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RAND EUROPE

Mental Health Retrosight

Case studies

Alexandra Pollitt, Stephanie Diepeveen, Susan Guthrie, Molly Morgan Jones, Siobhán Ní Chonaill, Stuart S. Olmsted, Dana Schultz, Harold Alan Pincus, Jonathan Grant, Steven Wooding

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Prepared for the Alliance of Mental Health Research Funders

The project described in this report was supported in Canada by the Graham Boeckh Foundation, Alberta Innovates Health Solutions, and the Canadian Institutes of Health Research; in the UK by the National Institute for Health Research; and in the USA by the National Institute of Mental Health.

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Preface

Mental Health Retrosight was a three-year international project that aimed to investigate the translation and payback from mental health and neuroscience research, with a particular focus on schizophrenia. It looked at the development of research over a 20-year period in Canada, the USA and the UK.

The project was supported in Canada by the Graham Boeckh Foundation, Alberta Innovates – Health Solutions, and the Canadian Institutes of Health Research; in the UK by the National Institute for Health Research; and in the USA by the National Institute of Mental Health. It was the first project funded through the Alliance of Mental Health Research Funders, a joint initiative between the Graham Boeckh Foundation and RAND Europe. The network was established as a 'think tank without borders' that would undertake research and analysis into mental health research funding.

This report presents the full set of forward-tracing case studies. This is intended to complement the other reports associated with this study, which describe the findings and policy provocations, the methods and methodology, and the backward-tracing perspectives.

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CHAPTER 1

Changes in striatal dopamine neurotransmission assessed with microdialysis following recovery from a bilateral 6-OHDA lesion: variation as a function of lesion size

This case study is based on the research that produced the paper:

Castañeda, E., Whishaw, I.Q., & Robinson, T.E. (1990). Changes in striatal dopamine neurotransmission assessed with microdialysis following recovery from a bilateral 6-OHDA lesion: variation as a function of lesion size. *Journal of Neuroscience*, 10(6), 1847–1854.

Information was gathered from an interview with the lead author, Edward Castañeda, an interview with co-author Ian Whishaw, and desk-based research.

1.1 Summary

The target paper studied the effects of the destruction of nerve cells that produce dopamine on extra-cellular dopamine levels and brain function. The work was done in a rat model of Parkinson's disease, but the dopamine pathway was also important to drug addiction and schizophrenia. A reduction of dopamine in the brain is associated with Parkinson's disease, while high levels of dopamine are associated with schizophrenia (Arias-Carrion, 2007). Typical antipsychotics to treat schizophrenia block dopamine receptors in the brain. In addition, dopamine has been implicated in drug addiction and reward-seeking behaviour (Arias-Carrion, 2007). The paper was ground-breaking because it was one of the first to look at pre-synaptic effects on dopamine production and because it measured actual biochemical changes in the brain, using a novel technique, not just changes in animal behaviour.

Throughout his research career, Castañeda's primary interest has been 'the plasticity of the brain, how it can compensate during damage and how it changes during episodes of learning'. His research has focused on neurotransmission, specifically the production, storage and release of the neurotransmitter dopamine. He has used a rat model for Parkinson's because it is well established, with well-described behaviours and neural circuitry, so questions about neural plasticity as it relates to human behavioural disorders show face, construct and predictive validity. According to Castañeda, looking at a specific

condition such as Parkinson's disease allows a researcher to maintain focus, but is also necessary to receive funding.

The target paper reports on a technique called intracerebral microdialysis, used in the lab of Castañeda's PhD advisor at the University of Michigan, Dr. Terry Robinson. Robinson's lab had refined the technique of collecting fluid from the brain by using a microdialysis technique, which allows collection of fluids from very specific regions of the brain. With a post-doctoral fellowship from the Alberta Heritage Foundation, Castañeda, also trained in high-performance liquid chromatography (HPLC), went to the University of Lethbridge in Alberta, Canada, from 1987–1990 to help set up microdialysis and HPLC facilities in Ian Whishaw's lab.

After completing his post-doctoral fellowship, Castañeda went to Arizona State University, where he continued to study dopamine. During this time, his funding was limited to primarily intramural sources. He continued to collaborate with his advisors, and was asked by other laboratories to help them set up microdialysis. However, much of his time was spent on administrative and career development activities. Given his Hispanic background, he was asked to do a lot of mentoring and served on numerous university committees. In 2007, he moved to University of Texas at El Paso to become chair of the Department of Psychology. While much of his time there is now spent on administration of the department, he recently won a large grant to fund the Vulnerability Issues in Drug Abuse (VIDA) Project, which is multidisciplinary in its approach to studying vulnerability factors that contribute to drug abuse and addiction.

Although this case study research did not lead directly to clinical practice or applications, it contributed to the body of knowledge related to the effects of dopamine production by measuring biochemical changes in the brain using a novel technique.

1.2 Introduction

1.2.1 Scientific background

This research examines neurotransmission of dopamine and the plasticity of the brain, including how the brain recovers function after a loss event. It derived from earlier work in Sweden in the 1970s by Urban Ungerstedt that pioneered a research method using radioactive ligands. At the time, it was known that Parkinson's patients exhibited a large (>80 percent) depletion of dopamine-producing nerve cells in the substantia nigra. A rat model, where rats exhibited similar loss of body functions to Parkinson's patients, had been developed and a non-linear relationship between loss of dopamine-producing nerve cells and behavioural symptoms was discovered. Rats that lost up to 80 percent of the nerve cells producing dopamine were able to function normally; in contrast, rats that had 95–97 percent of their dopamine-producing nerve cells destroyed experienced a permanent loss of many motor functions. However, rats that are depleted of 80–95 percent of their dopamine-producing cells are able to recover some function. Early studies of the rat model were based primarily on behavioural observations of gross motor functions and post-mortem analysis of brain tissue, and were not able to accurately measure extracellular dopamine concentrations from specific regions in the brain.

The relationship between this work and schizophrenia is also based on the dopamine system. While Parkinson's disease is related to a decrease in dopamine activity, one theory about schizophrenia relates to an increase in dopamine concentration in specific areas of the brain. The treatments for Parkinson's and schizophrenia are opposite to each other, and can lead to some symptoms of the other disease. For instance, some Parkinson's patients develop some of the symptoms of schizophrenia, including hallucinations (Poewe, 2003), although it is not clear if these are medication induced or result from other risk factors (Merims et al., 2004).

1.2.2 Researchers' backgrounds

Edward Castañeda has a BSc and MA in psychology from the University of Texas at El Paso. He completed his PhD in psychobiology at the University of Michigan in 1987. From 1987–1990, he completed a post-doctoral fellowship in the Department of Psychology at the University of Lethbridge in Canada. Castañeda's post-doc was funded by the Alberta Heritage Foundation, and included money to buy some of the necessary HPLC instruments to conduct his experiments. Castañeda was then at Arizona State University from 1990, before becoming chair of the Department of Psychology at the University of Texas at El Paso in 2007.

Castañeda wrote the target paper with his PhD advisor, **Terry Robinson**, and his post-doctoral advisor, **Ian Whishaw**. Robinson had been an undergraduate student of Whishaw's and has remained at the University of Michigan. He is currently the Elliot S. Valenstein Collegiate Professor of Behavioral Neuroscience and a Professor in the Department of Psychology and Neuroscience Program. Whishaw has remained at the University of Lethbridge and currently holds a Board of Governor's Research Chair in The Canadian Center for Behavioural Neuroscience and in the Department of Neuroscience.

1.3 Defining the research cloud

This case study covers the research carried out during Castañeda's post-doctoral fellowship at the University of Lethbridge to develop and use microdialysis to look at intracerebral dopamine levels in live rats and correlate those levels with behavioural characteristics. Much of this work was completed during Castañeda's post-doctoral fellowship from 1987 to 1990. A few later papers by Castañeda's and his co-authors continue the research around recovery of function after damage to dopamine-producing cells using microdialysis.

The publications included in the cloud for this case study are as follows:

1. Robinson, T.E., & Whishaw, I.Q. (1988). Normalization of extracellular dopamine in striatum following recovery from a partial unilateral 6-OHDA lesion of the substantia nigra: a microdialysis study in freely moving rats. *Brain Research*, 450(1–2), 209–224.
2. Castañeda, E., Whishaw, I.Q., Lermer, L., & Robinson, T.E. (1990). Dopamine depletion in neonatal rats: Effects on behavior and striatal dopamine release assessed by intracerebral microdialysis during adulthood. *Brain Research*, 508(1), 30–39.
3. Castañeda, E., Whishaw, I.Q., & Robinson, T.E. (1990). Changes in striatal dopamine neurotransmission assessed with microdialysis following recovery from a

bilateral 6-OHDA lesion: variation as a function of lesion size. *Journal of Neuroscience*, 10(6), 1847–1854.

4. Robinson, T.E., Yew, J., Paulson, P.E., & Camp, D.M. (1990). The long-term effects of neurotoxic doses of methamphetamine on the extracellular concentration of dopamine measured with microdialysis in striatum. *Neuroscience Letters*, 110(1–2), 193–198.
5. Castañeda, E., Whishaw, I.Q., & Robinson, T.E. (1992). Recovery from lateralized neocortical damage: dissociation between amphetamine-induced asymmetry in behavior and striatal dopamine neurotransmission in vivo. *Brain Research*, 571(2), 248–259.
6. Whishaw, I.Q., Fiorino, D., Mittleman, G., & Castañeda, E. (1992). Do forebrain structures compete for behavioral expression?: Evidence from amphetamine-induced behavior, microdialysis, and caudate-accumbens lesions in medial frontal cortex damaged rats. *Brain Research*, 576(1), 1–11.
7. Robinson, T.E., Mocsary, Z., Camp, D.M., & Whishaw, I.Q. (1994). Time course of recovery of extracellular dopamine following partial damage to the nigrostriatal dopamine system. *Journal of Neuroscience*, 14(5), 2687–2696.
8. Robinson, T.E., Noordhoorn, M., Chan, E.M., Mocsary, Z., Camp, D.M., & Whishaw, I.Q. (1994). Relationship between asymmetries in striatal dopamine release and the direction of amphetamine-induced rotation during. The first week following a unilateral 6-OHDA lesion of the substantia nigra. *Synapse*, 17(1), 16–25.
9. Tran-Nguyen, L.T.L., Castañeda, E., & MacBeth, T. (1996). Changes in behavior and monoamine levels in microdialysate from dorsal striatum after 6-OHDA infusions into ventral striatum. *Pharmacology, Biochemistry, and Behavior*, 55(1), 141–150.
10. Neisewander, J.L., Castañeda, E., Davis, DA., Elson, H.J., & Sussman, A.N. (1996). Effects of amphetamine and 6-hydroxydopamine lesions on reserpine-induced oral dyskinesia. *European Journal of Pharmacology*, 305(1–3), 13–21.

1.4 Stage 0: Opportunity identification/research needs assessment

Inspiration

This area of research grew from the work and techniques of Robinson's laboratory at the University of Michigan. A rat model for Parkinson's disease had previously been developed (Schultz, 1982). These rats displayed a non-linear relationship between behavioural function and extent of depletion of dopamine-producing nerve cells. Rats behaved normally with up to 80 percent of their dopamine producing nerve cells destroyed. They initially lost functions if 80–95 percent of their dopamine-producing cells were destroyed, but, if kept alive with feeding tubes, regained some function. Finally, they showed complete loss of function if 95–98 percent of dopamine-producing nerve cells were destroyed. This model had been characterised by post-mortem inspections of brain tissue, but actual levels of dopamine in the extracellular regions of the brain had not been measured. While others had shown that more dopamine was being produced in cells of rats that had 20–80 percent of their dopamine producing cells destroyed, nobody had been able to measure the release of that dopamine and the intracerebral concentration of

dopamine. The research conducted in Robinson's laboratory and developed further in Whishaw's laboratory at the University of Lethbridge by Castañeda resulted in a technique that allows researchers to measure intracellular dopamine levels and represented an obvious next step based on the existing research in this area. Castañeda reported that one researcher told him that he 'had the done the study that she had been wanting to do for a long time. But it was so technically challenging, that most people weren't going to do it.'

> And I was particularly interested in going to Michigan because I had always been interested in this dynamic process of release, and tried to profile changes in brain activity with changes in behaviour. (EC)

Feasibility

The research was possible because of Castañeda's skills and expertise, as well as the introduction of a new technique, microdialysis. Castañeda originally went to the University of Michigan to work in Robinson's laboratory, studying biochemical, especially dopamine, pathways in the brain and learning biochemical and other techniques including high-performance liquid chromatography (HPLC). HPLC is a method of identifying and analysing chemicals such as neurotransmitters that are present in samples of liquid (e.g. the fluid around cells in the brain). At the end of his PhD training, he also learned a microdialysis technique to measure intracerebral levels of neurotransmitters that had been refined by Robinson. Towards the end of Castañeda's graduate work, Whishaw from the University of Lethbridge also spent a semester at Michigan with Robinson to learn microdialysis for his laboratory in Canada. Previously, Whishaw's laboratory had been more focused on behavioural studies of rats with Parkinson-type disease. Whishaw offered Castañeda a post-doctoral position to come back to Lethbridge to assist him setting up HPLC and microdialysis in his lab. This was a challenge for Castañeda and Whishaw, as noted by Castañeda:

> It was really tough to do, and it's still really tough to do microdialysis. People say that if you rely on microdialysis in your laboratory, you're committing professional suicide. (EC)

The combined expertise of Castañeda and his mentors enabled them to conduct research studies that had not been attempted by other laboratories.

Potential value

The value of this research for Castañeda stemmed from his desire to advance the field and his career by conducting high-impact research that would lead to grant and job opportunities.

> I think my effort is more long term. I contribute to the literature, and I hope that people that are more at the translational process will be able to see some of those principles that they can adapt. (EC)

1.5 Stage 1: Inputs to research

Money, researcher time, lab/office space and consumables

Whishaw's work was supported by the Medical Research Council (MRC) for Canada, now the Canadian Institute for Health Research, and the National Research Council (NRC), now the National Science and Engineering Research Council. Whishaw's initial research was funded by the NRC to do basic science work to investigate pathways in the brain stem

that produce brainwaves. This included studies of brainwaves using electroencephalography (EEG) and behavioural studies of rats with various brain lesions. When he started working on dopamine and its link to Parkinson's disease, he also applied for funding from the MRC, which funds more medically related research. Both these funders allow researchers a fair amount of latitude to pursue the research topics and problems they like, providing general support that gives researchers more freedom.

When Castañeda arrived for his post-doctoral fellowship, Whishaw initially funded him through his NRC grants, which provided flexible funds for his laboratory. He then helped Castañeda successfully apply for funding from the Alberta Heritage Foundation for Medical Research, now Alberta Innovates Health Solutions. The Foundation supports research scientists and promotes research in Alberta, and it provided funding for both Castañeda's time and the HPLC instrument used to conduct the biochemical assays needed for their experiments.

Whishaw started working at the University of Lethbridge in 1971, based in a small classroom. By the 1980s, he had acquired a laboratory and a few test rooms. There were only three researchers working in the laboratory (himself, Castañeda and Bryan Kolb). Whishaw's success continued to grow, and in the mid-1990s, he and Bryan Kolb received a grant from the Canadian government to build the Canadian Centre of Behavioural Neuroscience. There are now over 100 people working in that centre.

Knowledge

The experiments described in the target paper required substantial knowledge and experience in two main areas. First, experience in conducting and understanding behavioural experiments with rats was important. One of the outputs of the experiments was the ability of the treated and control rats to perform specific motor functions. Secondly, a detailed understanding of the neurobiology of dopamine-producing nerve cells, how they operate and how to create lesions in the brain to reduce dopamine nerve cells was required.

Expertise and techniques

This research cloud required three main technical components: animal testing facilities, HPLC expertise, and microdialysis expertise. Whishaw had already developed a laboratory with animal testing facilities, but he did not have the biochemical assays required for these experiments. Castañeda brought two unique skills to Alberta for his post-doctoral fellowship. First, he was a well-trained biochemist with expertise in HPLC. Secondly, he had learned the microdialysis technique and equipment that Robinson had successfully modified. While the microdialysis apparatus was reasonably priced, the HPLC equipment, which was required to do the biochemical testing of the samples collected via the dialysis, was expensive. Funding from the Alberta Heritage Foundation for Castañeda included money to purchase an HPLC instrument.

Collaborators

Castañeda's primary collaborators were Whishaw and Robinson. From 1968–1971, Whishaw trained at the University of Western Ontario under Vanderwolf, who himself had been a student of Donald Hebb, a famous Canadian neuropsychologist. Vanderwolf was known for electrophysiology of the hippocampus and categorising behaviours based on EEG. Whishaw went on to a faculty position at the University of Lethbridge in 1970.

Robinson was an early undergraduate researcher with Whishaw, and then went on to work on his PhD with Vanderwolf at the University of Western Ontario. Later, Robinson was appointed to a position in Michigan. There he married a post-doctoral fellow, Jill Becker, a chemist who brought the HPLC technique to the collaboration. Castañeda completed his PhD in Robinson's laboratory and worked closely with Becker to develop his biochemistry skills. Robinson is currently the Elliot S. Valenstein Collegiate Professor of Behavioral Neuroscience and a Professor in the Department of Psychology and Neuroscience Program at the University of Michigan.

Whishaw has more than 400 publications and Robinson has 300.

1.6 Stage 2: Processes

This research cloud starts with the publication of the microdialysis technique (Robinson, 1988) and another early study of nerve cell death on behavioural characteristics in the rat model (Castañeda, 1990a).

The target paper (Castañeda, 1990b) reports the results of basic research on brain recovery and function using a previously developed animal model for Parkinson's disease. The team treated a group of the animals with varying amounts of 6-hydroxydopamine to kill some of the dopamine-producing nerve cells in the substantia nigra (a region of the brain). The rats were then allowed to recover for one month. After that, the levels of dopamine were measured using the microdialysis technique, which involved inserting a very small dialysis probe into the brain. The probe had fluid pumped through it, and because neurotransmitters could diffuse into the probe from the surrounding brain the level of neurotransmitters in the brain could be tested. The dialysate was then tested for dopamine and other neurotransmitters. The animals were also treated with *d*-amphetamine, which stimulates dopamine release to 'determine their ability to respond to an increased demand for dopamine release'. Treated animals were compared to control animals. Five days after the completion of testing, the rats were killed and their brains examined to determine the size of the lesion of cell death caused by the 6-hydroxydopamine.

At the time, these researchers were not the only group working on the effects of cell death on dopamine production. There was a friendly competition and 'tension' with the Zigmond laboratory at the University of Pittsburgh and an Italian laboratory. Both these laboratories were also trying to refine microdialysis to better measure intracerebral concentrations of neurotransmitters. It was a race to discover the details of the innate capacity of dopamine neurons to increase dopamine release.

Subsequently, the collaborators continued their work on the biochemical impact of cell death on dopamine levels, focusing on different aspects of the research questions including different regions of the brain, and length of time after initiating cell death (Robinson, 1990, 1994a, 1994b; Castañeda, 1992; Whishaw, 1992; Tran-Nguyen, 1996; Neiswander, 1996).

1.7 Stage 3: Primary outputs

Knowledge

The techniques used in the target paper allowed the researchers to measure extracellular dopamine levels in live rats. Using the intracerebral microdialysis technique, the team showed that, one month after treating rats with a chemical that kills some of the dopamine-producing nerve cells, some of the rats are able to continue to produce the same extracellular concentration of dopamine. To do this, the remaining live cells increase their production and release of dopamine and help the rats maintain normal motor functions. Specifically, rats depleted of 20–80 percent of their dopamine-producing cells are able to maintain the same amount of extracellular dopamine as control rats. Rats depleted of 80–95 percent of dopamine-producing cells show a slight decrease in dopamine production, but many of those rats are still within the control range of dopamine release. Rats with high levels of lesions (>95 percent) show a significant reduction in extracellular dopamine concentration. This was important in understanding the recovery of function of the dopamine system.

The authors reported that the paper was highly cited because it was focused on the pre-synaptic mechanisms and the changes that took place in the receptors. In addition, they reported that it was important because it helped to clarify conflicting reports from their laboratory and another laboratory, which had initially found a linear relationship between cell death and dopamine concentration. In addition, there was a large literature focused on recovery on depletion and this paper helped to understand that the system was robust even when severely depleted.

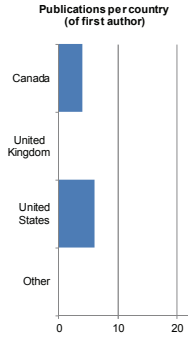
> I think it was because we were looking at pre-synaptic mechanisms in Lethbridge that really brought to life for the first time that there are changes taking place on the pre-synptic side of the connection that might be harnessed to improve recovery after damage or neurodegeneration. A lot of the research at that time was looking at changes in the other side of the synapse, namely post-synaptic receptors. And there was a huge literature on the receptor question. And people were just starting to get interested in what's happening on the pre-synaptic side. (EC)

Subsequent papers report findings based on similar studies examining different regions of the brain, or looking at different recovery timelines.

A bibliometric analysis of the papers produced from the research cloud is shown below.

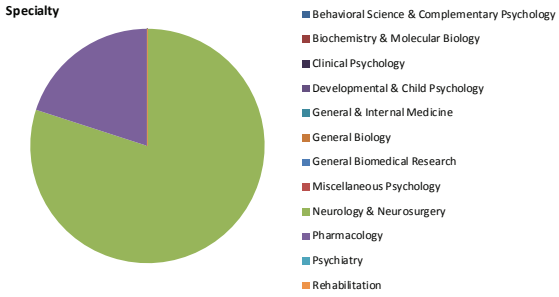
Research cloud:

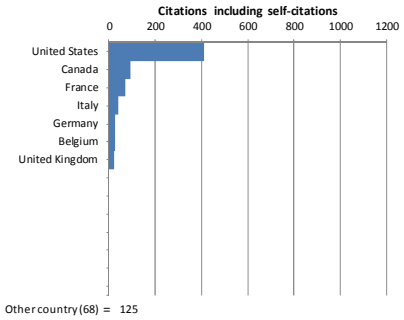
		Citations in:		% of total citations	Research level of cloud papers	
WoS Indexed papers:	10	**RCT:**	2	0%	Clinical **1:**	0%
Total citations of papers:	819	**Meta-analyses:**	0	0%	**2:**	0%
of which, self-citations:	2.7%	**Indexed practice guidelines:**	0	0%	**3:**	10%
Mean citations per paper:	82	**Review articles:**	81	10%	Basic **4:**	90%
Distinct cloud citations:	743					
Second-generation cloud citations:	25,732					
Third-generation cloud citations:	331,030					



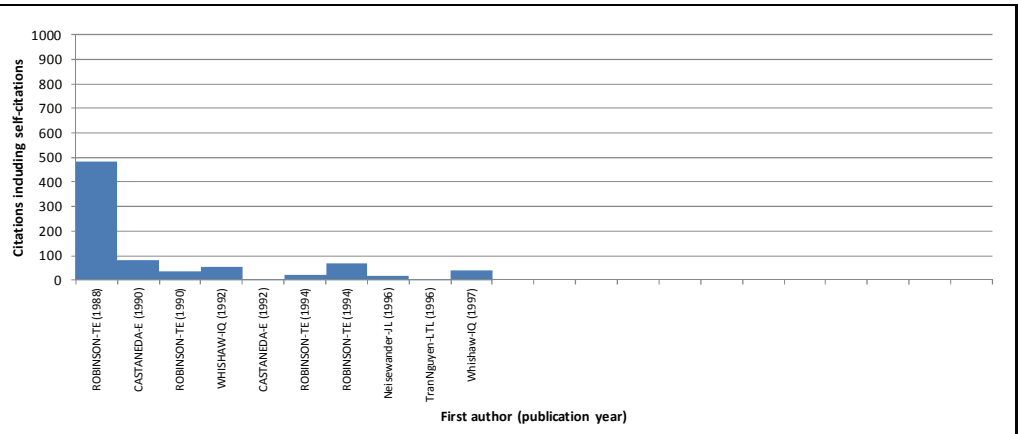
Most highly cited article: Terry E. Robinson, Ian Q. Whishaw (1988). Normalization of extracellular dopamine in striatum following recovery from a partial unilateral 6-OHDA lesion of the substantia nigra: a microdialysis study in freely moving rats, Brain Research, 450 (1-2): 209-224

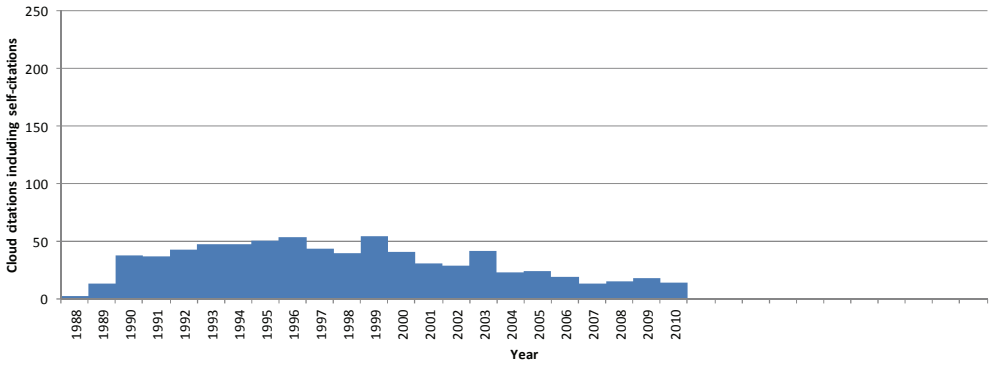
Times cited: 485





Note: Countries with more than 20 citations are displayed





Targeting future research

Effect on the researchers' careers

At the time of this paper, the scientific community was just beginning to explore the biochemical nature of diseases like Parkinson's. Techniques such as microdialysis were in the early stages of development. The papers that derived from this research cloud enabled Castañeda to get a tenure track position at a research university. His collaborators continued to do substantial work in the areas of biochemical and behavioural aspects of drug addiction and diseases, especially Parkinson's, each publishing over 300 papers.

After his post-doctoral fellowship, Castañeda worked at Arizona State University before moving to the University of Texas at El Paso. At Arizona State, he received start-up funding to cover equipment and space (especially for laboratory animals). Similarly, he received start-up funding from the university to build his laboratory. During this time, his research continued to focus on the recovery of function after depletion of dopamine-producing nerve cells. In part, Castañeda continued to collaborate with Whishaw. However, he also expanded his research to include the effects of cocaine on dopamine activity.

Castañeda's career also shifted from being focused primarily on research to also being very focused on administrative and career development activities. Beginning at the University of Lethbridge, Castañeda mentored undergraduate and graduate students.

> Certainly when I was a post-doc in Lethbridge, I had a cohort of students that learned this technique, that learned about the science, that got interested in research, and they went out and established their own independent research careers. So pushing forth the agenda that will ultimately benefit disease states like schizophrenia is going to depend on having the workforce that's out there, and that's competent to do really good research at all levels. Some of these students have gone on to more applied settings, or have stayed at the basic research level. (EC)

As a representative of a minority group, at Arizona State University and the University of Texas at El Paso, he has been asked to perform many duties involving improving the representation of minorities in science. Often these duties take considerable time and the result is a decreased research output. With the opportunity to become Chair, Castañeda felt that he was being compensated and recognised for these activities.

Castañeda has also helped to set up microdialysis in other labs. Collaborators on some of his studies have asked for assistance setting up the necessary equipment and training students in its use.

Future work

Currently, Castañeda is still working in the general field of brain function and its relationship to drugs and diseases. He has also expanded to more health policy work, leading the Hispanic Health Disparities Research Center, a cross-disciplinary centre at the University of Texas at El Paso, where one of his research projects examines the impact of drug addiction, Parkinson's and schizophrenia on the Hispanic population.

> I'm also co-director of the Hispanic Health Disparities Research Center here. And in the Hispanic Health Disparities Research Center, we're asking questions about why certain disease states are more prevalent in special populations, in this case, Hispanics, especially here in the border area. So I've got an opportunity to impact questions about drug

addiction, schizophrenia, neurodegenerative diseases like Parkinson's disease, specifically to Hispanic populations. (EC)

Robinson continues an active research career at the University of Michigan. Whishaw continues to perform research at the University of Lethbridge.

1.8 Interface B: Dissemination

Publications and talks were the main vehicles for disseminating the findings of the research cloud. Primarily the results were presented at basic science (cellular and behavioural) conferences such as those of the Society of Neurosciences and Psychological Associations.

Whishaw and Castañeda have both spoken to non-scientific audiences and support groups.

1.9 Stage 4: Secondary outputs

None identified.

1.10 Stage 5: Applications

None identified.

1.11 Stage 6: Public engagement

None identified.

1.12 Stage 7: Final outcomes

None identified.

1.13 Table of payback

Payback category	Impacts from case study
Knowledge Production	• Demonstrated the effects on dopamine production by measuring biochemical changes in the brain, using a novel technique.
Research Targeting and Capacity Building	• Critical to Castañeda's career during and after his post-doctoral fellowship. • Beneficial to other laboratories that Castañeda was able to support by setting up microdialysis after he had developed the technique and equipment.
Informing Policy and Product Development	• None identified.
Health and Health	• None identified.

Sector Benefits	
Broader Social and Economic Benefits	• None identified.

1.14 Timeline

1987	Castañeda completes his PhD in Psychobiology at the University of Michigan
1987–1990	Castañeda's post-doctoral fellowship at the University of Lethbridge
1988	Robinson and Whishaw publish first paper using microdialysis to measure dopamine in the brain
1990	Castañeda publishes results of the target paper
1990–1996	Castañeda is Assistant Professor at the Department of Psychology, Arizona State University
1992–1996	Castañeda and colleagues publish additional papers in the research cloud
1996–2007	Castañeda promoted to Associate Professor at the Department of Psychology, Arizona State University
2007	Castañeda accepts position as Professor & Chair at the Department of Psychology, University of Texas at El Paso

1.15 References

Arias-Carrión, O., & Pöppel, E. (2007). Dopamine, learning, and reward-seeking behavior. *Acta Neurobiologiae Experimentalis*, 67(4), 481–488.

Castañeda, E., Whishaw, I.Q., & Robinson, T.E. (1992). Recovery from lateralized neocortical damage: dissociation between amphetamine-induced asymmetry in behavior and striatal dopamine neurotransmission in vivo. *Brain Research*, 571(2), 248–259.

Castañeda, E., Whishaw, I.Q., & Robinson, T.E. (1990). Changes in striatal dopamine neurotransmission assessed with microdialysis following recovery from a bilateral 6-OHDA lesion: variation as a function of lesion size. *Journal of Neuroscience*, 10(6), 1847–1854.

Castañeda, E., Whishaw, I.Q., Lermer, L., & Robinson, T.E. (1990). Dopamine depletion in neonatal rats: Effects on behavior and striatal dopamine release assessed by intracerebral microdialysis during adulthood. *Brain Research*, 508(1), 30–39.

Merims, D., Shabtai, H., Korczyn, A.D., et al. (2004). Antiparkinsonian medication is not a risk factor for the development of hallucinations in Parkinson's disease. *Journal of Neural Transmission*, 111, 1447–1453.

Neisewander, J.L., Castañeda, E., Davis, DA., Elson, H.J., & Sussman, A.N. (1996). Effects of amphetamine and 6-hydroxydopamine lesions on reserpine-induced oral dyskinesia. *European Journal of Pharmacology*, 305(1–3), 13–21.

Poewe, W. (2003). Psychosis in Parkinson's disease. *Movement Disorders*, 18, S80–S87.

Robinson, T.E., & Whishaw, I.Q. (1988). Normalization of extracellular dopamine in striatum following recovery from a partial unilateral 6-OHDA lesion of the substantia nigra: a microdialysis study in freely moving rats. *Brain Research*, 450(1–2), 209–224.

Robinson, T.E., Mocsary, Z., Camp, D.M., & Whishaw, I.Q. (1994). Time course of recovery of extracellular dopamine following partial damage to the nigrostriatal dopamine system. *Journal of Neuroscience*, 14(5), 2687–2696.

Robinson, T.E., Noordhoorn, M., Chan, E.M., Mocsary, Z., Camp, D.M., & Whishaw, I.Q. (1994). Relationship between asymmetries in striatal dopamine release and the direction of amphetamine-induced rotation during. The first week following a unilateral 6-OHDA lesion of the substantia nigra. *Synapse*, 17(1), 16–25.

Robinson, T.E., Yew, J., Paulson, P.E., & Camp, D.M. (1990). The long-term effects of neurotoxic doses of methamphetamine on the extracellular concentration of dopamine measured with microdialysis in striatum. *Neuroscience Letters*, 110(1–2), 193–198.

Schultz, W. (1982). Depletion of dopamine in the striatum as an experimental model of parkinsonism: direct effects and adaptive mechanisms. *Progress in Neurobiology*, 18(2–3), 121–166.

Tran-Nguyen, L.T.L., Castañeda, E., & MacBeth, T. (1996). Changes in behavior and monoamine levels in microdialysate from dorsal striatum after 6-OHDA infusions into ventral striatum. *Pharmacology, Biochemistry, and Behavior*, 55(1), 141–150.

Whishaw, I.Q., Fiorino, D., Mittleman, G., & Castañeda, E. (1992). Do forebrain structures compete for behavioral expression?: Evidence from amphetamine-induced behavior, microdialysis, and caudate-accumbens lesions in medial frontal cortex damaged rats. *Brain Research*, 576(1), 1–11.

CHAPTER 2 Synaptic modulation by dopamine of calcium currents in rat pars intermedia

This case study is based on research related to the following paper:

Williams, P.J., MacVicar, B.A., & Pittman, Q.J. (1990). Synaptic modulation by dopamine of calcium currents in rat pars intermedia. *Journal of Neuroscience*, 10(3), 757–763.

Information was gathered from interviews with Peter Williams, Quentin Pittman and Jacco Keja, as well as desk-based research.

2.1 Summary

The target paper evaluates the modulation of currents by dopamine in pars intermedia cells in rats. This work was led by Peter Williams as part of his PhD research at the University of Calgary. He was supervised by Quentin Pittman and Brian MacVicar, who identified the general research questions prior to Williams joining MacVicar's lab for a PhD in neurophysiology. Williams' funding was through a full PhD scholarship from the Alberta Heritage Foundation.

Pittman and MacVicar did not begin this work with a specific hypothesis about the modulation of calcium currents in the pars intermedia, in particular. They thought it was likely that dopamine would be inhibitory to calcium currents as it was known that dopamine inhibited release of hormones from these cells and that calcium currents were also critical for hormone release. Primarily, they chose to examine modulation of calcium currents by dopamine because they had an interest in how it worked. Williams agreed to pursue the research question proposed by MacVicar and Pittman because he was interested in the science. While Pittman and MacVicar were familiar with electrophysiology techniques, Williams was not. Williams spent the first few months of his PhD learning and refining the technique; this was sufficient for him to learn how to successfully apply the technique to cells of the rat pars intermedia. After this initial training, he then applied a single electrode voltage clamp technique to stimulate isolated cells from the pars intermedia and measure T-, N- and L- type calcium currents. Williams measured the inhibition of calcium currents at high and low voltages, by dopamine antagonists and agonists, and also the role of G-proteins in mediating this relationship. He found that the research process was marked by a high degree of uncertainty about which experiments to run and which stimulations to test. Given this uncertainty, Williams found that time to

explore open research questions, access to up-to-date equipment to facilitate well-run experiments, and 'intuition' were critical for successful experiments.

The main findings of this research were that both low- and high-threshold peak inward calcium currents were inhibited from a holding potential of -90 mV. This was not the case with a holding potential of -30 mV. This pattern of inhibition was found to be consistent. They also found that the inhibition of calcium currents was reversed by an antagonist of dopamine, while a dopamine (D2) agonist (Quinpirole) inhibited calcium currents at a holding potential of -90mV, and that D2 dopamine stimulation of calcium currents was prevented by pertussis toxin, suggesting that G proteins play a role in synaptic modulation by dopamine.

This work has been cited as one of the early studies to demonstrate dopamine modulation of calcium currents in the pars intermedia. Williams, MacVicar and Pittman were one of the first groups to publish comprehensive, consistent and well-defined results on dopamine modulation of calcium currents in this area of the brain. By providing consistent results about the effect of dopamine, this study helped to accumulate the evidence of this particular function of dopamine, through robust exploratory research; synaptic modulation of calcium currents is now well accepted.

This particular work was discontinued at the lab once Williams left the University to take a post-doctoral position at the University of Colorado, Denver. Williams chose not to remain in neurophysiology and at present is a practicing counsellor in Calgary, Alberta.

In contrast to Williams, MacVicar and Pittman continued in research. While their subsequent work was informed by this research cloud, they chose to take it in new directions. MacVicar shifted to focusing on dopamine in areas of the brain important in emotional controls and behaviour. He applied aspects of the approach that Williams used in exploring cells of the pars intermedia to a different area of the brain, more relevant to mental disorders. Pittman remained head of a lab at the University of Calgary, but shifted his focus to synaptic pharmacology of endocrine and autonomic nuclei, and central autonomic controls.

While this specific research had little direct clinical application, the accumulation of basic research on the modulation of calcium currents has informed some early clinical studies looking at calcium currents as targets for chronic pain. However, most directly, the contribution of this research was to improve basic understanding of brain functioning. By expanding knowledge of processes and functioning in a specific area of the brain, investigations such as this can help to build a foundation for further research aimed at understanding neurological disorders and how they affect brain functioning.

2.2 Introduction

2.2.1 Scientific background

The research conducted in this case study explores functions of the nervous system through electrophysiology, a technique used to measure the electrical activity of neurons and the action potentials of cells. Experiments tested the effects of dopamine on calcium currents by applying dopaminergic agonist or synaptically released dopamine to tissues in vitro, and

then measuring their responses to the stimulus using single-electrode voltage clamp recordings.

Experiments were conducted using melanotroph cell tissues from the intermediate pituitary (also known as the pars intermedia) of the rat. The preparation was somewhat unique, in that it consisted of the intact pituitary with defined, afferent (incoming) connections, which could be placed in a dish where it could be perfused with known concentrations of drugs and potential transmitters whilst intricate intracellular recording was taking place. Very few mammalian preparations offer these advantages.

While these experiments were being conducted, there was also ongoing research in the MacVicar lab on a particular type of glial cell, astrocytes. Glial cells were first thought to simply hold neurons in place, but from the 1960s and particularly in the 1980s and 1990s it was discovered that they also released and responded to neurotransmitters. Astrocytes are a type of glial cell found in the brain that have been found to generate chemical signals, and their activation appears linked to calcium currents.

2.2.2 Researchers' backgrounds

Peter Williams was the primary investigator. The research cloud in question formed the basis for his PhD research at the University of Calgary. Williams conducted these experiments while at Brian MacVicar's lab at the university. Williams chose not to remain in neurophysiology, and is now a practicing counsellor in Calgary.

Quentin Pittman was one of Williams' PhD supervisors. He remains a synaptic neuroscientist at the University of Calgary, and continues to work in the areas of physiology and biophysics.

Brian MacVicar was the head of the lab at the University of Calgary where the research took place, and supervised Williams' PhD along with Pittman. MacVicar developed a research programme at the University of Calgary to explore the neurophysiology of astrocytes in the 1980s; the programme formed part of the landscape in which this research cloud was conducted. Since the 1980s, MacVicar has become increasingly interested in the study of active membranes of astrocytes and other glial cells, and calcium signalling. In 2003, MacVicar took up a position as a Professor in the Department of Psychiatry and the Brain Research Centre at the University of British Columbia.

2.2.3 Institution background

This research cloud took place within the Neuroscience Research Group at the University of Calgary. This was a multidisciplinary group that supported and encouraged collaboration and networking between researchers interested in neuroscience research, spanning a wide range of departments, including Cell Biology, Anatomy, Clinical Neurosciences, Physiology and Biophysics, etc. The group subsequently evolved into the Hotchkiss Brain Institute, launched in 2004.

The PI for this work, Williams, was a student in medical physiology associated with the Neuroscience Research Group. His primary supervisor, Pittman, was also a member of the group, and was associated with the Department of Physiology and Biophysics. At the time, the department was experiencing dynamic growth within the university, supported by wider efforts to form the Alberta Heritage Foundation for Medical Research (AHFMR). Through the 1980s, physiology research at the University of Calgary was able to attract

financial support in the form of grants for competitive salaries and some equipment grants from the AHFMR,[1] which was founded and began to fund students and fellows in 1980.[2]

2.3 Defining the research cloud

This research cloud consists of research done at MacVicar's lab at the University of Calgary to explore synaptic modulation of electric currents by dopamine in cells of the intermediate pituitary. The entry point for this case study is the publication 'Synaptic modulation by dopamine of calcium currents in rat pars intermedia', authored by Peter Williams, Brian MacVicar and Quentin Pittman. MacVicar and Pittman (1986) devised the research question, and Williams was the primary person conducting the experiments, which he did as part of his PhD research at the University of Calgary, supervised by Pittman and MacVicar.

The papers published from this research cloud were:

1. Williams, P.J., MacVicar, B.A., & Pittman, Q.J. (1990). Synaptic modulation by dopamine of calcium currents in rat pars intermedia. *Journal of Neuroscience*, 10(3), 757–763.
2. Williams, P.J., MacVicar, B.A., & Pittman, Q.J. (1990). Electrophysiological properties of neuroendocrine cells of the intact rat pars intermedia: multiple calcium currents. *Journal of Neuroscience*, 10(3), 748–756.
3. Williams, P.J., Pittman, Q.J., & MacVicar, B.A. (1993). Blockade by funnel web toxin of a calcium current in the intermediate pituitary of the rat. *Neuroscience Letters*, 157(2), 171–174.
4. Williams, P.J., Pittman, Q.J., & MacVicar, B.A. (1991). Ca(2+)- and voltage-dependent inactivation of Ca2+ currents in rat intermediate pituitary. *Brain Research*, 564(1), 12–18.

The research cloud itself was relatively contained; Williams felt it had a natural endpoint once he finished measuring the modulation of different calcium currents by dopamine:

> To a certain extent we'd done a pretty good job of characterising our system so then the next logical step would have been what do you use it for? (PW)

The research, focusing on calcium currents and dopamine in the intermediate pituitary, largely concluded with the completion of Williams' PhD research. Wider research activities at the lab evolved to new areas. Others in the lab turned to studying glial cells in the pituitary (Mudrick-Donnan, Williams et al., 1993). MacVicar and Pittman looked more widely at dopamine action in the brain. Their subsequent work included examination of sodium currents (Fraser, Hoehn et al., 1993; Horn, Bauce et al., 1995); glutamate synaptic transmission (Chen, Kombian et al., 1999; Price & Pittman, 2001); and peptide release

[1] http://www.ucalgary.ca/pp/history

[2] The founder of the Department of Physiology and Biophysics at the University of Calgary, Professor K.E. Cooper, took up a senior administrative post at the University as Associate Vice-President in 1978. While in this position, Cooper, along with others at the University of Calgary and the University of Alberta in Edmonton, was closely involved in setting up the AHFMR.

from dendrites of magnocellular neurons and its effects (Kombian, Mouginot et al., 1997); as well as activity in different areas of the brain, for example the parabrachial nucleus (a region of the pons) (Chen, Kombian et al., 1999), the prefrontal cortex (Kisilevsky, Mulligan et al., 2008) and the hypothalamus (Price & Pittman, 2001).

2.4 Stage 0: Opportunity identification/research needs assessment

Inspiration

In the 1980s, when this research began, the actions of dopamine in the brain were in the process of being identified. One of the components of this line of questioning was to ask if dopamine has an effect on membrane current (JK). Calcium currents were of particular interest, and a analysis of the modulation and function of calcium currents became fashionable among labs working in neurophysiology at the time (QP). It was confirmed in the early 1980s that calcium channels were important targets for hormones (Reuter, 1983; Tsien, 1983; Cota, 1986); researchers were also aware of the presence of calcium currents in the melanotroph, and their function in triggering secretion from these cells (Williams, MacVicar et al., 1990). However, beyond this general knowledge, little was known about their function in the pituitary, and no successful studies had yet been published on calcium currents in pituitary cells in primary cultures (Cota, 1986).

Within this wider landscape of scientific exploration, Pittman and MacVicar became interested in whether or not dopamine modulated calcium currents. This inspired them to develop and initiate the study of synaptic modulation by dopamine of calcium currents in cells of the intermediate pituitary, as an aside to their primary areas of interest and funded research.[3]

Pittman and MacVicar did not begin this work with a specific hypothesis about the modulation of calcium currents in the intermediate pituitary. They thought it was likely that dopamine would be inhibitory to calcium currents as it was known that dopamine inhibited release of hormones from these cells and that calcium currents were also critical for hormone release. Primarily, they chose to examine modulation of calcium currents by dopamine because they had an interest in how it worked:

> We did a paper where we identified the calcium currents in these cells and then we said, 'Geez wouldn't it be cool to actually see what dopamine does to these calcium currents'. (QP)

MacVicar and Pittman proposed this question to Williams as a potential focus for his PhD work. Williams' primary research interest was neurophysiology and drugs of abuse. Pittman and MacVicar suggested to Williams that these experiments on the synapse in the intermediate pituitary could eventually contribute to a model synapse that could be used in the future to pursue more specific research on drugs of abuse (QP).

[3] For example, MacVicar, the lab head, was primarily funded to research epilepsy, and potential differences in calcium channels in epileptic versus non-epileptic tissue. Pittman was working on experiments on the relationship between the hypothalamus and the pituitary.

Prior to the research cloud, Williams had been working for about ten years at an oil analysis laboratory at Petro Canada. When he was laid off, Williams was awarded as scholarship to return to school; he decided to approach Quentin Pittman at the University of Calgary about conducting PhD research based on informal recommendations through word of mouth. Williams agreed to pursue the research question proposed by MacVicar and Pittman because he was interested in the science:

> I was fascinated by how this system worked. I wanted to know how this thing operated. I [didn't care] if there [was] any application. (PW)

Feasibility

The research environment, facilities and expertise at MacVicar's lab at the University of Calgary made this a very feasible research project.

Pittman and MacVicar were experienced in conducting electrophysiology experiments. They had been applying this technique to cells from other areas of the brain. Pittman was interested in the relationship between the hypothalamus and the pituitary, while MacVicar was focussed more on the role of glial cells in controlling neuron activity.

2.5 Stage 1: Inputs to research

Money, researcher time, lab/office space and consumables

While infrastructure, time and funding were necessary to carry out their work, the researchers involved did not find access to these resources to be a major challenge. MacVicar's lab at the University of Calgary already had in place equipment and financial support (QP, PW). Funding was accessible through grants and support from the Canadian Medical Research Council (MRC), who supported the project through an operating grant. Each researcher involved in the study also had individual salary support: Williams through a PhD scholarship from the AHFMR, and MacVicar and Pittman as both AHFMR Scholars and MRC Scientists.

Stable funding for equipment and time helped to attract researchers to the university, because it allowed them to devote the majority of their time to research (versus teaching) (QP) and supported access to high-quality equipment with which to conduct rigorous experiments. Williams argues that he 'had the Cadillac of equipment' including hydraulic micro-drives and an air flotation table necessary for isolating and stabilizing cells of the intermediate pituitary.

Expertise and techniques

MacVicar and Pittman's ongoing research activities in the 1980s drew on electrophysiology techniques, the same required for this research. MacVicar and Pittman also were engaged in work on cells in the intermediate pituitary, specifically astrocytes, a type of glial cell. They chose to look at cells in the intermediate pituitary for several reasons – primarily due to their knowledge of the characteristics of the cell and its amenability to exploration through electrophysiology techniques: (i) the membrane of the cells could be controlled relatively well; (ii) the cells could survive for long periods of time outside of the body; (iii) the cells received monosynaptic inputs making it possible to focus on particular synapses rather than a complex combination of connections (QP); and (iv) the pituitary contained a homogenous population of intermediate pituitary cells that could be easily targeted in vitro

(QP). However, one challenge in experimenting on cells of the intermediate pituitary was that they are small, and require very still conditions and precision in order to successfully conduct electrophysiology experiments.

However, while Pittman and MacVicar were familiar with electrophysiology techniques, Williams was not. Williams spent the first few months of his PhD learning and refining the technique; this was sufficient for him to learn how to successfully apply the technique to cells of the rat pars intermedia.

Collaborators

Progress in neurophysiology research was enabled at the time by advances in the patch clamp approach, as well as the growing ability to study cells in vitro (QP). However, there were few labs specifically experimenting with the effect of dopamine on synaptic modulation of calcium currents, and collaboration with other labs and researchers did not play a major role in the conducting of this research. Interviewees identified the following competing labs working in parallel in this area:

- Vrije Universiteit, Amsterdam: Jacco Keja was recruited to the laboratory of J.C. Stoof as a PhD student to look at the effect of dopamine on receptors in the intermediate pituitary, and on electric currents. This was supported through a grant from the Dutch Association of Basic Science.
- Institut National de la Santé et de Recherche Médicale, Bordeaux, France.[4]
- Department of Pharmacology, School of Medicine, Yale University: led by research by W.W. Douglas.
- Stanford University: Richard W. Tsien worked more broadly on calcium currents, but not specifically modulation by dopamine in the pars intermedia.

Lab heads and senior researchers at these universities were aware other groups were pursuing similar research questions (JK, QP). Researchers in this area interacted at conferences (PW, JK), and would follow each other's publications. Pittman and MacVicar sought to maintain contact with researchers experimenting with calcium currents more widely, and many researchers working in this area visited the University of Calgary during this time. However, despite this, researchers tended to work in isolation (JK). One researcher, from a competing lab in the Netherlands at the time, suggests:

> In all honesty… we were working in the same field along the same research questions; what I remember is there was not much in terms of cooperation and coordination. We would have benefitted if we had specialised a bit more or had more frequent phone calls and more frequent communication. (JK)

2.6 Stage 2: Processes

The research experiments were conducted as part of Williams' PhD research and Williams found he had the freedom to take the lead in conducting the research:

> They gave me this little project and said, 'Run with it. See what you can do'. …I don't think they had any real clear cut expectations. (PW)

[4] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1189835/

Williams was guided by MacVicar and Pittman. Pittman suggests that the model was for the students to do the experiments, but for the more senior staff to review and supervise this work on an ongoing basis:

> MacVicar and my role was to make sure that there was funding for [the research] and we were supervising the work on a daily basis. We would discuss every day with Peter Williams what the outcomes of the experiments were, and where we should go ahead. It was a true collaboration. (QP)

As noted above, Williams first spent a few months being trained in the application of electrophysiology techniques. He then applied a single electrode voltage clamp technique to stimulate isolated cells from the pars intermedia and measure T-, N- and L- type calcium currents. Williams measured the inhibition of calcium currents at high and low voltages, by dopamine antagonists and agonists, and also the role of G-proteins in mediating this relationship.

Williams found the research process was marked by a high degree of uncertainty about which experiments to run and which stimulations to test. Using the analogy of a computer and a computer game, Williams suggests:

> The human brain… has 10 billion neurones, multiply redundant, and what possible chance have we got? It's like trying to figure out what a computer programme is doing. You're running World of Warcraft and you've got a voltmeter and you're poking the computer with your voltmeter and trying to figure out what World of Warcraft strategy to use. (PW)

Given this uncertainty, Williams found that time to explore open research questions, access to up-to-date equipment to facilitate well-run experiments, and 'intuition' were critical for successful experiments:

> You have to have good intuition because there is always going to be 50 or 60 leads presented from every experiment. And it's knowing which one to track down and which one to follow. And that's all intuition. It's not logic. (PW)

2.7 Stage 3: Primary outputs

Knowledge

The results of this study characterised the modulation at the synapse by dopamine of calcium currents in cells of the pars intermedia, looking at three types of currents: N, L and T. The work had several main findings:

- Both low- and high-threshold peak inward calcium currents were inhibited from a holding potential of -90 mV. This was not the case with a holding potential of -30 mV. This pattern of inhibition was found to be consistent.
- The inhibition of calcium currents was reversed by an antagonist of dopamine, while a dopamine (D2) agonist (Quinpirole) inhibited calcium currents at a holding potential of -90mV.
- D2 dopamine stimulation of calcium currents was prevented by pertussis toxin, suggesting that G proteins play a role in synaptic modulation by dopamine.

This work has been cited as one of the early studies to demonstrate dopamine modulation of calcium currents in the pars intermedia. Williams, MacVicar and Pittman were one of the first groups to publish comprehensive, consistent and well-defined results on dopamine modulation of calcium currents in this area of the brain:

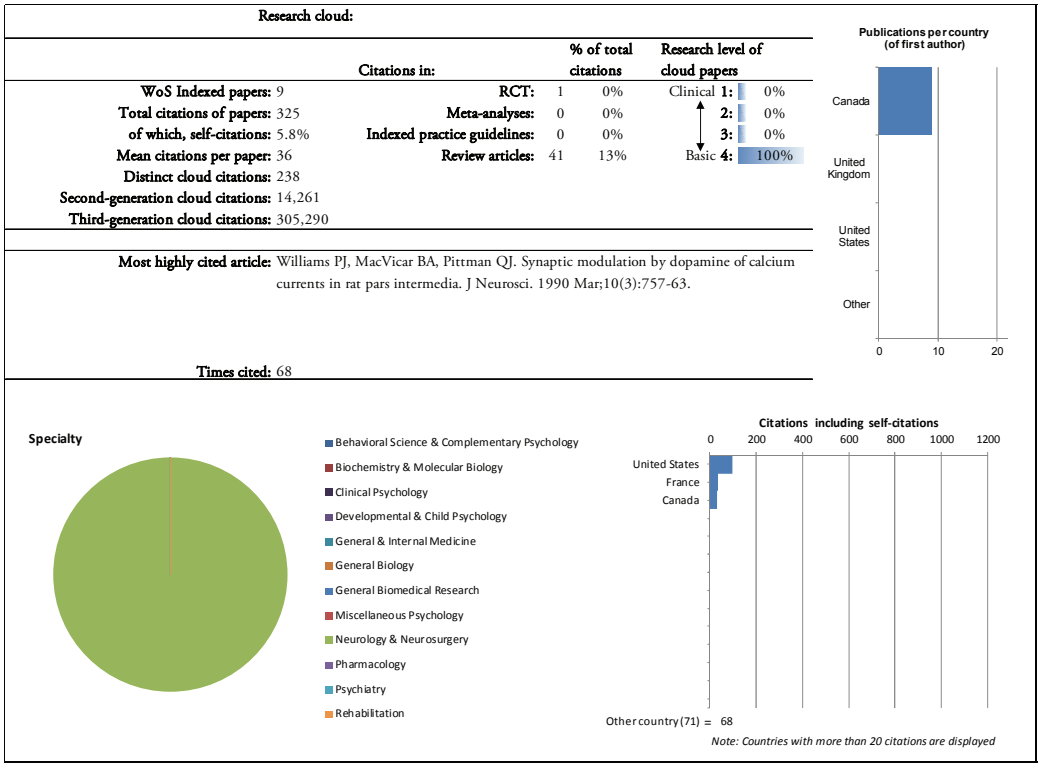
> I think that the data that came from this was so robust that I would like to think it made it easier for people to work on a dopamine system in areas of the brain that are much more difficult. (QP)

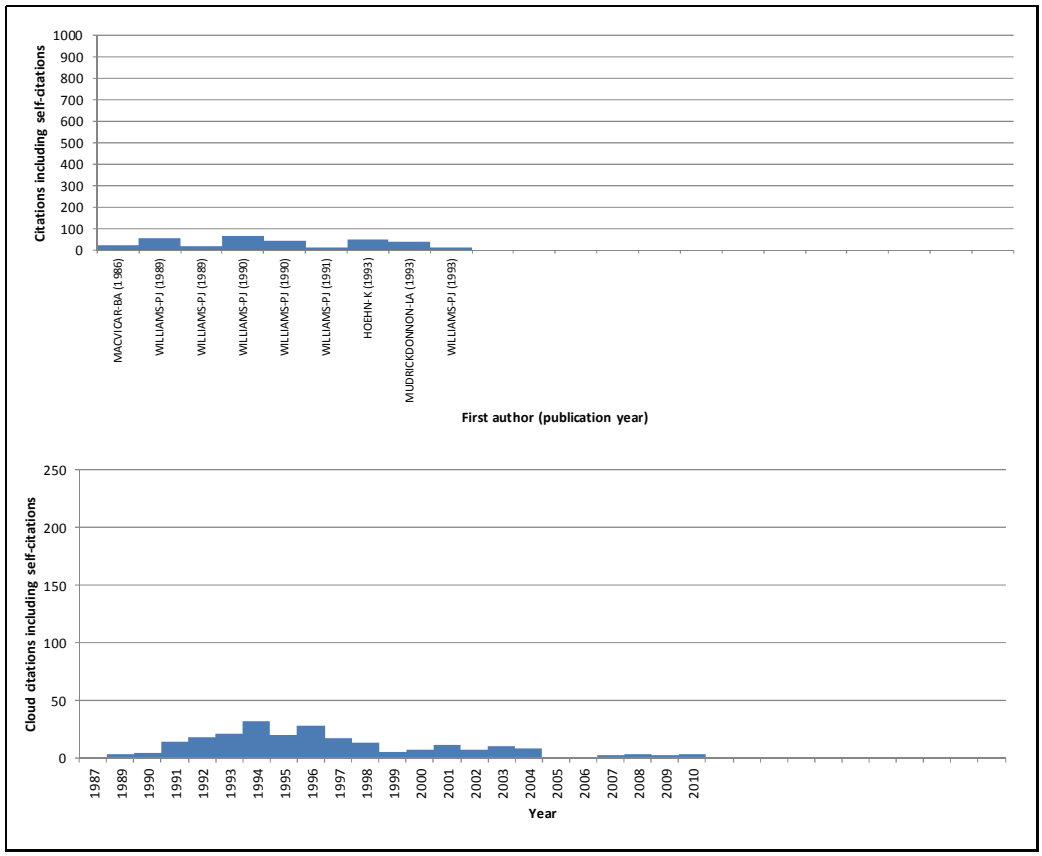
By providing consistent results through robust exploratory research, this study helped to accumulate evidence of this particular function of dopamine; synaptic modulation of calcium currents is now well accepted.

However, interviewees suggest that the importance of this particular field to wider knowledge creation is difficult to assess, particularly as they were not the only group exploring this specific question at the time. Pittman suggests,

> It's obvious a lot of people found [the paper] useful [but] the other thing of course is that science is inevitable. If we hadn't done it somebody else would have eventually done it. (QP).

A bibliometric analysis of the papers produced from the research cloud is shown below.





Targeting future research

Effect on the researchers' careers

Soon after, Williams ceased to pursue this work, and chose to leave the field of neuroscience. In his personal life, he met his future wife who introduced him to psychology and counselling; this sparked an interest in these areas, and a decline in his focus on basic science. Immediately following his PhD, Williams had intended continue to research calcium currents with a professor at Stanford, but was not accepted. He was offered a position by King, head of another lab at Stanford, but given his evolving interests, Williams chose to take up a post-doctoral position in Denver instead, which allowed him to simultaneously complete Neurolinguistic Programming training.

Initially, while in Denver, Williams continued to explore the pars intermedia due to equipment constraints (Williams, Dunwiddie et al., 1992). He used electrophysiology to examine post-synaptic potentials rather than calcium currents (Mudrick-Donnan, Williams et al., 1993), and measured postsynaptic response and dopamine release simultaneously, testing for variation in how drugs affected both sides of the synapse. During his post-doctoral fellowship, an exchange student from Astra Pharmaceuticals expressed interest in using Williams' model of pre- and post-synaptic modulation. Williams was invited to spend three months at Astra Pharmaceuticals, Sweden, to teach the application of this model to analysing differential responses of their drugs. At the end of his post-doctoral fellowship, Williams felt he was no longer fascinated with the research, and chose to pursue a career in counselling, psychology and hypnotherapy.

In contrast to Williams, MacVicar and Pittman continued in research. While their subsequent research was informed by this research cloud, they chose to take it in new directions. MacVicar shifted to focussing on dopamine in areas of the brain important in emotional controls and behaviour (QP). He applied aspects of the approach that Williams used in exploring cells of the intermediate pituitary to a different area of the brain, more relevant to mental disorders (QP). Pittman remained head of a lab at the University of Calgary, but shifted his focus to synaptic pharmacology of endocrine and autonomic nuclei, and central autonomic controls.

Future work

Though Pittman, MacVicar and Williams did not pursue this area of work much further, it was carried on by investigators at other labs. At the Vrije Universiteit, Huib Mansvelder continued to explore calcium currents and synaptic modulation by dopamine. However, in the 1990s, he moved away from the intermediate pituitary to look at the prefrontal cortex and ventral tegmental area.

Initially there was some suggestion that the research could have some clinical relevance (JK). Organon Pharmaceuticals discussed the work with a PhD student at Vrije Universiteit working on dopamine modulation of calcium currents in cells of the pars intermedia. Empirical study of synaptic modulation informed screening of potential new pharmaceutical agents by helping to identify how drugs might affect electric signalling in the brain. This in turn was thought to have potential to help identify the reasons why drugs have particular intended and unintended effects. However, such further application to pharmaceutical research did not materialise. There were several potential reasons why it was difficult to apply this to pharmaceutical industry R&D: specifically, animal models were unstable and the application of electrophysiology to screenings was labour intensive and tedious (JK).

Also, generally, wider sentiments were that molecular neurobiology was likely to be a more fruitful and feasible direction for pharmaceutical research; discussions about identifying electric currents and channels were overtaken by interest in the molecular biology of neurons and their activity in the brain. Imaging technologies also contributed to lessening some of the novelty of electrophysiology techniques, and affected the scope to which the latter were applied. Electrophysiology did continue to be applied functionally to understanding the synapse (JK).

2.8 Interface B: Dissemination

The researchers mainly disseminated findings from this research through publications and conferences. Williams, as a PhD student, was the primary person conducting the experiments; however, senior researchers played a more direct role in dissemination (QP).

When seeking to publish findings, Pittman and MacVicar became closely involved in structuring and communicating findings:

> When the time came to write up the paper, we [MacVicar and Pittman] play a critical role in helping to develop the paper, teaching the student writing skills, [and] trying to develop a storyline that's going to be seductive to the reviewers. (QP)

Still, as primary investigator, Williams wrote the first drafts of the papers and was given opportunities to attend conferences and network with other researchers pursuing similar interests. Williams attended two key conferences during his PhD: one in the Netherlands and a second in the United States. Williams treated these conferences as opportunities to share his work and exchange ideas:

> …I think those are productive. I think they're useful and you get to meet people and you get to exchange ideas and that's fun and that's useful. And that's really the only kind of perks to the job. (PW)

For example, at the first conference in the Netherlands, Williams met another PhD student working on the same question. At the second conference, Williams spoke with a researcher from New York interested in the potential effect of spider venom on calcium currents. Following this, he and Williams co-published a study testing this effect (Williams, Pittman et al., 1993).

2.9 Stage 4: Secondary outputs

None identified.

2.10 Stage 5: Applications

The research conducted in this cloud did not have any direct application to clinical practice or mental health outcomes. One interviewee suggests that the long-term aim was to contribute to a model system that could affect change for the wider public through the understanding of the action of illicit drugs in the brain, in line with Williams' initial area of interest. However, this was not possible due to the extent to which the researchers pursued the research question: it remained a very basic study looking at electrical currents and their modulation in cells in vitro.

> This doesn't really have much relevance other than it's basic science. It tells you how a certain part of the brain works. There may be other parts of the brain that work the same way, which is cool, but there is not necessarily any major, immediate relevance to disease [or] any curative process at all, as far as I was concerned. (PW)

Some attempts were made to link the research to wider clinical relevance on paper for funding proposals, but given the very basic nature of the research question, the primary investigator suggests the link was often distant (PW).

While this specific research had little direct clinical application, the accumulation of basic research on the modulation of calcium currents has informed some early clinical studies looking at calcium currents as targets for chronic pain (Zamponi, Lewis et al., 2009). However, most directly, the contribution of this research was to improve basic understanding of brain functioning. By expanding knowledge of processes and functioning in a specific area of the brain, investigations such as this can help to build a foundation for further research aimed at understanding neurological disorders and how they affect brain functioning.

> This is fundamental, basic research. This needs to be done. …If all research is geared to trying to figure out how diseases operate, then you never develop a groundwork

> understanding of how the brain works, which will then allow you to eventually figure out diseases like schizophrenia and… Parkinson's disease. …We need to have a fundamental understanding of how the brain works, before we can really target a specific disease. (PW)

2.11 Stage 6: Public engagement

None identified.

2.12 Stage 7: Final outcomes

None identified.

2.13 Table of payback

Payback category	Impacts from case study
Knowledge Production	• Among the first to characterise the synaptic modulation, by dopamine, of calcium currents in a mammalian intermediate pituitary. • Main finding: D2 dopamine agonists inhibit the certain calcium currents in cells of the intermediate pituitary through a G-protein mediated mechanism at the D-2 receptor.
Research Targeting and Capacity Building	• None identified.
Informing Policy and Product Development	• The primary investigator was invited to Astra Pharmaceuticals to teach the application of his pre- and post-synaptic model to analysing differential responses of their drugs.
Health and Health Sector Benefits	• None identified.
Broader Social and Economic Benefits	• None identified.

2.14 Timeline

1980	The Alberta Heritage Foundation for Medical Research (AHFMR) is founded and begins to fund students and fellows
early 1980s	Empirical studies confirm calcium channels as targets for hormones (Cota, 1986; Reuter, 1983; Tsien, 1983)
mid-1980s	Williams leaves his job at an oil analysis laboratory at Petro Canada and is offered a studentship by AHFMR
	Williams begins PhD research supervised by Pittman and MacVicar, at MacVicar's lab at the University of Calgary

1990	The first findings of this research cloud are published by Williams, MacVicar and Pittman in the *Journal of Neuroscience*
1991	Peter Williams founds Avilon Counselling
1993	The final paper describing findings from this research cloud is published by Williams, Pittman and MacVicar in *Neuroscience Letters*
early 1990s	Williams takes up a post-doctoral position in Denver, and simultaneously completes the Masters practitioner level in Neurolinguistic Programming
2003	MacVicar accepts a position as a Professor in the Department of Psychiatry and the Brain Research Centre at the University of British Columbia
2004	The Neuroscience Research Group at the University of Calgary is evolved into the Hotchkiss Brain Institute

2.15 References

Chen, X., Kombian, S., et al. (1999). Dopamine depresses glutamatergic synaptic transmission in the rat parabrachial nucleus in vitro. *Neuroscience*, 90(2), 457–468.

Cota, G. (1986). Calcium channel currents in pars intermedia cells of the rat pituitary gland. Kinetic properties and washout during intracellular dialysis. *Journal of General Physiology*, 88(1), 83.

Fraser, D.D., Hoehn, K., et al. (1993). Arachidonic acid inhibits sodium currents and synaptic transmission in cultured striatal neurons. *Neuron*, 11(4), 633–644.

Horn, T., Bauce, L., et al. (1995). Microdialysis with high NaCl causes central release of amino acids and dopamine. *Journal of Neurochemistry*, 64(4), 1632–1644.

Kisilevsky, A.E., Mulligan, S.J., et al. (2008). D1 receptors physically interact with N-type calcium channels to regulate channel distribution and dendritic calcium entry. *Neuron*, 58(4), 557–570.

Kombian, S.B., Mouginot, D., et al. (1997). Dendritically released peptides act as retrograde modulators of afferent excitation in the supraoptic nucleus in vitro. *Neuron*, 19(4), 903–912.

MacVicar, B.A., & Pittman, Q.J. (1986). Novel synaptic responses mediated by dopamine and [gamma]-aminobutyric acid in neuroendocrine cells of the intermediate pituitary. *Neuroscience Letters*, 64(1), 35–40.

Mudrick-Donnan, L.A., Williams, P.J., et al. (1993). Postsynaptic potentials mediated by GABA and dopamine evoked in stellate glial cells of the pituitary pars intermedia. *Journal of Neuroscience*, 13, 4660–4668.

Price, C.J., & Pittman, Q.J. (2001). Dopamine D4 receptor activation inhibits presynaptically glutamatergic neurotransmission in the rat supraoptic nucleus. *Journal of Neurophysiology*, 86(3), 1149–1155.

Reuter, H. (1983). Calcium channel modulation by neurotransmitters, enzymes and drugs. *Nature*, 301, 569–574.

Tsien, R. (1983). Calcium channels in excitable cell membranes. *Annual Review of Physiology*, 45(1), 341–358.

Williams, P.J., Dunwiddie, T.V., et al. (1992). Direct in vitro electrochemical measurement of dopamine overflow in intermediate pituitary: characterization and pharmacology. *Journal of Pharmacology and Experimental Therapeutics*, 261(2), 403.

Williams, P.J., MacVicar, B.A., & Pittman, Q.J. (1990). Electrophysiological properties of neuroendocrine cells of the intact rat pars intermedia: multiple calcium currents. *Journal of Neuroscience*, 10(3), 748–756.

Williams, P.J., MacVicar, B.A., & Pittman, Q.J. (1990). Synaptic modulation by dopamine of calcium currents in rat pars intermedia. *Journal of Neuroscience*, 10(3), 757–763.

Williams, P.J., Pittman, Q.J., & MacVicar, B.A. (1991). Ca(2+)- and voltage-dependent inactivation of Ca2+ currents in rat intermediate pituitary. *Brain Research*, 564(1), 12–18.

Williams, P.J., Pittman, Q.J., & MacVicar, B.A. (1993). Blockade by funnel web toxin of a calcium current in the intermediate pituitary of the rat. *Neuroscience Letters*, 157(2), 171–174.

Zamponi, G.W., Lewis, R.J., et al. (2009). Role of voltage-gated calcium channels in ascending pain pathways. *Brain Research Reviews*, 60(1), 84–89.

CHAPTER 3 Differential distribution of $GABA_A$ receptor mRNAs in bovine cerebellum

This case study is based on the research that produced the paper:

Wisden, W., McNaughton, L.A., Darlison, M.G., Hunt, S.P., & Barnard, E.A. (1989). Differential distribution of $GABA_A$ receptor mRNAs in bovine cerebellum-localization of $\alpha 2$ mRNA in Bergmann glia layer. *Neuroscience Letters*, 106(1–2), 7–12.

Information was gathered from interviews with William Wisden, Stephen Hunt, Mark Darlison and Brian Morris, as well as desk-based research.

3.1 Summary

This research analysed the expression of $GABA_A$ receptor subunit mRNA using the in situ hybridisation technique. It was initiated at the MRC Molecular Neurobiology Unit, Cambridge (UK), headed by Professor Eric Barnard, in collaboration with Genentech, and Professor Peter Seeburg, who began the work at Genentech but transferred to the University of Heidelberg while the research was ongoing. Although the research began as the focus for William Wisden's PhD at the University of Cambridge, it was completed during a long-term fellowship with Peter Seeburg at the University of Heidelberg. The work ended after mapping the expression of all 13 genes involved in the subunit $GABA_A$ receptors in the rat brain.

At the time the study was conducted, $GABA_A$ receptors were newly discovered, and there were questions arising in the scientific community about the molecular heterogeneity of the receptors, their distribution across brain regions, and their relevance to different brain circuits and behaviours. Wisden, a PhD student in Molecular Neuroscience at the University of Cambridge (funded through a MRC research studentship), supervised by Professor Steven Hunt and Mark Darlison, was tasked with attempting to address this topic by localising $GABA_A$ receptor subunit mRNA in the brain. The hypothesis was that by identifying the expression of the different mRNA in the brain, they could then determine how the different subunits were expressed. To do this, Wisden first had to refine the in situ hybridisation technique to be sensitive enough to differentiate between the protein subunits. Once the technique was refined, Wisden applied this to looking at $GABA_A$ receptor subunits in the bovine brain, switching to the rat brain as the protein sequences were made known and they had access to the cloned tissues.

The work on localisation of the expression of $GABA_A$ receptor subunit mRNA in the brain was novel in two ways. First, technically it provided a relatively simple way to localise mRNA in brain tissue (through in situ hybridisation). Secondly, the research provided information on the expression of $GABA_A$ receptor subunits in the brain, of particular interest because of the progress in cloning genes at the time, and also the receptors' binding affinity to benzodiazepines (depressant medications). This research on the molecular expression and function of the $GABA_A$ receptor had substantial potential value commercially (especially in relation to benzodiazepines), in terms of further research, and to researchers' careers. Also, pursuing work in molecular neurobiology had the potential for novel contributions to scientific discovery; the field was new and emergent in the 1980s. Key discoveries in this field were being made during this time, particularly at the MRC Unit and by its collaborators. Collaborative experiments conducted by Barnard's and Seeburg's labs contributed to the discovery that the GABA benzodiazepine receptor comprised a family of subunits. This discovery sparked wider scientific interest in the function and expression of $GABA_A$ receptor subunits, the number of different receptors, and their binding properties to benzodiazepines.

There were multiple competing groups also engaged in cloning techniques and in situ hybridisation histochemistry with the aim to map the expression of $GABA_A$ receptor subunit mRNA in the brain. The MRC Unit at Cambridge and its collaborators from Genentech were particularly well placed to engage in this work; the resources and researchers involved had a unique combination of technical and subject expertise.

After completing his post-doctoral fellowship, Wisden worked as a group leader at the MRC Laboratory of Molecular Biology, Cambridge, for seven years, before returning to the University of Heidelberg and then spending four years as head of the neurobiology programme at the Institute of Medical Sciences, University of Aberdeen. As of 2011, Wisden is a Professor of Molecular Neuroscience at Imperial College London, and head of the section on Cell Biology and Functional Genomics.

3.2 Introduction

3.2.1 Scientific background

The research conducted in this case study set out to identify the expression of genes encoding $GABA_A$ receptor subunits in the central nervous system. The $GABA_A$ receptor subunits form ligand-gated ion channels for the inhibitory neurotransmitter GABA, and are major receptors mediating neuronal inhibition in the brain. $GABA_A$ receptors are acted on by a number of therapeutic drugs, notably benzodiazepines, barbiturates and major clinical anaesthetics, such as propofol.

Benzodiazepines are depressant medications used therapeutically for a range of psychiatric disorders; in different dosages they can act as hypnotics, anxiolytics and sedatives. Clinical benefits of use include their high efficiency and rapid onset of action; negative effects include psychomotor impairment, and tolerance, dependency and withdrawal effects with long term use (Ashton, 1994). The use of benzodiazepines for therapeutic treatment of schizophrenia remains uncertain; a Cochrane Review published in 2010 suggests that results on the effects of benzodiazepines for schizophrenia are inconclusive (Volz, Khorsand et al., 2010). When this research took place, it had already been identified that

benzodiazepines act on the $GABA_A$ receptor (Haefely, Kulcsar et al., 1975; Hunkeler, Möhler et al., 1981). In the 1980s $GABA_A$ receptors were found to have different affinities for some benzodiazepines (Sieghart, Mayer et al., 1983; Fuchs, Möhler et al., 1988; Olsen & Tobin, 1990).

This research analysed the expression of $GABA_A$ receptor subunit mRNA using the in situ hybridisation technique. At the time the study was conducted, $GABA_A$ receptors were newly discovered, and there were questions arising in the scientific community about the molecular heterogeneity of the receptors, their distribution across brain regions, and their relevance to different brain circuits and behaviours. In situ hybridisation and immunohistochemistry were techniques that could be used to address these questions. In situ hybridisation detects the location of mRNA or DNA within heterogeneous cell tissue, where it is expressed or found. To locate the mRNA, a complementary strand of nucleic acid is used as a radioactive probe; it is tagged to allow for detection and hybridized within a tissue. The probe recognises cognate mRNA and forms a duplex. Excess probe is then washed away to expose the sites where the mRNA is expressed; the mRNA can be made visible by photographic film/emulsion (Wisden & Morris, 2002a; Wisden & Morris, 2002b).

3.2.2 Researchers' background

William Wisden was the primary investigator for this research cloud. The research began as the focus for his PhD, and was completed during a long-term fellowship he obtained at the University of Heidelberg afterwards. Wisden's PhD in Molecular Neuroscience at the University of Cambridge was supervised by Professor Stephen Hunt and funded through a MRC research studentship. He finished his PhD in 1989, and took up an EMBO long-term fellowship with Peter Seeburg at the University of Heidelberg. Wisden continued to work on the localisation of $GABA_A$ receptor subunit mRNA in the brain during his post-doctoral fellowship. After completing that, he worked as a group leader at the MRC Laboratory of Molecular Biology, Cambridge, for seven years, before returning to the University of Heidelberg and then spending four years as head of the neurobiology programme at the Institute of Medical Sciences, University of Aberdeen. As of 2011, Wisden is a Professor of Molecular Neuroscience at Imperial College London, and head of the section on Cell Biology and Functional Genomics. Currently, Wisden has funding from the BBSRC and the MRC, looking at several specific streams of work, on hippocampal function and hypothalamic function, GABAergic interneurons and ion channels.

Stephen P. Hunt was a senior scientific staff member working on molecular neurobiology at the MRC Molecular Neurobiology Unit during this research. He is an anatomist specialising in immunocytochemistry and was the first supervisor of Wisden's PhD. His work on anatomical analysis and early work on in situ hybridisation was crucial to the application of the in situ hybridisation method for the research (WW). Hunt remained at Cambridge following the absorption of the MRC Molecular Neurobiology Unit into the MRC Laboratory of Molecular Biology at Cambridge, becoming a staff member of the latter. He was the only staff member to remain at Cambridge following Barnard's retirement and the absorption of the MRC Molecular Neurobiology Unit. In 1998, Hunt took up a position at UCL as Professor of Molecular Neuroscience.

Mark G. Darlison was a staff scientist and group leader at the MRC Molecular Neurobiology Unit at Cambridge, and Wisden's second PhD supervisor, when this research was conducted. His contribution was in cloning $GABA_A$ receptor genes. At the time, Darlison was working to identify DNA sequences for $GABA_A$ receptor subunits. Darlison subsequently worked at the Institute for Cell Biochemistry and Clinical Neurobiology in Hamburg, and then Nottingham Trent University. He is now Professor of Neuroscience and Head of the School of Life, Sport & Social Sciences at Edinburgh Napier University.

Eric A. Barnard was head of the MRC Molecular Neurobiology Unit, Cambridge. Barnard retired in the early 1990s, and the MRC Unit was absorbed into the MRC Laboratory of Molecular Biology and became the Division of Neurobiology, under Nigel Unwin as Director. Barnard is now a Professor Emeritus at the University of Cambridge.

Peter Seeburg was an expert molecular biologist involved in this research; he became involved while employed at Genentech in the mid-1980s and continued in this work upon transferring to the University of Heidelberg in 1987. Seeburg has remained in Heidelberg, becoming a director at the Max Planck Institute for Medical Research there in 1996.

Brian Morris was a post-doctoral fellow at the MRC Unit at Cambridge between 1987 and 1990. For his post-doctoral studies, Morris was funded through a fellowship from the Mental Health Foundation to work mainly on nicotinic receptors. Morris assisted Wisden in refining the in situ hybridisation method. He moved to the University of Glasgow, where he is now Professor of Pharmacology.

Linda Ariza-McNaughton was a lab technician in the MRC Unit working on molecular neuroscience, and assisted in this research. Subsequently, she moved from the MRC Unit to the Laboratory of Developmental Neurobiology at the National Institute for Medical Research (UK). Ariza-McNaughton continued to work in molecular neuroscience, and is now a principal scientific officer with Cancer Research UK.

David Laurie was a post-doctoral fellow with Seeburg for this research. He took up the position with Seeburg after completing a PhD with Professor Judith Pratt at the University of Strathclyde, Glasgow. In 1997 he took up a position with Novartis with the Drug Regulatory Affairs department, and has remained there until the present.

3.3 Defining the research cloud

This case study is based on the research that produced the paper:

> Wisden, W., McNaughton, L.A., Darlison, M.G., Hunt, S.P., & Barnard, E.A. (1989). Differential distribution of $GABA_A$ receptor mRNAs in bovine cerebellum-localization of $\alpha 2$ mRNA in Bergmann glia layer. *Neuroscience Letters*, 106(1–2), 7–12.

The research was initiated at the MRC Molecular Neurobiology Unit, Cambridge (UK), headed by Professor Eric Barnard, in collaboration with Genentech, and Professor Peter Seeburg, who began the work at Genentech but transferred to the University of Heidelberg while the research was ongoing. (For the purpose of this case study, any reference to the

'MRC Unit' refers to the MRC Molecular Neurobiology Unit, Cambridge, headed by Barnard, unless otherwise specified.)

The underlying motivation for this research was to identify the expression of $GABA_A$ receptor subunits in the brain by localising the mRNA that encodes the subunits through in situ hybridisation. Wisden, a PhD student at the University of Cambridge, supervised by Stephen Hunt and Mark Darlison, was tasked with attempting to answer this question.

Alongside this work, researchers at the MRC Unit were engaged in ongoing research to identify and clone the DNA sequences for the $GABA_A$ receptor subunits; the newly identified sequences were accessible to Wisden to use for the localisation of mRNA. The work began with the use of bovine brains, and ended with the identification of the expression patterns of the mRNAs in rat brain. The researchers completed this particular body of research when they applied in situ hybridisation to identify the expression and development of 13 subunit mRNAs of the $GABA_A$ receptor in the rat brain (Laurie, Wisden et al., 1992; Laurie, Seeburg et al., 1992; Wisden, Laurie et al., 1992).

The following publications describe work completed within this research cloud:

1. Wisden, W., Laurie, D.J., Monyer, H., & Seeburg, P.H. (1992). The distribution of 13 $GABA_A$ receptor subunit mRNAs in the rat brain. I. Telencephalon, diencephalon, mesencephalon. *Journal of Neuroscience*, 12(3), 1040–1062.
2. Laurie, D.J., Seeburg, P.H., & Wisden, W. (1992). The distribution of 13 $GABA_A$ receptor subunit mRNAs in the rat brain. II. Olfactory bulb and cerebellum. *Journal of Neuroscience*, 12(3), 1063–1076.
3. Wisden, W., Morris, B.J., Darlison, M.G., Hunt, S.P., & Barnard, E.A. (1988). Distinct $GABA_A$ receptor α subunit mRNAs show differential patterns of expression in bovine brain. *Neuron*, 1, 937–947.
4. Wisden, W., McNaughton, L.A., Darlison, M.G., Hunt, S.P., & Barnard, E.A. (1989). Differential distribution of $GABA_A$ receptor mRNAs in bovine cerebellum-localization of α2 mRNA in Bergmann glia layer. *Neuroscience Letters*, 106(1–2), 7–12.
5. Wisden, W., Morris, B.J., Darlison, M.G., Hunt, S.P., & Barnard, E.A. (1989). Localization of $GABA_A$ receptor α-subunit mRNAs in relation to receptor subtypes. *Molecular Brain Research*, 5(4), 305–310.
6. Seeburg, P.H., Wisden, W., Verdoorn, T.A., Pritchett, D.B., Werner, P., Herb, A., Lüddens, H., Sprengel, R., & Sakmann, B. (1990). The $GABA_A$ receptor family: molecular and functional diversity. *Cold Spring Harbor Symposia Quantitative Biology*, 55, 29–40.
7. Wisden, W., Gundlach, A.L., Barnard, E.A., Seeburg, P.H., & Hunt, S.P. (1991). Distribution of GABA receptor subunit mRNAs in rat lumbar spinal cord. *Molecular Brain Research*, 10, 179–183.
8. Wisden, W., Herb, A., Wieland, H., Keinänen, K., Lüddens, H., & Seeburg, P.H. (1991). Cloning, pharmacological characteristics and expression pattern of the rat $GABA_A$ receptor α4 subunit. *FEBS Letters*, 289, 227–230.
9. Kato, K. (1990). Novel $GABA_A$ receptor α subunit is expressed only in cerebellar granule cells. Communication. *Journal of Molecular Biology*, 214(3), 619–624.

10. Ymer, S., Draguhn, A., Wisden, W., Werner, P., Keinanen, K., Schofield, P.R., Sprengel, R., Pritchett, D.B., & Seeburg, P.H. (1990). Structural and functional characterization of the -Y, subunit of GABAA/benzodiazepine receptors. *EMBO Journal*, 9, 3261–3267.
11. Shivers, B.D., Killisch, I., Sprengel, R., Sontheimer, H., Köhler, M., Schofield, P.R., & Seeburg, P.H. (1989). Two novel $GABA_A$ receptor subunits exist in distinct neuronal subpopulations. *Neuron*, 3, 327–337.
12. Bateson, A.N., Harvey, R.J., Wisden, W., Glencorse, T.A., Hicks, A.A., Hunt, S.P., Barnard, E.A., & Darlison, M.G. (1991). The chicken $GABA_A$ receptor $\alpha 1$ subunit: cDNA sequence and localization of the corresponding mRNA. *Molecular Brain Research*, 9, 333–339.
13. Lüddens, H. & Wisden, W. (1990). Function and pharmacology of multiple $GABA_A$ receptor subunits. *Trends in Pharmalogical Sciences*, 12(2), 49–51.
14. Laurie, D.J., Wisden, W., & Seeburg, P.H. (1992). The distribution of 13 $GABA_A$ receptor subunit mRNAs in the rat brain. III. Embryonic and postnatal development. *Journal of Neuroscience*, 12, 4151–4172.

3.4 Stage 0: Opportunity identification/research needs assessment

Feasibility

Molecular neurobiology was an 'infant science' at the time; $GABA_A$ and other receptors were just being cloned and their structures becoming known (BM). It was a dynamic and fast-paced area of research. However, the number of labs involved in the competition to sequence and localize receptors was limited to those with the capacity and expertise to apply the techniques. Each bit of information was difficult to obtain, and many labs did not have the equipment or technical knowledge to engage in protein chemistry and sequencing effectively.

The MRC Unit at Cambridge and its collaborators from Genentech were particularly well placed to engage in this work. The resources and researchers involved had a unique combination of technical and subject expertise.

Morris and Wisden, both based at the MRC Unit when the research began, were among those engaged in the early application of in situ hybridisation to the brain. Morris was one of the first researchers to refine in situ hybridisation for use on mRNA in the brain. He came to the MRC Unit in 1987 as a post-doctoral fellow from the Max Planck Institute for Psychiatry, where his main focus had been to set up in situ hybridisation to measure the expression of genes in the brain, with particular interest in opioidpeptides (BM). He honed this technique while at the MRC Unit. Wisden, with guidance from Morris, was then among the first to refine this further to be sensitive enough for use on GABA receptor subunit mRNAs (BM).

Learning and adapting the in situ technique for the research required skills development in anatomical analysis and protein chemistry. Hunt supported Wisden in this work by providing insights into anatomical techniques and equipment. Hunt's ongoing work on the effects of stimulation of rat primary sensory neurons on gene expression also was part of the wider landscape within which Wisden conducted his research (Hunt, Pini et al., 1987). Hunt's colleagues, staff scientists from the neighbouring MRC-LMB, Dr. Michel

Goedert[5] and Dr. John Rogers,[6] also taught Wisden some key methods (e.g. northern blotting, and some parts of the techniques required for in situ hybridisation) (Goedert & Hunt, 1987; Rogers & Hunt, 1987).

Adaptations of the in situ hybridisation technique (e.g. probes used, processing techniques) were being pursued by several labs during the 1980s (Wisden & Morris, 2002b) – for example, the use of synthetic oligodeoxyribonucleotides developed by researchers at the Max Planck Institute for Psychiatry and at the MRC Unit at Cambridge, the National Institute of Mental Health, Bethesda, and the University of Michigan (Lewis, Sherman et al., 1985; Morris, Haarmann et al., 1986; Young III, Mezey et al., 1986; Young III, 1986; Morris, 1989). In the 1980s, in situ hybridisation was modified to analyse peptide gene expression in the pituitary and hypothalamus (for example, Young III, Mezey et al., 1986; Young III, 1986). Successful adaptation of the technique for these other experiments suggested it might be possible to further refine it to look at genetic expression of $GABA_A$ receptor subunit mRNA. Wisden's ability to engage in work to refine in situ hybridisation then made it possible to consider performing experiments to localise GABA receptor subunits based on the expression of mRNA.

Additionally, researchers at the MRC Unit and Genentech were considered experts in the field, and are cited as the first to have identified the primary structures for the alpha and beta subunits of the $GABA_A$ receptor by purifying the proteins and determining their structures through cloning complementary DNA (Pritchett, Sontheimer et al., 1989; Olsen & Tobin, 1990; Levitan, Schofield et al., 1988; Ymer, Schofield et al., 1989). The MRC Unit at Cambridge and its collaborators had widespread expertise in molecular neuroscience; this breadth of expertise enabled them to tackle questions about $GABA_A$ receptors using a range of approaches. Barnard provided a focus for diverse research going on at the MRC Unit on the receptor's molecular structure (BM). Senior scientists were recruited with diverse expertise relevant to understanding molecular neurobiology (for example, immunocytochemistry, the binding properties of receptors, intracellular regulation, and protein structure, function and expression). Intra-Unit collaboration was encouraged, providing junior researchers with access to expertise from across the Unit.

Finally, stable funding and access to equipment and resources further made it feasible to consider this question. The MRC Unit had consistent funding for research, as well as the technology for molecular neurobiology experiments. Very few labs had the technology to engage in this work at that time (WW, MD).

Potential value

This research on the molecular expression and function of the $GABA_A$ receptor had substantial potential value commercially, to scientific discovery and further research, and to researchers' careers. The commercial potential was largely due to the receptor's properties in the binding of benzodiazepines (MD, BM), depressant medications used therapeutically for a range of psychiatric disorders. In the 1980s, they became one of the most prescribed medications in the US. Research in the 1980s showed that more than one $GABA_A$ receptor

[5] Goedart is still at the LMB.

[6] Rogers is now at the Physiology Department at the University of Cambridge.

existed and that these receptors had different affinities for some benzodiazepines (Sieghart, Mayer et al., 1983; Fuchs, Möhler et al., 1988; Olsen & Tobin, 1990).

Also, pursuing work in molecular neurobiology had the potential for novel contributions to scientific discovery; the field was new and emergent in the 1980s. Key discoveries in this field were being made in the 1980s, particularly at the MRC Unit and its collaborators. Collaborative experiments conducted by Barnard's and Seeburg's labs contributed to the discovery that the GABA benzodiazepine receptor comprised a family of subunits (Barnard, Darlison et al., 1987; Schofield, Darlison et al., 1987; Levitan, Schofield et al., 1988). This discovery sparked wider scientific interest in the function and expression of $GABA_A$ receptor subunits, the number of different receptors, and their binding properties to benzodiazepines. Professional ambition to be at the forefront of discoveries in this new and growing area of research was also a key driver for pursuing this work at the MRC Unit (WW).

Given the potential value of the research commercially and scientifically, molecular research on $GABA_A$ receptor subunits was a competitive field at the time (Fuchs, Möhler et al., 1988; Lolait, O'Carroll et al., 1989b). There were multiple competing groups also engaged in cloning techniques and in situ hybridisation histochemistry with the aim to map the expression of $GABA_A$ receptor subunit mRNA in the brain. Notable groups active in the area at the time included:

- Hans Möhler, at Hoffmann-La Roche, involved in cloning of $GABA_A$ mRNA and mapping the expression of specific subunits of the receptor. See: Séquier, Richards et al., 1988; Malherbe, Sigel et al., 1990a, 1990b.
- Ruth Siegel's research group, focussed on expression of mRNA of $GABA_A$ receptor subunits in the developing rat brain. See: Siegel, 1988; Nadler, Raetzman et al., 1996; Gambarana, Beattie et al., 1991.
- A group led by Allan Tobin, exploring the expression and size of subunit $GABA_A$ receptor mRNAs in the brain through in situ hybridisation histochemistry. See: Khrestchatisky, MacLennan et al., 1989; MacLennan, Brecha et al., 1991; Khrestchatisky, MacLennan et al., 1991.
- Lawrence Mahan and colleagues, using in situ hybridisation histochemistry to map the expression of mRNAs coding for specific subunits of the $GABA_A$ receptor. See: Montpied, Ginns et al., 1989; Lolait, O'Carroll et al., 1989a; Poulter, Barker et al., 1992.
- Masaya Tohyama's group at Osaka University Medical School, using in situ hybridisation histochemistry to map the expression of mRNAs coding for specific subunits of the $GABA_A$ receptor in the rat brain. See: Hironaka, Morita et al., 1990; Zhang, Sato et al., 1990; Zhang, Sato et al., 1991a, 1991b.
- Heinz Wassle and colleagues, at the Max Planck Institute for Brain Research, Frankfurt, focussed on the study of retinal mammalian organisation in rodents and primates. His work was not dissociated from the research group engaged in this case study; in fact, he published with Seeburg and Wisden at the time. See: Greferath, Müller et al., 1993; Müller, Greferath et al., 1992; Greferath, Grünert et al., 1995; Sassoe-Pgnetto, Kirsch et al., 1995.

Researchers at the MRC Unit were most aware at the time of the closely competing group at Hoffman-La Roche led by Hans Möhler.

The number and activity of competing groups contributed to a sense of urgency and a fear that a competitor might be first to sequence or localise the receptor subunits among the researchers involved (BM). Labs tended to be uncertain of each other's progress (MD):

> It was a brutal rivalry to be first, basically, in a way that I don't like [to work anymore]. (WW)

The desire to be at the forefront in this field, given its potential scientific and clinical value, helped motivate researchers to actively pursue their work.

3.5 Stage 1: Inputs to research

Money, researcher time, lab/office space and consumables

This research began at the MRC Molecular Neurobiology Unit in the 1980s. The Unit was formed under the leadership of Eric Barnard in 1985 and was funded until 1992, when it was closed after Barnard's retirement.

The MRC Unit was funded through intramural funding from the MRC, ensuring long-term financial support for infrastructure, salaries and consumables. The distribution of Unit funding was overseen by Barnard as Unit head. As a PhD student, Wisden's research activities had separate funding, provided by a MRC research studentship. The work conducted at Seeburg's lab at the Zentrum für Molekulare Biologie, University of Heidelberg, was also supported through a common budget at the centre for research and equipment.

Intramural funding enabled researchers to do research without concern about funding applications, in an area of research that was new and speculative (i.e. it was a new technique, and there was uncertainty whether it could produce the desired information about subunit gene expression), and also labour intensive (WW, MD).

> I think that it's important to be successful, if you're starting your career, you need to be in a maximally funded place so that you don't have to worry about if you can do it or not; you just should be able to do it. (WW)

Unit funding also supported acquisition of up-to-date technology and equipment for the research. Access to equipment contributed to the Unit's competitive advantage in conducting molecular neurobiology research in the UK:

> Technology and resources were the biggest issues at the time; [other] labs couldn't do what we did. (MD)

Researcher time was another particularly important input to experimentation with in situ hybridisation. The work was labour intensive. Wisden found that it took two years alone to refine in situ hybridisation to be appropriate to looking at $GABA_A$ receptor subunits; this investment was made without certainty as to whether the technique could even be successfully applied for this purpose.

Animal tissues (specifically bovine brain tissues) for experiments were accessed from the abattoir. Bovine brains were a key consumable for the initial research, because large

amounts of tissue were required for original cloning techniques and also for successfully obtaining signals on Northern blots (a technique used to help assess the specificity of the signal for in situ hybridisation). The nucleic acid sequences for the bovine receptor were also accessible to Wisden at the time. The sequences were not known for rat brain when the research began. Once the sequences for the $GABA_A$ receptor subunits were identified in the rat, Wisden moved to applying in situ hybridisation to gene expression in the rat brain.

Expertise and techniques

Tacit knowledge about how to refine and apply in situ hybridisation was a key to successful application of the technique to expression of mRNA for the $GABA_A$ receptor family of subunits. In situ hybridisation was a relatively new technique; when the work began it was not yet refined in such a way to be sensitive enough to identify the expression of different $GABA_A$ receptor subunits (WW). Specific skill and knowledge to guide efforts to refine and apply the technique was required. Wisden used the analogy of 'following a recipe' to describe this process. At the time, few people knew the recipe and how to follow it correctly; his work to understand how to apply this 'recipe' enabled him to effectively examine gene expression of the subunits.

Wider research activity and expertise in molecular biology and protein chemistry at the MRC Unit also supported the research by providing Wisden with access to the cloned DNA sequences required to do the experiments. A critical mass of expertise helped the researchers at the MRC Unit to stay at the forefront of new developments in the field:

> When the big work gets done it's done through multi-disciplinary teams. (MD)

The MRC Unit had the expertise and technical skills to purify the $GABA_A$ receptor, identify protein sequences and isolate clones, and apply in situ hybridisation techniques (albeit for different receptors). Stable and generous funding helped to attract a number of leading experts on molecular biology and biochemistry to the Unit. Barnard also sought out researchers with a range of expertise:

> [Barnard] brought a lot of people together with important skills. And I guess that gave us the edge, because there was nowhere in the UK that had all of that expertise in one place. (MD)

Particular expertise at the Unit relevant to Wisden's work on expression of $GABA_A$ receptor subunits included:

- Protein chemistry: Barnard was involved in purifying the $GABA_A$ (benzodiazepine) receptor in the mid-1980s. This was a challenging procedure at the time, as the protein was membrane bound. This expertise provided access to the purified protein that could then be used for protein sequencing.
- Protein sequencing: This was a difficult area of research at the time, and it was performed by experts at Genentech. Darlison, Wisden's second supervisor, was involved in the screening of libraries, which was done in collaboration with Seeburg's lab at Genentech (Schofield, Darlison et al., 1987; Levitan, Schofield et al., 1988; Olsen & Tobin, 1990). Protein sequencing allowed the lab to screen libraries to identify the structure of the receptor; the nucleic acid sequences obtained then informed experiments to identify expression of genes encoding the subunits in the brain.

- Anatomical analysis: Hunt specialised in immunocytochemistry, and also completed some early work on in situ hybridisation. Hunt's expertise in anatomical techniques, and associated equipment, were important in supporting Wisden's progress in refining and applying in situ hybridisation (WW).
- Other related research: Less directly supportive of Wisden's work, but part of the research landscape at the MRC Unit, were experiments on the affinity of ligands for the $GABA_A$ receptor by Ian Martin (Brown & Martin, 1983; Brown & Martin, 1984), and work on intracellular regulation by G-proteins, led by Michael Hanley (Hanley & Iversen, 1978; Hanley, 1985; Hanley, 1988; Thastrup, Dawson et al., 1989; Thastrup, Cullen et al., 1990).

Collaborators

The researchers at Cambridge involved in protein chemistry, anatomical analysis and DNA cloning collaborated extensively internally within the Unit, discussing progress, findings and emerging questions.

Leadership at the Unit was less open to external collaboration with competing labs. Collaboration with external labs had its challenges, given the competitive and fast-moving nature of the field. There were some limitations on what researchers were willing to share, and discussion over how their contributions should be recognised. However, when it occurred, collaboration was partially driven by the fear that another lab might identify the protein sequences 'first' as well as the need to access specific expertise.

In the mid-1980s, Barnard sought to collaborate externally in molecular neurobiology to support the MRC Unit's work in protein sequencing; there were only a few experts in molecular neurobiology at the time, and external collaboration was identified as important to staying competitive in this field. Barnard began to collaborate with Peter Seeburg, a molecular biologist at Genentech, based in south San Francisco, around the time he became Director of the MRC Unit at Cambridge (MD). Genentech had excellent protein chemistry facilities, and Seeburg's lab had demonstrated technical capacity and expertise to clone the GABA receptor subunits (Pritchett, Sontheimer et al., 1988; Pritchett, Sontheimer et al., 1989; Olsen & Tobin, 1990). Darlison found that the work with Genentech was genuinely collaborative: Seeburg designed oligonucleotide probes to screen libraries, Darlison's lab isolated partial sequences, which he would read out to Seeburg, and Seeburg's lab then isolated full-length clones for the $GABA_A$ receptor subunits. In 1987, Seeburg moved to the University of Heidelberg for family reasons (WW), and the collaboration followed him. This external collaboration was instrumental in determining the speed with which they progressed in protein sequencing (MD).

3.6 Stage 2: Processes

Directly preceding this research in the mid-1980s, researchers at Genentech and the Cambridge MRC Unit published work confirming that the $GABA_A$ receptor existed as a family of receptors (Schofield, Darlison et al., 1987; Levitan, Schofield et al., 1988). This discovery raised further questions about the number of subunits and their expression in the brain. There was the potential for a large number of subtypes to be formed from the products of the different genes (MD).

The motivation for this research cloud arose from this earlier work, and was twofold: (i) to help localise subunits of the GABA receptor by identifying where genes were expressed, and (ii) to determine which subunits combined to form which subtypes. The first task was to identify a suitable method for this work. It was hypothesised at the Unit that in situ hybridisation could be used to identify the expression of individual members of gene families in situations where there was high sequence similarity (Wisden & Morris, 2002b).

Having decided to approach this research by using in situ hybridisation techniques, the technique had to be refined to be appropriate to examination of $GABA_A$ receptor subunits. There is a high degree of sequence similarity between $GABA_A$ receptor subunits and the DNA sequences that encode them (Olsen & Tobin, 1990). The in situ signal had to be made specific enough to differentiate between the subunits; this required specific probes. For this reason, the researchers involved designed oligonucleotides and the methodology for oligonucleotide-based in situ hybridisation (MD).

Wisden, with input and advice from Morris, refined and applied in situ hybridisation to $GABA_A$ receptors. He assessed the specificity of the signal through Northern blots, and then once refining the technique successfully, Wisden could apply it to $GABA_A$ receptor subunits, beginning with the bovine brain, and then switching to the rat brain once the cloned protein sequences for the rat became known. Wisden continued to apply the technique to the different subunits for the duration of his PhD as well as a subsequent post-doctoral fellowship at the University of Heidelberg. The work was completed after he and his collaborators mapped the expression of 13 genes for $GABA_A$ receptor subunits in the rat brain.

3.7 Stage 3: Primary Outputs

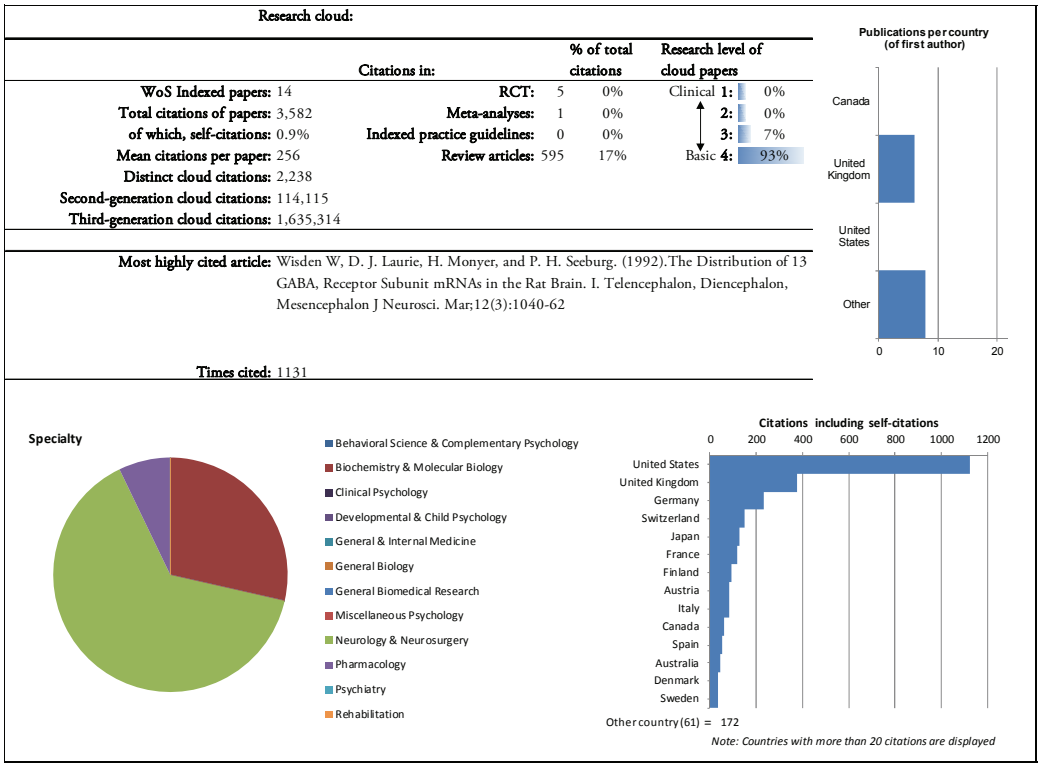
Knowledge

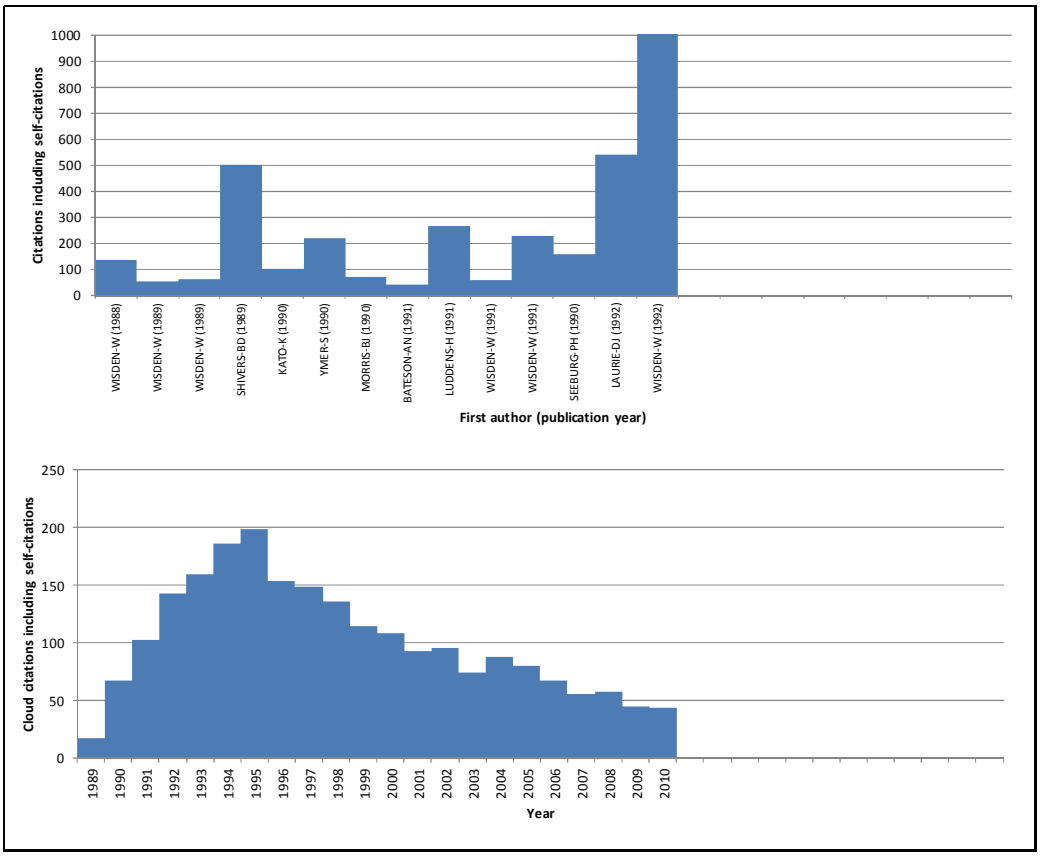
Both the findings and the methodology used in this research cloud were novel and contributed to scientific knowledge (SH). The research was novel technically because it provided a relatively simple way to localise mRNA in brain tissue using in situ hybridisation. One researcher involved suggests that science is driven by 'the devising of new technologies' (SH), suggesting innovations to methodologies and techniques have substantial value in furthering scientific exploration. This research also made a contribution through its findings about the expression of $GABA_A$ receptor subunits in the brain. It identified overlapping patterns of gene expression for the $GABA_A$ receptor subunits. Intuitively, the researchers involved had hypothesised that this research would allow them to identify particular subtypes of the $GABA_A$ receptor based on the expression of mRNA. As such, these findings were of particular interest due to the possibility they might further understanding the $GABA_A$ receptor family, and thereby the action of benzodiazepines that bound to it. While Wisden's group was not the only group to publish on the expression of the known subunits of the $GABA_A$ receptor (see Persohn, Malherbe et al., 1991; Persohn, Malherbe et al., 1992),[7] this research cloud was the first to publish on

[7] Specifically, Persohn, Malherbe and Richards, also drawing on findings from situ hybridisation, described the distribution of subunit mRNAs first in the rat spinal cord and dorsal root ganglia (Persohn, Malherbe et al., 1991), as well as of 11 subunit mRNA in the rat central nervous system (Persohn, Malherbe et al., 1992).

the expression of the 13 known subunit $GABA_A$ receptors in the rat brain, making a key contribution to scientific knowledge at the time.

A bibliometric analysis of the papers produced from the research cloud is shown below.





Targeting future research

Effect on the researchers' careers

This research cloud overlapped substantially with Wisden's PhD; as such, the skills and experience gained through the work on the expression of $GABA_A$ receptor subunits were crucial in establishing Wisden in the field of molecular biology. Broadly, Wisden has continued to conduct research to better understand brain function through molecular biology, and to develop and refine techniques for this. Initially, Wisden remained at Seeburg's lab at Heidelberg until 1992, working on the cloning of glutamate receptors, $GABA_A$ receptors and other types of ion channels. Wisden continued to be interested in the use and application of in situ hybridisation. He co-authored a textbook on the application of in situ hybridisation in the brain with Morris in 1994, publishing a second edition in 2002 (Wisden & Morris, 2002a; Wisden & Morris, 2002b). Wisden's line of questioning has become more focussed and complex over time, as he has moved to increasingly looking at how mutation affects brain function.

Most of the senior researchers who engaged with this research cloud left the MRC unit in the early 1990s. Barnard retired soon after the work was completed and the MRC placed the Unit under review. At this time, most senior researchers chose to leave to pursue their research elsewhere. Darlison left the lab in 1991. He continued to use the in situ hybridisation methodology. He also worked on mapping genes to specific human chromosomes looking for correlations between human genetic disease and where genes were located, invertebrate ligand-gated ion channels, and certain G-protein coupled receptors. Brian Morris remained at the MRC Unit from 1987–1990. In 1990, he received

a Wellcome Trust fellowship to work in Glasgow and has remained there since. His research interests evolved, and in the past 12–15 years he shifted to specialise in schizophrenia, experimenting with genetic and genomic analysis of neuronal function in psychiatric diseases. He analyses long-term changes in neuronal activity, and the expression of proteins and mRNA by cultured cells. Stephen Hunt remained at the MRC Unit in Cambridge until 1998, when he took up a post at UCL as Professor of Molecular Neuroscience. His specific interests have continued to focus on linkages between behaviour and molecular biology.

Upon leaving the Unit, researchers tended to pursue different lines of inquiry and rarely collaborated on research activities. Wisden and Darlison collaborated on one subsequent paper, published in 1996, on expression of γ-aminobutyric acid type A receptor cDNAs; the study used in situ hybridisation (Bahn, Harvey et al. 1996).

Future work

There was much interest and competition in publication of molecular research on $GABA_A$ receptors around this research cloud. There was some immediate follow-on research from the discoveries made about the expression of $GABA_A$ receptor subunit mRNA in the brain. For example, it remained unclear how subunits were assembled in the brain, and what the functions of the different subtypes were. Efforts to identify the expression of the subtypes and their roles in the brain were the subject of intense study through the early 1990s (McKernan & Whiting, 1996) (also MD). Siegel's research group has continued to study the onset and expression of $GABA_A$ receptors during cerebeller development, as well as molecular mechanisms regulating postnatal cerebellar differentiation. Also through subsequent study, Wisden identifies substantial progress made through anatomical and mouse genetics in identifying the presence of a limited number of $GABA_A$ receptor subunit combinations. Researchers are increasingly able to identify which subtypes of $GABA_A$ receptor are responsible for the different effects of different drugs, for example, benzodiazepines (Uwe, Crestasni et al., 1999; Möhler, Fritschy et al., 2002) and anaesthetics. There still remains uncertainty about the finer detail around the expression of subunit combinations (WW, MD), but progress towards better understanding their function and expression has been made (WW) (see, for example, Fritschy & Mohler, 1995; Rudolph & Möhler, 2004). The work on the expression of mRNA of the subunits of the $GABA_A$ receptor has continued to be relevant to pathology research. Tobin's laboratory took this area of research forward with the study of the function, regulation and degeneration of GABA-producing neurons in the brain and spinal cord, aiming to better understand issues around drug development for Huntington's disease, Parkinson's disease, epilepsy, and spinal cord injury. Darlison suggests, 'Until we understood the structure of those proteins you couldn't see if there was any real involvement [of the receptor in these diseases] and what their involvement was' (MD). A growing body of literature implicates $GABA_A$ receptor defects in schizophrenia, bipolar affective disorder, epilepsy, etc.

The contribution of the research to refining the in situ hybridisation technique for use in neuroscience has continued to be relevant to scientific inquiry. Wisden and Morris (2002) suggest the technique is ubiquitous across labs, who use it to analyse gene expression (BM). Though difficult to attribute the increased use of in situ hybridisation back to this particular piece of research, this was one of the early studies to refine the technique for use in the brain (Young III, Mezey et al., 1986; Young III, 1986). Various modifications of the

technique have been put forward, e.g. with different probes, processing and hybridizing techniques. The particular modified technique developed by this research cloud can result in a high throughput by labelling and hybridising large numbers of oligonucleotide probes at one time (Wisden & Morris, 2002b). A combination of studies done to refine in situ hybridisation, including this research cloud, helped to make the technique replicable and appropriate to examining mRNA in discrete brain regions.

3.8 Interface B: Dissemination

Academic publications were the main vehicle for publishing the findings of the research, and communicating key discoveries to the wider scientific community (WW). *Nature* and *Science* were viewed as the best publications (WW).

As a PhD student, Wisden was particularly keen to publish the results of this work. It was early in his career and academic publication was important to obtaining a future fellowship:

> I was interested in the biology of it, but I thrashed the method to death in order to maximise the publications from it. And then my aim was to get as many good papers as possible. (WW)

Alongside publications, researchers used conferences to communicate and promote their research. This was mainly done by more senior researchers, in this case often by Barnard. Darlison gave the first presentation on the lab's work cloning the $GABA_A$ receptor in San Francisco, in March 1987. This first presentation only stated the findings, and did not report on methods or data, as it was prior to publication in *Nature*. Following publication, the work was presented internationally.

3.9 Stage 4: Secondary Outputs

The research cloud was cited in three RCTs/meta-analyses. The work was referred to in the discussion section of articles on phase 2 RCT studies, when studies consider the linkages between a disorder, therapeutic drugs, and their effect on GABA receptors. Some subsequent work on 'knock out' mice has shown which subunits are responsible for certain actions of benzodiazepines and for some specific behaviours, but this remains an ongoing area for investigation (Rudolph & Möhler, 2004).

3.10 Stage 5: Applications

Research into the expression and functions of the $GABA_A$ receptor subunits has the potential to be relevant for treatment because of the way that benzodiazepines bind. Morris and Wisden suggest that it is likely that this research into the expression of subunits of the $GABA_A$ receptor could have informed work to develop selective benzodiazepines (BM). Drugs to act on specific subunits could be a mechanism by which to separate treatment effects from side effects, for example, a benzodiazepine that treated anxiety but did not cause drowziness (Möhler, 2011; Möhler, 2012).

There has been some progress in performing clinical trials on different tranquilisers, for example. Subtype selective benzodiazepines have been developed, with some evidence of effectiveness. For example, Merck Sharpe & Dohme developed and ran clinical trials for receptor-selective drugs; however, they cut off this work due to insufficient funds and the closure of their research institute at Harlow, UK, where the $GABA_A$ programme was taking place (WW) (Whiting, 2006). Progress in this area has continued at other pharmaceutical companies. For example, work by R Atack with Janssen Pharmaceuticals has continued in drug development in this area (R Atack, 2011), as well as work by Bjarke Ebert and colleagues on the drug gaboxadol, which promotes sleep onset, at Lundbeck in Denmark (see, for example, Krogsgaard-Larsen, Frolund et al., 2004; Ebert, Wafford et al., 2006; Wafford & Ebert, 2006).

3.11 Stage 6: Public Engagement

None identified.

3.12 Stage 7: Final Outcomes

None identified.

3.13 Table of payback

Payback category	Impacts from case study
Knowledge Production	• Refinement of the in situ hybridisation technique to be specific enough to differentiate between the expression of mRNAs for the $GABA_A$ receptor subunits. • Identification of the expression of mRNAs for $GABA_A$ receptor subunits in the brain.
Research Targeting and Capacity Building	• Capacity of the principal investigator to apply the in situ hybridisation technique. • Contribution to the development of a textbook to support use of this technique more widely.
Informing Policy and Product Development	• Provided knowledge that could be used to inform development of drugs acting specifically on $GABA_A$ receptor subtypes, drawing on their expression in the brain.
Health and Health Sector Benefits	• None identified
Broader Social and Economic Benefits	• None identified

3.14 Timeline

1986 Wisden begins his PhD in Molecular Neuroscience at the University of Cambridge

1989 Wisden completes his PhD in 1989 and takes up an EMBO long-term fellowship with Peter Seeburg at the University of Heidelberg

1987 Seeburg moves to the University of Heidelberg

1987 Brian Morris comes to the MRC Unit as a post-doctoral fellow

1987 Darlison makes the first presentation on the lab's work on cloning the $GABA_A$ receptor in San Francisco

1987/1988 First papers are published on cloning of the GABAA receptor (MD)

1989 The first articles presenting results from the research cloud are published (including the selected paper, Wisden, McNaughton et al., 1989)

1990 Brian Morris leaves the MRC Unit for a Wellcome Trust fellowship to work in Glasgow

1991 Mark Darlison leaves the MRC Unit to take up a position in Germany

1992 The final publications on the research cloud are published (Laurie, Wisden et al., 1992; Laurie, Seeburg et al., 1992; Wisden, Laurie et al., 1992)

1992 Wisden leaves Seeburg's lab at the University of Heidelberg

1994 Wisden and Morris co-author a textbook on the application of in situ hybridisation in the brain

1998 Stephen Hunt leaves Cambridge to take up a position at UCL

2002 Wisden and Morris's textbook on in situ hybridisation is re-issued by the publisher as a second edition (Wisden & Morris, 2002b)

3.15 References

Ashton, H. (1994). Guidelines for the rational use of benzodiazepines. When and what to use. *Drugs*, 48(1), 25.

Bahn, S., Harvey, R.J., et al. (1996). Conservation of γ-aminobutyric acid type A receptor α6 subunit gene expression in cerebellar granule cells. *Journal of Neurochemistry*, 66(5), 1810–1818.

Barnard, E.A., Darlison, M.G., et al. (1987). Molecular biology of the GABAA receptor: the receptor/channel superfamily. *Trends in Neurosciences*, 10(12), 502–509.

Bateson, A.N., Harvey, R.J., Wisden, W., Glencorse, T.A., Hicks, A.A., Hunt, S.P., Barnard, E.A., & Darlison, M.G. (1991). The chicken $GABA_A$ receptor α1 subunit: cDNA sequence and localization of the corresponding mRNA. *Molecular Brain Research*, 9, 333–339.

Brown, C., & Martin, I.L. (1984). Modification of pyrazoloquinolinone affinity by GABA predicts efficacy at the benzodiazepine receptor. *European Journal of Pharmacology*, 106(1), 167–173.

Brown, C., & Martin, I.L. (1983). Photoaffinity labelling of the benzodiazepine receptor cannot be used to predict ligand efficacy. *Neuroscience Letters*, 35(1), 37–40.

Ebert, B., Wafford, K.A., et al. (2006). Treating insomnia: current and investigational pharmacological approaches. *Pharmacology & Therapeutics*, 112(3), 612–629.

Fritschy, J.M., & Möhler, H. (1995). GABAA-receptor heterogeneity in the adult rat brain: differential regional and cellular distribution of seven major subunits. *Journal of Comparative Neurology*, 359(1), 154–194.

Fuchs, K., Möhler, H., et al. (1988). Various proteins from rat brain, specifically and irreversibly labeled by [3H]flunitrazepam, are distinct α-subunits of the GABA-benzodiazepine receptor complex. *Neuroscience Letters*, 90(3), 314–319.

Gambarana, C., Beattie, C.E., et al. (1991). Region-specific expression of messenger RNAs encoding $GABA_A$ receptor subunits in the developing rat brain. *Neuroscience*, 45, 423–432.

Goedert, M., & Hunt, S. (1987). The cellular localization of preprotachykinin A messenger RNA in the bovine nervous system. *Neuroscience*, 22(3), 983–992.

Greferath, U., Müller, F., et al. (1993). Localization of GABA-A receptors in the rat retina. *Visual Neuroscience*, 10, 102–112.

Greferath, U., Grünert, U., et al. (1995). GABA-A receptor subunits have differential distribution in the rat retina: *in situ* hybridization and immunohistochemistry. *Journal of Comparative Neurology*, 353, 553–571.

Haefely, W., Kulcsar, A., et al. (1975). Possible involvement of GABA in the central actions of benzodiazepines. *Advances in Biochemical Psychopharmacology*, 14, 131.

Hanley, M.R. (1988). Proto-oncogenes in the nervous system. *Neuron*, 1(3), 175.

Hanley, M.R. (1985). Growth factors: neuropeptides as mitogens. *Nature*, 315, 14–15.

Hanley, M.R., & Iversen, L. (1978). Muscarinic cholinergic receptors in rat corpus striatum and regulation of guanosine cyclic 3', 5'-monophosphate. *Molecular Pharmacology*, 14(2), 246.

Hironaka, T., Morita, Y., et al. (1990). Localization of GABA-A-receptor α1 subunit mRNA-containing neurons in the lower brainstem of the rat. *Molecular Brain Research*, 7(4), 335–345.

Hunkeler, W., Möhler, H., et al. (1981). Selective antagonists of benzodiazepines. Nature, 290(5806), 514–516.

Hunt, S.P., Pini, A., et al. (1987). Induction of c-fos-like protein in spinal cord neurons following sensory stimulation. Nature, 328(6131), 632–634.

Kato, K. (1990). Novel $GABA_A$ receptor α subunit is expressed only in cerebellar granule cells. Communication. *Journal of Molecular Biology*, 214(3), 619–624.

Khrestchatisky, M., MacLennan, A.J., et al. (1989). A novel alpha subunit in rat brain $GABA_A$ receptors. *Neuron*, 3(6), 745–753.

Khrestchatisky, M., MacLennan, A.J., et al. (1991). Sequence and regional distribution of the mRNA encoding the α2 polypeptide of rat gamma-aminobutyric acidA receptors. *Journal of Neurochemistry*, 56(5), 1717–1722.

Krogsgaard-Larsen, P., Frolund, B., et al. (2004). GABAA agonists and partial agonists: THIP (Gaboxadol) as a non-opioid analgesic and a novel type of hypnotic. *Biochemical Pharmacology*, 68(8), 1573–1580.

Laurie, D.J., Wisden, W., & Seeburg, P.H. (1992). The distribution of 13 $GABA_A$ receptor subunit mRNAs in the rat brain. III. Embryonic and postnatal development. *Journal of Neuroscience*, 12, 4151–4172.

Laurie, D.J., Seeburg, P.H., & Wisden, W. (1992). The distribution of 13 $GABA_A$ receptor subunit mRNAs in the rat brain. II. Olfactory bulb and cerebellum. *Journal of Neuroscience*, 12(3), 1063–1076.

Levitan, E.S., Schofield, P.R., et al. (1988). Structural and functional basis for GABAA receptor heterogeneity. *Nature*, 335(6185), 76–79.

Lewis, M.E., Sherman, T.G., et al. (1985). In situ hybridization histochemistry with synthetic oligonucleotides: strategies and methods. *Peptides*, 6, 75–87.

Lolait, S.J., O'Carroll, A.M., et al. (1989a). Pharmacological characterization and region-specific expression in brain of the α2- and α3-subunits of the rat GABAA receptor. *FEBS Letters*, 258(1), 17–21.

Lolait, S.J., O'Carroll, A.M., et al. (1989b). Cloning and expression of a novel rat GABAA receptor. *FEBS Letters*, 246(1–2), 145–148.

Lüddens, H. & Wisden, W. (1990). Function and pharmacology of multiple $GABA_A$ receptor subunits. *Trends in Pharmalogical Sciences*, 12(2), 49–51.

MacLennan A.J., Brecha, N., et al. (1991). Independent cellular and ontogenetic expression of mRNAs encoding three αpolypeptides of the rat $GABA_A$ receptor. *Neuroscience*, 43(2–3), 369–380.

Malherbe, P., Sigel, E., et al. (1990a). Functional characteristics and sites of gene expression of the alpha 1, beta 1, gamma 2-isoform of the rat GABAA receptor. *Journal of Neuroscience*, 10(7), 2330–2337.

Malherbe, P., Sigel, E., et al. (1990b). Functional expression and sites of gene transcription of a novel alpha subunit of the $GABA_A$ receptor in rat brain. *FEBS Letters*, 260(2), 261–265.

McKernan, R.M., & Whiting, P.J. (1996). Which GABAA-receptor subtypes really occur in the brain? *Trends in Neurosciences*, 19(4), 139–143.

Möhler, H. (2012). The GABA system in anxiety and depression and its therapeutic potential. *Neuropharmacology*, 62(1), 42–53.

Möhler, H. (2011). The rise of a new GABA pharmacology. *Neuropharmacology*, 60(7–8), 1042–1049.

Möhler, H., Fritschy, J.M., & Rodolph, U. (2002). A new benzodiazepine pharmacology. *Journal of Pharmacology*, 300(1), 2–8.

Montpied, P., Ginns, E.I., et al. (1989). Multiple $GABA_A$ receptor α subunit mRNAs revealed by developmental and regional expression in rat, chicken and human brain. *FEBS Letters*, 258(1), 94–98.

Morris, B., Haarmann, I., et al. (1986). Localization of prodynorphin messenger RNA in rat brain by in situ hybridization using a synthetic oligonucleotide probe. *Neuroscience Letters*, 69(1), 104–108.

Morris, B.J. (1989). Neuronal localisation of neuropeptide Y gene expression in rat brain. *Journal of Comparative Neurology*, 290(3), 358–368.

Müller, F., Greferath, U., et al. (1992). Glutamate receptor expression in the rat retina. *Neuroscience Letters*, 138, 179–182.

Nadler, L.S., Raetzman, L.T., et al. (1996). $GABA_A$ receptor subunit expression and assembly in cultured rat cerebellar granule neurons. *Developmental Brain Research*, 97, 216–226.

Olsen, R., & Tobin, A. (1990). Molecular biology of GABAA receptors. *FASEB Journal*, 4(5), 1469.

Persohn, E., Malherbe, P., & Richards, J.G. (1991). In situ hybridization histochemistry reveals a diversity of $GABA_A$ receptor subunit mRNAs in neurons of the rat spinal cord and dorsal root ganglia. *Neuroscience*, 42(2), 297–507.

Poulter, M.O., Barker, J.L., et al. 1992. Differential and transient expression of $GABA_A$ receptor α-subunit mRNAs in the developing rat CNS. *Journal of Neuroscience*, 12(8), 2888–2900.

Pritchett, D.B., Sontheimer, H., et al. (1989). Importance of a novel GABAA receptor subunit for benzodiazepine pharmacology. *Nature*, 338(6216), 582–585.

Pritchett, D.B., Sontheimer, H., et al. (1988). Transient expression shows ligand gating and allosteric potentiation of GABAA receptor subunits. *Science*, 242(4883), 1306.

R Atack, J. (2011). GABAA receptor subtype-selective modulators. I. 2/3-selective agonists as non-sedating anxiolytics. *Current Topics in Medicinal Chemistry*, 11(9), 1176–1202.

Rogers, J., & Hunt, S. (1987). Carbonic anhydrase-II messenger RNA in neurons and glia of chick brain: mapping by in situ hybridization. *Neuroscience*, 23(1), 343–361.

Rudolph, U., & Möhler, H. (2004). Analysis of GABAA receptor function and dissection of the pharmacology of benzodiazepines and general anesthetics through mouse genetics. *Annual Review of Pharmacology and Toxicology*, 44, 475–498.

Sassoe-Pognetto, M., Kirsch, J., et al. (1995). Colocalization of Gephyrin and GABA-A receptor subunits in the rat retina. *J Comp Neurol*, 357, 1–14.

Schofield, P.R., Darlison, M.G., et al. (1987). Sequence and functional expression of the GABAA receptor shows a ligand-gated receptor super-family. *Nature*, 328(6127), 221–227.

Seeburg, P.H., Wisden, W., Verdoorn, T.A., Pritchett, D.B., Werner, P., Herb, A., Lüddens, H., Sprengel, R., & Sakmann, B. (1990). The $GABA_A$ receptor family: molecular and functional diversity. *Cold Spring Harbor Symposia Quantitative Biology*, 55, 29–40.

Séquier, J.M., Richards, J.G., et al. (1988). Mapping of brain areas containing RNA homologous to cDNAs encoding the alpha and beta subunits of the rat $GABA_A$ y-aminobutyrate receptor. *Proceedings of the National Academy of Sciences*, 85, 7815–7819.

Shivers, B.D., Killisch, I., Sprengel, R., Sontheimer, H., Köhler, M., Schofield, P.R., & Seeburg, P.H. (1989). Two novel $GABA_A$ receptor subunits exist in distinct neuronal subpopulations. *Neuron*, 3, 327–337.

Siegel, R.E. (1988). The mRNAs encoding $GABA_A$/benzodiazepine receptor subunits are localized in different cell populations of the bovine cerebellum. *Neuron*, 1, 579–584.

Sieghart, W., Mayer, A., et al. (1983). Properties of [3H] flunitrazepam binding to different benzodiazepine binding proteins. *European Journal of Pharmacology*, 88(4), 291–299.

Thastrup, O., Cullen, P.J., et al. (1990). Thapsigargin, a tumor promoter, discharges intracellular Ca2+ stores by specific inhibition of the endoplasmic reticulum Ca2 (+)-ATPase. *Proceedings of the National Academy of Sciences*, 87(7), 2466.

Thastrup, O., Dawson, A., et al. (1989). Thapsigargin, a novel molecular probe for studying intracellular calcium release and storage. *Inflammation Research*, 27(1), 17–23.

Uwe, R., Crestasni, F., et al. (1999). Benzodiazepine actions mediated by specific [gamma]-aminobutyric $acid_A$ receptor subtypes. *Nature*, 401, 496–800.

Volz, A., Khorsand, V., et al. (2010). *Benzodiazepines for Schizophrenia*. Cochrane Database of Systematic Reviews.

Wafford, K.A., & Ebert, B. (2006). Gaboxadol--a new awakening in sleep. *Current Opinion in Pharmacology*, 6(1), 30–36.

Whiting, P.J. (2006). GABA-A receptors: a viable target for novel anxiolytics? *Current Opinion in Pharmacology*, 6(1), 24–29.

Wisden, W., & Morris, B.J. (2002a). In situ hybridization with oligonucleotide probes. *International Review of Neurobiology*, 47, 3–59.

Wisden, W., & Morris, B.J. (2002b). *In Situ Hybridization Protocols for the Brain*. Academic Press.

Wisden, W., Gundlach, A.L., Barnard, E.A., Seeburg, P.H., & Hunt, S.P. (1991). Distribution of GABA receptor subunit mRNAs in rat lumbar spinal cord. *Molecular Brain Research*, 10, 179–183.

Wisden, W., Herb, A., Wieland, H., Keinänen, K., Lüddens, H., & Seeburg, P.H. (1991). Cloning, pharmacological characteristics and expression pattern of the rat $GABA_A$ receptor α4 subunit. *FEBS Letters*, 289, 227–230.

Wisden, W., Laurie, D.J., Monyer, H., & Seeburg, P.H. (1992). The distribution of 13 $GABA_A$ receptor subunit mRNAs in the rat brain. I. Telencephalon, diencephalon, mesencephalon. *Journal of Neuroscience*, 12(3), 1040–1062.

Wisden, W., McNaughton, L.A., Darlison, M.G., Hunt, S.P., & Barnard, E.A. (1989). Differential distribution of $GABA_A$ receptor mRNAs in bovine cerebellum-localization of α2 mRNA in Bergmann glia layer. *Neuroscience Letters*, 106(1–2), 7–12.

Wisden, W., Morris, B.J., Darlison, M.G., Hunt, S.P., & Barnard, E.A. (1989). Localization of $GABA_A$ receptor α-subunit mRNAs in relation to receptor subtypes. *Molecular Brain Research*, 5(4), 305–310.

Wisden, W., Morris, B.J., Darlison, M.G., Hunt, S.P., & Barnard, E.A. (1988). Distinct $GABA_A$ receptor α subunit mRNAs show differential patterns of expression in bovine brain. *Neuron*, 1, 937–947.

Ymer, S., Draguhn, A., Wisden, W., Werner, P., Keinanen, K., Schofield, P.R., Sprengel, R., Pritchett, D.B., & Seeburg, P.H. (1990). Structural and functional characterization of the -Y, subunit of GABAA/benzodiazepine receptors. *EMBO Journal*, 9, 3261–3267.

Ymer, S., Schofield, P.R., Draguhn, A., Werner, P., Köhler, M., & Seeburg, P.H. (1989). GABAA receptor 3 subunit heterogeneity: functional expression of cloned cDNAs. *EMBO Journal*, 8, 1665–1670.

Young III, W.S. (1986). Vasopressin and oxytocin mRNAs in adrenalectomized and Brattleboro rats: analysis by quantitative in situ hybridization histochemistry. *Molecular Brain Research*, 1(3), 231–241.

Young III, W.S., Mezey, E., et al. (1986). Quantitative in situ hybridization histochemistry reveals increased levels of corticotropin-releasing factor mRNA after adrenalectomy in rats. *Neuroscience Letters*, 70(2), 198.

Zhang J.H., Sato, M., et al. (1990). The differential expression patterns of the mRNAs encoding α subunits (beta 1, beta 2 and beta 3) of $GABA_A$ receptors in the olfactory bulb and its related areas in the rat brain. *Neuroscience Letters*, 119, 257–260.

Zhang, J.H., Sato, M., et al. (1991). Region-specific expression of the mRNAs encoding β subunits (β1, β2, and β3) of $GABA_A$ receptor in the rat brain. *Journal of Comparative Neurology*, 303(4), 637–657.

Zhang, J.H., Sato, M., & Tohyama, M. (1991). Different postnatal development profiles of neurons containing distinct $GABA_A$ receptor β subunit mRNAs (β1, β2, and β3) in the rat forebrain. *Journal of Comparative Neurology*, 308(4), 586–613.

CHAPTER 4

Identification and distribution of 5-HT_3 receptors in rat brain using radioligand binding

This case study is based on the research that produced the paper:

Kilpatrick, G.J., Jones, B.J., & Tyers, M.B. (1987). Identification and distribution of 5-HT_3 receptors in rat brain using radioligand binding. *Nature*, 330, 746–748.

Information was gathered from interviews with Gavin Kilpatrick, Brian Jones, Brenda Costall and Daniel Hoyer, as well as from desk-based research.

4.1 Summary

Serotonin or 5-hydroxytryptamine (5-HT) is a neurotransmitter found primarily in the central nervous system, gastrointestinal tract and blood platelets. The research covered in this case study provided the first direct evidence of the existence of 5-HT_3 receptors (one class of serotonin receptor) in the brain, previously only believed to exist in the peripheral nervous system.

A number of research groups, including teams at Glaxo, Sandoz, Beecham and Merrell-Dow,[8] were investigating therapeutic uses of 5-HT_3 antagonists, which although initially targeted in relation to pain (and particularly migraine relief) had shown promise in psychiatric disorders including schizophrenia and anxiety. These findings suggested that such compounds were active in the brain, in contrast to previous evidence, and Kilpatrick and colleagues set out to demonstrate the existence of central 5-HT_3 receptors. They achieved this in 1987 and published their findings in a highly cited *Nature* paper the same year.

The finding that 5-HT_3 receptors were present in brain areas likely to be implicated in anxiety and psychosis added weight to the belief that they might be involved in psychiatric conditions. Much of the previous evidence to this end had come from behavioural research using animal models, and clinical trials in humans soon followed. However, the initial findings of clinical trials were disappointing, with no consistent evidence of positive effects, and pharmaceutical companies soon moved to focus on other areas instead.

[8] Glaxo and Beecham are both now part of GlaxoSmithKline; Sandoz merged with Ciba-Geigy in 1996 to form Novartis; and following a number of mergers Merrell-Dow is now part of Sanofi-Aventis.

By this time, the primary indication for which 5-HT_3 antagonists were being developed was emesis, and in particular chemotherapy-induced and post-operative nausea and vomiting. A related stream of work on 5-HT_3 antagonists at Glaxo produced the antiemetic compound ondansetron, which was hugely successful and revolutionised the care of cancer patients undergoing chemotherapy.

Despite the initial failure of 5-HT_3 antagonists in psychiatry, there has been something of a recent revival of interest in the area, and there are some indications that this work could potentially lead to clinical applications in disorders such as schizophrenia.

4.2 Introduction

4.2.1 Scientific background

Serotonin or 5-hydroxytryptamine (5-HT) is found mainly in the central nervous system (where it acts as a neurotransmitter), in enterochromaffin cells in the gastrointestinal tract (where it regulates smooth muscle function), and in blood platelets. The actions of 5-HT are mediated through a number of different cell membrane receptors, of which there are now thought to be around fifteen in seven functional classes.

The differentiation of 5-HT receptor types began in the 1950s, when Gaddum and Picarelli at the University of Edinburgh published a paper identifying two distinct subtypes of receptor in the guinea pig intestine (Gaddum & Picarelli, 1957). They termed the two types D receptors and M receptors.

This classification remained unchallenged for over 20 years, and it was not until the work of Fozard and colleagues at Merrell-Dow in the late 1970s that interest in the activity of 5-HT at the M receptor was revived. They worked to develop selective 5-HT antagonists and identified a receptor in the rabbit heart that appeared equivalent to the M receptor found in the guinea pig ileum (Fozard & Mobarok Ali, 1978; Fozard, Mobarok Ali & Newgrosh, 1979). In the years that followed, Fozard's group and a number of other research teams, including groups at Glaxo, Sandoz and Beecham, began working to develop more specific M receptor antagonists, and the first potent selective compound, MDL 72222 (bemestron), was described in 1984 (Fozard, 1984). This was followed shortly after by ICS 205930 (tropisetron) (Richardson, Engel, Donatsch, & Stadler, 1985), GR38032 (ondansetron) (Brittain et al., 1987) and BRL43694 (granisetron) (Fake, King & Sanger, 1987). The research model in pharmaceutical companies at the time tended to be to develop a selective compound first, and then define the direction of the research and investigate what indication the compound might be useful in (DH).

The development of these compounds, as well as of a number of potent agonists, provided the tools to further characterise the receptor, and as the body of knowledge grew, the M receptor was reclassified as the 5-HT_3 receptor (Bradley et al., 1986). The D receptor was reclassified as the 5-HT_2 receptor, whilst a third class resembling neither of Gaddum and Picarelli's subtypes was termed 5-HT_1. At the time of this work in the early 1980s, the 5-HT_3 receptor was still believed to exist only peripherally (in contrast to the 5-HT_1 and 5-HT_2 classes of receptor, which had been identified in the brain). The 5-HT_3 receptor differs from other 5-HT receptors in that it is the only one that is a ligand-gated ion

channel – the other classes are all G protein coupled receptors. This does have its advantages for research, in that compounds acting at 5-HT_3 receptors do not tend to cross-react with other receptors.

Initial work on developing 5-HT_3 antagonists clinically had focused on their potential use in pain relief, particularly in migraine treatment, and it was for this purpose that MDL 72222 was first trialled (Fozard, 1994). Based on Fozard's findings, Glaxo had developed ondansetron with the same aim, but a pilot study at a migraine clinic in West Germany in 1985 produced a surprising result: there was no major effect on patients' headaches, but ondansetron did appear useful in relieving nausea and vomiting in some instances (*GlaxoSmithKline v Teva*, 2004[9]). Mike Tyers, head of the neuropharmacology department at Glaxo at the time, believed that the 5-HT_3 antagonist properties of ondansetron could be having an antiemetic effect, and despite initial scepticism at Glaxo, he and his colleagues persuaded a senior committee to take forward ondansetron for evaluation for antiemetic activity (*GlaxoSmithKline v Teva*, 2004). The subsequent trials in both animals and humans supported the theory that ondansetron could relieve nausea and vomiting and Glaxo patented the compound in 1986.

Around the same time, the earliest 5-HT_3 antagonists, MDL 72222 and ICS 205930, were also being evaluated for antiemetic activity in animal models, and it was established that both these compounds blocked emesis induced by the chemotherapeutic agent cisplatin in the ferret (Costall, Domeney, Naylor & Tattersall, 1986; Miner & Sanger, 1986). This cumulative body of evidence led to emesis becoming the main indication for which 5-HT_3 receptor antagonists were investigated by pharmaceutical companies.

Throughout this period, research had continued to look at other potential targets for 5-HT_3 antagonists, particularly psychiatric disorders. Industry–academia collaborations were common in the field at the time (discussed further below), and the development for clinical use of 5-HT_3 antagonists relied on this kind of partnership. Brenda Costall (at Bradford University), Mike Tyers (at Glaxo) and their colleagues had begun a research programme in 1983 looking at the use of ondansetron in treating anxiety using animal models (Costall & Naylor, 2004). This produced promising results, as did initial work looking at animal models of schizophrenia. Raised dopamine activity has long been implicated in contributing to schizophrenia symptoms, with dopamine receptors being the primary target of the main pharmacological treatments. Early work in animal models demonstrated that ondansetron and other 5-HT_3 receptor antagonists block the activity of dopamine (as well as amphetamine and 2-methyl-5-HT) in limbic areas of the rat and marmoset brain. This suggested that serotonin might be involved in the modulation of dopamine activity, and highlighted 5-HT_3 receptors as another potential target receptor for drug development in treating schizophrenia.

Because there was still no definitive evidence for the existence of 5-HT_3 receptors in the brain at this time; it was believed that the antiemetic properties of 5-HT_3 receptor antagonists were a result of activity at receptors in the gut. However the promising findings

[9] This patent infringement and validity case was not related specifically to the case study research, but provided useful background information on the 5-HT_3 work being carried out by Glaxo in the 1980s.

from animal models of apparent effects in anxiety and psychosis suggested that these compounds were active in the brain as well.

4.2.2 Researchers' backgrounds

Gavin Kilpatrick was the corresponding author on the paper initially selected. He had completed his PhD in neuropharmacology at the Institute of Psychiatry, King's College London in 1985. At that time, the pharmacology field was quite applied due to the heavy involvement of industry. This was an environment that suited Kilpatrick well, and in the absence of any post-doc opportunities that were of particular interest, he opted to join Glaxo as a Senior Scientist.

Brian Jones was head of the group that Kilpatrick joined at Glaxo. After completing his PhD in pharmacology, he taught for a few years before joining Glaxo in 1973. At Glaxo he worked on CNS drug research, in particular in depression and anxiety, before leaving for Beecham in 1989.

Mike Tyers was head of the neuropharmacology department at Glaxo when Kilpatrick joined and had responsibility for approving work to happen in the department.

Daniel Hoyer was a senior research biochemist at Sandoz, where he was also trying to characterise/localise 5-HT_3 receptors using similar techniques to the Glaxo team, although his main emphasis was on non 5-HT_3 receptors. With Hans Neijt, a PhD student from Holland, J.M. Palacios and other colleagues he showed in 1987–1989 that 5-HT_3 receptors were expressed in neuronal cells, brain and peripheral nervous system of various species, including humans, using radioligand binding, autoradiography and electrophysiology (e.g. Hoyer & Neijt, 1987; Hoyer & Neijt, 1988; Waeber et al., 1988).

Brenda Costall and **Robert Naylor**, professors at the University of Bradford, carried out much of the behavioural work on 5-HT_3 in animal models. They collaborated with a number of pharmaceutical companies, including both Glaxo and Sandoz.

Ed Sellers at the University of Toronto, Canada, was studying the role of 5-HT_3 receptors in addiction. He worked with Glaxo to look at the effects of ondansetron on alcohol and drug intake in animals.

4.2.3 Institution background

The case study research took place at Glaxo's Ware research facility in the UK. At the time that Kilpatrick joined (coinciding with the start of the research cloud), the team was in the process of moving from their previous research base in Greenford. The CNS group was the last to move to Ware.

Kilpatrick characterises the research environment within Glaxo at the time as being fairly academic. Collaboration across groups was encouraged and although the company had a clear commercial drive to develop drugs, researchers were afforded a reasonable degree of freedom to experiment in new areas.

> At the time at Glaxo there weren't that many people who had a PhD, so if you came in with a PhD you tended to get a very easy ride in terms of freedom. So I guess I was very lucky. I was a first year post-doc really. (GK)

The Ware group was also particularly successful at the time:

> There were maybe 150 people at that site in Ware who came up with at least four genuine blockbusters in less than ten years, and Glaxo made an absolute fortune from the drugs that came out of there… in that sort of environment, management recognised the benefits of allowing scientists a fair degree of freedom. (GK).

4.3 Defining the research cloud

This case study covers the research carried out at Glaxo that showed the existence of 5-HT_3 receptors in the brain. The research cloud begins when Gavin Kilpatrick joined Glaxo in 1985 and includes the work done there to map the distribution of 5-HT_3 receptors in a number of species and using several techniques. Work on the functional role of 5-HT_3 receptor antagonists and the concurrent development through to clinical use of ondansetron form separate but related research clouds, which are not the primary focus of the case study.

The publications from the research cloud are as follows:

1. Kilpatrick, G.J., Jones, B.J., & Tyers, M.B. (1987). Identification and distribution of 5-HT_3 receptors in rat brain using radioligand binding. *Nature*, 330, 746–748.
2. Kilpatrick, G.J., Jones, B.J., & Tyers, M.B. (1988). The distribution of specific binding of the 5-HT3 receptor ligand [3H]GR65630 in rat brain using quantitative autoradiography. *Neuroscience Letters*, 94(1–2), 156–160.
3. Kilpatrick, G.J., Jones, B.J., & Tyers, M.B. (1989). Binding of the 5-HT3 ligand, [3H]GR65630, to rat area postrema, vagus nerve and the brains of several species. *European Journal of Pharmacology*, 159(2), 157–164.
4. Barnes, J.M., Barnes, N.M., Costall, B., Deakin, J.F.W., Ironside, J.W., Kilpatrick, G.J., et al. (1990). Identification and distribution of 5-HT3 recognition sites within the human brainstem. *Neuroscience Letters*, 111(1–2), 80–86.
5. Kilpatrick, G.J., Bunce, K.T., & Tyers, M.B. (1990). 5-HT3 receptors. *Medicinal Research Reviews*, 10(4), 441–475.
6. Kilpatrick, G.J., Butler, A., Hagan, R.M., Jones, B.J., & Tyers, M.B. (1990). [^{3}H] GR67330, a very high affinity ligand for 5-HT_3 receptors. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 342(1), 22–30.
7. Pratt, G.D., Bowery, N.G., Kilpatrick, G.J., Leslie, R.A., Barnes, N.M., Naylor, R.J., et al. (1990). Consensus meeting agrees distribution of 5-HT3 receptors in mammalian hindbrain. *Trends in Pharmacological Sciences*, 11(4), 135–137.
8. Kilpatrick, G.J., Barnes, N.M., Cheng, C.H.K., Costall, B., Naylor, R.J., & Tyers, M.B. (1991). The pharmacological characterization of 5-HT3 receptor-binding sites in rabbit ileum – comparison with those in rat ileum and rat-brain. *Neurochemistry International*, 19(4), 389–396.
9. Jones, D.N.C., Barnes, N.M., Costall, B., Domeney, A.M., Kilpatrick, G.J., Naylor, R.J., et al. (1992). The distribution of 5-HT3 recognition sites in the marmoset brain. *European Journal of Pharmacology*, 215(1), 63–67.
10. Kilpatrick, G.J., & Tyers, M.B. (1992). Interspecies variants of the 5-HT3 receptor. *Biochemical Society Transactions*, 20(1), 118–121.

4.4 Stage 0: Opportunity identification/research needs assessment

Inspiration

As discussed above, after the revival of interest in 5-HT in the late 1970s, research on characterising receptor subtypes had gathered momentum and was being advanced rapidly by a number of research groups. Several pharmaceutical companies, including Glaxo, Sandoz, Merrell-Dow and Beecham had initiated research programmes to synthesise 5-HT_3 antagonists, which it was widely believed would have a role in managing pain, particularly in association with migraine. Early findings soon suggested an additional role in the treatment of emesis. In these indications it was assumed initially that compounds were active only peripherally (and not in the central nervous system), as it was well established that 5-HT_3 receptors existed in the gut. However, work done by Costall and Naylor at the University of Bradford using animal models also indicated a possible application in psychiatric disorders, including anxiety, schizophrenia and Alzheimer's disease, findings that seemed to suggest that 5-HT_3 receptors might also be present in the brain. This accumulation of knowledge formed the basis for carrying out the case study work.

Collaborations between industry and academia, such as much of the work done by Costall and Naylor in this area, were particularly common at the time. This situation existed partly out of need: pharmaceutical companies developed compounds, but often relied on the expertise of leading academic researchers to investigate their clinical application.

> It was a strange time because industry was seen very much as second class citizens in pharmacology, even though some of the best scientists were in industry; they just didn't carry the weight or authority of a professor in a university. It certainly isn't like that now; I think industry is respected as being equal, or in many ways far more advanced in some areas than universities. (BC)

However, this was a two-way relationship, as even if an academic group had a suitable compound, it is unlikely that they would have the resources to develop it through clinical trials:

> [For] a team in academia to take a compound and develop it full blown in indications as complex as anxiety, depression and schizophrenia is almost impossible. (DH)

This mutually beneficial relationship created an 'exciting time for research, with academic leaders joining with industry leaders to get literally "from molecules to man"… the 5-HT_3 story was when research was at its peak' (Costall, personal communication).

The Glaxo group worked closely with Costall and Naylor at the University of Bradford on testing 5-HT_3 antagonists in animal models. At the time the Bradford group was leading the field in this area of work, with over 60 staff and sophisticated models to evaluate compounds across the entire spectrum of CNS indications. The Glaxo team isolated 5-HT ligands on peripheral receptors and sent them through to the Bradford group to test for effects on the brain in anxiety, memory enhancement, depression and schizophrenia.

> It literally was a series of bottles of coded compounds and a question: what do they do in the brain? It was really exciting. It was done within days. We gave the information to Glaxo; Glaxo bosses moved it. From the head of neuropharmacology, who was then Mike Tyers, it went straight up to the very top and they got funding to do it very quickly. That wouldn't happen now. (BC)

Neuropharmacology was advancing rapidly in the 1980s and the 5-HT field was small and competitive. The group at Glaxo was in competition with a team at Sandoz, where there was a similar effort to localise 5-HT_3 receptors through radioligand binding. Costall and Naylor worked extensively with both groups, testing new compounds in animal models, and Costall confirmed the competiveness that existed:

> Robert Naylor was doing the work for Sandoz on emesis while I was doing the work for Glaxo on anxiety…. Brian Richardson, who developed that work at Sandoz actually did know that they had an antiemetic, but he didn't get the backing of senior management and so they fell behind in the race…. I was actually at Sandoz when a newsflash came through that Glaxo had done it first, the first publication on the antiemetic effect of their compound, and you could just see that the entire Sandoz group went 'oh no…'. It really was neck and neck, but it was just about who was prepared to go the fastest, put more resource in line. (BC)

Feasibility

The team at Glaxo had substantial experience in identifying and characterising receptors and developing drugs, but Kilpatrick brought the specific technique of radioligand binding into the lab. His experience in using the technique during his PhD at the Institute of Psychiatry (London), in which he studied dopamine receptors, was a key reason for his recruitment on to the team at Glaxo, as it was recognised that this would be vital expertise for the 5-HT_3 work.

The technique of radioligand binding requires a high-affinity compound for the receptor of interest which can be made in a highly radioactive form, i.e. with a high specific activity. Finding the right compound is time consuming and expensive, and so it was advantageous that Glaxo already had numerous compounds which could potentially be used, including GR38032 (ondansetron), which was looking extremely promising in peripheral 5-HT_3 work.

Potential value

There was clear value to carrying out the case study research, both clinically through the potential to develop drugs to help alleviate mental disorders, and commercially through the marketing potential that such a product would have. As mentioned previously, Glaxo's research efforts in the UK were highly successful at the time, and a number of blockbuster drugs had recently been developed.

4.5 Stage 1: Inputs to research

Money, researcher time, lab/office space and consumables

The research was funded solely by Glaxo, with head of department Mike Tyers approving work to take place in neuropharmacology. Kilpatrick estimated that the initial work on localising 5-HT_3 receptors in the brain probably took the equivalent of two FTEs (Kilpatrick and a technician) for around 18 months, plus the lab overheads and cost of synthesis of the radioligand used. Tyers acted as a champion for 5-HT_3 antagonists within Glaxo, including in convincing more sceptical senior management of the potential commercial value of developing these compounds. Costall discussed the importance of this in driving forward a particular area of research:

> We handled quite a lot of 5-HT_3 receptor antagonists, but none of them went as fast as Glaxo. They're the ones who really led everyone else, even though the others were there at about the same time. You need a champion inside who has weight and Mike Tyers was that in Glaxo. (BC)

The research was carried out at Glaxo's research headquarters in Ware. As mentioned previously, the CNS group had been the last remaining research group based at Glaxo's previous site in Greenford, so during that time had a lot of space to conduct their work. The move to Ware meant that they became more constrained in terms of space, but benefitted from being close to other research groups and the opportunities for cross-fertilisation of ideas that this brought.

Knowledge

As mentioned above, a body of knowledge about the nature of 5-HT receptors had built up over the previous ten years or so, and the suggestion from animal models that 5-HT_3 receptors might exist centrally was important in directing the case study research.

The neuropharmacology group at Glaxo were also able to draw on the knowledge of other groups based at Ware (and became close to the cardiovascular group who were already working on 5-HT_3 receptors), as well as on the skills of Glaxo's radiochemical experts in developing a radioligand. Working on a radioligand of high specific activity was a new venture for the radiochemistry group, who at that time worked mainly in developing low specific activity compounds from metabolic studies.

Expertise and techniques

The neuropharmacology department at Glaxo consisted of around 40 people. Prior to Kilpatrick joining Glaxo, the technique of radioligand binding was not used within the company, although competitors, most notably Sandoz, had been conducting such studies with 5-HT for some time. In fact, a group at Sandoz led by Hoyer was using the technique to investigate 5-HT_3 receptors at the same time, and despite submitting their paper just after Kilpatrick et al.'s *Nature* paper, it appeared in the *European Journal of Pharmacology* just a few weeks earlier, becoming the first published account of using radioligand binding to investigate 5-HT_3 receptors (Hoyer & Neijt, 1987).

Collaborators

As noted above, the move of the CNS group to Ware created opportunities for discussion and informal collaboration with other research groups within Glaxo. In particular, the move strengthened relations with the cardiovascular group, who were looking at similar receptors.

The 5-HT field as a whole was similarly close at the time.

> That was one of the great things about 5-HT – that there were people from across the board in both academia and industry that worked closely together, in competition of course, but really closely together. (DH)

4.6 Stage 2: Processes

The general research model in use at Glaxo at the time was receptor based, which meant that a group would work on any indications associated with a particular receptor (in this case 5-HT_3). This was in contrast to some other pharmaceutical companies at the time; for

example, Beecham used a project system, in which a group would be given a therapeutic indication that would be addressed through a number of different approaches. Although the kind of project system used by Beecham was an efficient model at the time, as new technologies emerged it became necessary to recruit specific expertise in applying each and such a broad approach became unrealistic.

The specific method of radioligand binding was a new technique within Glaxo at the time. A number of promising 5-HT_3 antagonists had already been developed at the company, and Kilpatrick's initial binding work used GR38032 (ondansetron), but this was unsuccessful. However, within a year or so of his arrival at Glaxo, GR65630 was developed and the radiochemical group was tasked with developing a version that had a high specific activity. As noted previously, in order to do this, Mike Tyers had persuaded the group to depart somewhat from its usual work in developing low specific activity compounds for metabolic studies. From this, Kilpatrick was able to develop a binding assay and demonstrate the presence and distribution of 5-HT_3 receptors in the brain.

Subsequent work in the research cloud repeated the radioligand binding work in other species (Kilpatrick, Jones & Tyers, 1989a) and supported the findings reported in the *Nature* paper with autoradiography (Kilpatrick, Jones & Tyers, 1988).

4.7 Stage 3: Primary outputs

Knowledge

The first publication emerging from the research cloud was a paper published in *Nature* in 1987 by Kilpatrick, Jones and Tyers. This paper described the team's work to identify 5-HT_3 receptors through radioligand binding and was the first to provide direct evidence for their existence in the brain. Binding of the 5-HT_3 receptor antagonist GR65630 was found to be differentially localised throughout the rat brain, with the highest density of binding sites found in the entorhinal cortex. Significant binding was also demonstrated in other areas of the cortex, as well as the amygdala, hippocampus and nucleus accumbens/tuberculum olfactorium. The paper briefly speculated on the functional role of 5-HT_3 receptors in the brain, noting that the areas identified as having the highest receptor densities were also those likely to be involved in the behavioural effects of 5-HT_3 antagonists found in studies of anxiety and psychosis in animal models (eg. Costall, Domeney, Kelly, Naylor & Tyers, 1987; Jones, Oakley & Tyers, 1987). Kilpatrick suggested that the research team had further suspicions at the time regarding the function of the receptors, but due to the brevity of the article and *Nature*'s strict editorial policy the final paper included only the bare facts of the research.

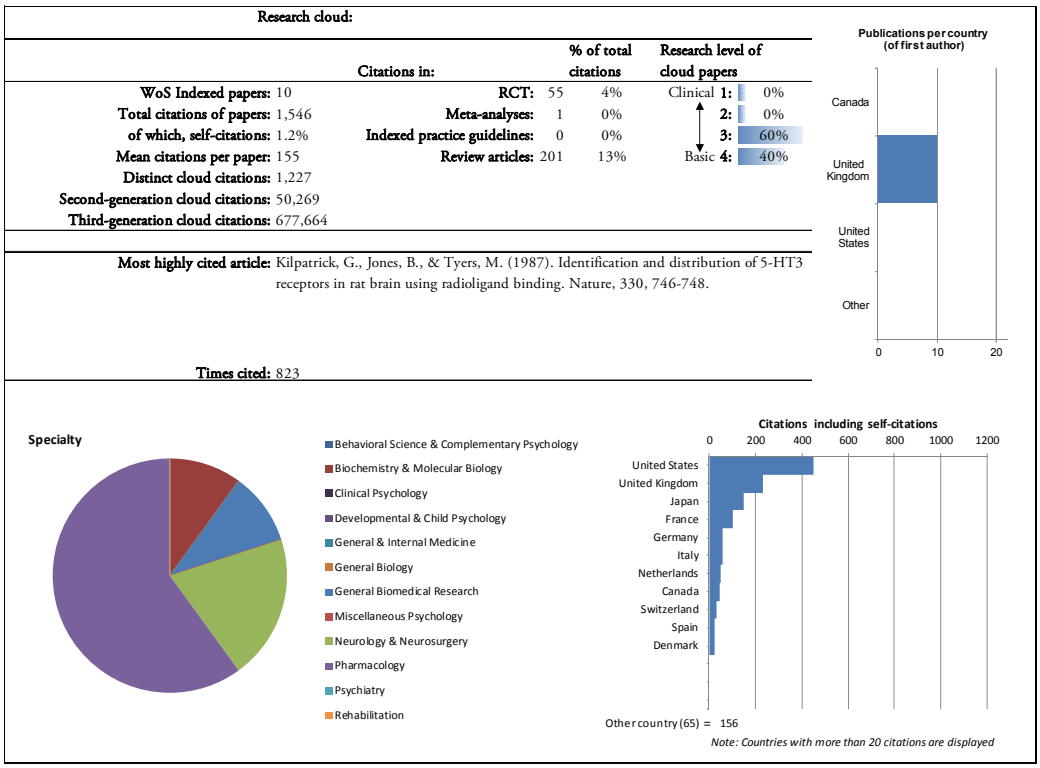
The same issue of *Nature* also included an editorial discussing whether or not the Glaxo team had actually found evidence of a *functional* receptor, arguing that they might have only identified a 5-HT_3 binding site (Bradley, 1987). The fact that radioligand binding studies did not test for a physical or biochemical response (in contrast to early pharmacology research showing, for example, the contraction of a piece of gut) created a reluctance in much of the pharmacology community to trust these methods. This attitude was also prevalent within Glaxo: the technique was not in use within the company until Kilpatrick joined in 1985, despite having been fairly widely used in characterising receptors for a number of years. Kilpatrick commented that although some misleading results had

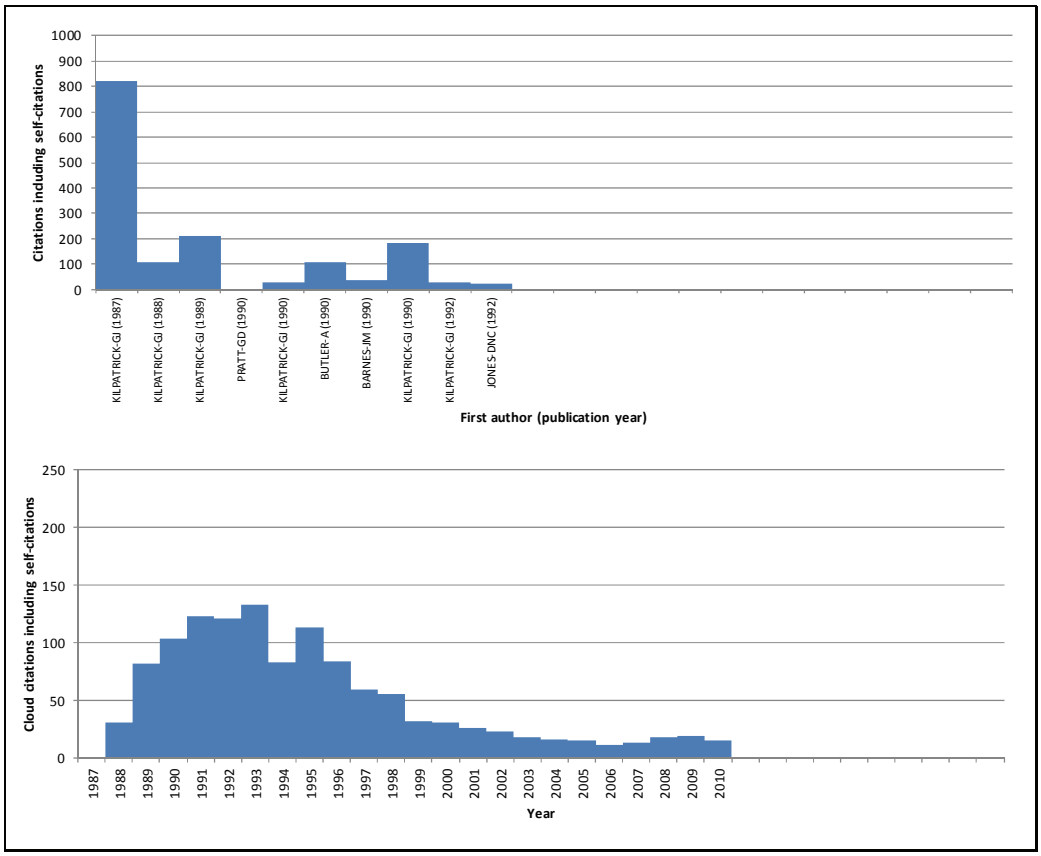
been obtained in early work (binding where there was not actually a functional receptor), these had been in the very early days, before the receptors had been properly characterised and before the technique was well understood.

In line with these concerns the editorial specifically mentioned that GR65630 had not been shown to produce any behavioural effects, and that this might suggest no activity in the central nervous system. However, Jones argued that such findings could also indicate a compound that is psychoactive, but with a very good side effect profile. For example, in the case of an antidepressant, the drug should have no observable effect on someone who is not depressed (BJ).

The discovery of 5-HT_3 receptors in the rat brain led to the publication of a stream of related papers in rapid succession by the Glaxo team. These publications expanded on the *Nature* paper through replicating the findings using autoradiography (Kilpatrick et al., 1988), by identifying 5-HT_3 receptors in the brains of humans (Barnes et al., 1990) and other species (Kilpatrick, Jones & Tyers, 1989b), and by developing new, higher affinity ligands for 5-HT_3 receptors (Kilpatrick, Butler, Hagan, Jones & Tyers, 1990).

A bibliometric analysis of the papers produced from the research cloud is shown below.





Targeting future research

Effect on the researchers' careers

The case study work was important in Kilpatrick's career, as it gave him a highly cited *Nature* paper within two years of joining Glaxo, his first position after completing has PhD at the Institute of Psychiatry. Although his early breakthrough raised hopes of a number of possible therapeutic applications in psychiatry, the follow-up clinical work proved disappointing. Glaxo began to decrease their investment in 5-HT_3 work and by the early 1990s the stream of work had completely ceased. Kilpatrick moved on to an entirely different area – H_3 receptors, which are widespread in the central nervous system and are involved in the control of histamine levels, as well as modulating other neurotransmitters, including dopamine, serotonin, GABA and acetylcholine.

The 1990s was a time of rapid change in the pharmaceutical industry. Molecular biology and genetics were becoming the preferred research approaches and a series of mega-mergers (including Glaxo's merger with Wellcome) and the introduction of new regulations dramatically altered the market. As psychiatry became less of a priority within Glaxo and the emphasis shifted away from pharmacological research, many of the senior people involved were made redundant. This was not the case for Kilpatrick, who by this point had worked his way up to Research Manager on the back of his 5-HT_3 and H3 work, but he recognised that there would be little demand within the company for his particular skills, and left to lead psychiatry research at Roche. This was a much more diverse role, although using a research model similar to that previously used at Glaxo, and provided opportunities to do some academic work as well.

As of November 2011, Kilpatrick is doing consulting work for his own company, GJK Pharma Ltd, as well as helping some small start-up companies. Prior to this he was Chief Scientific Officer of the biopharmaceutical company PAION, where much of his research was around the development of a sedative agent with very fast onset and offset.

The 5-HT_3 work was also important in the career of Brian Jones. He left Glaxo in 1989 to join Beecham, shortly before their merger with SmithKline Beckman, where he became Director of Neurochemical Pharmacology in Neurosciences Research. The research set-up at Beecham was quite different to that of Glaxo, in that they adopted a project system using a number of different approaches to address a particular therapeutic target.

The research on localising 5-HT_3 receptors was also beneficial to the careers of Mike Tyers, who was head of department at Glaxo at the time, and Russell Hagan, who went on to a senior position at the pharmaceutical company BTG.

Future work – in psychiatry

Building on the finding that 5-HT_3 receptors are present in the brain, research proceeded in a number of distinct directions, both through the work of the team at Glaxo and in other industry and academic labs. The prospect of developing drugs targeting 5-HT_3 receptors in CNS-mediated conditions held great potential, while confirmation that these receptors existed centrally provided the opportunity to explore (and potentially explain) a range of physiological phenomena.

The work by Brenda Costall and Robert Naylor at Bradford University during the 1980s had provided promising evidence of the behavioural effects of 5-HT_3 antagonists in animal models of anxiety and psychosis. Taken alongside the evidence for the existence of these same receptors in the brain, the logical conclusion was that compounds acting at 5-HT_3 receptors might well prove useful in the treatment of psychiatric conditions such as schizophrenia, anxiety and depression. Kilpatrick felt that the case study research was important in facilitating the subsequent clinical trials in psychiatry, as without this evidence of 5-HT_3 antagonists acting centrally it would have been difficult to recruit good investigators to carry out the work. However, these trials, for which Kilpatrick and Jones both often acted as pre-clinical consultants, ultimately failed to replicate the expected effects and by the early to mid-1990s it had become fairly clear to the Glaxo team that a commercial product was not going to emerge (GK).

The Glaxo team also collaborated with a group at the University of Toronto led by Ed Sellers. Sellers' group was investigating the use of 5-HT_3 receptor antagonists in treating drug and alcohol dependence, but despite producing some evidence of their beneficial effects (Sellers et al., 1992), this has yet to be adopted as a standard treatment.

Kilpatrick and his colleagues also developed a potent 5-HT_3 receptor agonist (Kilpatrick, Butler, Burridge & Oxford, 1990). Although this would be of little clinical use (as it causes people to vomit), it has been used extensively as a pharmaceutical tool in studying the 5-HT_3 receptor (e.g. Ali et al., 1996; Campbell & McBride, 1995).

One of the challenges in conducting clinical trials of 5-HT_3 receptor antagonists is that many are characterised by a bell-shaped dose response curve (Barnes & Sharp, 1999); that is, after reaching a certain optimum dose, further increasing dosage decreases the effects of

the drug. This can complicate the interpretation of negative results and Jones suggested that this could potentially have been an issue in some of the early unsuccessful trials (BJ). Costall agreed, adding:

> I do know that the anxiety trials came in quite positive but there was a big worry about how you would put together the document for the FDA or wherever for a compound which didn't have a normal sigmoid response curve. Pharmacologically we couldn't explain it; we still can't explain it. And what if somebody overdosed? There is a tendency [to do so] if you're feeling really good on a medication, but then what if you take the full packet and lose the effect? (BC)

A second challenge in selecting the correct dosage for clinical trials was related to the fact that animal models showed 5-HT_3 receptor antagonists to be particularly potent in psychiatric disorders, a finding that meant that the effective psychoactive dose was likely to be far lower than the clinical dose used in emesis (BJ). In such instances, the usual clinical trial strategy of using the maximum tolerated dose would not be appropriate. An ideal approach would involve comparing the effective antiemetic and psychoactive doses in animals, then using this ratio to estimate an appropriate range of doses to test in human trials. This may, however, be complicated by the fact that psychiatric disorders are often examined in rat models, which are not suitable for emesis.

Future work – in other areas

As discussed previously, by the time the Glaxo team demonstrated the presence of 5-HT_3 receptors in the brain, the antiemetic properties of 5-HT_3 antagonists had already been revealed through looking at the effects of ondansetron in animal models, primarily ferrets (eg. Costall, Domeney, Gunning et al., 1987), and through clinical trials initially conducted by Professor John Smyth at Western General Hospital in Edinburgh (*GlaxoSmithKline v Teva*, 2004).

The finding that receptors were particularly densely clustered in the dorsal vagal complex of the brain stem (Pratt et al., 1990), a region of the brain that controls vomiting, added further weight to emesis being the primary indication on which research efforts in the 5-HT_3 field were focussed. Similar work was being carried out at other companies, including at Sandoz where Daniel Hoyer's group was also using radioligand binding to identify 5-HT_3 receptors, and where tropisetron, one of the first 5-HT_3 antagonists to show antiemetic effects, was developed in the early 1980s. Both ondansetron and tropisetron went on to be used clinically in treating chemotherapy-induced nausea and vomiting and postoperative emesis. Both are still in use today, the former becoming particularly successful for Glaxo and grossing over a billion dollars a year.

This success, though, may have hindered progress in investigating the use of 5-HT_3 receptor antagonists more widely. As new compounds are costly to develop, the fact that ondansetron (and other early 5-HT_3 antagonists, such as tropisetron and bemesetron) had already been licensed and had been well characterised in the literature meant that it was commonly used in any trial requiring a 5-HT_3 receptor antagonist. However, other compounds developed subsequently may have been better suited to the treatment of other conditions:

> Ondansetron possibly isn't the best drug to use for CNS effects, because it probably gave us the worst dose response curve of all… it is relatively weak compared to some of the

> other 5-HT_3 receptor antagonists that are available and the more potent ones seem to give a better dose range. There are better compounds that could be used for CNS problems. (BJ)

Additionally, there may be a tendency within pharmaceutical companies to focus only on the primary indication for any particular experimental compound, and for their competitors to also concentrate on these same areas (DH). This is partly due to the fact that major drug breakthroughs are rare enough and commercially valuable enough to generate intense competition and attract huge investment in areas showing promise, but there may also have been a culture of silo-based working in some organisations.

> There's a lot of stuff out there but it seems that for whatever political or internal strategic reason, the main players decided not to follow up and this is something that happens fairly classically in Big Pharma. A team will take a compound on board, say for instance ondansetron in Glaxo, and go for the primary indication, which is chemotherapy-induced vomiting… if in the same company another team in psychiatry or CNS would take the compound, this would be seen as almost competition, internal competition, and these kind of things don't always work well. Actually, it's pretty unusual that these things work well and so you have to have someone who has an interest in both fields to strongly push in both directions. (DH)

The negative results of the early clinical trials in anxiety and psychosis may also have been seen as potentially damaging to the image of a drug and may have discouraged further investigation for other indications (BC).

> The concept that it didn't work somewhere would really hurt the marketing.… Considering the difficulties in psychiatry, wouldn't it be better to make your money in emesis, which is there in all cancer patients? There are two sides to this: there's what the companies must do, and I can't say that that is wrong in terms of their survival, but in terms of psychiatry it was a disaster because we stopped all the trials. (BC)

4.8 Interface B: Dissemination

Publications and talks were the main vehicles for disseminating the findings of the research cloud. Management at Glaxo's Ware research facility were keen for researchers to publish in order to build the group's credibility in the academic world. Kilpatrick gave ten to twelve talks at major meetings in the years following the publication of the *Nature* article, something which he said was very beneficial for his career.

New knowledge was well disseminated within what was a fairly small field. Many of the groups working on 5-HT_3 receptors had, despite being in competition, collaborated on certain projects, and most met up regularly at meetings of societies including the British Pharmacological Society (BPS) and the International Union of Basic and Clinical Pharmacology (IUPHAR). While it was not possible to share everything with competitors, there was a consensus in the field that sharing as much knowledge as possible was beneficial to everyone. Hoyer recalled the BPS meetings being particularly well attended at the time by both industry and academia, and suggested that even in instances where information couldn't be shared with the wider field, there was an unwritten understanding that researchers would not intentionally allow competitors to follow a line of enquiry that they knew would not work (DH).

4.9 Stage 4: Secondary outputs

None identified.

4.10 Stage 5: Applications

Despite Glaxo's substantial investment in clinical trials of 5-HT_3 receptor antagonists in psychiatric disorders, the research ultimately came to little and no commercial drugs were produced.

> That was quite a lesson. It was a lesson personally, but I think a lesson to the industry about animal models in psychiatric diseases – that they needed improvement and also much more care when it came to translating and moving from the animal work into the human work. (GK)

Costall commented that other animal models her group had used had very successfully translated and brought drugs to market, and that the failure of 5-HT_3 receptor antagonists in psychiatry at the time of the case study research may have been due in part to the particular conflict model in use at Glaxo at the time. She suggested that the punishment element of this model may create a level of fear that was not on a par with anxiety in psychiatric disorders, but that findings like these contributed to the development of future trials.

> Whilst those first 5-HT_3 receptor antagonists might not have been out there looking successful in psychiatry, there have been other things which have followed because they allowed us to develop tests. (BC)

The first 5-HT_3 receptor subunit was cloned in 1991 (Maricq et al., 1991), an advance that made their study considerably easier. However, one case study reviewer commented that if multiple subunits had been cloned at that time it might have been possible to develop drugs that were more selective or worked in different therapeutic areas. Further subunits were cloned in the late 1990s and early 2000s, but by this time the focus of the field had shifted away from 5-HT_3 receptors. Glaxo focussed on ondansetron and its use in chemotherapy-induced emesis, which rapidly became a very profitable area. It was one of a number of successes emerging from the Ware research facility at the time, where the team of around 150 people developed at least four blockbuster drugs in less than ten years (GK). Glaxo was awarded the European Prix Galien in oncology for ondansetron in 1990.

Before Glaxo ended their 5-HT_3 work, this stream of research did produce another drug that made it to the clinic: alosetron. This compound was licensed for use in the US in treating irritable bowel syndrome, and despite being withdrawn from the market in 2000 due to adverse gastrointestinal effects, was reinstated in 2002 and is still in use today (although GSK sold the license to American company Prometheus in 2007). This is arguably the closest that a 5-HT_3 antagonist has come to being used clinically in psychiatric disorders: although the underlying cause of IBS remains unknown, there is increasing support for the theory that it involves a dysregulation of the interaction between brain and gut (Drossman et al., 1999), as well as evidence that up to 94 percent of IBS patients have a comorbid psychiatric condition (Whitehead, Palsson & Jones, 2002). Alosetron was also originally trialled by Glaxo (at its US research base in North Carolina)

for use in schizophrenia patients in conjunction with the antipsychotic haloperidol (Gupta et al., 1995). However, this did not lead to clinical use.

In recent years, there has been something of a revival of interest in alternative uses (besides antiemetic properties and IBS use) of 5-HT_3 antagonists. Despite earlier clinical trials failing to support the use of ondansetron in schizophrenia, a number of recent studies have evaluated its use both on its own and as an adjunct to an antipsychotic. A recently published article reviewed six clinical trials of ondansetron use in schizophrenia treatment (Bennett & Vila, 2010). The authors concluded that although further large, randomised, double-blind controlled trials are needed, findings relating to the use of ondansetron in combination with an antipsychotic were promising, particularly in treating negative symptoms and cognitive impairments (eg. Zhang et al., 2006 as an adjunct to haloperidol; Akhondzadeh et al., 2009 as an adjunct to risperidone).

> I think it is still an open question, to be honest, whether these things have psychoactive properties. (BJ)

One of the challenges in taking forward promising compounds in psychiatric disorders is the difficulty of conducting rigorous, controlled clinical trials. This stems from the lack of homogeneity across patient populations: disorders such as schizophrenia are not tightly defined and are diverse in their occurrence, making it difficult to recruit comparable patient populations. Hoyer suggested that this may be one reason behind the reluctance of pharmaceutical companies to pursue the use of 5-HT_3 receptor antagonists in psychiatric disorders (DH). Costall agreed, highlighting the particularly complex nature of schizophrenia:

> If you put together a large group of people who have got complex symptoms, who have got different drug histories, and quite often chronic with acute, young with old, male with female – and this is what one has to do to get sufficient numbers – then you will end up with a variety of outcomes… and with very dirty data, which when analysed really gives you very little effect. (BC)

Costall went on to add that when subgroups of patients are separated out, for example, young people newly admitted with a particular subtype of schizophrenia, the data obtained tend to be consistent. However, such trials are very difficult to set up and in the late 1980s the importance of setting tight selection criteria may not have been fully appreciated (BC).

In a somewhat roundabout way, tropisetron (the 5-HT_3 antagonist developed by Sandoz at the same time as Glaxo was working on ondanestron) has also recently been considered for use in schizophrenia. Shiina et al. (2010) published findings from a randomised, placebo-controlled study of tropisetron in patients with chronic schizophrenia who were taking risperidone. Although there was no improvement observed in direct schizophrenia symptoms (as measured by the Positive and Negative Syndrome Scale; PANSS), they did find a significant improvement in a visual attention task and a reduction in auditory sensory gating P50 deficits (a correlate of attention deficits), suggesting that tropisetron may be useful in addressing cognitive deficits associated with schizophrenia. They do, however, speculate that these effects may be due not to tropisetron's effects as a 5-HT_3 antagonist, but instead to its action at the α7 nicotinic acetylcholine receptor.

This acknowledgement of the action of compounds at multiple receptor types may be indicative of another issue in the early clinical trials of 5-HT_3 antagonists in psychiatry.

Costall suggested that those drugs that have proven most effective often tend to also be fairly non-specific, acting at a number of different receptor types, and that research had perhaps focussed too narrowly in the past in an effort to identify pure compounds. A good example of this is clozapine, which in addition to acting upon the dopamine system, is also active at serotonergic, adrenergic, histaminergic and cholinergic receptors.

> I think we maybe got too narrow, and we almost had to park the concept of pure compounds. We also needed to get it out of the minds of the registering bodies that we needed that level of purity, because it seems not to be giving the answers that we want. It gave us the pharmacological lead and we have enough clinical trial data to know that we're on the right lines, but we still need the right compounds. (BC)

4.11 Stage 6: Public engagement

None identified.

4.12 Stage 7: Final outcomes

Although the case study research did not lead directly to improvements for patients or wider economic benefits, other drugs developed from Glaxo's 5-HT_3 receptor work did. Ondansetron revolutionalised care for cancer patients undergoing chemotherapy and has made billions of dollars for Glaxo over the past 20 years. It is still widely used today and exists in a number of generic forms (since the expiry of Glaxo's patent in 2006). Alosetron, while having a smaller impact and temporarily being withdrawn from the US market, is still in use today for some irritable bowel syndrome patients.

4.13 Table of payback

Payback category	Impacts from case study
Knowledge Production	• A number of papers were published showing the existence of 5-HT_3 receptors centrally in a number of species and using various methods.
Research Targeting and Capacity Building	• Instrumental in Kilpatrick's career not long after completing his PhD and beneficial to others on the research team who went on to good positions in other companies. • First to demonstrate the existence of 5-HT_3 receptors in the brain, a finding that stimulated substantial further research on their functional properties by a number of groups and led to clinical trials in several psychiatry indications. • Led to the development of a potent 5-HT_3 agonist, since used extensively as a tool in pharmaceutical research.
Informing Policy and Product Development	• Although a related stream of work led to the clinical development of ondansetron and alosetron, the case study research had little direct effect on these developments.

Health and Health Sector Benefits	• As above, ondansetron and alosetron brought substantial health benefits, but the case study research had little direct influence in this.
Broader Social and Economic Benefits	• Although only indirectly related, ondansetron and alosetron are both still in clinical use today.

4.14 Timeline

1957	Gaddum & Picarelli identify two distinct 5-HT receptors in the guinea pig ileum: D and M receptors
Late 1970s	Revival of interest in 5-HT. At Merrell Dow, Fozard identifies an equivalent of the M receptor in rabbit heart. Various groups, including at Glaxo, Sandoz and Beecham, begin trying to synthesise selective M receptor agonists and antagonists
1982	Fozard at Merrell Dow patents the first potent selective M receptor antagonist, MDL 72222 (bemesetron)
1982/3	Sandoz develops the compound ICS 205930 (tropisetron) (Richardson, 1985)
1983	Hoyer joins Sandoz and works primarily on 5-HT_1 and 5-HT_2 receptors
1983	Tyers at Glaxo develops ondansetron (GR38032)
1985	Kilpatrick joins Glaxo, tries to identify 5-HT_3 receptors in the brain through radioligand binding using ondansetron
1985	Glaxo pilots ondansetron for migraine treatment at a clinic in Germany. Results show no effect on headache, but relief of nausea and vomiting in some patients. Glaxo proceeds to evaluate ondansetron in patients for antiemetic activity
Mid–late 1980s	5-HT_3 antagonist work on animal models of psychiatric disorders looks promising, but no direct evidence of receptors in the brain. Much of this work done by Costall and Naylor at the University of Bradford
1986	M receptor reclassified as 5-HT_3 receptor (Bradley et al., 1986)
1986	Development of compound GR65630 at Glaxo
1987	Fozard leaves Merrell Dow for Sandoz
Sept 1987	Glaxo patents ondansetron in the US for treatment of migraine and psychotic disorders
Oct 1987	Hoyer & Neijt publish first report of using radioligand binding to identify 5-HT_3 receptors (using tropisetron)
Dec 1987	Kilpatrick et al.'s *Nature* paper on discovery of 5-HT_3 receptors in the brain

June 1988	Glaxo patents ondansetron in US for relief of nausea
1989	Jones leaves Glaxo for Beecham
1990	Glaxo introduces ondansetron to the market as Zofran and is awarded the European Prix Galien in oncology
January 1991	Ondansetron granted FDA approval as Zofran
Early 1990s	Clinical work on role of 5-HT_3 receptors in psychiatric disorders leads to nothing
1995	Glaxo merges with Wellcome and psychiatry becomes less of a priority; Kilpatrick leaves Glaxo for Roche
December 2006	Glaxo's exclusivity on ondansetron expires and first generic versions approved by FDA

4.15 References

Akhondzadeh, S., Mohammadi, N., Noroozian, M., Karamghadiri, N., Ghoreishi, A., Jamshidi, A.-H., et al. (2009). Added ondansetron for stable schizophrenia: a double blind, placebo controlled trial. *Schizophrenia Research*, 107(2-3), 206–212.

Ali, Z., Wu, G., Kozlov, A., & Barasi, S. (1996). The role of 5HT3 in nociceptive processing in the rat spinal cord: results from behavioural and electrophysiological studies. *Neuroscience Letters*, 208(3), 203–207.

Barnes, N.M., & Sharp, T. (1999). A review of central 5-HT receptors and their function. *Neuropharmacology*, 38(8), 1083–1152.

Barnes, J.M., Barnes, N.M., Costall, B., Deakin, J.F.W., Ironside, J.W., Kilpatrick, G.J., et al. (1990). Identification and distribution of 5-HT3 recognition sites within the human brainstem. *Neuroscience Letters*, 111(1–2), 80–86.

Bennett, A.C., & Vila, T.M. (2010). The Role of Ondansetron in the Treatment of Schizophrenia. *Ann Pharmacother*, 44(7), 1301–1306.

Bradley, P.B. (1987). 5-HT3 receptors in the brain? *Nature*, 330(6150), 696–696.

Bradley, P.B., Engel, G., Feniuk, W., Fozard, J.R., Humphrey, P.P.A., Middlemiss, D.N., et al. (1986). Proposals for the classification and nomenclature of functional receptors for 5-hydroxytryptamine. *Neuropharmacology*, 25(6), 563–576.

Brittain, R.T., Butler, A., Coates, I.H., Fortune, D.H., Hagan, R., Hill, J.M., et al. (1987). GR38032F, a novel selective 5-HT_3 antagonist. *British Journal of Pharmacology*, 90, 87P.

Campbell, A.D., & McBride, W.J. (1995). Serotonin-3 receptor and ethanol-stimulated dopamine release in the nucleus accumbens. *Pharmacology Biochemistry and Behavior*, 51(4), 835–842.

Costall, B., & Naylor, R.J. (2004). 5-HT3 Receptors. *Current Drug Targets – CNS & Neurological Disorders*, 3, 27–37.

Costall, B., Domeney, A.M., Gunning, S.J., Naylor, R.J., Tattersall, F.D., & Tyers, M.B. (1987). GR38032F: a potent and novel inhibitor of cisplatin-induced emesis in the ferret. *British Journal of Pharmacology*, 90, 90P.

Costall, B., Domeney, A.M., Kelly, M.E., Naylor, R.J., & Tyers, M.B. (1987). The antipsychotic potential of GR38032F, a selective antagonist of 5-HT_3 receptors in the central nervous system. *British Journal of Pharmacology*, 90, 89P.

Costall, B., Domeney, A.M., Naylor, R.J., & Tattersall, F.D. (1986). 5-hydroxytryptamine m-receptor antagonism to prevent cisplatin-induced emesis. *Neuropharmacology*, 25(8), 959–961.

Drossman, D.A., Creed, F.H., Olden, K.W., Svedlund, J., Toner, B.B., & Whitehead, W.E. (1999). Psychosocial aspects of the functional gastrointestinal disorders. *Gut*, 45 Suppl 2, II25–30.

Fake, C.S., King, F.D., & Sanger, G.J. (1987). BRL 43694: a potent and novel 5-HT_3 recptor anatagonist. *British Journal of Pharmacology*, 91, 335P.

Fozard, J.R. (1994). Role of 5-HT_3 receptors in nociception. In King, F.D.G., Jones, B.J., & Sanger, G.J. (eds.), *5-Hydroxytryptamine-3 Receptor Antagonists*, Boca Raton: CRC Press, 241–254.

Fozard, J.R. (1984). MDL 72222: a potent and highly selective antagonist at neuronal 5-hydroxytryptamine receptors. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 326(1), 36–44.

Fozard, J.R., & Mobarok Ali, A.T.M. (1978). Blockade of neuronal tryptamine receptors by metoclopramide. *European Journal of Pharmacology*, 49(1), 109–112.

Fozard, J.R., Mobarok Ali, A.T.M., & Newgrosh, G. (1979). Blockade of serotonin receptors on autonomic neurones by (-)-cocaine and some related compounds. *European Journal of Pharmacology*, 59(3–4), 195–210.

Gaddum, J.H., & Picarelli, Z.P. (1957). Two kinds of tryptamine receptor. *British Journal of Pharmacology and Chemotherapy*, 12(3), 323–328.

Glaxo Group Ltd. and Smithkline Beecham Corp. v Teva Pharmaceuticals USA, Inc. and Teva Pharmaceuticals Industries Ltd., United States District Court for the District of Delaware (2004).

Gupta, S.K., Kunka, R.L., Metz, A., Lloyd, T., Rudolph, G., & Perel, J.M. (1995). Effect of alosetron (a new 5-HT3 receptor antagonist) on the pharmacokinetics of haloperidol in schizophrenic patients. *Journal of Clinical Pharmacology*, 35(2), 202–207.

Hoyer, D., & Neijt, H.C. (1988). Identification of serotonin 5-HT3 recognition sites in membranes of N1E-115 neuro-blastoma cells by radioligand binding. *Molecular Pharmacology*, 33(3), 303–309.

Hoyer, D., & Neijt, H.C. (1987). Identification of serotonin 5-HT3 recognition sites by radioligand binding in NG108-15 neuroblastoma-glioma cells. *European Journal of Pharmacology*, 143(2), 291–292.

Jones, B.J., Oakley, N.R., & Tyers, M.B. (1987). The anxiolytic activity of GR38032F, a 5-HT_3 receptor antagonist, in the rat and cynomolgus monkey. *British Journal of Pharmacology*, 90, 88P.

Jones, D.N.C., Barnes, N.M., Costall, B., Domeney, A.M., Kilpatrick, G.J., Naylor, R.J., et al. (1992). The distribution of 5-HT3 recognition sites in the marmoset brain. *European Journal of Pharmacology*, 215(1), 63–67.

Kilpatrick, G.J., & Tyers, M.B. (1992). Interspecies variants of the 5-HT3 receptor. *Biochemical Society Transactions*, 20(1), 118–121.

Kilpatrick, G.J., Barnes, N.M., Cheng, C.H.K., Costall, B., Naylor, R.J., & Tyers, M.B. (1991). The pharmacological characterization of 5-HT3 receptor-binding sites in rabbit ileum – comparison with those in rat ileum and rat-brain. *Neurochemistry International*, 19(4), 389–396.

Kilpatrick, G.J., Bunce, K.T., & Tyers, M.B. (1990). 5-HT3 receptors. *Medicinal Research Reviews*, 10(4), 441–475.

Kilpatrick, G.J., Butler, A., Burridge, J., & Oxford, A.W. (1990). 1-(m-Chlorophenyl)-biguanide, a potent high affinity 5-HT3 receptor agonist. *European Journal of Pharmacology*, 182(1), 193–197.

Kilpatrick, G.J., Butler, A., Hagan, R.M., Jones, B.J., & Tyers, M.B. (1990). [^{3}H] GR67330, a very high affinity ligand for 5-HT_3 receptors. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 342(1), 22–30.

Kilpatrick, G.J., Jones, B.J., & Tyers, M.B. (1989). Binding of the 5-HT3 ligand, [3H]GR65630, to rat area postrema, vagus nerve and the brains of several species. *European Journal of Pharmacology*, 159(2), 157–164.

Kilpatrick, G.J., Jones, B.J., & Tyers, M.B. (1988). The distribution of specific binding of the 5-HT3 receptor ligand [3H]GR65630 in rat brain using quantitative autoradiography. *Neuroscience Letters*, 94(1–2), 156–160.

Kilpatrick, G.J., Jones, B.J., & Tyers, M.B. (1987). Identification and distribution of 5-HT_3 receptors in rat brain using radioligand binding. *Nature*, 330, 746–748.

Maricq, A., Peterson, A., Brake, A., Myers, R., & Julius, D. (1991). Primary structure and functional expression of the 5HT3 receptor, a serotonin-gated ion channel. *Science*, 254(5030), 432–437.

Miner, W.D., & Sanger, G.J. (1986). Inhibition of cisplatin-induced vomiting by selective 5-hydroxytryptamine M-receptor antagonism. *British Journal of Pharmacology*, 88(3), 497–499.

Pratt, G.D., Bowery, N.G., Kilpatrick, G.J., Leslie, R.A., Barnes, N.M., Naylor, R.J., et al. (1990). Consensus meeting agrees distribution of 5-HT3 receptors in mammalian hindbrain. *Trends in Pharmacological Sciences*, 11(4), 135–137.

Richardson, B.P., Engel, G., Donatsch, P., & Stadler, P.A. (1985). Identification of serotonin M-receptor subtypes and their specific blockade by a new class of drugs. *Nature*, 316(6024), 126–131.

Sellers, E.M., Higgins, G.A., & Sobell, M.B. (1992). 5-HT and alcohol-abuse. *Trends in Pharmacological Sciences*, 13(2), 69–75.

Shiina, A., Shirayama, Y., Niitsu, T., Hashimoto, T., Yoshida, T., Hasegawa, T., et al. (2010). A randomised, double-blind, placebo-controlled trial of tropisetron in patients with schizophrenia. *Annals of General Psychiatry*, 9(1), 27.

Waeber, C., Dixon, K., Hoyer, D., & Palacios, J.M. (1988). Localization by autoradiography of neuronal 5-HT3 receptors in the mouse CNS. *European Journal of Pharmacology*, 151(2), 351–352.

Whitehead, W.E., Palsson, O., & Jones, K.R. (2002). Systematic review of the comorbidity of irritable bowel syndrome with other disorders: What are the causes and implications? *Gastroenterology*, 122(4), 1140–1156.

Zhang, Z.-J., Kang, W.-H., Li, Q., Wang, X.-Y., Yao, S.-M., & Ma, A.-Q. (2006). Beneficial effects of ondansetron as an adjunct to haloperidol for chronic, treatment-resistant schizophrenia: A double-blind, randomized, placebo-controlled study. *Schizophrenia Research*, 88(1–3), 102–110.

CHAPTER 5 PET scanning and schizophrenia

This case study is based on the research that produced the paper:

Cohen, R.M., Semple, W.E., Gross, M., Nordahl, T.E., DeLisi, L.E., Holcomb, H.H., King, A.C., Morihisa, J.M., & Pickar, D. (1987). Dysfunction in a prefrontal substrate of sustained attention in schizophrenia. *Life Sciences*, 40(20), 2031–2039.

Information was gathered from interviews with Robert Cohen and David Pickar, as well as from desk-based research.

5.1 Summary

The research cloud described in this case study draws on studies carried out over a 10- to 15-year period, from the early 1980s to the late 1990s. Dr. Robert Cohen used PET scanning to determine regional brain metabolism while the patient conducted a simple continuous performance task. While he was not the only researcher at the time using PET scanning techniques to examine schizophrenic brains, Cohen's innovation and unique contribution to the field was to develop the continuous performance task that could be used to control, as best as possible, for the thoughts that went on in someone's mind. By keeping the patients focused on the task, they could have a clearer sense of how blood flowed in the brain, as measured by glucose metabolism in the brain, under similar conditions from patient to patient. Thus, his was one of the first studies to show how regional brain metabolism varies in situ when controlling for patient thinking. The main paybacks of this research cloud were in knowledge production, research targeting and capacity building. There are some possible benefits in the health sector due to the contribution to knowledge about the pathophysiology of schizophrenia.

5.2 Introduction

Scientific background

At the time the research in this cloud was started, the US National Institutes of Health (NIH) had recently purchased a large positron emission tomography (PET) scanner, which was shared among the different institutes, including the US National Institutes of Mental Health (NIMH). PET scanning is a method that measures glucose metabolic rates and thereby allows one to determine the relative performance of different bodily functions, such as blood flow, oxygen use, and, ultimately, performance of different organs, including the brain. In the 1980s, PET scanning was increasingly used to study the functioning of

the brain, and in particular to understand the pathophysiology of schizophrenia. Advances had been made in characterising the nature of schizophrenia as an illness, but the failure to elucidate other elements of the disease's causal pathway continued to be a stumbling block that frustrated researchers.

The Intramural Research Programme (IRP) at the NIMH recognised the potential of PET scanning to provide insights into the pathophysiology of schizophrenia and in the early 1980s initiated a research programme in this field.

> We have made this commitment because we believe that PET, a brain-imaging technology of unsurpassed ability to localize and quantify tracers in space and thereby physiological processes in the human brain, offers the greatest promise for delineating the pathophysiology of schizophrenia. (Cohen et al., 1988, 169)

One of the main reason researchers believed that PET scanning could help them elucidate the pathophysiology of schizophrenia was because it provided a literal 'window' into the functioning of the brain as an organ. Evidence was beginning to suggest that there were regional differences in blood flow and dopamine levels in the brain in patients with schizophrenia. It was thought these differences could play an important role in the progression of schizophrenia as a disease. Therefore, using PET scanning to look at the parameters under which the brain uses oxygen would enable comparative and further analysis of brain function in schizophrenic patients and its effects. Cohen was one of many prominent researchers conducting various kinds of research trying to understand the pathophysiology through different techniques, including imaging and PET scanning. Another was Danny Weinberger, who used PET and regional cerebral blood flow to describe and characterise abnormalities in the prefrontal cortex. Both worked at the NIMH and the cumulative effect of their work led to advances in understanding how glucose metabolism, and hence cerebral blood flow, was impacted in schizophrenic patients, particularly under conditions where the brain was activated. This led to advances in understanding the pathophysiology of schizophrenia, especially in relation to hypofrontality in the prefrontal cortex and the implications for the dopaminergic system.

In addition, there were a much broader series of research efforts developing before and during the time of Cohen and Pickar's work that may have contributed different types of knowledge (although a detailed discussion of these is outside the scope of this case study). First, there was a rapidly developing field around metabolic brain imaging and advances in PET scanning itself. Secondly, there were major PET-driven advances in the understanding of schizophrenia at the time, which contributed to better knowledge about the chemical processes underlying physiological and pathological processes in schizophrenia (see, for example, Farde et al., 1988).

The research in the cloud was part of a broader programme at the NIMH and occurred alongside other developments in the field mentioned above. Specifically, the cloud assessed the brain functioning of patients with schizophrenia while they carried out an auditory discrimination task. A baseline was established and brain functioning in schizophrenic patients was compared against that of normal individuals. From there, additional comparisons were made between the patients and the effects of different psychopharmalogical treatments, for example the effect of neurolpetics on brain functioning, as well as the effects of different types of neuroleptics on different patient

populations. The research cloud described in this case study draws on work carried out over a 10- to 15-year period, from the early 1980s to the late 1990s.

Researchers' backgrounds

Robert Cohen has an undergraduate degree in chemistry, a PhD in biochemistry and a medical degree. After medical school his residency was done at the University of Chicago in the Department of Psychiatry. He joined the NIMH in 1977 as a staff psychiatrist in the Clinical Neuropharmacology Branch, moving in 1980 to become chief of the Unit on Clinical Psychopharmacology within the Neuropharmacology Branch and then moving in 1983 to become chief of the Clinical Brain Imaging Section. It was during this time that the majority of the work in the research cloud was undertaken. His early and late career interests were in memory disorders, in particular Alzheimer's and Parkinson's disease, and it was only during his time running the clinical imaging group that he came to focus on schizophrenia. In the early 1990s he chose to shift the focus of his career back to Alzheimer's and memory disorders, the primary focus of his current work.

While Cohen had a background in biochemistry and PET scanning, **David Pickar** had substantial clinical experience working with patients and supplied the patient population used in the studies. PET scanning research was just one part of a wider body of clinical work Pickar was pursuing at the time. His clinical research was about the psychopharmacological effects of schizophrenia, in particular trying to understand the biological basis of neuroleptic action.

Pickar did his medical training at Yale University and started working at the NIMH on the same day as Cohen in 1977. Though neither of them started out working in schizophrenia, during the period within which the research cloud took place, he ran a clinical research programme and a clinical in-patient unit in the IRP at the NIMH. He was Chief of the Experimental Therapeutics Branch in the clinical studies section and had a self-described primary focus on clinical and 'before the term was fashionable, "translational" aspects of schizophrenia (DP). The patients that Pickar oversaw were the population used in the studies.

Other researches who worked on the research cloud, or made a significant contribution in some way, but were not interviewed for this case study included:

- William Semple – Worked with Cohen on the PET scanning
- Michael Gross – Worked with Cohen on the PET scanning
- Thomas Nordahl – Worked with Cohen on the PET scanning
- Lynn DeLisi – Worked with Cohen on the PET scanning
- Henry Holcomb – Worked with Cohen on the PET scanning
- John Morihisa – Worked with Pickar with the clinical population.

5.3 Defining the research cloud

There are two overlapping research clouds that contributed to, and followed on from, the initial target paper:

- One related to the use of PET scanning for schizophrenia patients.

- A second related to the research around PET scanning for various psychiatric and mental health disorders, particularly the methodological innovation of developing a continuous performance task for patients to do while they are being scanned.

Though the main focus of this case study is on the first research cloud, the outcomes and outputs of the second cloud are important to keep in mind when thinking about the secondary outputs of the research.

Research cloud for PET scanning in schizophrenia

This research cloud sought to understand where glucose metabolism varied in the brain in patients with schizophrenia in relation to sustained attention deficits, if at all, and if it did, how this variation was altered when patients were under different treatment conditions (e.g., taking neuroleptics or not). The cloud's publications cover a period of about 10 years, but according to the authors this was simply because the studies themselves took a long time to conduct due to the patient population.

1. Cohen, R.M., Semple, W.E., Gross, M., Nordahl, T.E., DeLisi, L.E., Holcomb, H.H., King, A.C., Morihisa, J.M., & Pickar, D. (1987). Dysfunction in a prefrontal substrate of sustained attention in schizophrenia. *Life Sciences*, 40(20), 2031–2039.
2. Cohen, R.M., Semple, W.E., Gross, M., Nordahl, T.E., Holcomb, H.H., Dowling, M.S., & Pickar, D. (1988). The effect of neuroleptics on dysfunction in a prefrontal substrate of sustained attention in schizophrenia. *Life Sciences*, 43(14), 1141–1150.
3. Cohen, R.M., Semple, W.E., Gross, M., & Nordahl, T.E. (1988). From syndrome to illness: delineating the pathophysiology of schizophrenia with PET. *Schizophrenia Bulletin*, 14(2), 169–176.
4. DeLisi, L.E., et al. (1985). Positron emission tomography in schizophrenic patients with and without neuroleptic medication. *Journal Of Cerebral Blood Flow And Metabolism*, 5(2), 201–206.
5. Cohen, R.M., et al. (1989). Evidence for common alterations in cerebral glucose metabolism in major affective disorders and schizophrenia. *Neuropsychopharmacology*, 2(4), 241–254.
6. Cohen, R.M., et al. (1997). The brain metabolic patterns of clozapine- and fluphenazine-treated patients with schizophrenia during a continuous performance task. *Archives Of General Psychiatry*, 54(5), 481–486.
7. Cohen, R.M., et al. (1998). Abnormalities in the distributed network of sustained attention predict neuroleptic treatment response in schizophrenia. *Neuropsychopharmacology*, 19(1), 36–47.
8. Cohen, R.M., et al. (1999). The brain metabolic patterns of clozapine- and fluphenazine-treated female patients with schizophrenia: evidence of a sex effect. *Neuropsychopharmacology*, 21(5), 632–640.
9. Cohen, R.M., Semple, W.E., & Gross, M. (1986). Positron emission tomography. *Psychiatric Clinics of North America*, 9(1), 63–79.
10. Holcomb, H.H., et al. (1996). Functional sites of neuroleptic drug action in the human brain: PET/FDG studies with and without haloperidol. *American Journal of Psychiatry*, 153(1), 41–49.

Research cloud in PET scanning for mental health and psychiatric disorders

This research cloud built on that established in the primary research cloud. Once Cohen and his colleagues had demonstrated that PET scanning could be used to see where and how metabolic rates differed in the brains of schizophrenic patients, they applied the technique to several other mental disorders. The most prominent of these studies was that done for attention deficit disorder.

11. Cohen, R.M., Semple, W.E., Gross, M., Holcomb, H.H., Dowling, M.M., & Nordahl, T.E. (1988). Functional localization of sustained attention: comparison to sensory stimulation in the absence of instruction. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*, 1(1).
12. Cohen, R.M., et al. (1989). Evidence for common alterations in cerebral glucose metabolism in major affective disorders and schizophrenia. *Neuropsychopharmacology*, 2(4), 241–254.
13. Benkelfat, C., et al. (1990). Local cerebral glucose metabolic rates in obsessive compulsive disorder – patients treated with clomipramine. *Archives of General Psychiatry*, 47(9), 840–848.
14. Cohen, R.M., et al. (1992). Preliminary data on the metabolic brain pattern of patients with winter seasonal affective-disorder. *Archives Of General Psychiatry*, 49(7), 545–552.
15. Goyer, P.F., et al. (1992). Cerebral glucose metabolism in patients with summer seasonal affective disorder. *Neuropsychopharmacology*, 7(3), 233–240.
16. Zametkin, A.J., Nordahl, T.E., Gross, M., King, A.C., Semple, W.E., Rumsey, J., Hamburger, S., & Cohen, R.M. (1990). Brain metabolism in hyperactive adults with childhood onset. *New England Journal of Medicine*, 323(20), 1361–1366.

5.4 Stage 0: Opportunity identification/research needs assessment

Inspiration

At the time of this research there were rapid developments in knowledge about the pathophysiology of schizophrenia and it was a combination of these developments, and the new questions they posed, that served as inspiration for the work. One of these developments was early work in schizophrenia research by Sokoloff and Kety that showed that regional blood flow did vary in the brain – but they didn't know where or how. On reflection many years later, Cohen remarked how striking it was that Sokoloff and Kety had chosen to focus on schizophrenia as one of their first patient groups. It had the effect of setting Sokoloff 'on the trail' (RC) of searching for a method that would allow him to understand what was happening with cerebral blood flow. In fact, it was the failure of Sokoloff to fully understand cerebral blood flow in schizophrenics that inspired Cohen and his colleagues.

One area being looked at for differences in blood flow was the frontal cortex. The frontal cortex is an important area of the brain for higher level functioning (the more 'executive functions' of the brain). Some resting state studies had shown hypofrontality in schizophrenia – lower functional activities in the frontal cortex than in more posterior areas of the brain – than in normal controls. This knowledge supported the hypothesis that

frontal cortex abnormality was responsible for schizophrenia, but not all patients showed this pattern and there were still gaps in knowledge about how to identify the nature of the abnormality, as no one knew how to control for what people were thinking during testing, which could skew results.

There was also a lack of knowledge at the time of the study about what actions neuroleptics had in the brain, and in particular on the dopaminergic system. Increasingly a wide body of evidence was pointing to the role of dopamine in the progression of psychosis (see Seeman case study). Included in this was interesting evidence from Pickar's research group showing that the effects of neuroleptics on the brain were delayed (Pickar et al., 1984), which suggested that the antipsychotic effects of neuroleptics was actually more to do with the delayed effect of blocking presynaptic activity as opposed to their more immediate effect of blocking postsynaptic dopamine receptors. However, this finding was counter to what many others thought was the primary action for neuroleptics, which was blocking the D2 receptor in sub-cortical areas. Pickar was inspired to pursue this line of research because he noticed that within hours of giving someone an antipsychotic you could show post-synaptic blockage of dopamine, but clinically the patients were not getting better for weeks. It made him think that something else was going on in the dopaminergic system that was far more complex than the effect of neuroleptics blocking post-synaptic receptor binding.

Against this background, Cohen, Pickar and colleagues began to think about ways they could actually get into the brain to see what was happening in patients with schizophrenia.

> As I used to say, there's no question what organ was ill on this disease: the brain was ill. But how do you get to it, you couldn't see it. Normal x-rays were not terribly helpful although we started observing that there was some cerebral atrophy in patients with schizophrenia…. The promise of PET [was] to be able to look into a human brain to see dysfunctional regions…. (DP)

It was hoped a series of PET scanning studies would help in elucidating the pathophysiology of the brain, the specific actions of neuroleptics and the relationship they had with the dopamine system.

Feasibility

There are three interrelated scientific breakthroughs integral to the development of PET and, subsequently, important for the feasibility of conducting the PET scanning work: the development of the Kety-Schmidt method for measuring cerebral blood flow; the development of PET scanning itself; and the discovery of deoxyglucose as a suitable molecule for measuring glucose uptake in the brain.

In 1948, the development of the Kety-Schmidt method allowed for the quantitative determination of cerebral blood flow and metabolism in unanesthetised people. In other words, one could determine how and where blood flow, and hence, metabolism, varied across brain regions and conditions. This could lead to a better understanding of brain functioning. The next major breakthrough was the development of PET scanning itself. The first PET scanners were developed in the 1970s by a few different groups, but in particular the work of Kuhl, Ter-Pogossian and Phelps done between the Universities of Pennsylvania, Washington and UCLA made important breakthroughs on the physics behind PET scanners and moved the field away from single photon emission tomography

to scanners that were able to have two emitting sources and thus reduction in attenuation (or noise). Finally, Sokoloff, Wolf and Fowler all contributed to the development of the fluorodeoxyglucose method on which the PET scanning technique used in Cohen's study was dependent. Deoxyglucose can be taken up into a cell for metabolism (and at the same rate as glucose molecules), but it cannot be metabolised once inside the cell. By tagging the molecule with a radionuclide, scientists can measure the amount of glucose being taken up by the cell and, therefore, measure cerebral glucose utilization.

Another contributing factor to the feasibility of the study was the environment at the NIMH. At the time at which Cohen began the study, the NIMH had two significant programmes in the field of schizophrenia. A special issue of the *Schizophrenia Bulletin* published in 1988 set out the rationale and components of the research programme. The introduction to the issue stated that, 'One of the major reasons for the existence of National Institute of Mental Health's Intramural Research Program is the study of schizophrenia. The programme provides relatively stable funding for the long-term examination of the basic and clinical sciences as they relate to this major public-health problem' (Wyatt, 1988, 145). The fact that Cohen's work was funded out of this programme contributed to its ultimate feasibility.

The final element of feasibility was Pickar's knowledge of the patient population. He ran a large clinical in-patient unit with the IMP at the NIMH and eventually became Chief of the Experimental Therapeutics Branch. This is discussed in further detail below.

Potential value

The potential value of the research was multifaceted. Cohen was more interested in dementia at the time of this study in his career, but he accepted the position of running the PET laboratory for NIMH because he thought he might ultimately be able to develop a tracer for dopamine, which would help him look at its contribution to the progression of dementia as an illness. However, despite his interest in dementia, Cohen selected to work on schizophrenia first. One reason he did this was because schizophrenia was a severe disorder and any findings would add real value to the field.

> Schizophrenia was the first one we chose to do, because it is the most severe, in our minds the most severe neuropsychotic disorder that we deal with. Therefore it was the most likely to yield the most interesting results. (RC)

Second, Cohen mentioned that there was a bit of a 'cachet' about doing PET with schizophrenia because Kety and Sokoloff had attempted to image the brain in this way and had not wholly succeeded.

> …It had, in my mind it had the cachet of having been attempted by Lou Sokoloff and Seymour Kety and had been unsuccessful in terms of global metabolism. Here we had an opportunity. So schizophrenia is the one we settled on. I mean one could have imagined studying other illnesses, but in my mind that seemed to be the most interesting one to start with. But you know, you never do know. (RC)

Cohen's work also occurred during a time when there was a transition in thinking about schizophrenia from psychoanalytic traditions to modern observations that were based in biology.

> My generation was the first generation to sort of be fully into the biology of it at the same time we learned other aspects…. The research ward that I took over and tried to shape was a unique phenomena – to study schizophrenia from a biological point of view. (DP)

Ultimately, though, Cohen and Pickar felt that the value the research would add was that it could provide a window into the brain and, potentially, be something you could use as a diagnostic tool to understand how schizophrenia was developing and how you could treat it. 'That was the dream' (DP).

5.5 Stage 1: Inputs to research

Money, researcher time, lab/office space and consumables

Cohen and Pickar were part of the Intramural Research Programme at the NIMH. Cohen had to apply for the position to run the PET scanning programme within the NIMH and it was Pickar who nominated him. The application process included consideration of who had the best ideas about how to use the newly acquired PET scanner the NIH (RC). Several leading academics were brought in for the interview process, including Seymour Kety, which Cohen reflected upon when thinking about how he then went on to work on schizophrenia.

The study was funded internally and funding per se was not a concern for the researchers. Funding was something they only initially had to compete for in order to get the study running. After that, the researchers were in a position of having enough money to do interesting scientific research without many restrictions.

> I was in a unique situation in that in the intramural programme basically scientists were given an allocation per year. At the time there was no direct payment to the core facility (the scanner facility). In a lot of places you have to pay a fee to use a scanner. But since everything was paid for in the intramural programme in the first place – the scanner was purchased, the technicians, etc – all were being supported by various institutes…. [So] scientifically it was an easy position to be in. Financially it was a very easy position to be in. Position-wise it was very easy because the Directors – I had two Directors who really believed in the programme, I never felt restricted in terms of resources. It was a wonderful time period in terms of that. (RC)

The only resource restriction they had was time and access to the PET scanning machine itself. As head of the group, Cohen became a sort of gatekeeper.

> Everybody wanted time on the scanners for their patient population. It was a process of trying to keep people happy. (RC)

However, in the early period of research using the PET scanner, it was mainly only Cohen and Pickar's group in the NIMH who were using it. At a later stage, Weinberger, another prominent researcher at NIMH, began doing work with PET scanning and so competition for scanning time became more intense.

The decision to buy the PET scanner was an interesting one, and is worth briefly reflecting on it as it was a key input to the research. The NIMH had come to recognise in the early 1980s, probably based in part on the work of Kety, Sokoloff and others, but also the success PET was having in other fields, that it could be of use in studying people with mental health disorders. However, at the time there were only a few PET scanners in the

entire world. One of these belonged to the NIH Intramural Research Programme. The NIH had originally purchased three machines, initiated by the Head of the Neurology Institute at the NIH, Donald Tower.

Different institutes were each given an allocation of time on the scanner, which was housed in a central clinical centre. So though they all recognised they were in an extremely fortunate position of not having to pay for the scanner, there were still other issues to think about.

> So the Nuclear Medicine Department was given the scanner as a non-research institute…. So the way NIH was divided up at the time – there were a variety of research institutes and then the clinical centre, which was essentially like a research hospital. They [the clinical centre] were departments that were basically service departments, [they] weren't meant primarily for research purposes because in a hospital you need various services, whether it be nursing services etc. So at that time the clinical centre was chosen to house this as a non-competing entity in which the other institutes would then participate in PET scanning. They developed a team of physicists, chemists, etc, to make the fluorodeoxyglucose and to engineer and keep maintenance of the scanner, and then the institutes were the ones intended to be the users for research purposes. So that is how it developed. Each institute would have a liaison person who would decide an allocation. In other words there might be allocation for the Mental Health Institute, a certain amount of allocation for the Neurology Institute, or for the Diabetes Institute, etc, etc. They could decide what to use with their particular allocation at that time. (RC)

Knowledge

Much of the knowledge that served as an input to this study has been summarised above. It is worth emphasising that Cohen was a promising young clinician-scientist at the NIMH who had a background in biochemistry. Pickar was a clinical researcher who had good knowledge of the patient population and characteristics of the disease. Therefore, together the two of them had a good knowledge base with which to work on the research cloud.

The general level of knowledge at the NIMH as a result of their broader research programme into understanding the pathophysiology of schizophrenia was also likely to provide inputs. In particular, the work of Weinberger mentioned above was happening alongside Cohen's, and together the two made important advances in the use of PET scanning for understanding the way cerebral blood flow occurs in the brain (see Weinberger & Berman, 1988, for a review; also, Knable & Weinberger, 1997).

Expertise and techniques

As mentioned above, the NIMH was undertaking major research programmes in schizophrenia, so the Cohen and Pickar's research was drawing on the knowledge that already existed in the NIMH about schizophrenia. It seems to have been important that Pickar had nominated Cohen to be the director of the scanning section and that the two had worked together before. In addition, Pickar worked with a population of patients who would be used for the study and had detailed clinical knowledge of the challenges of working with them. This clinical knowledge was important in understanding what to look for and what the significance of the findings might be.

> It was what I loved – a mixture of real clinical medicine with a piece of biology and pharmacology…. We were committed to working with ill schizophrenic patients and the

> disease not working [only] with biological techniques of which schizophrenia might be useful. (DP)

Cohen had a background in biochemistry that he thinks may have been important to his selection as the person to lead the PET scanning group for the NIMH. However, since PET scanning was relatively new, at least at the beginning of the research cloud, expertise and techniques had to be developed by everyone.

Samples/patients

As mentioned above, Pickar worked in clinical research ward at the NIMH. People would come to the hospital and essentially sign up to be part of different clinical research studies. So an individual patient might be a part of two or three different studies at any one time. There were hundreds of beds, especially for mentally ill patients, and as Pickar described it, it was a unique point in time and wards like that don't exist anymore.

> Research wards at the NIMH were, particularly for schizophrenia, were unique in the world and it required a huge amount of cost as you might imagine. (DP)

Working with the schizophrenic patients was particularly difficult, especially once the research team began doing studies that required the patients to be off medication and sit through a PET scanning study (see below). It required several doctors under Pickar, as well as many well-trained nurses and social workers.

> Yes and how about you want to go to a big machine now it's not like MRIs that make clanking noises but it was a big machine in its day. And it wasn't on our ward. [The patients] had to be, they had to be well enough. They were sick but they had to be well enough that I could transport them there…. And we had a very dedicated staff. It was really a unique piece of history. (DP)

Collaborators

There were no collaborators outside the NIMH working on the research.

5.6 Stage 2: Processes

Though there are a number of publications and areas of focus that fall under this research cloud, they all shared a similar research process. Cohen and his colleagues completed several PET scanning studies of patients with schizophrenia from the mid-1980s when the research programme using PET scanning began through to the late 1990s when the final papers comparing fluphenazine and clozapine effects on the brain were published. The lapse in time between these papers was simply due to how difficult it was to work with patient population.

The studies started by looking at patients with schizophrenia and comparing glucose metabolism in different regions of the brain to those of normal patients (Cohen et al., 1987). This research was done to determine whether, and where, glucose metabolism varied in the brain for schizophrenic patients. Having established that glucose metabolism did differ from normal patients, they then looked at how it differed in schizophrenic patients who were and were not taking neuroleptics (Cohen et al., 1988). Several other papers were then published looking at different aspects of cerebral blood flow and glucose metabolism, including a final set of papers in the late 1990s that compared fluphenazine, a first-generation antipsychotic, with clozapine, a second-generation antipsychotic, to see if

there were any differences in the effects in the brain (Cohen et al., 1998; Cohen et al., 1999). Both classes of drugs were found to have similar mechanisms of action in the brain and the differences between them were not significant in relation to overall effect.

The methodology of the research shared a common principle. Previous PET studies had not been able to control for the thoughts that went on in people's minds. This was methodologically problematic.

> So for example, if I have you sitting in a scanner and you are scared to death and you are thinking about ghosts coming out of the walls to attack you, your mind is going to look different than if you were thinking about a sunny day on the beach and you are having a good time. (RC)

Cohen's innovation in this regard was to apply a simple continuous performance task that could be used to control, as much as possible, for the thoughts that went on in someone's mind. By keeping the patient focussed on the task, the researchers could have a clearer sense of how blood flowed in the brain under similar conditions from patient to patient. So while they made use of advances in PET that had been developed by other people and are described above, Cohen's application of this task within an imaging paradigm was a unique methodological contribution.

> We decided that we wanted to do a study in which subjects would be doing exactly – the mind would be doing exactly the same thing in the two cases: one, the healthy control… and [two,] the patient with schizophrenia. Then the problem, the issue, was devising a task, because with this particular tracer, you have to have people engaged in whatever they are doing for a period of about 30 minutes. So you have to have a task that is easy enough for subjects to be able to continue to do over a period of 30 minutes. [It also] has to be easy enough for patients with schizophrenia to do well in, because again if they just stop and they don't work on it, that is a problem. But it has to hold their attention. …So we came up and I will take credit for doing that, we came up with a test for – a continuous performance test to make it really easy. (RC)

The continuous performance task was as an auditory discrimination task. Auditory stimuli were used instead of visual stimuli because this would help to ensure equivalent stimulus presentation to each subject. At the time many people had used continuous performance tasks, but often with the purpose of testing people's mental capacities to their limits. Cohen and his colleagues wanted to do just the opposite.

> Most of the time with [a] continuous performance test, people want to push people to their limits, because they want to see who has got an abnormality in concentration and speed of processing, etc. Our idea was just the reverse. So we basically programmed a situation which was three tones, fairly easy to identify. A low, medium, high tone and the subject had to identify one tone and when they identified a tone they pressed a button. So basically we could keep track, which was another thing that hadn't been done, is to keep track actually how accurately the subject responded in the scan. (RC)

Using this task also provided a novel way of keeping track, in real-time, of what people were responding to in the continuous task. This allowed the researchers to examine relationships in performance and relate these to brain function and metabolic rates, as well. Moreover, the researchers were able to effectively 'isolate' a part of the frontal cortex that is responsible for maintenance of directed attention. This isolation was important because the

frontal cortex was known to control many higher executive functions of human behavior, including information processing.

Once the research team had established that there were differences between schizophrenic patients and normal individuals, they went on to look at the effects of different treatments on metabolic blood flow, primarily focusing on the effect of neuroleptics. In these studies patients were given different doses of neuroleptics or they remained off of medication and then were put through the same auditory discrimination task while in the PET scanner.

5.7 Stage 3: Primary Outputs

Knowledge

Cohen and his colleagues were able to provide evidence that there really was an abnormality in the brains of patients with schizophrenia, independent of their thinking. In addition to this, the research cloud also introduced a methodological innovation that showed how you could measure glucose metabolism in real time, independent of thought, to examine 'the relationship between different rates of metabolism in different parts of the brain and the accuracy' (RC). Cohen's application of this methodology within the imaging paradigm was a unique contribution and it is this aspect of the study to which Cohen attributes the high citation of the target paper of the research cloud.

> So I think that was the basic innovation if you will that maybe would have caused it to be cited, if it was going to be cited, [it was] this idea…. (RC)

The first paper in the research cloud established that there were differences in the metabolism of schizophrenic patients compared to normal individuals. It also showed that schizophrenic patients did not differ in their global glucose metabolic rates, a finding that confirmed earlier work in the field (see above). However, they then evaluated 55 regions of the brain for glucose metabolic rates and found that these regional rates differed from normal patients in the medial parietal cortex, the left anterior temporal cortex and in five regions of the mid-frontal cortex. This confirmed that glucose metabolism, and therefore cerebral blood, flow varied in the brain, and in particular that these rates were different in schizophrenic patients. Moreover, this variation was pronounced in the midfrontal cortex areas in schizophrenics, providing support for the idea that hypofrontality was a characteristic of schizophrenia (an idea also being developed by Weinberger at the same time (Weinberger & Berman, 1988)).

They were also able to demonstrate that glucose metabolic rates in the midfrontal cortex were directly related to quantitative measures of a normal subject's performance on a cognitive task. On this basis they could then 'directly examine the functional activity of this region in patients with schizophrenia during the performance of auditory discrimination' (Cohen et al., 1987, 2037). In schizophrenic patients they found no relationship between performance on the task and metabolic rates in the midfrontal cortex. Moreover, there was a wide performance range on the task by the schizophrenic patients and the fact that there was still no relationship between high- and low-performing patients and glucose metabolism in the midfrontal cortex strengthened their finding that dysfunction of the middle prefrontal cortex was at least one basis for the disorder of sustained attention in schizophrenia.

A follow-on study looked at the effect of neuroleptics and showed that there were some differences in metabolic rates in schizophrenic patients treated with fluphenazine and those not treated. Again, global glucose metabolism did not differ between patient groups. In addition, there were no significant differences in glucose metabolism between the two groups in those regions of the brain that had shown significant differences in metabolism from normal patients in the earlier study. However, significant differences were found between medicated and non-medicated patients in other regions. Medicated patients had higher glucose metabolism throughout the temporal cortex and in the subcortical structures of the basal ganglia and thalamus. Medicated patients also showed lower metabolic rates in the superior frontal cortex. A relationship between performance on the auditory discrimination task and mid-prefrontal cortex metabolism was not found for non-medicated patients, but there was a relationship for medicated patients. Here, performance accuracy was closely coupled to mid-prefrontal cortex activity at a similar level to that found in normal subjects in the previous study. In other words, the higher the performance accuracy of a patient, the higher the metabolic rate was in the mid-prefrontal cortex.

Since neuroleptics act on the dopaminergic system, Cohen and his research team demonstrated 'an important function of the dopamine neurotransmitter pathway in the biological determination of sustained attention as mediated by the mid-prefrontal cortex' (Cohen et al., 1988, 1149). The findings suggest that one specific action of fluphenazine is to improve coupling of activity in the mid-prefrontal cortex and actual performance. However, this correction was not as significant as one might have expected.

> Yes and one of the… important findings was that neuroleptics do not correct the deficit that we saw. This is, in my mind, one of the very important contributions we tried to make in the field. …There was still this idea and question mark whether [and] how neuroleptics were working. Do they correct a deficit that actually happens? Is this like a Vitamin A deficiency and we give them Vitamin A and they improve? What we could see by looking at patients, both on and off drugs – and again the important part of this initial study was that we had patients who were off medications for a period of time… we could see that the changes we were seeing, the abnormalities we were seeing off drug, were not related to those… we see on drug. (RC)

It was on this basis that the authors suggested that there was a broader inability of the prefrontal cortex to direct higher-level motivations and rewards in patients with schizophrenia. This inability may have been related to a different amount of dopamine receptors in different areas of the brain and it was thought that blocking dopamine receptors could help to improve psychotic symptoms (Cohen et al., 1988, 174). It has been suggested that these findings relate to various levels of hyper or hypofrontality in the frontal cortex area in schizophrenia, contributing to a wider shift in the field that helped to advance understanding of the complex neurochemical alterations within different brain regions.

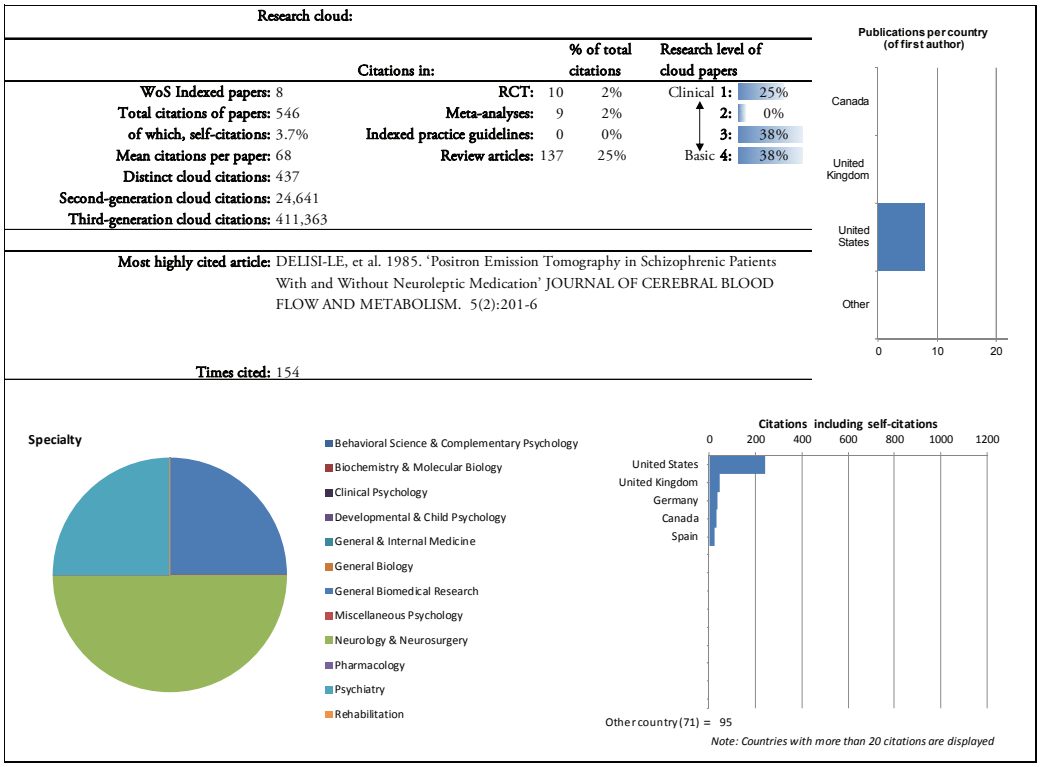
After this initial group of publications, the research cloud 'went quiet' in terms of publications. This did not mean the work was not continuing, but that it was becoming more difficult to get the required number of patients and time on the PET machine for the studies.

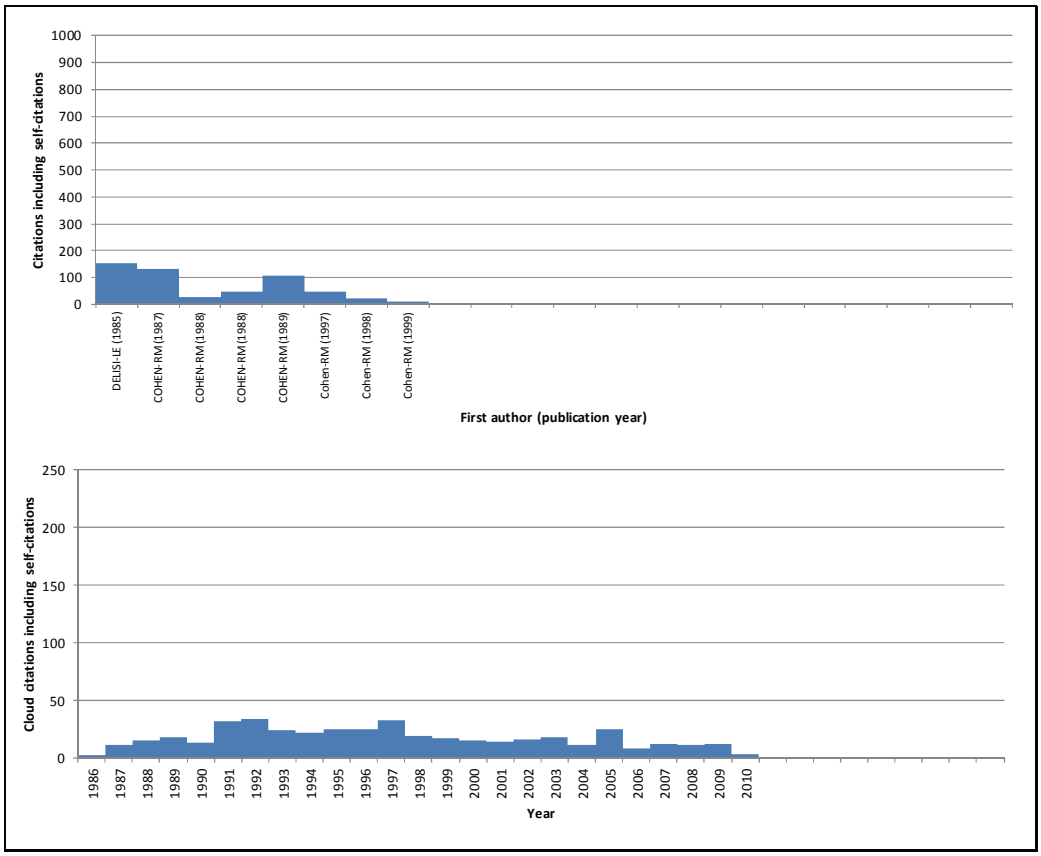
Ten years after the first publications, a new group of papers came out that reported on the effects on sustained attention of antipsychotics in male and female patients. The authors

found that male schizophrenic patients had lower metabolic rates in their prefrontal cortex and higher rates in their posterior putamen compared to healthy male subjects. They also found that differences in regional metabolic rates were a predictor of clinical outcomes in some cases. These findings implied that the sustained attention pathway and its distributed network of brain structures are likely to play an important role in the expression of psychotic symptoms.

Cohen, Pickar and colleagues also compared the effects of two neuroleptics on sustained attention. This study found that brain metabolic patterns of clozapine and fluphenazine did not differ significantly, though small differences in the metabolic rates of different areas might explain the differences in side effects of the two drugs. Comparison between male and female patients on clozapine and fluphenazine also revealed evidence of a sex effect that was consistent with other findings at the time showing that men and women had different reactions to neuroleptic treatment. The main findings of these studies, though, was to show that neuroleptics led to a 'compensation' effect in the brain, not a 'normalisation' one. In other words, neuroleptics helped the brain compensate for dopamine deficiencies, but did not normalise brain functioning.

A bibliometric analysis of the papers produced from the research cloud is shown below.





Targeting future research

Effect on the researchers' careers

Cohen went on to apply the PET scanning technique using the auditory discrimination task to different psychiatric disorders. He was very successful in this regard and used the methodology to understand what was going on in the brain in a whole range of different mental illnesses.

But eventually the group became too big and many more people wanted to use the scanner. Cohen felt his role was transitioning into being only about running an imaging programme. This feeling was compounded by the fact that a new director of the NIMH wanted to make the PET group even bigger than it was. Cohen wasn't interested in this kind of role, as he disliked running big groups.

> I am not someone that likes to run big groups. I decided in the early 1990s to – as he took over – to ask him if I could slip out of my position…. The work that we had – my original interest was in memory disorders, primarily. The imagining was important to get at that goal. We had developed quite a few things that were of interest and that, but part of what I was doing was helping with administering a larger programme. It was taking me further away from direct science. With the new Scientific Director, they wanted to make the programme even bigger. I decided that was not something that I particularly wanted to do. (RC)

Interestingly, Cohen took a new path even in the face of being offered more funding. His new career saw him taking time out to work in a molecular biology lab (of Dr. Michael Brownstein) so that he could refocus on Alzheimer's research.

This research cloud did not have a specific effect on Pickar's career, but Pickar did train many clinicians, nurses and others as part of the work. In Cohen's laboratory there were some researchers who went on to have prominent academic careers, but it is hard to say whether this research cloud was a direct causal factor (though it probably made a contribution).

Future work

As mentioned above, Cohen went on to apply the technique he developed in the research cloud to a whole range of other mental illnesses. His aim was to use the simple continuous performance task to look across a range of disorders for patterns in metabolic changes.

> So one of the things we did, and our job was to do, was to develop the technology and make it accessible to people with different clinical questions…. (RC).

This led to a whole new research cloud. One of the most significant pieces of work within this cloud looked at patients with ADHD using the continuous performance task approach in the PET scanner. This work was published in the *New England Journal of Medicine* and had high impact. It received national press (Zametkin et al., 1990) because it showed for the first time that ADHD really was a biological development disorder, and not one brought on by social effects.

> So we could look at – and we did look at manic depressive and sort of obsessive compulsive, seasonal affective disorder. We went on to do a whole series of studies. So we can see that there was a unique patterns of metabolic changes among the different disorders which very few other groups were able to do. We were able to do it primarily because the NIMH was such a productive programme in terms of having a variety of wards and groups working on the different disorders. Whereas other places around the country, probably more financial restrictions and issues, and not as large a group of investigators, they had to specialise more. (RC)

Eventually, though, Cohen began to feel like he'd gone as far as he could with PET scanning at NIMH. He felt that for diagnostic purposes there was a certain point at which you need hundreds of patients in order to establish significance and this just wasn't feasible. There also wasn't the interest from clinical psychiatrists to look at that many patients. Cohen thought that the reason for this is that, with the psychiatric diagnostic tools available to classify people, until you get a large population of patients where there are still diagnostic questions, you aren't going to get the large-scale research programme that will allow you to see how well the tools work in a biologically diagnostic fashion. Another barrier to further application of this research area was that there was a lot of background noise in the findings, and they could never come close to statistically significant results.

> We never really had, in all the scanning that we had done, never really reached anything close to three standard deviations from a healthy normal, in any of our studies. So what we were looking at was the biology, an important part of the biology. But it wasn't yet at a point where there is going to be a diagnostic tool. So that is both the good part and the disappointing part. I remember looking at the first scans of patients with schizophrenia. Like I said, there was one slice at a time. It would slowly develop over time, you could see it in the CRT monitor. …We were all looking for a hole in the brain where patients with schizophrenia would be and what we are seeing is, you know, 7% differences. These are

> small differences and there is a lot of noise. Why is there a lot of noise? Because people basically – everybody has – biologically every human being is different. (RC)

Pickar echoed these views. He knew that a lot of the biological findings were interesting, but without layering clinical knowledge onto them they weren't going to get anywhere. However, Pickar did continue trying to understand the clinical and biological implications of neuroleptics. In particular, he was very interested in understanding how and why dopamine worked differently in subcortical areas of the brain. There was some research, including that resulting from the PET scanning, that pointed to a varied effect of dopamine in contributing to the development of schizophrenia. Essentially, in schizophrenic patients, there was too much dopamine in the subcortical areas. Neuroleptics were blocking this uptake, but Cohen thought there was also too little dopamine in the prefrontal areas, and neuroleptics weren't doing much to address this situation. The real trick, in Pickar's view, would be to figure out how to get dopamine levels up in the prefrontal area, but keep them down in the subcortical areas. Out of these observations he developed a new drug, Idazoxan, which is in Phase II clinical trials and is discussed further below. Though Pickar points out that the PET scanning work was not critical to these developments, his collaboration with Cohen was an important contributory avenue of research that helped to establish hypofrontality in the frontal cortex and gave further clues about the dopamine imbalance.

After the PET scanning work, Cohen went on to have a successful research career in memory disorders and molecular biology. He has now developed a rat model for studying Alzheimer's and does clinical work and sees patients on a regular basis. He is widely regarded as being a highly successful researcher and a few years ago received a prize for being one of the most highly cited researchers in the US.

In other areas outside psychiatry, as Cohen and Pickar's research developed, PET scanning was becoming widely used, particularly in cardiology and cancer screening. Within psychiatry, PET scanning is used today as a diagnostic tool for Alzheimer's disease, but both interviewees dismissed this technique to a certain extent as not widely used or of clinical value. The work of Weinberger and other groups has been mentioned throughout, but is worth echoing again here as during the entire time of Cohen and Pickar's work, other major advances in PET imaging throughout the field, and particularly at the NIMH, were contributing to growing knowledge about the pathophysiology of schizophrenia and its implications for treatment of the illness.

5.8 Interface B: Dissemination

Academic dissemination

Cohen did not do very much active dissemination. Most that was done was through traditional means of presenting at conferences, but he let post-docs and junior faculty do the talks. He wrote the occasional review paper, but he was generally not keen on going to big meetings or conferences.

Pickar felt he was disseminated 'to', or in other words that people were constantly coming to him and asking him to present at things, give talks, provide advice, etc. He felt there was

less of a need to disseminate the research because people wanted his results and often came to him for them before the work was published.

5.9 Stage 4: Secondary outputs

Secondary outputs of the research cloud are those that result from the direct knowledge outputs and might include citation in clinical guidelines or systematic reviews. There were few secondary outputs from this research. Both Cohen and Pickar felt their work contributed to changing the way people saw schizophrenia, but this was part of a broader shift in the field at the time that saw people realise that it wasn't just about family life or something people did, but rather that it was a developmental disorder in origin.

The work on ADHD that arose from the secondary research coming out of the cloud was cited in the European Consensus Statement on Attention Deficit Hyperactivity Disorder (ADHD) (Kooij et al., 2010), which aimed to increase awareness of the disorder for adults and improve knowledge and patient care across Europe.

Cohen also felt that the early work in PET helped contribute to the side-by-side use of imaging with clinical treatment.

> I think functional MRI has become a much bigger tool for behavioural research than PET has. But in the other areas of medicine, it has been PET. So I would say, 'Yes, the idea of using imaging with clinical research has become an integrated activity.' There is no question about where the roots are. (RC)

Not only has this use of imaging with clinical research become more integrated, but the idea of controlling for 'restive' versus 'active' states of the brain had a significant impact on the field of functional imaging, including fMRI, by introducing the basic distinction between these two states and what the implications of this are for the brain. This is still an active area of research (Jones & Rabiner, 2012).

5.10 Stage 5: Applications

PET scanning is now used diagnostically and clinically for Alzheimer's disease, but the contribution of the research cloud to this development is likely to be small. Neither Cohen nor Pickar ever thought about patenting or licensing the technology of their PET scanning method.

> You know in those days we did not think that anything we did should be patented. We were working for the Government. It was being paid for by tax dollars and we thought – and I thought – that whatever we did should be freely open and in the public domain…. It is a big generational gap issue…. (RC)

Pickar is working to develop his new drug, which is in Phase IIb clinical trials. In the mid-1990s he was doing some experiments with different dosing of neurolpetics together with Idazoxan when he realised that norepinephrine could have the effect of increasing release of dopamine in the prefrontal cortex, independent of what was happening in the subcortical areas. It had to do with the simultaneous release of the α_2 molecule that would, effectively, let dopamine back into the system. Since then, Pickar has been trying to get FDA approval

for a drug that will simultaneously block dopamine and allow dopamine back into the prefrontal cortex. The main hurdle in moving to Phase III trials at the moment is funding.

5.11 Stage 6: Public engagement

There is little evidence of public engagement of this research. Pickar did engage with different advocacy and patient groups over the course of his career, but not in any significant way that might have shaped the course of his research.

5.12 Stage 7: Final outcomes

Today Cohen does clinical and research work. To a certain extent his earlier work has contributed to his current approach to research of using PET and clinical applications side by side; in other words, the idea of using imaging in clinical research has become an integrated activity.

5.13 Table of payback

Payback category	Impacts from case study
Knowledge Production	• Evidence of glucose metabolism in the brain in different regions. • Evidence that dopamine has a complex effect in the prefrontal cortex. • Methodological innovation in how mental disorders can be studied to understand their biological effect on the brain. • Improved understanding of schizophrenia as a biological, not a psychological, disorder.
Research Targeting and Capacity Building	• Improved capacity within the NIH to do PET scanning, including contributing to the successful careers of some researchers in the lab. • Many doctors were trained by Pickar through his clinical research lab. • Cohen's appointment to run the PET scanning group in the NIMH clearly had a significant impact on his future career trajectory.
Informing Policy and Product Development	• No impacts on policy directly from the research cloud, but the related stream of work. • Potential impact on product development from Idazoxan, but not solely related to the PET scanning work.
Health and Health Sector Benefits	• Potential impacts from Idazoxan, if approved. • Benefits to the health sector in helping to elucidate the pathophysiology of schizophrenia and providing a 'window' into the brain. • PET scanning has health benefits for patients with Alzheimer's and for patients with cancer, but this is not necessarily an attributable result of Cohen's work.
Broader Social and	• Contributions to the advancement of the field of PET imaging and its

Economic Benefits	acceptance in research and clinical practice, including diagnostic use and guided surgeries. Related, contributions to the acceptance and use of MRI in the brain. • Potential benefits from development of Idazoxan.

5.14 Timeline

1977	Cohen joins NIMH as Staff Psychiatrist, Clinical Neuropharmacology Branch
1977	Pickar joins NIMH as Clinical Associate, Clinical Neuropharmacology Branch, IRP, NIMH
1980	Cohen becomes Chief, Unit on Clinical Psychopharmacology, Clinical Neuropharmacology Branch, NIMH
1982	Pickar becomes Chief, Section on Clinical Studies, Experimental Therapeutics Branch (Formerly Clinical Neuroscience Branch), IRP, NIMH
1983	Cohen becomes Chief, Clinical Brain Imaging Section, Laboratory of Cerebral Metabolism, NIMH
Mid-1980s	NIMH purchases PET scanning machine
1988	Pickar becomes Acting Chief, Clinical Neuroscience Branch, IRP, NIMH
1990	Cohen leaves PET scanning section and becomes Section Chief, Clinical, Laboratory of Cell Biology, NIMH
1991	Pickar becomes Chief, Experimental Therapeutics Branch, IRP, NIMH
1993	Cohen becomes Section Chief, Clinical, Laboratory of Cerebral Metabolism, NIMH
1998	Cohen becomes Section Chief, Geriatric Psychiatry Branch, NIMH
1999	Pickar leaves NIMH to pursue private sector drug development
2005	Cohen leaves NIMH to become Director of Research, Psychiatry and Behavioral Neurosciences, Cedars, Sinai Medical Center

5.15 References

Benkelfat, C., et al. (1990). Local cerebral glucose metabolic rates in obsessive compulsive disorder – patients treated with clomipramine. *Archives of General Psychiatry*, 47(9), 840–848.

Cohen, R.M. (2011). *RE: Personal interview.* Communication with Morgan Jones, M., & Olmsted, S.

Cohen, R.M., et al. (1997). The brain metabolic patterns of clozapine- and fluphenazine-treated patients with schizophrenia during a continuous performance task. *Archives Of General Psychiatry*, 54(5), 481–486.

Cohen, R.M., et al. (1992). Preliminary data on the metabolic brain pattern of patients with winter seasonal affective-disorder. *Archives Of General Psychiatry*, 49(7), 545–552.

Cohen, R.M., et al. (1989). Evidence for common alterations in cerebral glucose metabolism in major affective disorders and schizophrenia. *Neuropsychopharmacology*, 2(4), 241–254.

Cohen, R.M., Nordahl, T.E., Semple, W.E., Andreason, P., & Pickar, D. (1998). Abnormalities in the distributed network of sustained attention predict neuroleptic treatment response in schizophrenia. *Neuropsychopharmacology*, 19(1), 36–47.

Cohen, R.M., Nordahl, T.E., Semple, W.E,. & Pickar, D. (1999). The brain metabolic patterns of clozapine- and fluphenazine-treated female patients with schizophrenia: evidence of a sex effect. *Neuropsychopharmacology*, 21(5), 632–640.

Cohen, R.M., Semple, W.E., & Gross, M. (1986). Positron emission tomography. *Psychiatric Clinics of North America*, 9(1), 63–79.

Cohen, R.M., Semple, W.E., Gross, M., Holcomb, H.H., Dowling, M.M., & Nordahl, T.E. (1988). Functional localization of sustained attention: comparison to sensory stimulation in the absence of instruction. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*, 1(1).

Cohen, R.M., Semple, W.E., Gross, M., & Nordahl, T.E. (1988). From syndrome to illness: delineating the pathophysiology of schizophrenia with PET. *Schizophrenia Bulletin*, 14(2), 169–176.

Cohen, R.M., Semple, W.E., Gross, M., Nordahl, T.E., DeLisi, L.E., Holcomb, H.H., King, A.C., Morihisa, J.M., & Pickar, D. (1987). Dysfunction in a prefrontal substrate of sustained attention in schizophrenia. *Life Sciences*, 40(20), 2031–2039.

Cohen, R.M., Semple, W.E., Gross, M., Nordahl, T.E., Holcomb, H.H., Dowling, M.S., & Pickar, D. (1988). The effect of neuroleptics on dysfunction in a prefrontal substrate of sustained attention in schizophrenia. *Life Sciences*, 43(14), 1141–1150.

DeLisi, L.E., et al. (1985). Positron emission tomography in schizophrenic patients with and without neuroleptic medication. *Journal Of Cerebral Blood Flow And Metabolism*, 5(2), 201–206.

Farde, L., Wiesel, F.A., Halldin, C., Sedvall, G. (1988). Central d2-dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs. *Archives of General Psychiatry,* 45(1), 71–76.

Goyer, P.F., et al. (1992). Cerebral glucose metabolism in patients with summer seasonal affective disorder. *Neuropsychopharmacology*, 7(3), 233–240.

Holcomb, H.H., et al. (1996). Functional sites of neuroleptic drug action in the human brain: PET/FDG studies with and without haloperidol. *American Journal of Psychiatry*, 153(1), 41–49.

Jones, T., & Rabiner, E.A. (2012). The development, past achievements, and future directions of brain PET. *Journal of Cerebral Blood Flow and Metabolism,* 32(7), 1426–1454.

Knable, M.B., & Weinberger, D.R. (1997). Dopamine, the prefrontal cortex and schizophrenia. *Journal of Psychopharmacology,* 11, 123–131.

Kooij, S., Bejerot, S., Blackwell, A., et al. (2010). European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD. *BMC Psychiatry,* 10, 67.

Pickar, D. (2011). *RE: Telephone Interview 1 with David Pickar.* Communication with Morgan Jones, M., & Olmsted, S.

Pickar, D., Labarca, R., Linnoila, M., Roy, A., Hommer, D., Everett, D., & Paul, S. (1984). Neuroleptic-induced decrease in plasma homovanillic acid and antipsychotic activity in schizophrenic patients. *Science,* 225, 954–957.

Weinberger, D.R., & Berman, K.F. (1988). Speculation on the meaning of cerebral metabolic hypofrontality in schizophrenia. *Schizophrenia Bulletin,* 14, 157–168.

Wyatt, R.J. (1988). Schizophrenia research in the intramural research program, National Institute of Mental Health: editor's introduction. *Schizophrenia Bulletin,* 14, 145–150.

Zametkin, A.J., Nordahl, T.E., Gross, M., King, A.C., Semple, W.E., Rumsey, J., Hamburger, S., & Cohen, R.M. (1990). Brain metabolism in hyperactive adults with childhood onset. *New England Journal of Medicine*, 323(20), 1361–1366.

CHAPTER 6

Organisation of dopamine D1 and D2 receptors in human striatum: receptor autoradiographic studies in Huntingdon's disease and schizophrenia

This case study is based on research related to the following highly cited publication, which was identified from a bibliometric analysis:

Joyce, J.N., Lexow, N., Bird, E., & Winokur, A. (1988). Organization of dopamine D1 and D2 receptors in human striatum: receptor autoradiographic studies in Huntington's disease and schizophrenia. *Synapse*, 2, 546–557.

Information was gathered from interviews with the lead author, Dr. Jeffrey Joyce, as well as desk-based research.

6.1 Summary

The target paper describes early basic clinical research on the organization of dopamine D1 and D2 receptors in the striatum region of the human brain, comparing control patients with patients with Huntington's disease and patients with schizophrenia. The work was led by Jeffrey Joyce, at the time a junior faculty member at the University of Pennsylvania, in the Departments of Psychiatry and Pharmacology. Previously, researchers had shown that the receptor levels of dopamine were elevated in schizophrenic patients, but these studies were on patients who had been treated with neuroleptics, so it was not clear if the changes were a result of the disease or the drugs. The work reported in this paper was novel for a number of reasons: they were the first studies to show that the changes in dopamine receptor concentration were different in different regions of the brain; it also showed that that the changes in dopamine receptor concentration were not drug induced, as the patients tested had not been treated with neuroleptics; and it used a relatively novel technique, quantitative autoradiography, although this was not the first paper to describe that technique.

At the time of the paper, Joyce's research focused on the behavioural and neurochemical analysis of the plasticity of dopamine systems using both rodent and human tissue. He was also establishing a human brain tissue bank to expand his work on the molecular neurochemistry of the human brain, especially related to neuropsychiatric and neurodegenerative illnesses. For the target paper, the researchers used quantitative

autoradiography to measure the concentration of the D1, D2, and muscarinic receptors in thin tissue sections from different regions of the brain of 10 patients. Quantitative autoradiography measures the amount of a radioactive substance that has bound to a target molecule and had rarely been used in human studies prior to this research. A radioactively labelled ligand is allowed to bind to its receptor in a tissue sample, the tissues are then exposed to radioactive sensitive film, the film is developed, and the concentration of bound ligand is measured with a computer-based image analysis tool. The concentration of D2 receptors was higher in brain tissue from schizophrenic patients than controls or Huntington's disease patients. The concentration of D1 receptors was lower in Huntington's disease patients than controls or schizophrenic patients. Ultimately, the authors showed that the ratio of D2/D1 receptors was increased in both schizophrenic and Huntington's disease patients. This paper also showed for the first time that the distribution of receptors was different in the different regions of the brain.

Joyce remained at the University of Pennsylvania for about a decade, successfully securing grant funding from various sources. Initial data from this paper helped him secure a grant from the Scottish Rite Schizophrenia Research Program and the paper was a key step in securing a follow-on R-29 grant from the NIH (US). Later he moved to Arizona to start a Parkinson's disease research centre associated with the Sun Health Research Institute. He remained at Sun Health for about 10 years before becoming the director of the Department of Research at the Maricopa Integrated Health System, his current position. Joyce does not conduct research in this position, but manages the systems research portfolio, develops strategic partnerships, and supports the research training of medical residents and physicians.

The research described in the target paper employed a technique rarely used in human post-mortem studies to localize dopamine D3 receptors in the brain and the ratio of D2 to D1 receptors. The anatomical localization of the D3 receptors in the human brain contributed substantively to the field. While the ratio of D2 to D1 receptors was thought to be important at the time, it has not turned out to be meaningful. Although this case study research did not lead directly to clinical practice or applications, it contributed to the body of knowledge related to the role, distribution and function of dopamine receptors (D1, D2, and D3) in the human brain, and the variation of this in various mental disorders such as schizophrenia, Huntington's disease and Alzheimer's disease.

6.2 Introduction

6.2.1 Scientific background

This research cloud examines the neurochemistry of the brain, specifically comparing brain specimens from humans without chronic mental conditions (controls) with specimens from patients with schizophrenia and Huntington's disease. The research focused on the roles of the three dopamine receptors. The D2 receptor is the primary target for antipsychotic drugs that block D2 and for anti-Parkinson stimulant drugs that stimulate D2. The D1 receptor works with the D2 receptor to enhance the action of anti-Parkinson drugs. The D3 receptor is not known to be involved in antipsychotic drug action but may have a role in the formation of addictive behaviour.

At the time of the research, dopamine had been identified as an important neurotransmitter in the brain with D2 receptors found to be elevated in post-mortem brains that had not undergone treatment (Lee & Seeman, 1980; Seeman et al., 1984). Other researchers had shown that D2 receptors were increased in the striatum for schizophrenia patients on neuroleptics, while D1 receptors were decreased in Huntington's disease patients. Neuroleptics, which block dopamine receptors, were already being used to treat patients with symptoms of both diseases. At the time, the mechanism through which dopamine acted within the brain was less well known. Furthermore, the relationship between dopamine and different mental health conditions was not well understood. Researchers were trying to develop a more in-depth understanding of the role of the dopamine system in schizophrenia and Huntington's disease.

Autoradiography, the technique of radio-labelling molecules and then using them to image specific features of a cell, had been developed in the 1950s. The availability of radio-labelled compounds increased substantially in the 1970s, although quantification of the amount of bound substances had not been developed. Just prior to Joyce's work on the target paper, he completed a post-doctoral fellowship at the University of California at Irvine (UCI), where he collaborated with researchers who were developing a computer-assisted method to quantify autoradiography, the amount of ligand bound to receptors in the brain (Altar et al., 1984; Joyce et al., 1986).

The target paper describes a relatively small sample of subjects: four with Huntington's disease, three with schizophrenia, and three normal controls.

6.2.2 Researchers' background

Jeffrey Joyce earned his PhD from the University of Florida, Gainesville, in the Department of Psychology, where he studied dopamine as a neurotransmitter. Joyce completed his PhD in physiological psychology in 1983. He then completed a post-doctoral fellowship in the Department of Psychobiology at the University of California, Irvine. During this fellowship (1983–1986), he learned two new techniques that became very important for this paper and his career – he started using human brain tissue sections in his research and he worked with the team that developed a quantitative method to measure ligand binding using autoradiography. In 1986, he accepted a position as a Research Assistant Professor in the Department of Pharmacology, University of Pennsylvania School of Medicine, to work in the Laboratory of Behavioral Pharmacology and Neurochemistry. The expertise he developed as a post-doc was a critical factor in his obtaining this position.

Andrew Winokur was a psychiatrist at the University of Pennsylvania who inherited parts of a NIMH programme project grant when the PI, Tom Rainbow, died. Currently, Winokur is the Director of the Neuropsychopharmacology Treatment, Research and Training Center in the Department of Psychiatry at the University of Pennsylvania.

John Marshall was Joyce's post-doctoral advisor at UCI and influenced Joyce's thinking and career more than anyone else. Marshall has remained at UCI throughout his career of more than 35 years.

6.3 Defining the research cloud

The research cloud for this study focuses on the work that Joyce and colleagues conducted studying the molecular neurochemistry of the human brain, particularly related to neuropsychiatric and neurodegenerative illnesses. Specifically, this research cloud examines the role, distribution and function of dopamine receptors (D1, D2, and D3) in the human brain, and the variation of this in various mental disorders such as schizophrenia, Huntington's disease and Alzheimer's disease. This is part of a larger research cloud within which there are three other identified sub-clouds: (1) regulation of dopamine receptors in neuropsychiatric disorders; (2) TRH, substance P, Monoaminergic systems; and (3) localization of dopamine receptors.

The research cloud includes one earlier paper that is cited by the target paper for its methods. The remaining papers were published between 1988 and 2001. The first few papers continued describing work that identifies where dopamine receptors are located in the brain. A highly cited 1999 paper references changes in D3 receptors in schizophrenia and the effects of antipsychotic drugs, building on the selected paper. A few of the later papers focus somewhat on the effects of antipsychotic drug on dopamine receptors. Interestingly, none of the other papers in the cloud include any of Joyce's co-authors on the target paper.

The publications included in the cloud for this case study are as follows:

1. Joyce, J.N., Sapp, D.W., & Marshall, J.F. (1986). Human striatal dopamine receptors are organized in compartments. *Proceedings of the National Academy of Sciences,* 83(20), 8002–8006.
2. Joyce, J.N., Lexow, N., Bird, E., & Winokur, A. (1988). Organization of dopamine D1 and D2 receptors in human striatum: receptor autoradiographic studies in Huntington's disease and schizophrenia. *Synapse*, 2, 546–557.
3. Joyce, J.N., Janowsky, A., & Neve, K.A. (1991). Characterization and distribution of [125I]epidepride binding to dopamine D2 receptors in basal ganglia and cortex of human brain. *Journal of Pharmacology and Experimental Therapeutics,* 257(3), 1253–1263.
4. Murray, A.M., Roo, H., & Joyce, J. (1992). Visualization of dopamine D3-like receptors in human brain with epidepride. *European Journal of Pharmacology: Molecular Pharmacology,* 227(4), 443–445.
5. Goldsmith, S.K. & Joyce, J.N. (1994). Dopamine D2 receptor expression in hippocampus and parahippocampal cortex of rat, cat, and human in relation to tyrosine hydroxylase-immunoreactive fibers. *Hippocampus*, 4(3), 354–373.
6. Murray, A.M., Ryoo, H., Guyrevich, E., & Joyce, J. (1994). Localization of dopamine D3 receptors to mesolimbic and D2 receptors to mesostriatal regions of human forebrain. *Proceedings of the National Academy of Science*, 91(23), 11271–11275.
7. Goldsmith, S.K., & Joyce, J.N. (1996). Dopamine D2 receptors are organized in bands in normal human temporal cortex. *Neuroscience*, 74(2), 435–451.

8. Gurevich, E.V., Bordelon, Y., Shapiro, R.M., Arnold, S.E., Gur, R.E., & Joyce, J.N. (1997). Mesolimbic dopamine D3 receptors and use of antipsychotics in patients with schizophrenia: a postmortem study. *Archives of General Psychiatry*, 54(3), 225–232.
9. Joyce, J.N., & Meador-Woodruff, J.H. (1997). Linking the family of D2 receptors to neuronal circuits in human brain: insights into schizophrenia. *Neuropsychopharmacology*, 16(6), 375–384.
10. Goldsmith, S.K., Shapiro, R.M., & Joyce, J.N. (1997) Disrupted pattern of D2 dopamine receptors in the temporal lobe in schizophrenia: a postmortem study. *Archives of General Psychiatry*, 54(7), 649–658.
11. Joyce, J.N., Myers, A.J., & Gurevich, E. (1998). Dopamine D2 receptor bands in normal human temporal cortex are absent in Alzheimer's disease. *Brain Research*, 784(1–2), 7–17.
12. Gurevich, E.V., & Joyce, J.N. (1999). Distribution of dopamine D3 receptor expressing neurons in the human forebrain: comparison with D2 receptor expressing neurons. *Neuropsychopharmacology*, 20, 60–80.
13. Joyce, J.N., & Gurevich, E.V. (1999). D3 receptors and the actions of neuroleptics in the ventral striatopallidal system of schizophrenics. *Annals of the New York Academy of Sciences*, 877, 595–613.
14. Joyce, J.N. (2001). Dopamine D3 receptor as a therapeutic target for antipsychotic and antiparkinsonian drugs. *Pharmacology & Therapeutics*, 90(2–3), 231–259.
15. Joyce, J.N. (2001). D2 but not D3 receptors are elevated after 9 or 11 months chronic haloperidol treatment: influence of withdrawal period. *Synapse*, 40(2), 137–144.

6.4 Stage 0: Opportunity identification/research needs assessment

Inspiration

Joyce's research examined clinical processes and disturbances in clinical process by understanding changes in neural networks. At the time of the research, dopamine had been identified as an important neurotransmitter in the brain. Other researchers had shown that D2 receptors were increased in the striatum of schizophrenia patients on neuroleptics, while D1 receptors were decreased in Huntington's disease patients. Neuroleptics, which block dopamine receptors, were already being used to treat patients with symptoms of both diseases. At the time, the mechanism through which dopamine acted within the brain was less well known. Furthermore, the relationship between dopamine and different mental health conditions was not well understood. Researchers were trying to develop a more in-depth understanding of the role of the dopamine system in schizophrenia and Huntington's disease. In his work, Joyce was interested in explaining and using techniques that would allow him to look at system changes with respect to neuropharmacology. Since the dopamine system was so strongly implicated in schizophrenia, it was a natural clinical disorder to explore.

Feasibility

Joyce, whose graduate work was in understanding dopamine as a neurotransmitter, arrived at UC Irvine just as a group of scientists were developing quantitative receptor autoradiography. Joyce spent his time at UCI helping develop this tool to conduct studies on the dopamine system in human tissues. This was a unique skill set that the University of Pennsylvania recruited him for:

> While I was doing work with animal models of varying kinds, what I got immediately known for was an ability to do it in human tissue which was very rare at that time and got brought to the University of Pennsylvania School of Medicine to be on a program project, in order to do those kinds of studies. (JJ)

Potential value

The value of this research to Joyce was two-fold. He was interested in doing basic research that would help understand neurological processes in clinically relevant situations. However, in part, he chose to work on schizophrenia because of professional ambition.

> I also thought, frankly at that time, that [schizophrenia] was an area I could make an impact in whereas at that time, there were still many other people in other neurological disorders, that that it [schizophrenia] would be something I could make an impact in, from a purely selfish point. (JJ)

6.5 Stage 1: Inputs to research

Money, researcher time, lab/office space and consumables

At the University of Pennsylvania, Perry Molinoff, the Chair of Pharmacology, had a NIH Research Program Project awarded by the National Institute of General Medical Sciences on the pharmacology of receptor/effector systems. This grant mechanism provides support for a long-term, multidisciplinary, and broad-based research programme centred around a basic theme. These research projects are typically led by an established investigator and support the basic resources used by the involved researchers. Molinoff's programme project grant included a section on receptor autoradiography that Tom Rainbow was supposed to lead. When he died unexpectedly, Joyce, one of the few other scientists in the country who knew the technique, was recruited to the University to do the work. Joyce then established a Laboratory of Behavioural Pharmacology and Neurochemistry that was funded through the programme project grant as well as support from a Training Grant for a Postdoctoral Fellow, and foundation and pharmaceutical grants.

The funding for the target paper came primarily from the Scottish Rite Schizophrenia Research Program grant 'Visualization of Neurochemical and Neuropathological Changes in Post Mortem Schizophrenic Tissue Utilizing Neurotransmitter Autoradiography.' This was a two-year grant spanning from August 1987 to July 1989 in the amount of $35,000 per year. The Scottish Rite grants were fast turn-around grants designed for young investigators without R01's from NIH (US). In order to get the Scottish Rite grant, Joyce used preliminary data collected with resources from the Research Program Project grant described above. The Scottish Rite grant enabled him to complete the study and publish the results in *Synapse*.

The data presented in the identified paper were then responsible for the award of a First Independent Research Support and Transition (FIRST) award (also known as an R29 at

the time) from NIMH on 'Neurotransmitter Disorders in Schizophrenia' in 1988. The FIRST awards were designed for newly independent biomedical and behavioural science investigators to support their research agenda. These were five-year awards that supported 50 percent of the researchers' time. For Joyce, the R29 helped support the establishment of the shared human tissue laboratory in pharmacology for molecular neurochemistry of the human brain. With the laboratory, Joyce became involved in multiple programme projects that helped support further work in this research cloud.

Joyce was given a small laboratory (400 square feet) in pharmacology when he arrived at the University of Pennsylvania. After developing his own funding sources, he also acquired a laboratory in psychiatry, which is where he started building his brain tissue bank. The research required special facilities to handle human tissue. For example, the cryostat for examining human tissue was different from the one used for animal tissue, requiring a negative pressure room where scientists were capped and gowned. The human tissue lab grew very large, with 19 people working in it at one point. The programme project grants provided support for the equipment and materials needed for the human tissue studies.

Joyce's work was of interest to pharmaceutical companies, because they had ligands that they wanted to test in binding studies in the human brain. He noted that it was common for funds in excess of the costs for completing industry-sponsored studies to be utilized by investigators to support novel research projects. Thus, these resources were able to be stretched to develop new lines of research and it also provided access to novel compounds being developed by industry.

Knowledge

Joyce's understanding of the neurochemistry of the dopamine system, including that there might be multiple dopamine receptors, was key to conducting this research. This included in-depth understanding of receptor-ligand biochemistry, including binding chemistry and equilibrium. In addition, the researchers' knowledge of the structure of the brain, different regions of the brain and how to label and identify those regions was critical.

Expertise and techniques

As a post-doc, Joyce published a paper in the *Proceedings of the National Academy of Sciences* (Joyce, Sapp, & Marshall, 1986) on using radio-ligands to bind to human brain tissue sections and analysing the result with quantitative receptor autoradiography. He collaborated with Sapp and Marshall at UCI to develop techniques to perform the quantitative receptor autoradiography in human brain tissue sections.

> When I then went to do my post-doc at UC Irvine I was very lucky in that they had just developed the technique – with a number of other labs – of quantitative receptor autoradiography… but the quantification had not been delineated, just the techniques for doing the binding of ligands to tissue and visualization. I happened to be lucky, there was a lab upstairs doing laser technology that had, at that time what we would consider a very sophisticated computer imaging that nobody else had. So I worked with them on how you'd actually image the films and then from that, derive a quantifiable numbers and develop the mathematical modelling for doing that. (JJ)

Based on this paper, Joyce became known for his ability to apply this technique to human tissue and in 1986, when Tom Rainbow died, the University of Pennsylvania recruited

him to its behavioural pharmacology and neurochemistry laboratory to conduct human tissues studies. This set the stage for the vast majority of his research for the next 20 years.

Collaborators

Joyce had a number of key collaborators who contributed to the target paper specifically and the research cloud more broadly. At the University of Pennsylvania, there was a unique relationship between the Departments of Pharmacology and Psychiatry. When Joyce arrived in 1986, he and his key collaborators had primary appointments in the Department of Pharmacology and secondary appointments in the Department of Psychiatry. He also shared a human tissue laboratory for collecting human tissue and doing studies in the field of pharmacology and psychiatry with Winokur, who had inherited the laboratory when Rainbow died. His collaboration with Winokur in the Psychiatry Department produced several papers (including the target paper) that allowed Joyce to generate his own research funding.

In 1989, the basic science research groups in psychiatry consolidated into one facility. At that time, Joyce and many of the other basic science researchers switched to have primary appointments in Psychiatry and secondary appointments in Pharmacology. This was rather unusual for a neuropharmacology training programme but came about because there were a number of investigators within psychiatry who were interested in brain disorders. With this transition, Joyce became an Associate Professor of Psychology and Neuroscience in the Department of Psychiatry and also became director of the laboratory since it was not Winokur's skill set or interest. Joyce also forged relationships with researchers in neuropathology (John Trojanowski and Virginia Lee) who later become renowned scientists in Alzheimer's disease and Parkinson's disease, meaning access to human tissue and the conducting of more post-mortem studies in schizophrenia.

Joyce credits the collaborative environment at the University of Pennsylvania with guiding his thinking on conducting translational research. During the late 1980s, much of the research was funded through NIH Research Program Project grants that required large groups of people with a sustained interest in developing a brain donor programme. The brain donor programmes required a lot of resources and time from investigators over an extended period of time. Funding for these programmes came from multiple sources. The collaborative environment at Penn allowed basic science researchers with an interest in the clinical outcomes of their research to connect to clinical researchers. Joyce considers these types of collaborations as valuable because they lead to large grants and important research. Pooling talent, funding and resources in a core area allows for cutting edge research.

> So I think the environment influenced me but it was also an environment I chose and was very comfortable being in and liked, and was forged in the concept of that's how you initiated translational research. At the same time I really drove part of that, not everybody had those kinds of interests, so I think that research really allowed people to think about doing research in mental illness in a way they had not really even thought was able to be done before. (JJ)

6.6 Stage 2: Processes

While others were focussing on animal studies, Joyce made his name by using the autoradiography technique to understand the distribution and concentration of dopamine

receptors in human post-mortem studies. He used radio-ligands (radioactively labelled molecules) to measure the concentration of dopamine and other receptors in thin tissue sections from different regions of the brain. The radio-ligand was allowed to bind to their receptor, the tissues exposed to radioactive sensitive film, the film developed, and the concentration of bound ligand measured with a novel computer-based image analysis tool that he had helped develop as a post-doctoral fellow. This work was considered cutting edge in terms of the technique and in its use of human tissue. While many of Joyce's studies were disease-specific, more generally his work pushed the field of neurobiology forward in understanding the neurobiology of clinical disorders. Joyce was an expert in both the neurochemistry of dopamine and a novel technique that he applied across multiple diseases, while still focusing somewhat on schizophrenia.

> I think actually the more important part of it really was not disease-specific but rather that what you were doing was viewed as being cutting edge, that you were pushing they feel whatever it was forward significantly. If this had been bipolar disorder or something, the program officer would have been as equally interested in it, I think the more important was you were driving a field forward, that everybody recognizes as being of big fundamental importance to… and that you really were likely to have an impact on understanding neurobiology of a disease. (JJ)

6.7 Stage 3: Primary outputs

Knowledge

The target paper reported on research that localized D3 receptors in the human brain and showed that the concentration of D2 receptors was higher in brain tissue from schizophrenic patients than controls or Huntington's disease patients. At the same time, the concentration of D1 receptors was lower in Huntington's disease patients than controls or schizophrenic patients. Ultimately, the research indicated that the ratio of D2/D1 receptors is increased in both schizophrenic and Huntington's disease patients. While this ratio was thought to be important at the time, it was not as important as the localization of the D3 receptors. The target paper utilized Huntington's disease to demonstrate that quantitative autoradiographic techniques could discriminate between receptor types and neuronal loss dependent changes. It also showed that the distribution of receptors was different in the different regions of the brain in schizophrenia, which had not been shown before and was key to understanding that there was a different biology behind schizophrenia and antipsychotic drug effects.

The anatomical localization of the D3 receptors in the human brain contributed substantively to the field. While the ratio of D2 to D1 receptors was thought to be important at the time, it has not turned out to be meaningful.

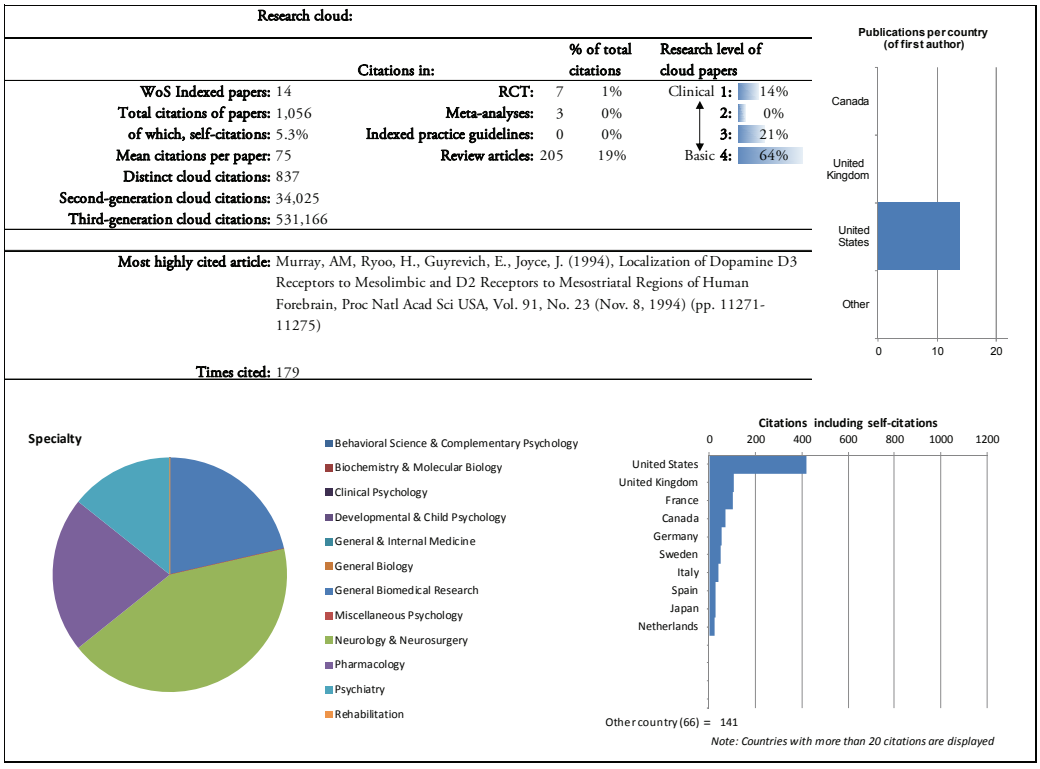
Overall, however, the scientific impact of Joyce's work was modest, but significant. In particular, his anatomical localisation of D3 receptors in the human brain was helpful, although French workers had already delineated the anatomical localization in brain regions (Schwartz et al., 1993; Sokoloff et al., 1992).

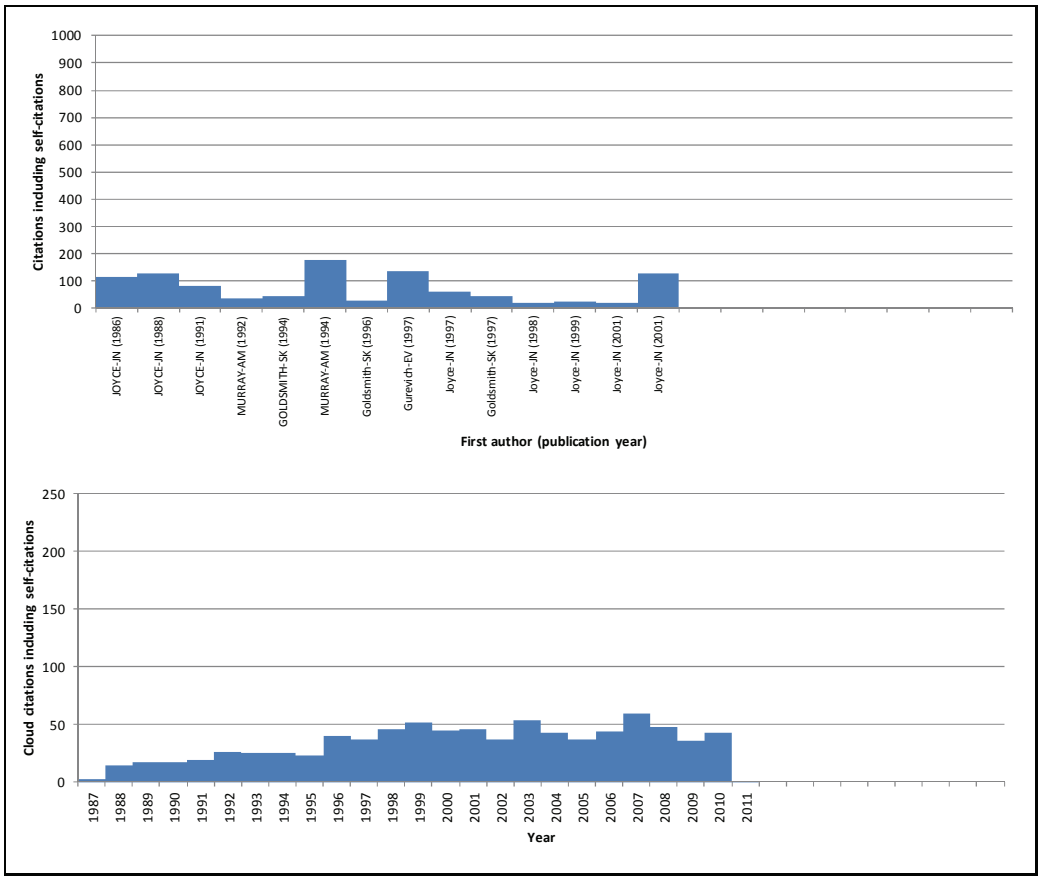
> That's part of it, I think probably a bigger impact simply was it got people to thinking about that anatomy was important in understanding changes in the brain for this disorder, because the dopamine hypothesis of schizophrenia had been around for a long time, there

> was nothing novel about that but the idea that it was not a global change, that it was a region specific change probably a neural specific change then led you to start thinking about neural circuits and the neural circuits have been what I pushed from then on. (JJ)

The rest of the research cloud included more studies that focussed on understanding the distribution of dopamine receptors (D1, D2, and D3) throughout different regions of the brain under different conditions (control, schizophrenia, Alzheimer's). Joyce was one of the first researchers to characterize a novel dopamine receptor (D3) in 1993. The other papers in this cloud also characterized some of the changes to dopamine receptors caused by schizophrenia drugs.

A bibliometric analysis of the papers produced from the research cloud is shown below.





Targeting Future Research

Effect on the researchers' careers

This work directly and positively affected Joyce's research career. The data presented in the *Synapse* paper enabled him to obtain a R29 FIRST award for research on neurotransmitter disorders in schizophrenia in 1988. The R29 helped him establish a laboratory for molecular neurochemistry of the human brain and allowed him to get involved in multiple projects in psychiatry, pathology and neurosurgery. The R29 in turn led to several NIH R01 research projects. A NIH R01 grant provides five years of funding to support a principal investigator's work on a well-defined project. The first, on developmental plasticity of dopamine systems, was awarded in 1993, and a second, on mesolimbic Da and the D3 receptor in schizophrenia, was awarded in 1996 after he had left the University of Pennsylvania (see below).

In 1995, Joyce left academic research to join and build the Sun Health Research Institute within the Sun Health Corporation healthcare network. The Institute focussed on translational research in neurodegenerative disorders. Despite his track record in obtaining research funding, Joyce was uncertain whether he would be able to lead translational research in a clinician led environment. He elected to join a research institute led by PhDs. and gravitated towards research that utilized cell culture, animal models and human post-mortem tissue. Human post-mortem tissue programmes were costly, requiring multiple sources of funding. At the Institute, Joyce was able to establish a Brain Donor Program to support clinical research on Parkinson's disease. He was able to secure two R-01s from

NIMH and a centre grant at the institute. He helped build the faculty from 3 to 36 researchers during his time there.

The work reported in the *Synapse* paper had more limited impact on the careers of other researchers. Among the co-authors, one author was a technician and one was a senior researcher at Harvard, who supplied the brain tissue. The senior author on the paper was Andy Winokur, whose interests did not lie directly in this area.

As Joyce's laboratory grew, he had many technicians, students, post-docs and junior collaborators who went on to successful careers. Angela Murray, a researcher who joined the University of Pennsylvania laboratory shortly after Joyce and conducted some of the initial work on the D3 receptor, went on to become a successful intramural researcher at the NIMH. S. Barak Caine was a technician who went on to graduate school and is now a well-known researcher in the field at Harvard. Another (medical/graduate student), Yvette Bordelon completed her MD/PhD at the University of Pennsylvania and is currently a physician-researcher at UCLA. Steve Arnold was a junior faculty member who collaborated with Joyce; he is now a tenured faculty member at the University of Pennsylvania.

Future work

Joyce maintained multiple lines of research throughout his career. While building the human brain tissue laboratory, he continued to pursue his research in animal models and cell culture. During the rest of his time at the University of Pennsylvania (1989–1995), Joyce's pharmacology work focused on the organization of dopamine and cholinergic receptors in basal ganglia of the adult rodent brain, publishing five papers describing the differential regulation on dopaminergic and muscarinic receptor subtypes. In his psychiatry work, Joyce used novel radio-ligands to conduct research on TRH, serotonin and noradrenergic systems in schizophrenia and alterations of the dopamine system (pre- and postsynaptic) in parkinsonian disorders (human) and animal models.

6.8 Interface B: Dissemination

Joyce disseminated the findings from the research cloud through publications, professional networks and conferences. The American College of Neuropsychopharmacology is an influential society with limited membership and an invitation-only annual conference. Joyce was invited to attend the conference for the first time in 1989 and became a member in 1992. He was also a member of the College of International Psychopharmacology, which was the European equivalent although not nearly as influential. The annual meetings of these organizations brought together all of the key researchers working in this small area.

Joyce also presented frequently to industry. Pharmaceutical companies had an interest in this research cloud because they were interested in both the techniques Joyce used and developed and the research findings. Drugs for schizophrenia and Huntington's and Parkinson's diseases often targeted dopamine receptors. Five different pharmaceutical companies funded Joyce on seven different occasions to test their drugs on his brain tissue samples using his techniques.

In terms of public engagement, advocacy groups such as the National Alliance for Research on Schizophrenia and Depression (NARSAD), now the Brain and Behavior Research

Foundation, were just developing during this time period. NARSAD was one of the first real advocacy groups for human subjects involved in clinical research. At the time, there was a lot of discussion about whether they should really be impacting research policy or not. NARSAD and other patient advocacy groups were starting to become influential and drive collaborations and policy starting around this time. However, public engagement was not a part of Joyce's research and did not influence its direction.

6.9 Stage 4: Secondary outputs

There were no specific secondary impacts from the identified paper. However, drugs targeting the D3 receptor are being developed. The *Archives of General Psychiatry* paper (1997) was of high interest to the pharmaceutical industry. Throughout his career, Joyce received funding from pharmaceutical companies, who were interested in both his techniques and the findings from his research.

6.10 Stage 5: Applications

None identified.

6.11 Stage 6: Public engagement

None identified.

6.12 Stage 7: Final outcomes

None identified.

6.13 Table of payback

Payback category	Impacts from case study
Knowledge Production	• Demonstrated that the ratio of D2/D1 receptors is increased in both schizophrenic and Huntington's disease patients. • Showed that the change in D2 and D1 receptor density is different in different regions of the brain. • Conducted studies on schizophrenic and Huntington's disease patients who had not been treated with neuroleptics.
Research Targeting and Capacity Building	• Critical to Joyce's appointment to a junior faculty position and his ability to secure extramural funding. • Beneficial to other researchers who learned to use the technique and conduct post-mortem human tissues studies. • Enabled Joyce to start a human tissue bank to support post-mortem

	studies
Informing Policy and Product Development	• Research techniques were used to test potential drug compounds.
Health and Health Sector Benefits	• None identified.
Broader Social and Economic Benefits	• None identified.

6.14 Timeline

1983–1986 Joyce completes his post-doctoral fellowship at the University of California, Irvine

1986 Joyce named a Research Assistant Professor of Pharmacology, University of Pennsylvania

1987 Joyce receives a two-year Scottish Rite Schizophrenia Research Program grant to complete the research for the identified paper

1988 Identified paper results published; Joyce receives a First Independent Research Support and Transition award from the NIMH

1989 Joyce becomes an Associate Professor of Psychiatry and Director of the Laboratory of Molecular Neurochemistry

1993 Joyce receives his first NIH (US) R01 grant on developmental plasticity of dopamine systems

1995 Joyce leaves academia to become the Associate Director of the Sun Health Research Institute and develop a brain donor programme

1996 Joyce receives a second NIH (US) R01 grant on Mesolimbuc Da and the D3 receptor in schizophrenia

2006–present Joyce becomes Director of the Department of Research at Maricopa Integrated Health System

6.15 References

Altar, C.A., Walter, R.J. Jr, Neve, K.A., & Marshall, J.F. (1984). Computer-assisted video analysis of [3H]spiroperidol binding autoradiographs. *Journal of Neuroscience Methods,* 10(3), 173–188.

Goldsmith, S.K. & Joyce, J.N. (1994). Dopamine D2 receptor expression in hippocampus and parahippocampal cortex of rat, cat, and human in relation to tyrosine hydroxylase-immunoreactive fibers. *Hippocampus*, 4(3), 354–373.

Goldsmith, S.K., & Joyce, J.N. (1996). Dopamine D2 receptors are organized in bands in normal human temporal cortex. *Neuroscience*, 74(2), 435–451.

Goldsmith, S.K., Shapiro, R.M., & Joyce, J.N. (1997) Disrupted pattern of D2 dopamine receptors in the temporal lobe in schizophrenia: a postmortem study. *Archives of General Psychiatry*, 54(7), 649–658.

Gurevich, E.V., Bordelon, Y., Shapiro, R.M., Arnold, S.E., Gur, R.E., & Joyce, J.N. (1997). Mesolimbic dopamine D3 receptors and use of antipsychotics in patients with schizophrenia: a postmortem study. *Archives of General Psychiatry*, 54(3), 225–232.

Gurevich, E.V., & Joyce, J.N. (1999). Distribution of dopamine D3 receptor expressing neurons in the human forebrain: comparison with D2 receptor expressing neurons. *Neuropsychopharmacology*, 20, 60–80.

Joyce, J.N., Sapp, D.W., & Marshall, J.F. (1986). Human striatal dopamine receptors are organized in compartments. *Proceedings of the National Academy of Sciences,* 83(20), 8002–8006.

Joyce, J.N., Lexow, N., Bird, E., & Winokur, A. (1988). Organization of dopamine D1 and D2 receptors in human striatum: receptor autoradiographic studies in Huntington's disease and schizophrenia. *Synapse*, 2, 546–557.

Joyce, J.N., Janowsky, A., & Neve, K.A. (1991). Characterization and distribution of [125I]epidepride binding to dopamine D2 receptors in basal ganglia and cortex of human brain. *Journal of Pharmacology and Experimental Therapeutics,* 257(3), 1253–1263.

Joyce, J.N., & Meador-Woodruff, J.H. (1997). Linking the family of D2 receptors to neuronal circuits in human brain: insights into schizophrenia. *Neuropsychopharmacology*, 16(6), 375–384.

Joyce, J.N., Myers, A.J., & Gurevich, E. (1998). Dopamine D2 receptor bands in normal human temporal cortex are absent in Alzheimer's disease. *Brain Research*, 784(1–2), 7–17.

Joyce, J.N., & Gurevich, E.V. (1999). D3 receptors and the actions of neuroleptics in the ventral striatopallidal system of schizophrenics. *Annals of the New York Academy of Sciences*, 877, 595–613.

Joyce, J.N. (2001). Dopamine D3 receptor as a therapeutic target for antipsychotic and antiparkinsonian drugs. *Pharmacology & Therapeutics*, 90(2–3), 231–259.

Joyce, J.N. (2001). D2 but not D3 receptors are elevated after 9 or 11 months chronic haloperidol treatment: influence of withdrawal period. *Synapse*, 40(2), 137–144.

Lee, T., & Seeman, O. (1980). Elevation of brain neuroleptic/dopamine receptors in schizophrenia.*American Journal of Psychiatry*, 137(2), 191–197.

Murray, A.M., Roo, H., & Joyce, J. (1992). Visualization of dopamine D3-like receptors in human brain with epidepride. *European Journal of Pharmacology: Molecular Pharmacology,* 227(4), 443–445.

Murray, A.M., Ryoo, H., Guyrevich, E., & Joyce, J. (1994). Localization of dopamine D3 receptors to mesolimbic and D2 receptors to mesostriatal regions of human forebrain. *Proceedings of the National Academy of Science*, 91(23), 11271–11275.

Schwartz, J.C., Levesque, D., Martres, M.P., & Sokoloff, P. (1993). Dopamine D3 receptor: basic and clinical aspects. *Clinical Neuropharmacology*, 16(4), 295–314.

Seeman, P., Ulpian, C., Bergeron, C., Riederer, P., Jellinger, K., Gabriel, E., Reynolds, G.P., & Tourtellotte, W.W. (1984). Bimodal distribution of dopamine receptor densities in brains of schizophrenics. *Science*, 225(4663), 728–731.

Sokoloff, P., Giros, B., Martres, M.P., et al. (1992). Localization and function of the D3 dopamine receptor. *Arzneimittelforschung*, 42(2A), 224–230.

CHAPTER 7 Auditory P300 in borderline personality disorder and schizophrenia

This case study is based on the research that produced the following initially selected paper:

Kutcher, S.P., Blackwood, D.H.R., St Clair, D.M., Gaskell, D.F., & Muir, W.J. (1987). Auditory P300 in borderline personality disorder and schizophrenia. *Archives of General Psychiatry*, 44(7), 645–650.

Information was gathered from interviews with Stan Kutcher, Douglas Blackwood and David St Clair, as well as from desk-based research.

7.1 Summary

This case study covers the work done at the MRC Brain Metabolism Unit in Edinburgh using electrophysiology to detect and quantify brain dysfunction in mental illness. In particular, the research team looked at abnormality in the P300 response and compared this across disorders and within families with the aim of establishing a biological marker for psychiatric disorders. In doing so they uncovered common abnormalities between a number of disorders and established clear differences between the P300 response in others, findings which (i) challenged the existing diagnostic classification of some disorders, and (ii) helped to validate the existence of some diagnoses that previously were not considered by some to be distinct conditions.

In further research they also demonstrated that similar P300 abnormalities may be present in unaffected family members, suggesting that it was possible to identify a group of unaffected relatives who may be carriers of a genetic vulnerability to schizophrenia. As techniques advanced, some members of the team moved on to look briefly at high-resolution imaging, then focused on DNA studies of schizophrenia in families, where they were instrumental in the discovery of DISC1, a gene shown to be related to schizophrenia and other disorders. Many studies by a range of research groups have since confirmed and extended these findings. Although the case study research did not impact directly upon policymaking or clinical practice, it may have contributed to the thinking at the time around the way mental disorders are conceptualised and categorised, which may in time lead to a diagnostic classification based on biological features. The major impact of the follow-on DNA studies has yet to materialise, but progress is being made and the researchers are confident that the first genetic markers for schizophrenia will be developed.

Kutcher's work went in a quite different direction, focusing on child and adolescent psychiatry, and although not directly related to the case study research, his ideas on clinical models for mental health care have had a substantial impact on understanding of adolescent mental disorders and mental health policy and service delivery in Canada.

7.2 Introduction

7.2.1 Scientific background

Electrophysiology is the study of the electrical properties of cells. Transmission of signals in the brain occurs when electrical impulses travel along nerve cells, triggering the release of neurotransmitters that convey the signal to adjacent cells. These electrical impulses begin as rapid changes in the polarisation (electrical charge) of the nerve cell membrane and are termed 'action potentials'. While these individual action potentials are too small to detect non-invasively, when they occur in synchrony across a population of cells the resulting overall 'wave' can be detected on the scalp. The recording of the wave via electrodes placed on the scalp is called electroencephalography (EEG). When these signals are recorded in response to a sensory stimulus (e.g., a sound) they are referred to as event-related potentials (ERPs). The ERP waveform recorded can thus be considered a measure of the cognitive processing of the stimulus.

Some particular components of the ERP waveform can be reliably observed following the presentation of a visual or auditory stimulus. These components are named according to the direction the waveform shifts in (positive or negative) and the delay at which they occur. As such, the P300 is a positive spike occurring around 300ms after a stimulus and is elicited in response to a stimulus that is either relevant to a task or is unexpected (Pfefferbaum et al., 1995).

Although EEG has been in use since the 1930s, it had been used relatively little in the study of mental disorders before the 1980s (DB). As the technology improved and researchers in psychiatry began the hunt for biomarkers as a basis for diagnosis (see below), the study of ERP components became more widely pursued as a means of investigating the biological basis of mental illness.

Some of the first work on ERPs in mental disorders was done by Charles Shagass and his colleagues, first at McGill University in Montreal, then at the University of Iowa, and Temple University, Philadelphia. Shagass started working in this area as early as the 1950s and documented systematic differences between psychiatric diagnoses (e.g., Shagass et al., 1979; Shagass et al., 1985). Other groups working on evoked potentials at the time of the case study research included Walton Roth, Adolf Pferfferbaum and Judith Ford at Stanford, Robert McCarley and colleagues at Harvard and David Friedman at New York State Psychiatric Institute.

7.2.2 Researchers' Backgrounds

Douglas Blackwood's background was initially in biochemistry before he studied medicine, and he maintained an interest in neurochemistry. After doing his clinical training in neurology in Edinburgh, he did a neuropharmacology PhD in experimental epilepsy, a topic very similar in terms of brain structures to schizophrenia. From this his

interest in psychiatry grew and he took up a position at the Maudsley Hospital (London, UK) in 1980, before returning to the MRC Brain Metabolism Unit and the Royal Edinburgh Hospital as a clinical psychiatrist in 1982. At the start of the case study research, Blackwood was a Member of Scientific Staff at the Unit, before becoming Senior Lecturer (1985), Reader (1994) and Professor (1998) in psychiatry at the University of Edinburgh. After using EEG during his PhD, Blackwood pioneered the use of the P300 component as a measure of cognitive processing in schizophrenia at the Unit.

David St Clair qualified in medicine then surgery and neurosurgery, before training in psychiatry in Edinburgh. He joined the MRC Brain Metabolism Unit to focus on schizophrenia, and in particular its genetic basis, and teamed up with Blackwood. Like the others in the team, St Clair continued his clinical work in addition to research.

Stanley Kutcher was a corresponding author on the target paper. From 1984–1985 he was a Visiting Clinical Scientist at the MRC Brain Metabolism Unit and a Senior Registrar in the Young Peoples' Unit at the Royal Edinburgh Hospital. Kutcher had recently completed his training in psychiatry at the University of Toronto, where there was encouragement from his institution for him to add extra research components to his work. He applied for and won a research fellowship (the McLaughlin Fellowship) from the university, and although NIMH was his initial first choice, his wife preferred Edinburgh as a location. As a result he spent a year working at the MRC Brain Metabolism Unit, where work on the thyroid and depression, an area of interest for him, was just beginning. Kutcher was the only member of the team who was a child psychiatrist by training; all of the others practised adult psychiatry.

Walter Muir completed his medical training in Edinburgh before joining the Wellcome Trust research registrar scheme, which allowed him to combine clinical training at the Royal Edinburgh Hospital with research. When he qualified in psychiatry in 1987, Muir was awarded a six-year (extramural) MRC Clinician Scientist Fellowship to continue his work at the MRC Brain Metabolism Unit.

David Gaskell joined the team for a short time during his clinical training and worked on a few studies before going on to be a psychiatrist (DB).

7.2.3 Institution background

The research took place at the Medical Research Council Brain Metabolism Unit in Edinburgh. The Unit housed around 55 researchers and was directed by George Fink, a specialist in neuroendocrinology, neuropharmacology and psychopharmacology, between 1980 and 1999. It had originally been set up by the MRC around 1970, under the direction of George Ashcroft and Donald Ecclestone, who were both academic psychiatrists at the Royal Edinburgh Hospital. The Unit closed upon Fink's departure in 1999.

Although the case study research concentrated on electrophysiological measures in mental disorders, much of the work in the Unit at the time was focussing on investigating peripheral neuroendocrine abnormalities as potential biomarkers for psychiatric disorders. This line of research has expanded knowledge about the relationship between brain function, endocrine activity and mental disorders, but has not yet fulfilled initial promise in the domain of disease specific neuroendocrine biomarkers (SK).

When Kutcher arrived at the Unit he found the atmosphere generally hostile towards the concept of borderline personality disorder (the part of the case study work he was involved in). He suggested that the diagnosis was looked at dubiously because of the strong hierarchical classification approach to mental disorders and the focus on dimensional constructs of personality that characterised UK psychiatry at the time, in contrast to diagnostic concepts that saw personality in categorical terms and allowed for diagnostic comorbidities to explain symptom constellations more commonly held in North America. In the USA and Canada, the concept of borderline personality disorder was still in flux, combining various considerations derived from psychoanalytic theory with research that linked this construct to mood disorders – primarily depression (SK).

7.3 Defining the research cloud

This case study focuses on the work done by the research team at the MRC Brain Metabolism Unit in Edinburgh in the late 1980s and early 1990s. Specifically, the cloud concerns the use of electrophysiology, and in particular the P300 response, to detect and quantify brain dysfunction in mental illness. It begins when the team first started this work and ends when the advancement of technology in the field led to a greater emphasis on methods such as high-resolution imaging and genetic linkage.

The publications from the research cloud are as follows:

1. St Clair, D.M., Blackwood, D.H.R., & Christie, J.E. (1985). P3 and other long latency auditory evoked potentials in presenile dementia Alzheimer type and alcoholic Korsakoff syndrome. *British Journal of Psychiatry*, 147(6), 702–706.
2. Blackwood, D.H.R., & Christie, J.E. (1986). The effects of physostigmine on memory and auditory P300 in Alzheimer-type dementia. *Biological Psychiatry*, 21(5-6), 557–560.
3. Blackwood, D.H.R., St Clair, D.M., & Kutcher, S.P. (1986). P300 in depression, schizophrenia and borderline personality disorder. *Biological Psychology*, 23(1), 104–104.
4. Blackwood, D.H.R., St Clair, D.M., & Kutcher, S.P. (1986). P300 event-related potential abnormalities in borderline personality disorder. *Biological Psychiatry*, 21(5), 560–564.
5. Blackwood, D.H.R., Whalley, L., Christie, J., Blackburn, I., St Clair, D.M., & McInnes, A. (1987). Changes in auditory P3 event-related potential in schizophrenia and depression. *British Journal of Psychiatry*, 150(2), 154–160.
6. Blackwood, D.H.R., St Clair, D.M., Blackburn, I.M., & Tyrer, G.M.B. (1987). Cognitive brain potentials and psychological deficits in Alzheimer's dementia and Korsakoff's amnesic syndrome. *Psychological Medicine*, 17(02), 349–358.
7. Kutcher, S.P., Blackwood, D.H.R., St Clair, D.M., Gaskell, D.F., & Muir, W.J. (1987). Auditory P300 in borderline personality disorder and schizophrenia. *Archives of General Psychiatry*, 44(7), 645–650.

8. St Clair, D.M., Blackwood, D.H.R., Oliver, C.J., & Dickens, P. (1987). P3 Abnormality in fragile X syndrome. *Biological Psychiatry*, 22(3), 303–312.

9. Blackwood, D.H.R., & Christie, J.E. (1988). Physostigmine, auditory P300, and Alzheimer's disease – response. *Biological Psychiatry*, 23(3), 322–324.

10. Blackwood, D.H.R., St Clair, D.M., & Muir, W.J. (1988). Auditory P300 and smooth pursuit eye tracking abnormalities in schizophrenic subjects and their relatives. *Schizophrenia Research*, 1(2-3), 177–178.

11. Blackwood, D.H.R., St Clair, D.M., Muir, W.J., Oliver, C.J., & Dickens, P. (1988). The development of Alzheimer's disease in Down's syndrome assessed by auditory event-related potentials. *Journal of Intellectual Disability Research*, 32(6), 439–453.

12. Muir, W.J., Squire, I., Blackwood, D.H.R., Speight, M.D., St Clair, D.M., Oliver, C., et al. (1988). Auditory P300 response in the assessment of Alzheimer's disease in Down's syndrome: a 2-year follow-up study. *Journal of Intellectual Disability Research*, 32(6), 455–463.

13. Kutcher, S.P., Blackwood, D.H.R., Gaskell, D.F., Muir, W.J., & St Clair, D.M. (1989). Auditory P300 does not differentiate borderline personality disorder from schizotypal personality disorder. *Biological Psychiatry*, 26(8), 766–774.

14. St Clair, D.M., Blackwood, D.H.R., & Muir, W.J. (1989). P300 abnormality in schizophrenic subtypes. *Journal of Psychiatric Research*, 23(1), 49–55.

15. Blackwood, D.H.R., & Muir, W.J. (1990). Cognitive brain potentials and their application. *British Journal of Psychiatry*, 157, 96–101.

16. Blackwood, D.H.R., St Clair, D.M., Muir, W.J., & Duffy, J.C. (1991). Auditory P300 and Eye Tracking Dysfunction in Schizophrenic Pedigrees. *Archives of General Psychiatry*, 48(10), 899–909.

17. Muir, W.J., St Clair, D.M., & Blackwood, D.H.R. (1991). Long-latency auditory event-related potentials in schizophrenia and in bipolar and unipolar affective disorder. *Psychological Medicine*, 21(04), 867–879.

18. Roxborough, H., Muir, W.J., Blackwood, D.H.R., Walker, M.T., & Blackburn, I.M. (1993). Neuropsychological and P300 abnormalities in schizophrenics and their relatives. *Psychological Medicine*, 23(2), 305–314.

19. Blackwood, D.H.R., Muir, W.J., Roxborough, H.M., Walker, M.R., Townshend, R., Glabus, M.F., et al. (1994). Schizoid personality in childhood – auditory P300 and eye tracking responses at follow-up in adult life. *Journal of Autism and Developmental Disorders*, 24(4), 487–500.

20. Glabus, M.F., Blackwood, D.H.R., Ebmeier, K.P., Souza, V., Walker, M.T., Sharp, C.W., et al. (1994). Methodological considerations in measurement of the P300 component of the auditory oddball ERP in schizophrenia. *Electroencephalography and Clinical Neurophysiology*, 90(2), 123–134.

21. De Souza, V.B.N., Muir, W.J., Walker, M.T., Glabus, M.F., Roxborough, H.M., Sharp, C.W., et al. (1995). Auditory P300 event-related potentials and neuropsychological performance in schizophrenia and bipolar affective disorder. *Biological Psychiatry*, 37(5), 300–310.

22. Shajahan, P.M., Ocarroll, R.E., Glabus, M.F., Ebmeier, K.P., & Blackwood, D.H.R. (1997). Correlation of auditory 'oddball' P300 with verbal memory deficits in schizophrenia. *Psychological Medicine*, 27(3), 579–586.

7.4 Stage 0: Opportunity identification/research needs assessment

Inspiration

At the time of the case study research, mental disorders were categorised according to diagnostic classification systems such as the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) (American Psychiatric Association Committee on Nomenclature and Statistics, 1980), but, as is still the case today, diagnosis was syndromal, based on clinical presentation of signs and symptoms. The lack of knowledge of underlying causes led the team at the Brain Metabolism Unit and many other groups at the time to begin looking for biological markers that might allow for an earlier diagnosis or a classification of disorders supported by an underlying biological substrate.

The status of some diagnoses was hotly disputed in the field. This was particularly the case for borderline personality disorder, one of the conditions studied by the research team and a particular interest of Kutcher's. In addition to differences in diagnostic considerations between the UK and North America (SK), the relationship of borderline personality disorder to other psychiatric disorders such as schizophrenia and depression was unclear (Gunderson & Elliott, 1985). Kutcher commented that in his clinical work he had observed that many features of borderline personality disorder were similar in nature, albeit less severe, to those seen in schizophrenia, while the two disorders also have a similar age of onset (DB). Clinical observations such as these led to the decision to compare P300 response across different disorders. When Kutcher arrived in Edinburgh he happened to be given an office near Blackwood's, which led to discussions about biomarkers for personality disorders and the similarities between borderline personality disorder and schizophrenia. Kutcher added that an additional incentive for studying the relationship between the two was the attitude of one of the senior professors in the department:

> He had absolutely no time for this concept of borderline, which made it even more interesting to study. (SK)

The case study research took place at a time of substantial change in the psychiatry field: empirical research was being seen as increasingly important and there was a shift, particularly in child and adolescent psychiatry, away from traditional psychodynamic theories towards a more biological explanation for psychiatric disorders (SK). As a consequence of this change, a school of thought emerged proposing that it might be possible to identify physiological markers indicating the early onset of or increased risk for developing a particular disorder.

There were growing research efforts to find markers by which psychiatric diagnoses could be made at an earlier stage, as diagnostic systems based on signs and symptoms only allow

an assessment to be made when the symptoms are relatively advanced. This hunt for schizophrenia markers saw findings from a range of fields being drawn together, including endocrinology, physiology and neuropsychology, while the advent of improved imaging techniques brought a better understanding of the structure of the living brain.

Feasibility

Douglas Blackwood had used EEG recording to study epilepsy during his PhD, and this existing expertise made using the same technique in schizophrenia and other disorders a natural step. From the early stages of the work it was clear that psychotic patients were demonstrating P300 abnormalities in comparison to controls (DB).

This was also around the time that David St Clair was beginning his involvement in genetics research, his main focus throughout his career, the aim of which was to identify heritability markers for schizophrenia in families.

Stan Kutcher's interest was primarily in child and adolescent psychiatry, a field that was shifting towards biological theories and the search for physiological markers that might facilitate earlier diagnosis of a range of conditions. He also brought a particular interest in personality disorders, a category that was both controversial and at that time heavily influenced by psychodynamic theory.

Potential value

As discussed above, finding biomarkers for particular mental disorders would have immense clinical value in creating a better understanding of the underlying disease processes of and relationships between disorders, enabling more accurate diagnosis, and facilitating the development of better-targeted treatments.

7.5 Stage 1: Inputs to research

Money, researcher time, lab/office space and consumables

The P300 work was fairly inexpensive to conduct, but was funded from a number of different sources. The recordings themselves required few resources, and so the primary cost of the work was the recruitment of participants. Although the work took place within an MRC Unit, only Blackwood's salary was covered intramurally; the team had to apply for all other funding.

Muir was supported by a six-year Clinician Scientist Fellowships from the MRC, while St Clair was a Wellcome Trust Fellow. Additional funding came from the MRC, the Scottish Home and Health Department, the Mental Health Foundation, SANE, the European Science Foundation, the European Commission and a US fund called the Scottish Rite Schizophrenia Research Program. The team felt they ought to apply for the latter, given that it seemed relevant to Scotland, but subsequently found out that this was a Masonic fund that was entirely unrelated to Scotland. The majority of this funding was project grants for specific pieces of work and was obtained through open calls with a peer review process. Around the time that genetics research was beginning and the accumulation of data sets was being encouraged, the team won an MRC grant through a specific call on the collection of family data.

Although the majority of the team's funding was for specific projects, Blackwood commented on the importance of having team members funded on long-term fellowships as well, as these grants brought with them extra funding for consumables. The funding available to the team was fairly flexible and the various grants could overlap, allowing the research team some flexibility in projects undertaken. It also enabled the team to attract PhD students and trainees to their projects, many of whom came from clinical psychology backgrounds.

It was not until the UK-based research team's DNA studies began that they needed to start applying for larger amounts of funding in earnest, something that initially proved fairly unsuccessful (DSC).

The MRC Brain Metabolism Unit had purchased a state-of-the-art Nicolet EEG recording machine and the team took advantage of this to begin their work on the P300 response. The equipment was not bought with any particular project in mind, something that St Clair commented would no longer happen today. Blackwood suggested, however, that the motivation for purchasing the equipment was a general interest at the Unit in researching phenotypes of different disorders, and that other groups in the field had begun using EEG recording to do this. At the same time as the work in the MRC unit, St Clair was also looking at P300 response in HIV-positive patients at another hospital. This meant that every week he had to dismantle the equipment and transport it back and forth between the two locations. The Unit also had a soundproofed room in which auditory ERP studies could be conducted.

Knowledge

As mentioned in Stage 0 above, the team's clinical work had made them aware of the similarities and differences between different diagnoses. The next step was to characterise the different phenotypes and search for biomarkers associated with them.

Expertise and techniques

Blackwood had looked at ERPs in epilepsy for his PhD so had some experience of using the technique. For the others on the team, as the method had been used little in psychiatry and the equipment was new to the lab, enthusiasm for the topic and motivation were initially likely to have been a more important factor than specific expertise – which developed over time with the research (DSC).

The use of EEG measures in psychiatry was still fairly rare when the research began. Although the technique was not itself new and work had been done in, for example, demonstrating the heritability of EEG characteristics, its application in detecting and quantifying brain abnormalities in mental disorders was a recent development. In addition, St Clair suggested that many researchers in the EEG field at that time had little clinical focus to their work, concentrating more on the technicalities of the method than its potential applications. There may also have been some influence from trends in psychiatry: EEG studies were not a 'fashionable' area for research at that time. Many believed that important findings would only come from more powerful studies and interest in fields such as molecular biology, which was growing rapidly (DSC).

Samples/patients

The team collected data on patients and their families over a number of years across Scotland. As blood samples were maintained in long-term storage in the lab, when laboratory techniques advanced the team were able to use the existing samples to carry out DNA analysis. This allowed the subsequent research to proceed more quickly and with fewer resource demands. Research participants were primarily patients who had been admitted to the Royal Edinburgh Hospital (where the team all worked as clinicians), and their families.

7.6 Stage 2: Processes

The EEG method has been in use since the 1930s, but at the time of the case study research relatively little work had been carried out in psychiatry, particularly in relation to the P300 response. The research team travelled around Scotland collecting blood samples and data on families of people with schizophrenia (and other disorders). This included EEG recordings, eye tracking data and other physiological and psychological measures. Building up this large bank of data meant that as new techniques became available, the research team already had much of the material needed to begin using them.

The work on borderline personality disorder, a particularly controversial diagnosis at the time, saw the research team use a new method of sample selection. At the time of the research, three different diagnostic classifications were being used for borderline personality disorder, each with slightly different criteria: the DSM-III criteria (American Psychiatric Association Committee on Nomenclature and Statistics, 1980), the Diagnostic Interview for Borderline patients (Gunderson et al., 1981) and the Borderline Ego Functions Inventory (Perry & Klerman, 1980). Kutcher considered that the team was more likely to find biomarkers in a tightly homogeneous population and so they applied all three sets of criteria to the patient population, selecting only those who met the diagnostic threshold on all three measures as the sample for the study.

All research team members also continued with clinical work while carrying out the research. St Clair described maintaining the balance between the two as quite challenging: clinicians would find it strange if a colleague devoted a lot of time to research, but full-time researchers could feel that someone spending part of their time on clinical work was not fully onboard with the research.

However, there were also positive aspects of combining the two positions. Having access to the patient population was essential for the research, and Blackwood commented that approaching the work from two quite different perspectives enabled the team to link the abnormalities found to clinical symptoms. Kutcher explained that the knowledge he has gained from seeing patients has been an important guiding factor throughout his research career:

> I couldn't have done any of this research if I didn't see patients, because I had this corpus of learning that had been given me and then I saw the people who I was working with and these things did not compute…. What I was being taught by my professors and what was in the books and what I saw in front of me didn't make any sense – they weren't the same thing. (SK)

He gave as an example here his experience in describing the course of adolescent bipolar disorder, identifying rapid cycling of mood within a manic episode, which had not previously been acknowledged.

Blackwood agreed, suggesting that the nature of their particular work made the contact with patients even more influential:

> It is very much like that. Even more so going to see families, because going back to people's homes, driving around in the middle of the night, it gives a completely different perspective – seeing families at home and degrees of illness. (DB)

7.7 Stage 3: Primary Outputs

Knowledge

The time of the case study research was an extremely productive period for the research team. They looked at P300 amplitude and latency across a number of disorders and alongside several other physiological and cognitive measures, including eye tracking and tests of memory and verbal fluency.

The team used the differences found in P300 amplitude and latency to demonstrate a common physiological process underlying a number of different disorders. For example, the same P300 latency abnormality was found in schizophrenia and borderline personality disorder (Kutcher et al., 1987), in schizophrenia and bipolar disorder (Muir et al., 1991), and in borderline and schizotypal personality disorders (Kutcher et al., 1989).

In addition to highlighting similarities, the research team was also able to demonstrate differences in auditory processing in various disorders. For instance, patients with Alzheimer-type dementia showed abnormal P300 latency and amplitude in comparison to controls and those with Korsakoff syndrome (St Clair et al., 1985), borderline personality disorder was differentiated from non-borderline by both amplitude and latency of the P300 wave (Blackwood et al., 1986b), and unipolar and bipolar affective disorders were found to be characterised by differences in P300 latency (Muir et al., 1991).

In total, 22 papers were published on the P300 response before the team started including newer methods such as high-resolution imaging and linkage analysis.

The papers produced from the case study research also discuss the implications of each of these findings for the conceptualisation of mental disorders. These implications fall broadly into two groups. First, the P300 research demonstrated that two diagnoses considered to be quite different from one another may still be characterised by abnormalities in the same physiological processes, something that might suggest a common underlying biological substrate. This appears to be the case in, for example, schizophrenia and borderline personality disorder, a finding that challenges the logic upon which syndromal diagnostic classification systems are structured. Secondly, in some instances the team's findings can be considered a validation of the existence of a particular diagnostic category. For example, in differentiating at the physiological level between borderline personality disorder and non-borderline personality disorders, the findings supported the existence of borderline as a credible, biologically-based disorder, but also provided evidence for a clear distinction between it and other personality disorders with which it might have been considered to overlap.

As the evidence for the complex heritability of schizophrenia mounted, the research team also published three papers that looked not only at individuals with a schizophrenia diagnosis, but also used the same ERP measures in their relatives (Blackwood et al., 1988; Blackwood et al., 1991; Roxborough et al., 1993). In these they showed that the proportion of first-degree relatives with P300 abnormalities was much higher than the incidence in the general population (Blackwood et al., 1991) and that relatives with a prolonged P300 latency performed significantly worse on neuropsychological tests than relatives with normal P300 latency, thus showing a similar impairment profile on both physiological and psychological measures to people with schizophrenia (Roxborough et al., 1993). In showing that it was possible to identify a group of relatives who may be carriers of a genetic vulnerability to schizophrenia, the team hoped that the measures used might assist in genetic linkage studies looking at its transmission.

The target paper of this case study has been cited 85 times as of October 2011. The topics of the citing papers reflect a number of different aspects addressed in the paper: while many focus on measuring ERPs in schizophrenia, others look at the characterisation of borderline personality disorder, the search for biomarkers for personality disorders, the potential of EEG recording in differentiating between a range of disorders, and the use of ERP measures in investigating cognition more generally. As mentioned previously, interest in biomarkers was growing in psychiatry but the study of ERPs in the field was still a fairly recent development, a factor that may have contributed to high citation of the team's early work.[10]

A bibliometric analysis of the papers produced from the research cloud is shown below.

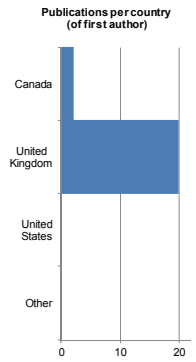
[10] The case study's reviewers suggested that the work may have been well cited because it used a rigorous methodology to produce clean and novel findings. It was also among the first pieces of evidence of markedly altered brain function in borderline personality disorder.

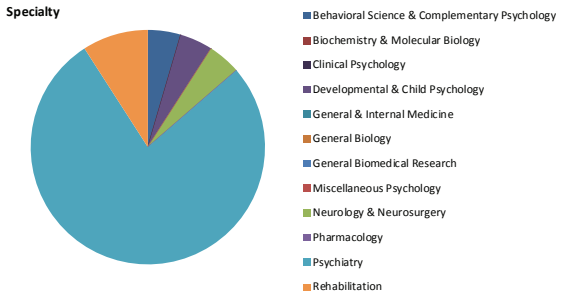
Research cloud:

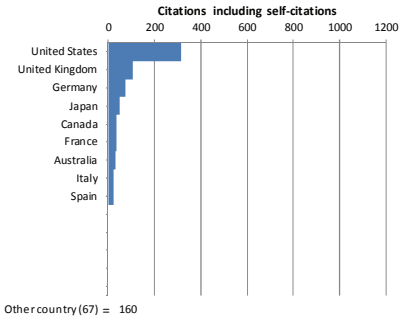
	Citations in:		**% of total citations**	**Research level of cloud papers**
WoS Indexed papers: 22	**RCT:**	20	2%	Clinical **1:** 45%
Total citations of papers: 1,139	**Meta-analyses:**	25	2%	**2:** 41%
of which, self-citations: 2.5%	**Indexed practice guidelines:**	0	0%	**3:** 5%
Mean citations per paper: 52	**Review articles:**	195	17%	Basic **4:** 0%
Distinct cloud citations: 732				
Second-generation cloud citations: 26,017				
Third-generation cloud citations: 334,268				

Most highly cited article: Blackwood, D., Whalley, L., Christie, J., Blackburn, I., St Clair, D., & McInnes, A. (1987). Changes in auditory P3 event-related potential in schizophrenia and depression. The British Journal of Psychiatry, 150(2), 154-160.

Times cited: 252

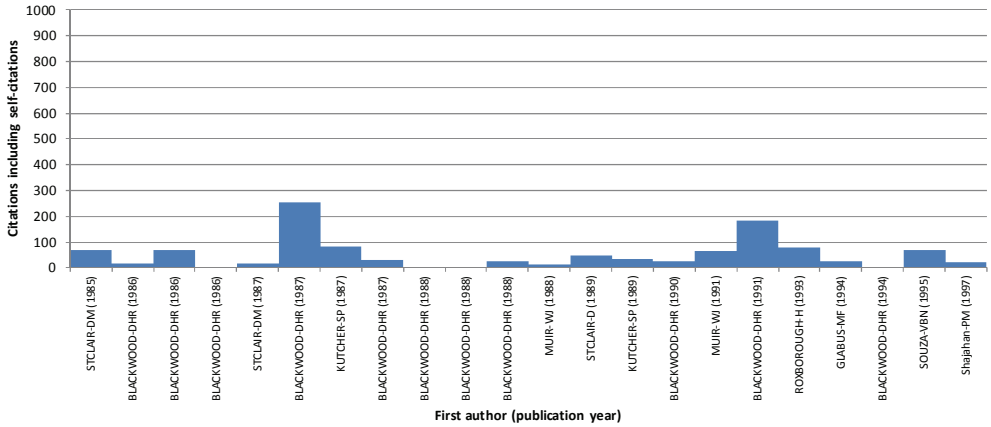


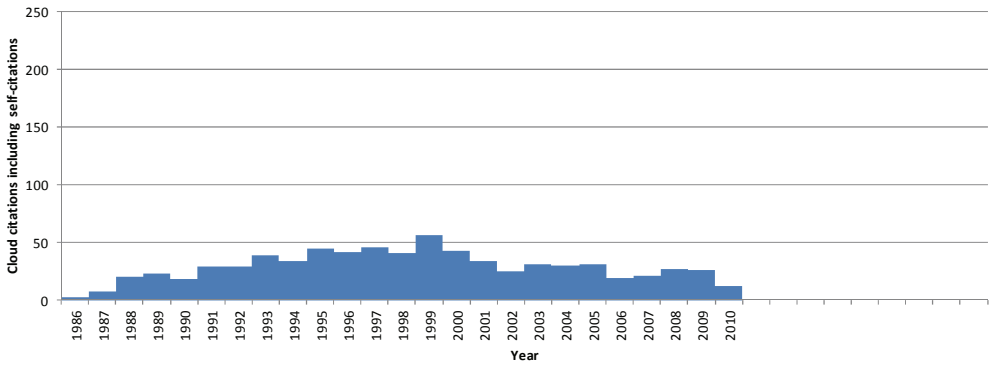




Other country (67) = 160

Note: Countries with more than 20 citations are displayed





Targeting future research

Effect on the researchers' careers

The team in Edinburgh continued the stream of work, taking advantage of new methods as they became available and beginning to look at DNA alongside their existing physiological and psychological measures in families. Blackwood and Muir remained in Edinburgh, continuing to collect data on families across Scotland. Many of the original families involved in the P300 work are still in contact with researchers in Edinburgh and continue to participate in the genetics research today.

St Clair had also initially hoped to continue this work in Edinburgh, but ended up taking up a position at the University of Aberdeen in 1995, where he has continued looking at both environmental and genetic factors in schizophrenia, particularly in relation to the DISC1 gene.

David Gaskell left research to go into full-time clinical practice.

Kutcher was involved in little direct follow-up work, primarily because he returned to Toronto, where there were no potential collaborators. Had he stayed in the UK, he would probably have continued with the work, particularly with the advent of fMRI and other new tools (SK). Kutcher went on to focus on child and adolescent psychiatry, having noted from his clinical work that many major mental disorders appeared to first manifest during adolescence, an observation not widely accepted in the field at the time. Kutcher went on to conduct research in many aspects of adolescent mental disorders including but not limited to: depression; psychopharmacology and therapeutics. He also developed an integrated model for adolescent mental health care linking acute hospital services to community programmes and school-based interventions (the first such programme in Canada). He emphasised the importance to him of always using what he has observed in patients to 'push the paradigm' and change thinking in the field. His interest in health policy has led to him leading the development of a national child and youth mental health policy framework and participating in the development of the Institute of Neuroscience, Mental Health and Addictions of CIHR, as well as work with the World Health Organization on various aspects of mental health policy. This interest developed when he became head of the psychiatry department at Dalhousie University in Halifax:

> It became very obvious that in order to change systems you had to change policy… so that's what I had to learn: what is policy, how do you deal with policy, how do you create policy, how do you change policy level frameworks that then will lead to effective plans and interventions. So I learned it. (SK)

Indeed, Kutcher unsuccessfully ran for Canadian parliament in the 2011 federal election. His decision to run for federal office was based in large part upon his conviction that it was necessary to influence the political process in order to advance health policies to support health, improve health care and advance scientific research.

Future work – in psychiatry

The case study research led in two quite distinct directions due to the differing focusses of the researchers involved.

The team in Edinburgh began combining imaging data with their P300 work to examine structural changes and attempt to localise abnormalities in the brain, and although this

work initially seemed to be picking up promising evidence of frontal lobe deficits, it was fairly quickly superseded by newer methods.

Eventually, by around 2000, the group's main EEG work came to an end, primarily because they would have had to buy new equipment and probably employ a full time-physicist to do the analysis, but also because they simply found the genetic work more interesting and more promising (DB). The P300 work had gone about as far as it could: it could only indicate that there was an abnormality, and to some extent the severity of it, but could provide no information on the cause or underlying mechanism causing the abnormality.

> It was quite striking at the time that the P300 abnormalities were clearly showing up in psychotic patients in a different way from controls. The problem then was to decide what it meant, and it turns out you can't localise P300 very much in the brain – you are never quite sure where it is coming from. So in a way it is overtaken by imaging and other methods. (DB)

To take the ERP work any further would have required a huge investment into investigating the physiology of the P300 component, which is most likely caused not by a single waveform, but by multiple waveforms generated in different areas of the brain. Other imaging techniques (e.g., MRI) with a greater spatial resolution soon overtook ERP recording and its use in clinical research diminished.

As methods advanced and the possibilities afforded by genetics research became apparent, the team in Edinburgh began focussing on this area alongside their work using ERPs, eye tracking and other physiological measures. They were helped in this by John Evans, who was Director of another MRC research centre in Edinburgh at the time, the Human Genetics Unit. He was very encouraging at a time when many people were quite sceptical about the potential benefit of genetics research in schizophrenia and provided lab space for the team to start their work. This work was underpinned by essentially the same principles as their earlier research: the aim was still to identify biomarkers for psychiatric disorders, but through looking at DNA instead of (or alongside) other physiological measures (DSC).

As the group had collected data on families for a number of years, they already had much of the material they needed to start looking at heritability of genetic characteristics in families with multiple diagnoses of schizophrenia. This body of data was important due to the challenges in finding large enough families in schizophrenia, where there tend to be lower reproductive rates than in, for example, bipolar disorder. They initially carried out linkage studies, then as the field advanced and the number of markers increased, moved on to genome-wide association studies and sequencing. They also continued to collect more data across Scotland, both for their own research and to contribute to wider international efforts (e.g., Moises et al., 1995; Schizophrenia Collaborative Linkage Group (Chromosome 22), 1996; International Schizophrenia Consortium, 2009).

The Edinburgh team went on to make a number of important discoveries in the burgeoning field of psychiatric genetics. In particular, they discovered that one of the large families followed up over many years by the Human Genetics Unit had a high incidence of mental illness and a particular chromosomal abnormality (St Clair et al., 1990). This finding led directly to the discovery of the DISC1 (Disrupted-In-Schizophrenia 1) gene around 10 years later, one of the best-validated genes yet implicated in schizophrenia

(Millar et al., 2000). It was subsequently found that the clinical phenotype of the gene in the original family also included bipolar disorder, schizoaffective disorder and unipolar depression, and that family members with the reported chromosomal abnormality, regardless of diagnosis, tended to show reduced P300 amplitude (Blackwood & Muir, 2004). These findings were in keeping with the team's earlier demonstration of P300 abnormality in unaffected relatives, adding to the evidence that this physiological response might act as a marker for an underlying genetic vulnerability to schizophrenia and other disorders.

As was the case with the group's earlier work, their genetic research allowed an analysis across diagnostic categories and examination of the overlap between different conditions, both within psychiatry and more widely across a wide range of medical conditions. For example, literature has recently drawn commonalities between schizophrenia and inflammation, auto-immunity, arthritis and some infections (DSC; e.g., Lencz et al., 2007; Saetre et al., 2007). Similar connections had been suggested as far back as the 1920s, but have re-emerged more recently as new knowledge and methods have come to the fore.

Genetics studies have the advantage of making possible the study large cohorts in a short time, with a simple diagnostic interview and blood test. In contrast, EEG and imaging require a substantial time commitment to get detailed phenotypes of a small sample of individuals. The cost of imaging studies is also prohibitive to the study of large samples.

However, St Clair commented that physiological measures are still useful today and he continues to use measures of eye movement in his research. These can easily be conducted on large samples (compared to, say, imaging) and are simpler and quicker to set up than EEG equipment. St Clair added that there is the potential for a direct clinical application of eye tracking, and even though one measurement on its own may not be specific or sensitive enough for clinical use, the aggregation of many can provide a powerful tool, particularly as new technology allows vast quantities of data to be integrated and modelled.

The search for biomarkers for mental disorders and the efforts to devise a better diagnostic classification system remain interdependent challenges: while diagnosis could be more robust if based on underlying biological features, identifying relevant genes or other physiological abnormalities relies on patient populations being accurately and reliably diagnosed.

Kutcher's work led in a quite different direction. Following his year in Edinburgh he returned to Toronto to work in child and adolescent psychiatry. His work in this area was very broad, covering a range of disorders and methods. He explained this in terms of the lack of evidence existing in the field at the time:

> In order for me to be an effective clinician I actually had to help create the data that we needed to be able to treat people. One of the reasons that you see my work is broad is because the field was broad. It was a data-free zone. It had no end of opinion, but it was a data-free zone. (SK)

Kutcher suggested that the impact of the case study research on the field extended far beyond the knowledge about particular disorders it generated.

> I don't see its impact, potential impact, or importance being the application of P300 to cognition. I see its potential impact being the change in paradigms of the field. (SK)

Kutcher considered an important part of challenging the conceptual approach to the field to be the demonstration that it is possible to relate cognitive conditions to underlying neurological substrates – which might be seen as a shift in perspective to thinking from inside the brain out, rather than outside the brain in. Challenging long-standing thinking is something that Kutcher has tried to do throughout his career since, using his experiences with patients to change how people approach the field of child and adolescent psychiatry (SK).

The work on personality disorders specifically was also important in challenging a prevailing psychoanalytically driven belief that personality disturbances had no biological basis, despite evidence for the heritability of personality traits. The finding that people diagnosed with borderline personality disorder showed cognitive processing abnormalities common to schizophrenia and other disorders was important both in validating borderline personality disorder as a diagnostic category and in demonstrating that it should be considered a serious mental illness alongside the likes of schizophrenia (SK).

7.8 Interface B: Dissemination

The team's work was mainly disseminated through publications, although they also presented findings at numerous international conferences. As the UK-based team began to focus more on genetics they fed their data from families around Scotland into high-profile European collaborations that pooled data across several countries.

7.9 Stage 4: Secondary outputs

The case study research has not directly informed policy, but may have contributed to a change in the conceptualisation of mental disorders, and may in future influence their diagnosis and the systems by which they are classified.

As the diagnosis of psychiatric conditions is based solely on observable signs and self-reported symptoms, the discovery that similar physiological features underlie multiple distinct diagnoses naturally led to a questioning of the diagnostic categories in use at the time. Although it was hoped that physiological markers would be uncovered that would allow diagnosis on the basis of biological traits, this would appear to still be some way off (for example, DSM-V is set to maintain a primarily phenomenological approach to diagnosis).

Indeed, following the case study research, the majority of which was conducted during the lifetime of DSM-III, Kutcher believes diagnostic categories became more vague:

> DSM-IV, in my opinion, is more of a political document than a medical classification system… it took well-established categories and pushed the boundaries wider…. It created a spurious comorbidity which has, I think, taken our field down the wrong path for decades…. There are true comorbidities in diseases, where you have two diseases spontaneously, but so much of DSM comorbidity is artifactual. You pull the categories back, you lose the comorbidity. (SK)

Kutcher also suggested that the demonstration that abnormal cognitive processing was a component of several different disorders suggested to the research team that focussing

therapies on cognition and how cognitive capacities can be used to control a variety of psychiatric symptoms may be a fruitful approach. The dominant therapeutic approach at the time was to focus psychotherapies such as Cognitive Behavioral Therapy on affective components (such as depression), but some years later, effective cognition-focussed therapies for a wide range of different psychiatric disorders did emerge (SK).

7.10 Stage 5: Applications

Although the research team did demonstrate the heritability of P300 response abnormalities in relatives of people with schizophrenia, the method was never precise or reliable enough at the individual level to be used as a clinical tool in assessing risk (DB).

Despite this, there have been a number of attempts to commercialise P300 measurement as a general measure of 'brain health', and even an indicator of particular 'neurological imbalances' that might then be treated (e.g., Braverman). It is unclear what impacts such endeavours might have had on individuals being assessed or in a wider economic context.

However, at the time of the research the team did consider the possibility that the P300 measure might have a potential application in screening response to treatment for schizophrenia, but this seemed very far off at the time (DB). They did, in fact, do some work towards this, investigating the effect various drugs had on the P300 response, but this work was soon superseded by new techniques. The field's focus turned to genetic markers, rather than physiological, although some more recent high-profile research has also looked at the potential use of proteins in plasma (Domenici et al., 2010) and cerebrospinal fluid (Huang et al., 2006).

Blackwood was optimistic for the future application of this line of research. Biological markers are still very much a research target in schizophrenia and he suggested that within the next few years we are likely to see the first genetic markers coming into clinical use. St Clair also commented that with recent advances in technology the investment in DNA research is now producing promising results.

St Clair commented that one of the important lessons to come from the ongoing search for biomarkers in psychiatry is the realisation that the timelines for this kind of research are far longer than people expect:

> You're really talking about one generation investing for the benefit of the next generation. The idea that you can get results, unless you're very, very lucky, that have an immediate impact is just…. For example, it's fifty years since Watson and Crick discovered the structure of DNA, and the payoff is still to come. It's speeding up now, but it is still a long process. (DSC)

7.11 Stage 6: Public engagement

None identified.

7.12 Stage 7: Final outcomes

None identified.

7.13 Table of payback

Payback category	Impacts from case study
Knowledge Production	• Demonstrating that two diagnoses considered to be quite different from one another may still be characterised by abnormalities in the same physiological processes. • Showing different physiological process characteristics in different disorders supported distinctions between diagnostic categories. • By identifying similar P300 abnormalities in unaffected family members, showing that it was possible to identify a group of relatives who may be carriers of a genetic vulnerability to schizophrenia.
Research Targeting and Capacity Building	• Move into DNA studies by the UK-based team, leading to discovery of the DISC1 gene's significance in schizophrenia. • The family data collected throughout the case study work was essential for the genetics studies and was fed into major international collaborative studies. • All of the research team continued very successful academic careers.
Informing Policy and Product Development	• None directly, but contributed to the debate on the way mental disorders are conceptualised and may still influence diagnostic classification in future. • Kutcher influential in child and adolescent mental health policy in Canada, but did not attribute this directly to the case study research.
Health and Health Sector Benefits	• As above, Kutcher has influenced child and adolescent mental health care in Canada, but not through the case study research specifically.
Broader Social and Economic Benefits	• None identified.

7.14 Timeline

1982	Blackwood joins the MRC Brain Metabolism Unit in Edinburgh
1984/5	Kutcher spends one year Fellowship at the Unit
1987	Target paper published in *Archives of General Psychiatry* (Kutcher et al.)
1987	Muir qualifies in psychiatry and is awarded six-year Fellowship at the Unit
1987	Most highly cited paper in the research cloud published, comparing P300 in schizophrenia and depression (Blackwood et al.)
1988	Team first publish on P300 in relatives of people with schizophrenia
1989	Edinburgh team begin working with MRC Human Genetics Unit

1990	Edinburgh team publish key paper on chromosomal abnormality co-segregating with schizophrenia in a large family (St Clair et al.)
1995	David St Clair moves to University of Aberdeen
1996	Kutcher moves to Dalhousie University as Chair of the Department of Psychiatry
2000	Scottish team publish discovery of DISC1 gene (Millar et al.)

7.15 References

American Psychiatric Association Committee on Nomenclature and Statistics. (1980). *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed.). Washington, DC: American Psychiatric Association.

Blackwood, D.H.R., & Christie, J.E. (1988). Physostigmine, auditory P300, and Alzheimer's disease – response. *Biological Psychiatry*, 23(3), 322–324.

Blackwood, D.H.R., & Christie, J.E. (1986). The effects of physostigmine on memory and auditory P300 in Alzheimer-type dementia. *Biological Psychiatry*, 21(5-6), 557–560.

Blackwood, D.H.R., & Muir, W.J. (2004). Clinical phenotypes associated with DISC1, a candidate gene for schizophrenia. *Neurotoxicity Research*, 6(1), 35–41.

Blackwood, D.H.R., & Muir, W.J. (1990). Cognitive brain potentials and their application. *British Journal of Psychiatry*, 157, 96–101.

Blackwood, D.H.R., Muir, W.J., Roxborough, H.M., Walker, M.R., Townshend, R., Glabus, M.F., et al. (1994). Schizoid personality in childhood – auditory P300 and eye tracking responses at follow-up in adult life. *Journal of Autism and Developmental Disorders*, 24(4), 487–500.

Blackwood, D.H.R., St Clair, D.M., Blackburn, I.M., & Tyrer, G.M.B. (1987). Cognitive brain potentials and psychological deficits in Alzheimer's dementia and Korsakoff's amnesic syndrome. *Psychological Medicine*, 17(02), 349–358.

Blackwood, D.H.R., St Clair, D.M., & Kutcher, S.P. (1986a). P300 in depression, schizophrenia and borderline personality disorder. *Biological Psychology*, 23(1), 104–104.

Blackwood, D.H.R., St Clair, D.M., & Kutcher, S.P. (1986b). P300 event-related potential abnormalities in borderline personality disorder. *Biological Psychiatry*, 21(5), 560–564.

Blackwood, D.H.R., St Clair, D.M., & Muir, W.J. (1988). Auditory P300 and smooth pursuit eye tracking abnormalities in schizophrenic subjects and their relatives. *Schizophrenia Research*, 1(2-3), 177–178.

Blackwood, D.H.R., St Clair, D.M., Muir, W.J., & Duffy, J.C. (1991). Auditory P300 and Eye Tracking Dysfunction in Schizophrenic Pedigrees. *Archives of General Psychiatry*, 48(10), 899–909.

Blackwood, D.H.R., St Clair, D.M., Muir, W.J., Oliver, C.J., & Dickens, P. (1988). The development of Alzheimer's disease in Down's syndrome assessed by auditory event-related potentials. *Journal of Intellectual Disability Research*, 32(6), 439–453.

Blackwood, D.H.R., Whalley, L., Christie, J., Blackburn, I., St Clair, D.M., & McInnes, A. (1987). Changes in auditory P3 event-related potential in schizophrenia and depression. *British Journal of Psychiatry*, 150(2), 154–160.

Braverman, E. *The brain controls the body*. As of 17 September 2013: http://www.encognitive.com/node/2810

De Souza, V.B.N., Muir, W.J., Walker, M.T., Glabus, M.F., Roxborough, H.M., Sharp, C.W., et al. (1995). Auditory P300 event-related potentials and neuropsychological performance in schizophrenia and bipolar affective disorder. *Biological Psychiatry*, 37(5), 300–310.

Domenici, E., Willé, D.R., Tozzi, F., Prokopenko, I., Miller, S., McKeown, A., et al. (2010). Plasma protein biomarkers for depression and schizophrenia by multi analyte profiling of case-control collections. *PLoS ONE*, 5(2), e9166.

Glabus, M.F., Blackwood, D.H.R., Ebmeier, K.P., Souza, V., Walker, M.T., Sharp, C.W., et al. (1994). Methodological considerations in measurement of the P300 component of the auditory oddball ERP in schizophrenia. *Electroencephalography and Clinical Neurophysiology*, 90(2), 123–134.

Gunderson, J., & Elliott, G. (1985). The interface between borderline personality disorder and affective disorder. *American Journal of Psychiatry*, 142(3), 277–288.

Gunderson, J., Kolb, J., & Austin, V. (1981). The diagnostic interview for borderline patients. *American Journal of Psychiatry*, 138(7), 896–903.

Huang, J.T.J., Leweke, F.M., Oxley, D., Wang, L., Harris, N., Koethe, D., et al. (2006). Disease biomarkers in cerebrospinal fluid of patients with first-onset psychosis. *PLoS Med*, 3(11), e428.

International Schizophrenia Consortium. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*, 460(7256), 748–752.

Kutcher, S.P., Blackwood, D.H.R., St Clair, D.M., Gaskell, D.F., & Muir, W.J. (1987). Auditory P300 in borderline personality disorder and schizophrenia. *Archives of General Psychiatry*, 44(7), 645–650.

Kutcher, S.P., Blackwood, D.H.R., Gaskell, D.F., Muir, W.J., & St Clair, D.M. (1989). Auditory P300 does not differentiate borderline personality disorder from schizotypal personality disorder. *Biological Psychiatry*, 26(8), 766–774.

Lencz, T., Morgan, T.V., Athanasiou, M., Dain, B., Reed, C.R., Kane, J.M., et al. (2007). Converging evidence for a pseudoautosomal cytokine receptor gene locus in schizophrenia. *Molecular Psychiatry*, 12(6), 572–580.

Millar, J.K., Wilson-Annan, J.C., Anderson, S., Christie, S., Taylor, M.S., Semple, C.A.M., et al. (2000). Disruption of two novel genes by a translocation co-segregating with schizophrenia. *Human Molecular Genetics*, 9(9), 1415–1423.

Moises, H.W., Yang, L., Kristbjarnarson, H., Wiese, C., Byerley, W., Macciardi, F., et al. (1995). An international two-stage genome-wide search for schizophrenia susceptibility genes. *Nature Genetics*, 11(3), 321–324.

Muir, W.J., Squire, I., Blackwood, D.H.R., Speight, M.D., St Clair, D.M., Oliver, C., et al. (1988). Auditory P300 response in the assessment of Alzheimer's disease in Down's syndrome: a 2-year follow-up study. *Journal of Intellectual Disability Research*, 32(6), 455–463.

Muir, W.J., St Clair, D.M., & Blackwood, D.H.R. (1991). Long-latency auditory event-related potentials in schizophrenia and in bipolar and unipolar affective disorder. *Psychological Medicine*, 21(04), 867–879.

Perry, J., & Klerman, G. (1980). Clinical features of the borderline personality disorder. *American Journal of Psychiatry*, 137(2), 165–173.

Pfefferbaum, A., Sullivan, E.V., & Mathalon, D.H., et al. (1995) Longitudinal changes in magnetic resonance imagin brain volumes in abstinent and relapsed alcoholics. *Alcoholism: Clinical and Experimental Research* 16, 1177-1191.

Roxborough, H., Muir, W.J., Blackwood, D.H.R., Walker, M.T., & Blackburn, I.M. (1993). Neuropsychological and P300 abnormalities in schizophrenics and their relatives. *Psychological Medicine*, 23(2), 305–314.

Saetre, P., Emilsson, L., Axelsson, E., Kreuger, J., Lindholm, E., & Jazin, E. (2007). Inflammation-related genes up-regulated in schizophrenia brains. *BMC Psychiatry*, 7(1), 46.

Schizophrenia Collaborative Linkage Group (Chromosome 22). (1996). A combined analysis of D22S278 marker alleles in affected sib-pairs: Support for a susceptibility locus for schizophrenia at chromosome 22q12. *American Journal of Medical Genetics*, 67(1), 40–45.

Shagass, C., Roemer, R.A., Straumanis, J.J., & Amadeo, M. (1979). Temporal variability of somatosensory, visual, and auditory evoked potentials in schizophrenia. *Archives of General Psychiatry*, 36(12), 1341–1351.

Shagass, C., Roemer, R.A., Straumanis, J.J., & Josiassen, R.C. (1985). Combinations of evoked potential amplitude measurements in relation to psychiatric diagnosis. *Biological Psychiatry*, 20(7), 701–722.

Shajahan, P.M., Ocarroll, R.E., Glabus, M.F., Ebmeier, K.P., & Blackwood, D.H.R. (1997). Correlation of auditory 'oddball' P300 with verbal memory deficits in schizophrenia. *Psychological Medicine*, 27(3), 579–586.

St Clair, D.M., Blackwood, D.H.R., & Christie, J.E. (1985). P3 and other long latency auditory evoked potentials in presenile dementia Alzheimer type and alcoholic Korsakoff syndrome. *British Journal of Psychiatry*, 147(6), 702–706.

St Clair, D.M., Blackwood, D.H.R., Muir, W.J., Walker, M., Carothers, A., Spowart, G., et al. (1990). Association within a family of a balanced autosomal translocation with major mental illness. *The Lancet*, 336(8706), 13–16.

St Clair, D.M., Blackwood, D.H.R., & Muir, W.J. (1989). P300 abnormality in schizophrenic subtypes. *Journal of Psychiatric Research*, 23(1), 49–55.

St Clair, D.M., Blackwood, D.H.R., Oliver, C.J., & Dickens, P. (1987). P3 Abnormality in fragile X syndrome. *Biological Psychiatry*, 22(3), 303–312.

CHAPTER 8 Elevation of human brain D2 dopamine receptors in schizophrenia

This case study is based on the research that produced the paper:

Seeman, P. (1987). Dopamine receptors and the dopamine hypothesis of schizophrenia. *Synapse*, 1(2), 133–152.

Information was gathered from an interview with Philip Seeman, another informant, and desk-based research.

8.1 Summary

The target paper measured D1 and D2 dopamine receptor densities in post-mortem brains with schizophrenia, Alzheimer's disease, Huntington's disease and Parkinson's disease. It tried to tease apart whether elevation of D2 is attributable to treatment, or occurs in schizophrenia without treatment. The main finding from this work suggested that D2 receptors were elevated in brains with schizophrenia, separate from the treatment effect. However, early PET scanning and meta-analyses have challenged this, suggesting that there remains ambiguity in the evidence to support this finding.

Seeman's research career was defined by a singular aim to identify the cause of schizophrenia from the 1960s onwards. He sought to better understand the disorder at the molecular level. Seeman started this research by examining antipsychotics, which were known to affect the symptoms of schizophrenia at the time, but the mechanism by which they had this effect was not known. In the mid-1970s Seeman's lab at the University of Toronto, Canada, made a breakthrough, discovering that antipsychotics consistently acted on dopamine receptors at concentrations directly related to their daily doses to control the clinical signs and symptoms of schizophrenia. From this point, Seeman's research evolved into a focussed trail of questioning, through which he sought to understand the nature of the link between dopamine receptors and schizophrenia. This case study focusses on the aggregate of publications from Seeman's lab, as it was not possible to completely separate the contribution of the research on dopamine receptor density from Seeman's wider research activities on dopamine and schizophrenia.

Evidence that antipsychotics had a common target in dopamine receptors created interest more widely into the relationship between the dopamine system and schizophrenia, with the hope that it could improve scientific understanding of the abnormalities in the brain

specific to schizophrenia. This research had particular relevance to drug discovery and development: if the cause of schizophrenia could be worked out, then resources for drug development and screening could be aimed more specifically at affecting the particular abnormalities in the disorder. As such, it could help make screening new drugs for treatment more efficient. Given the potential value of looking at dopamine receptor density and schizophrenia to scientific knowledge and commercially, Seeman's lab was not the only one examining the elevation of dopamine receptors.

By the 1990s, however, technology appeared to render the potential value of the post-mortem studies on density of receptors less relevant. Development of imaging technology transformed the approach to researching receptor density as PET and SPECT studies allowed for experiments to be conducted in living humans, who had not yet taken neuroleptics.

While Seeman found some consistent evidence of a relationship between D2 receptor densities and schizophrenia, these findings were limited by the methodological and logistical challenges of post-mortem brain and animal model studies. The particular effect of schizophrenia on density has continued to be questioned. Early PET studies showed conflicting results. Studies considering differences by high and low affinity states of dopamine receptors have continued to add to the ambiguity around schizophrenia and elevation of dopamine receptors. For example, animal models suggest the D2High state of the D2 receptor is elevated with psychosis, associated with behavioural dopamine supersensitivity; however, evidence of this in humans is not documented through human brain imaging data.

Seeman's choice to focus his work solely the dopamine system limited the directions with which he took his research, but also helped him to make a very definite contribution to understanding a particular area. For example, while his research could not provide full clarity on the link between D2 receptor density and schizophrenia, it did help to refine understanding of some of the changes within the dopaminergic system with schizophrenia, other mental disorders, and treatment with neuroleptic drugs.

Other researchers involved in this work moved in different directions afterwards: most were students or early career researchers at the time, or had peripheral roles (for example, providing expertise on particular disorders or facilitating access to brain tissues for the research). However, many of the collaborators with Seeman on this work, including the graduate students, did go on to make notable contributions to psychopharmacology research.

8.2 Introduction

8.2.1 Scientific background

Dopamine is one of a collection of neurotransmitters responsible for transmitting and modulating signals in the brain. The **Dopamine system** refers to the systems producing, regulating and affected by dopamine. The dopamine system is known to modulate cognitive processes, primarily in the frontal cortex, striatum and associated structures.[11]

[11] See (as of 21 September 2013): http://www.utdallas.edu/~tres/papers/cropley.2006.pdf

D2 dopamine receptors. There are multiple subtypes of dopamine receptors in the brain. D2 is one subtype, and is one of five currently known subtypes of the dopamine receptor family. The receptors exist in states of high and low affinity for dopamine (Wreggett & Seeman, 1984; George, Watanabe et al., 1985).

Neuroleptic drugs are antipsychotic medications used to manage psychosis, for example, in individuals with schizophrenia or bipolar disorder.

Radioligands are highly radioactive compounds that will to bind to particular receptors. This allows the amount of receptor to be determined by measuring the level of radioactivity in a washed sample. Radioligands may stimulate (agonists) or block (antagonists) a particular transmitter.[12]

8.2.2 Researchers' backgrounds

Philip Seeman was the principal investigator for this case study research. For most of his research career, Seeman was head of a lab at the Department of Pharmacology, University of Toronto. Seeman took up a post at the University of Toronto in 1967, after completing a PhD at Rockefeller University in Life Sciences (1966) with Dr. George Palade and a post-doctoral fellowship at the University of Cambridge with Sir Arnold Burgen. Seeman remained at the University of Toronto until his official retirement. Seeman was the consistent presence for this case study research, and provided overall direction. During the research process, he collaborated with researchers externally to allow for the use of different and new approaches, and also with technicians and PhD students at the University of Toronto to implement the research.

The graduate students who worked with Seeman on this case study research included:

- **Natalie Bzowej** (Medicine). Bzowej measured the number of dopamine receptors in 247 post-mortem human tissues from individuals who died at different ages (Seeman, Bzowej et al., 1987a; Seeman, Bzowej et al., 1987b)
- **Tyrone Lee** (Pharma industry)
- **Stephen List** (Psychiatry)
- **Hyman B Niznik** (Pharmacology). Niznik was a PhD student with Seeman from 1988 to 1992.

Two post-doctoral fellows and trainees at the lab also contributed to this case study research:

- **H.C. Guan**. Guan was also associated with the Department of Pharmacology, Beijing Medical College, China. He is a trained MD with a specialisation in pharmacology research.
- **Mark Guttman**. Guttman is an MD and trained in Neurology. At the time, he was affiliated with the Department of Medicine, University of Toronto. Guttman joined Seeman's lab in 1985 and stayed for one year. He measured D2 receptors in post-mortem brain tissues from patients who had died with Parkinson's disease.

External collaborators who cooperated with Seeman to conduct the case study research were:

[12] See (as of 21 September 2013): http://www-davenport.medschl.cam.ac.uk/documents/R20.PDF

Catherine Bergeron was a researcher at the Department of Pathology, University of Toronto and the Canadian Brain Tissue Bank. Bergeron was instrumental in setting up the Canadian Brain Tissue Bank (Seeman & Seeman, 2009, 63). Currently, Bergeron is a principal investigator at the Center for Research in Neurodegenerative Diseases, University of Toronto, focussing on neuropathology of neurodegenerative diseases.

Gavin Reynolds was affiliated with the Department of Pathology, University of Nottingham and Nottingham University Hospitals at the time of the case study research. From 1985 Reynolds held academic positions at the Universities of Nottingham and Sheffield. He now has an honorary professorship in the Biomedical Research Centre at Sheffield Hallam University, and is Past-President of the British Association for Psychopharmacology (President 2008–2010). Reynolds' research has mainly focussed on the pathology of neurotransmitter systems in psychiatric disorders and on the receptor mechanisms of antipsychotic drug action.

Peter Riederer was the Chief of Clinical Neurochemistry at the Ludwig Boltzmann Institute for Clinical Neurobiology in Vienna from 1971 to 1986. From 1986, he was appointed Chief of Neurochemistry at the Psychiatry and Psychotherapy Polyclinic, Medicine School of Würzburg, Germany.

Kurt Jellinger was an assistant professor at the Institute of Neurology in Vienna from 1966 to 1972, full professor of neuropathology at the Medical University of Vienna from 1973 to 1976, and director of the Department of Neurology and the Ludwig Boltzmann Institute for Clinical Neurobiology, Vienna from 1977 to 2002. His institutional affiliation for this research was the Ludwig Boltzmann Institute for Clinical Neurobiology.

Edward D. Bird was based at the Brain Tissue Resource Center, Harvard University, for this research. This is a centralised, federally funded centre for collecting and distributing human brain specimens for research. He is currently Director Emeritus at the Harvard Brain Tissue Resource Center.

Wallace Tourtellotte was the Director (and also Founding Director) of the National Neurological Research Bank, V.A. Wadsworth Medical Center, Los Angeles California, at the time this research was conducted. The National Neurological Research Bank contributed brain tissues for the research.

8.3 Defining the research cloud

The entry point for this case study is a paper published by Seeman et al. (1987), which measured D1 and D2 dopamine receptor densities in post-mortem brains with schizophrenia, Alzheimer's disease, Huntington's disease and Parkinson's disease. This paper is one output from a long research trail pursued by Seeman throughout his research career.

Seeman's research career was defined by a singular aim to identify the cause of schizophrenia from the 1960s onwards. He sought to better understand the disorder at the molecular level. Seeman started this research by examining antipsychotics, which were known to affect the symptoms of schizophrenia at the time, but the mechanism by which they had this effect was not known.

In the mid-1970s Seeman's lab made a breakthrough, discovering that antipsychotics consistently acted on dopamine receptors at concentrations directly related to their daily doses to control the clinical signs and symptoms of schizophrenia. From this point, Seeman's research evolved into a focussed trail of questioning, through which he sought to understand the nature of the link between dopamine receptors and schizophrenia:

> Basically, I was a monomaniac about D2 and how far it could go. You see, I'm wedded to D2, [and] I'm wedded to the idea to see how far we can go and treat psychiatric disease with D2. And if we get to the limit, we'll move to another receptor. (PS)

Seeman pursued a broad range of hypothesises about how dopamine receptors were linked to antipsychotics and schizophrenia. For example, he examined the structure and genetics of dopamine receptors, receptor density and elevation (i.e., an increase in receptor density), high- and low-affinity states of receptors (known as D2High and D2Low, respectively), pre- and post-synaptic effects, and much else throughout the years. Seeman pursued many of these questions in parallel and would return to different hypotheses over time.

The target paper is part of one line of questioning about the link between dopamine receptors and schizophrenia. It tried to tease apart whether elevation of D2 is attributable to treatment, or occurs in schizophrenia without treatment. Medication was known to elevate the number of receptors; determining if there was a link between elevation of D2 and schizophrenia required separating out the treatment effect. To do this, Seeman took several approaches, including examining receptor density in animal models, as well as comparing the elevation of receptor density across disorders. This work began in the late 1970s and continued to be part of Seeman's ongoing research activities into the 2000s.

This case study focuses on the aggregate of publications from Seeman's lab that examine the density of dopamine receptors, and the link to psychosis. Table 1 lists the publications on the elevation of dopamine receptors with schizophrenia, published by Seeman's lab at the University of Toronto; it also summarises the main contribution of each publication to the wider body of knowledge on schizophrenia and dopamine receptor density.

It is not possible to completely separate the contribution of the research on dopamine receptor density from Seeman's wider research activities on dopamine and schizophrenia. Seeman treated his work as a continuous and connected research programme. As such, while in this case study we seek to detail the process and major impacts of the research on receptor density, it is necessary to also situate this within the context of Seeman's wider body of research. Thus we will isolate a particular line of questioning (elevation of receptors), but clearly discuss its trajectory and effects within the overall research trail (described in Stages 0 and 1, below).

Table 1. Publications in the research cloud

Year	Authors	Title	Methodology and main findings
1978	Lee, T., Seeman, P., Tourtellotte, W.W., Farley, J., & Hornykeiwicz, I.J.	Binding of ^{3}H-neuroleptics and ^{3}H-apomorphine in schizophrenic brains	- A letter to *Nature* on the use of post-mortem brains from schizophrenic patients to provide evidence on abnormalities in brain dopamine receptors, measured by the binding of ^{3}H-apomorphine and ^{3}H-haloperidol or ^{3}H-spiperone
1980	Seeman, P., Lee, T., Bird, E.D., &	Elevation of brain neuroleptic/dopamine receptors	- Post-mortem neurochemical study reporting increased numbers of dopamine receptors,

Year	Authors	Title	Methodology and main findings
	Tourtellotte, W.W.	in schizophrenia	measured as butyrophenone binding sites
1980	Lee, T., & Seeman, P.	Elevation of brain neuroleptic/dopamine receptors in schizophrenia	- Post-mortem neurochemical study, which measures specific ^{3}H-neuroleptic/dopamine binding sites using ^{3}H-haloperidol and 3H-spiperone in 59 post-mortem control and 50 post-mortem brains from schizophrenic patients. Reports a significant elevation of binding of 2 nM 3H-haloperidol and of 1 nM ^{3}H-spiperone in brains from schizophrenic patients
1984	Seeman, P., Ulpian, C., Bergeron, C., Riederer, P., Jellinger, K., Gabriel, E., Reynolds, G.P., & Tourtellotte, W.W.	Bimodal distribution of dopamine receptor densities in brains of schizophrenics	- Post-mortem neurochemical study using 91 control subjects and 59 schizophrenic subjects, measuring dopamine receptor density in the caudate nucleus, putamen and nucleus accumbens. Finds a bimodal distribution of dopamine receptors in these regions of the brain and suggests this provides evidence of two categories of schizophrenia
1984	Dumbrille-Ross, A., & Seeman, P.	Dopamine receptor elevation by cholecystokinin	- Study of the effect of cholecystokinin (a hormone secreted by cells in the small intestine, which plays a role in digestion) on dopamine D2 receptors in the rat brain in vitro and in vivo in cells of the striatum and nucleus acumens, by looking at the binding of ^{3}H-spiperone. Reports an elevated density of D2 receptors in the accumbens and the striatum
1985	Guttman, M., & Seeman, P.	L-DOPA reverses the elevated D2 dopamine receptor density in Parkinson's diseased striatum	- Post-mortem study of striatal dopamine receptors of 36 patients with Parkinson's disease, using ^{3}H-spiperone. Finds an elevation of D2 dopamine receptors in the caudate nucleus and putamen compared in non-treated patients compared to controls. Elevated density was reversed with dopamine agonist therapy
1986	Guttman, M., & Seeman, P.	Dopamine D2 receptor density in Parkinsonian brain is constant for duration of disease, age and duration of L-DOPA therapy	- Post-mortem study of dopamine D2 receptor densities, looking at relationships to age, duration of the disease and duration of L-dopa therapy
1986	Guttman, M., Seeman, P., Bergeron, C., Riederer, P., Jellinger, K., & Tourtellotte, W.W.	Dopamine D2 receptor density remains constant in treated Parkinson's disease	- Post-mortem study of D2 dopamine receptor densities in the caudate nucleus and putamen from 36 parkinsonian patients, looking at relationships to age, duration of the disease and duration of L-dopa therapy, using ^{3}H-spiperone. Results suggest receptor density in parkinsonian tissues and control tissues was constant between the ages 56-90 years; also L-dopa treatment did not cause progressive reduction in receptor density
1987	Seeman, P., Bzowej, N.H., Guan, H.-C., Bergeron, C., Reynolds, G.P., Bird, E.D., Riederer, P., Jellinger, K., & Tourtellotte, W.W.	Human brain D1 and D2 dopamine receptors in schizophrenia, Alzheimer's, Parkinson's and Huntington's diseases	- Post-mortem study of the density of dopamine D1 and D2 receptors. Findings suggest elevation of D2 receptors due to schizophrenia, but unable to provide evidence in schizophrenia independent of treatment
1990	Seeman, P., & Niznik, H.B.	Dopamine receptors and transporters in Parkinson's disease and schizophrenia	- A review article on the evidence from post-mortem, PET and SPECT studies on dopamine receptors and transporters in Parkinson's disease

Year	Authors	Title	Methodology and main findings
			and schizophrenia. Review suggests evidence for a consistent elevation of D2 receptor density in brain putamen and caudate nucleus in schizophrenia
1990	Seeman, P., Niznik, H.B., & Guan, H.-C.	Elevation of D2 dopamine receptors in schizophrenia is underestimated by radioactive raclopride	- A letter to the editor commenting that dopamine D2 receptor densities are elevated in schizophrenia, with and without neuroleptic medications. Also suggests unequal elevation in the left and right putamen in patients with schizophrenia
1992	Seeman, P.	Dopamine receptor sequences. Therapeutic levels of neuroleptics occupy D2 receptors, clozapine occupies D4	- A review of the literature, suggests that antipsychotic drugs at their therapeutic concentrations, measured in cerebrospinal fluid or plasma water, act mainly at D2 receptors, except clozapine, which is suggested to act at D4 receptors
1993	Seeman, P., Guan, H.-C., & Van Tol, H.H.M.	Dopamine D4 receptors elevated in schizophrenia	- Study of the binding of ^{3}H-raclopride to D2, D3 and D4 receptors in schizophrenia. Findings suggest the combined density of D2 and D3 receptors is increased by only 10% in schizophrenia brain, but the density of dopamine D4 receptors is six-fold elevated in schizophrenia
1995	Schoots, O., Seeman, P., Guan, H.-C., Paterson, A., & Van Tol, H.H.M.	Long-term haloperidol elevates dopamine D4 receptors by two-fold in rats	- Study of the effect of neuroleptics on the density of the dopamine D4 receptor, using haloperidol on dopamine D4 receptor mRNA and protein levels in the rat striatum. Find that treatment elevates the density of dopamine D4 receptor mRNA; also shows an increase in density of D2 and D3 receptors
1995	Seeman, P., & Van Tol, H.H.M.	Dopamine D4-like receptor elevation in schizophrenia: cloned D2 and D4 receptors cannot be discriminated by raclopride competition against [3H]nemonapride	- Responding to a study using raclopride to compete against the binding of 1 nM ^{3}H-nemonapride to schizophrenia tissue, which challenged evidence on the elevation of D4 dopamine receptors in schizophrenia - Tests if the competition method distinguishes between dopamine D2 and D4 receptors by using a mixture of these two cloned receptors. Finds the method could not resolve components up to a level of 48% D4 receptors; suggests this invalidates findings from the previous study
1995	Seeman, P., Guan, H.-C., & Van Tol, H.H.M.	Schizophrenia: Elevation of dopamine D4-like sites, using [3H]nemonapride and [125I]epidepride	- Uses ^{3}H-nemonapride to measure dopamine D2 and D3 receptors and D4-like sites, and ^{125}I-epidepride to measure D2 and D3 sites in 10 control and 9 schizophrenia post-mortem brain putamen tissues. Finds a three-fold elevation of dopamine D4-like sites in schizophrenia
1997	Seeman, P., Guan, H.-C., Nobrega, J., Jiwa, D., Markstein, R., Balk, J.-H., Picetti, R., Borelli, E., & Van Tol, H.H.M.	Dopamine D2-like sites in schizophrenia, but not in Huntington's, Alzheimer's or control brains, for [3H]benzquinoline	- Study using ^{3}H-benzo[g]quinoline, a new radioligand, to measure the elevation of dopamine receptors in schiozphrenia. Finds elevated levels of a D2-like site in striata of brains with schizophrenia. This was not detected in control human post-mortem brains or in Alzheimer's, Huntington's, or Parkinson's disease brains
2002	Seeman, P., Tallerico, T., Oise Ko, F., Tenn, C., & Kapur, S.	Amphetamine-sensitized animals show a marked increase in dopamine D2 high receptors	- Testing the hypothesis that, in amphetamine-sensitised rats, an apparent decrease in dopamine D2 receptors may be apparent, but that the

Year	Authors	Title	Methodology and main findings
		occupied by endogenous dopamine, even in the absence of acute challenges	receptors could still be present but occupied by endogenous dopamine - Finds an increase in dopamine D2 receptors in the high-affinity state occupied by dopamine, and suggests this could explain why the amphetamine-sensitised rats are more responsive to dopamine agonists even though the absolute number of receptors is unchanged and the apparent receptor number is decreased
2008	Seeman, P.	Dopamine D2High receptors moderately elevated by sertindole	- Looks at behavioural dopamine supersensitivity in rats in the homogenised striata. Finds that sertindole increases the proportion of D2 (high) receptors, but that the total population of D2 receptors does not change
2008	Seeman, P.	Dopamine D2High receptors moderately elevated by bifeprunox and aripiprazole	- Examines behavioural dopamine supersensitivity in human cloned D2Long receptors and in control rat striata, with the administration of partial dopamine D2 agonists with antipsychotic activity. Increase in human cloned D2 receptors, but no significant change in the total population of D2 receptors. This increase appears to be of smaller magnitude than those seen previously with D2 antagonist antipsychotics
2008	Seeman, P.	Dopamine D2High receptors measured *ex vivo* are elevated in amphetamine-sensitized animals	- Study into the molecular basis of dopamine supersensitivity in schizophrenia and Parkinson's disease. Conducts an ex vivo study of D2High receptors in rats sensitised to amphetamines. Finds the specific binding of ^{3}H(1)PHNO displaced was higher for amphetamine-sensitised rats than control rats
2009	King, M., Seeman, P., Marsden, C.A., & Fone, K.	Increased dopamine DHigh2 receptors in rats reared in social isolation	- Begins from the premise that post-weaning social isolation in the rat induces alterations similar to some of the core symptoms of human schizophrenics (hyperreactivity to novel environments, cognitive impairment, and deficits in sensorimotor gating) - Studies if changes in the rat with social isolation correspond with an elevation in the proportion of striatal dopamine D2 receptors in the high affinity state. Findings suggest a highly significant elevation in the proportion of striatal D2High receptors
2010	Novak, G., & Seeman, P.	Hyperactive mice show elevated D2High receptors, a model for schizophrenia: calcium/calmodulin-dependent kinase II alpha knockouts	- Examines if an alteration in the levels of CaMKIIβ could lead to altered levels of D2High receptors in the rat striatum. - Finds a 2.8-fold increase in D2 high receptors and an increase in CaMKIIβ mRNA levels in the striata, but a reduction in CaMKIIα mRNA levels in the frontal cortex. Suggests elevated levels of CaMKIIβ mRNA in the striatum may increase D2High receptors
2011	Seeman, P.	All roads to schizophrenia lead to dopamine supersensitivity and elevated dopamine D2High receptors	- A review of the evidence on why individuals with schizophrenia tend to be supersensitive to dopamine-like drugs, and if the D2High state is a common basis for dopamine supersensitivity in the animal models of schizophrenia

Year	Authors	Title	Methodology and main findings
			- Suggests animal models of schizophrenia reveal elevations in D2High receptors. Models include brain lesions, sensitisation by drugs (amphetamine, phencyclidine, cocaine, corticosterone), birth injury, social isolation and gene deletions in pathways for NMDA, dopamine, GABA, acetylcholine and norepinephrine

8.4 Stage 0: Opportunity identification/research needs assessment

Inspiration

Seeman's decision to research the cause of schizophrenia by examining the target for antipsychotics was inspired by his wife, Mary Seeman, a researcher and medical doctor, with a primary interest in gender-based biopsychosocial differences. Initially, Seeman's PhD research at Rockefeller University (1962) looked at the content of granules in white blood cells. At this time, his wife and her colleagues at the Manhattan State hospital suggested Seeman might consider looking at the target for antipsychotics. Seeman then probed this issue further, and his interest in antipsychotics and schizophrenia grew. Also, at the time, his research on white blood cells was not progressing; this provided scope for Seeman to shift his PhD from granules in white blood cells to red blood cells, antipsychotic drugs and tranquillisers more widely (PS).

From this point, Seeman sought to better understand the cause of schizophrenia, beginning by looking for a common target for antipsychotics, which were known to alleviate symptoms of schizophrenia. The specific direction taken by Seeman – to look at dopamine and antipsychotics – was informed by indirect evidence of a link between dopamine and antipsychotics (see, for example, Van Rossum, 1966). Seeman suggests that:

> My kindergarten strategy was very naïve, very simple, and it survives to this day. The idea is to find out where the drugs work. …So, I studied that very carefully in the 1960s and the 1970s, and came out with this paper showing the precise target for antipsychotic drugs. (PS)

In 1967, Seeman took up a position at the University of Toronto, where he continued to research the effects of antipsychotic drugs on cell membranes. Each new experiment built on his previous work and wider discoveries in the field. For example, Seeman began experiments looking at Parkinson's disease following clinical observations that identified antipsychotics could cause parkinsonian signs.

In the mid-1970s, Seeman's lab achieved a breakthrough with the discovery of a dopamine receptor (then termed the 'antipsychotic/dopamine receptor'), labelled by tritiated haloperidol, which was sensitive to antipsychotic drug concentrations that directly related to the clinical potencies for the average dosage for antipsychotic drugs (Seeman, Chau-Wong et al., 1975). To do this, Seeman first determined a low concentration of haloperidol of 1nM (nanomoles per litre) was the therapeutic concentration of haloperidol in human spinal fluid, and then arranged with Dr. Paul Janssen to access a radioactive form of haloperidol. He reported this finding in *Proceedings of the National Academy of Sciences* in 1975. In an informal discussion with Sol Synder, Seeman shared the fact that he

had accessed radioactive haloperidol, and that it was available. Synder also requested this form of the drug, and arrived at similar findings. In the 1970s, Synder's lab at John Hopkins University was very active in the development and application of the ligand-binding technique, particularly using it to identify different major neurotransmitters in the brain. By 1976, Seeman, as well as Snyder, independently identified the binding sites for antipsychotics to be dopaminergic, and that the binding sites to dopamine receptors predicted the clinical efficacy of the drugs.[13]

Once direct evidence indicated a link between dopamine receptors and schizophrenia, the logical next step was for researchers to examine what the nature of this link was: were there particular abnormalities in the dopamine system with schizophrenia, acted on by antipsychotics? Labs followed up on Seeman's and Snyder's discoveries with experiments seeking to identify the reason for the apparent overactivity of the dopamine system. Seeman suggests that '[the work on dopamine and neuroleptics] caught on like wild fire' (PS).

Seeman's objective became 'to examine whether there were any differences in dopamine D2 receptors in the human brain of individuals with schizophrenia' (Seeman & Seeman, 2009, 61). He put forward a series of hypotheses for consideration at this time (Seeman & Seeman, 2009, 62). Through a multipronged approach, Seeman hoped to contribute to improved clinical practice in treating individuals with schizophrenia (PS). One of the hypotheses he put forward was that dopamine D2 receptor density was elevated in brains with schizophrenia. This hypothesis and its related discoveries were identified by Seeman as 'just one signpost on the way', within his broader ongoing research trail (PS). Seeman saw research to improve understanding of the link between dopamine D2 receptors and schizophrenia as the logical next step from his earlier discovery.

Seeman has maintained a strong personal interest in the dopamine hypothesis for schizophrenia, in particular the relationship between dopamine receptors and the disorder. Seeman's commitment to looking at domaine receptors and schizophrenia took precedence, overriding any external suggestions to take research in a different direction. More widely in the field, Seeman indicated there were competing pressures from political and funding bodies to take research on psychiatric disorder in different directions. Another interviewee suggests that researchers and funders were attracted to newer technologies and their potential to lead to different insights into the disorder, and hence the research would often change directions as a result of technological changes (IC). In contrast, Seeman suggests his approach was guided by the premise:

> You've got to be focussed in science. I tested many antipsychotics on the receptor to see if there were any exceptions to the relation between the antipsychotic binding concentration and the antipsychotic clinical dose. After all, as Linus Pauling advised, you have to try to kill your theory, and if it does not die, then the theory gets stronger. (PS)

Potential value

Evidence that antipsychotics had a common target in dopamine receptors created interest more widely into the relationship between the dopamine system and schizophrenia, with

[13] This was later confirmed to be the D2 receptor; however, at the time, this was referred to as the neuroleptic/dopamine receptor.

the hope that it could improve scientific understanding of the abnormalities in the brain specific to schizophrenia. This research had particular relevance to drug discovery and development: if the cause of schizophrenia could be worked out, then resources for drug development and screening could be aimed more specifically at the particular abnormalities in the disorder. As such, it could help make screening new drugs for treatment more efficient (IC, PS).

Seeman was also motivated to do this research because of its potential to contribute to scientific knowledge. In the 1970s and 1980s, contradictory findings were published on the elevation of dopamine receptors in post-mortem brains with schizophrenia. A few studies reported an elevation of dopamine and/or homovanillic acid (a dopamine metabolite) in the striatum in post-mortem brains with schizophrenia (Farley, Price et al., 1977; Crow, Baker et al., 1979), but not in the nucleus accumbens (Crow Baker et al., 1979). Other studies did not find a significant change in density of dopamine receptors in the striatum, but did find an increase in concentration of receptors in the nucleus accumbens in post-mortem brains with schizophrenia (Bird, Barnes et al., 1977; Bird, Spokes et al., 1979b). Crow, Longden et al. (1978) and Farley, Price et al. (1977) also found an increase in dopamine in the nucleus accumbens.

Inconsistent evidence on receptor density and schizophrenia was linked to methodological and logistical difficulties with the experiments. First, the disorder itself is heterogeneous, as were the subjects (e.g., by sex, age, etc.) and their treatment histories. Different medical histories of patients could contribute to variation in the elevation of dopamine receptors, but the relationships between medical histories and this outcome was difficult to unpick (McGeer & McGeer, 1977; Seeman, 1980). Given this heterogeneity, the number of subjects needed to arrive at definite conclusions about the disorder was unclear. Secondly, it was difficult, if not impossible, to separate out the treatment effect from the effect of the disorder in the post-mortem brains (Bird, Barnes et al., 1977; Bird, Spokes et al., 1979a). These challenges made further study to help clarify the actual relationship between the disorder and elevation of receptors particularly valuable to progressing scientific knowledge.

Given the potential value of looking at dopamine receptor density and schizophrenia to scientific knowledge (as well as commercially), Seeman's lab was not the only one examining the elevation of dopamine receptors with schizophrenia. For example, Leslie Iversen's and Snyder's labs, at the MRC Neurochemical Pharmacology Unit, Cambridge, and John Hopkins University respectively, also conducted experiments using animal brains and post-mortem human brains (Creese, Burt et al., 1976; Bird, Barnes et al. 1977; Bird, Spokes et al., 1979a; Bird, Spokes et al., 1979b; Mackay, Iversen et al., 1982). By the 1990s, however, technology appeared to render the potential value of the post-mortem studies on density of receptors less relevant. Development of imaging technology transformed the approach to researching receptor density as PET and SPECT studies allowed for experiments to be conducted in living humans, who had not yet taken neuroleptics.

8.5 Stage 1: Inputs to research

Money, researcher time, lab/office space and consumables

Consistent access to equipment, lab space and funding were key inputs to supporting and sustaining this case study research over time. The work was conducted at Seeman's lab at the University of Toronto. The initial decision to be based in Toronto was both personal and professional. First, Seeman was Canadian and hoped to live close to his family; secondly, he sought a location that was close to the northeast corner of North America, as it was a productive area for research, spanning Boston, New York and Montreal.

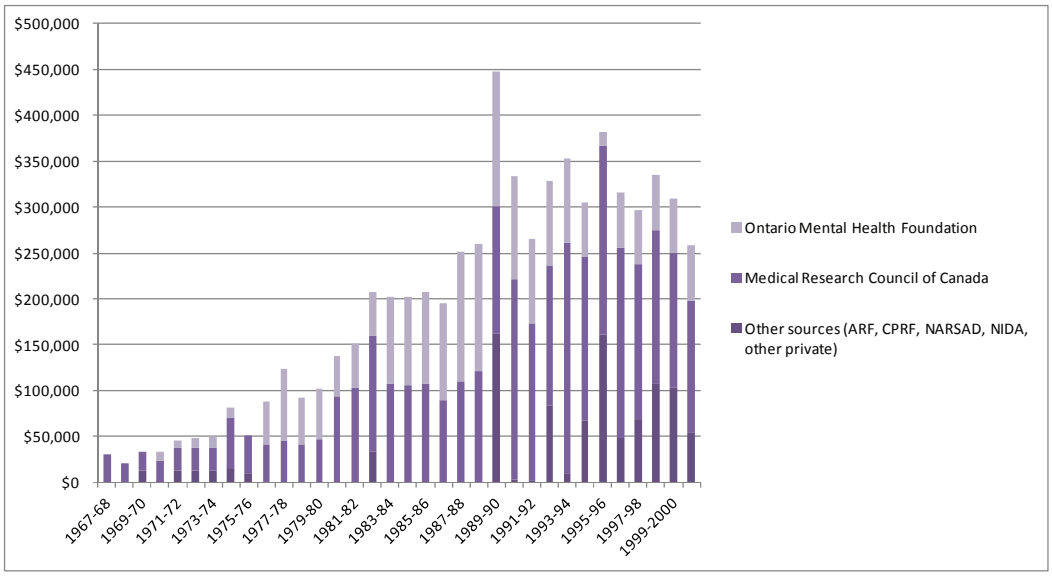
Once Seeman acquired funding, the University of Toronto provided him with a high level of independence to conduct his research (PS). He found that, prior to his discovery of the link between dopamine and antipsychotics, American- and UK-based funding bodies were unwilling to finance his research approach as they saw little potential value in it (PS). Instead, he accessed consistent funding through grants from the Medical Research Council of Canada, and the provincial equivalent, the Ontario Mental Health Foundation, throughout his research career. Figure 1 below provides an overview of the source and amount of funding to Seeman, sufficient for sustaining his research on dopamine receptors and schizophrenia over time.

Seeman began to receive grants from the Canadian Medical Research Council (MRC) in 1967. From 1967 to 1978, these MRC grants were mainly for research on schizophrenia; from 1978 onwards Seeman was awarded grants to look both at schizophrenia and D2 dopamine receptors. He began to be awarded regular funding from the Ontario Mental Health Foundation in 1970. This funding body also initially provided funding for research on schizophrenia, awarding Seeman grants for research on D2 from 1982 onwards. It also allocated funding for research fellowships, between 1990 and 1994.

Seeman also was awarded ad hoc funding from foundations and charities, for example, the Canadian Psychiatric Research Foundation (Health Minds) (CPRF) provided funding for a post-doctoral fellow in 1989/1990, and Seeman was awarded a NARSAD grant from the Brain and Behavior Research Foundation in 1989/1990 to research D1 and D2.

Seeman would amalgamate funding from multiple sources to support his ongoing research into different hypotheses for the specific link between dopamine D2 and schizophrenia. For example, the target paper alone was supported by the Parkinson Foundation of Canada, the Canadian Friends of Schizophrenics, the Medical Research Council of Canada and the Ontario Mental Health Foundation. The research in general did not require a lot of money, and grants were usually small to medium in size (CAN$40,000 to CAN$90,000). Seeman identifies that the aggregate amount of funding acquired for this work between 1967 and 2007 amounted to CAN$7.7 million.

Figure 1. The source and amount of research grants to Philip Seeman, 1967–2001



Source: Philip Seeman's personal records

Access to consumables for the research required Seeman to cooperate with pharmaceutical companies, in order to access radioactive forms of antipsychotic drugs. He would contact pharmaceutical companies directly, by phone or in writing, to request drugs necessary for the research, and he found pharmaceutical companies were willing to provide what he required. Another interviewee suggests that pharmaceutical companies would develop radioligands available for sale for research purposes, and therefore that these were accessible to labs at the time (IC).

Technology imposed limits on who could engage in different research approaches on dopamine receptors and schizophrenia (IC), and seems to have influenced the nature and scope of Seeman's research activities. For example, Seeman tended to work with animal models and with post-mortem brain tissues to experiment on receptor density, even after imaging technologies were developed. Other labs engaged in this area of research took different directions; for example, at John Hopkins University, where a PET unit was set up and used to study receptors in brain tissues of living humans.

Expertise and techniques

This case study consists of basic research using post-mortem brains and animal models. The techniques used to measure receptor binding were generally accessible and well known in the field at the time. Interviewees suggest that with access to appropriate technology, it was possible for labs to relatively easily conduct experiments to measure receptor density (IC). It was more challenging to decide how to shape the questions and experiments to overcome methodological and logistical difficulties. In particular, research on the cause of schizophrenia was complicated by heterogeneity of the disorder, treatment regimes and subject population, and the lack of a clear animal model.

Samples/patients

Access to post-mortem brains was necessary for the research. Seeman collected brain tissues between 1980 and 1986, acquiring material from tissue banks in Boston (US), Cambridge (UK), Los Angeles (US) and Vienna (Austria). The main source for brain tissue was the National Neurological Research Specimen Bank, Wadsworth Hospital, Los Angeles. In the 1980s, Seeman's lab acquired and measured D2 densities in 242 control brains and 92 brains with schizophrenia. Heterogeneity and lack of information about the samples remained a challenge when conducting experiments with post-mortem brains. For example, detailed clinical case records were not always available. Seeman, Bzowej et al. (1987b) report that accurate neuroleptic doses for the post-mortem brains were only available for 15 patients with Huntington's disease, 20 with Alzheimer's disease and 20 with schizophrenia.

Collaborators

Because of his singularly focussed approach to research, Seeman tended not to collaborate in the formation of research questions. The work began as an individual project and Seeman found that initially there was little support for his approach:

> This 1975 paper was a solo act. There was literally, everyone was saying, 'You're looking for an antipsychotic receptor, are you nuts, are you crazy? There's no such thing and you're wasting your time.' (PS)

Seeman's external collaboration on this case study research continued to be limited. He primarily cooperated with other researchers and with pharmaceutical companies to gain access to sample populations, techniques and consumables. For example, he cooperated extensively with researchers from a number of brain tissue banks internationally.

At his lab, Seeman tended to work only with a small number of graduate students and technicians:

> There were never more than 5 or 6 graduate students present at any time [in Seeman's lab in Toronto]. In order to discover the antipsychotic receptor, the strategy was always 'less is more'. Fewer projects, less people, less distraction, stay focused. (Seeman & Seeman, 2009, 95)

Graduate students were involved in discrete tasks for the research. Bzowej measured the number of dopamine receptors in 247 post-mortem human tissues from individuals who died at different ages (Seeman, Bzowej et al., 1987a; Seeman, Bzowej et al., 1987b). Guttman, a neurologist, measured D2 receptors in post-mortem brain tissues from patients who had died with Parkinson's disease. He found more D2 receptors in tissues from patients who had received little or no L-DOPA treatment before they died, but a low/normal level if the patient had been treated with L-DOPA.

Finally, the research required a capable lab technician to complete the experiments. In the 1970s, Margaret Chau-Wong worked with Seeman as a technician.

8.6 Stage 2: Processes

Studies within this research cloud were completed using post-mortem brains, as well as animal (rat) models.

The research process for post-mortem studies involved saturating tissues with increasing concentrations of dopamine agonists and antagonists, and measuring the densities of the dopamine receptors in the post-mortem tissue, from brains with schizophrenia, other disorders, as well as control brains. The researchers faced two main challenges in precisely measuring the elevation of dopamine receptors in the post-mortem brains, particularly those from individuals with schizophrenia. First, it was rare (and continues to be so) to obtain post-mortem tissue from a schizophrenic person who had never received neuroleptics. As such, the working assumption for the research was that all schizophrenic patients had received substantial neuroleptic medication within the last two years of their life. Secondly, the researchers did not have access to detailed and complete clinical neuroleptic dosage information with all of the post-mortem findings. Not only were post-mortem brains likely to have received antipsychotic treatment, but the dosage was not fully known across the sample of brains, nor the patient's demographic characteristics, clinical history, experience of the disorder, and even potentially details on the treatment of the post-mortem brain tissue. For this research, the data on the complete dosage of neuroleptics was available for 55 patients with Huntington's disease, 20 patients with Alzheimer's disease and 20 patients with schizophrenia.

Studies done using animal models tended to follow on from the post-mortem studies, beginning to be implemented in the 1990s. In these studies, Seeman and his collaborators examined the density of dopamine receptors by studying the binding of various radioactive forms of neuroleptics. These studies could use pure forms of the dopamine receptors, which were first cloned in the early 1990s. They were conducted in vivo and in vitro and sought to identify the effect of schizophrenia on the density of receptors, independent of treatment, which had not been possible in the post-mortem studies. A challenge in studies using animal models was the lack of a clearly applicable animal model for schizophrenia. Seeman experimented with a few different models, testing for how they reflected changes in elevation of receptors. For example, he used rats in postweaning social isolation (e.g., King, Seeman et al., 2009) and rats that were amphetamine-sensitised (e.g., Seeman, 2008), as they paralleled some of the symptoms of schizophrenia.

Over time, both post-mortem and animal model studies became more nuanced in their consideration of the elevation of receptors: for example, by shifting from looking at elevation of receptor subtypes to looking at elevation of receptor subtypes in their high- and low-affinity states.

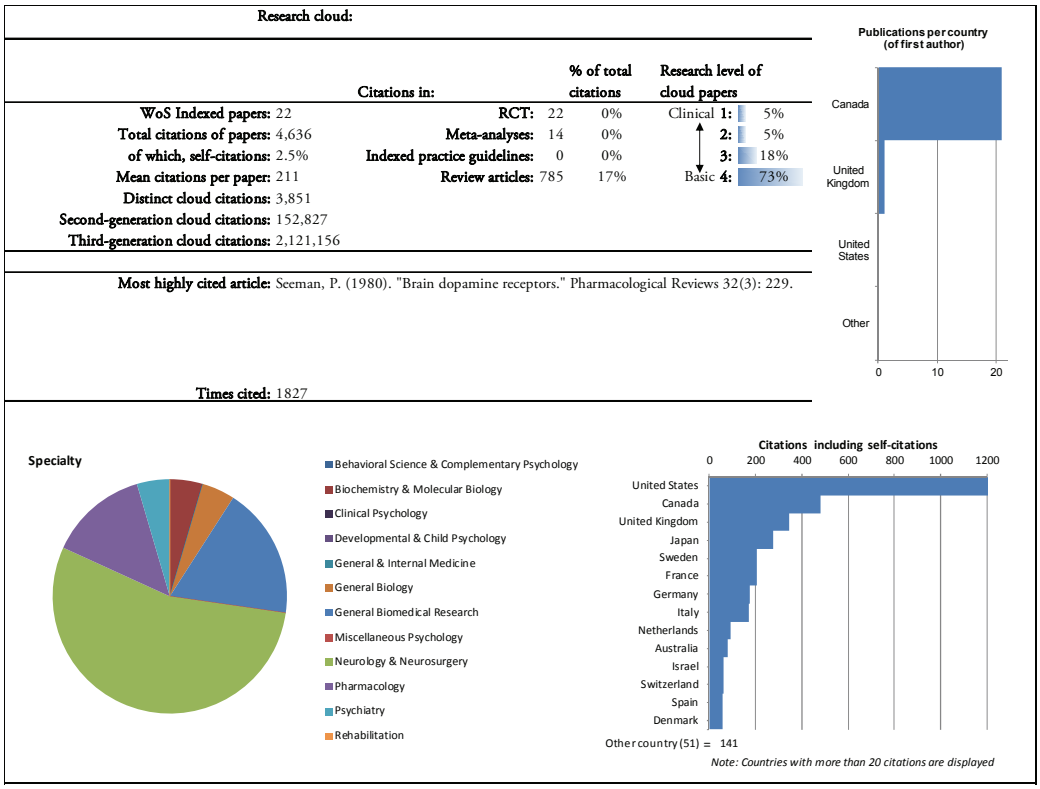
8.7 Stage 3: Primary outputs

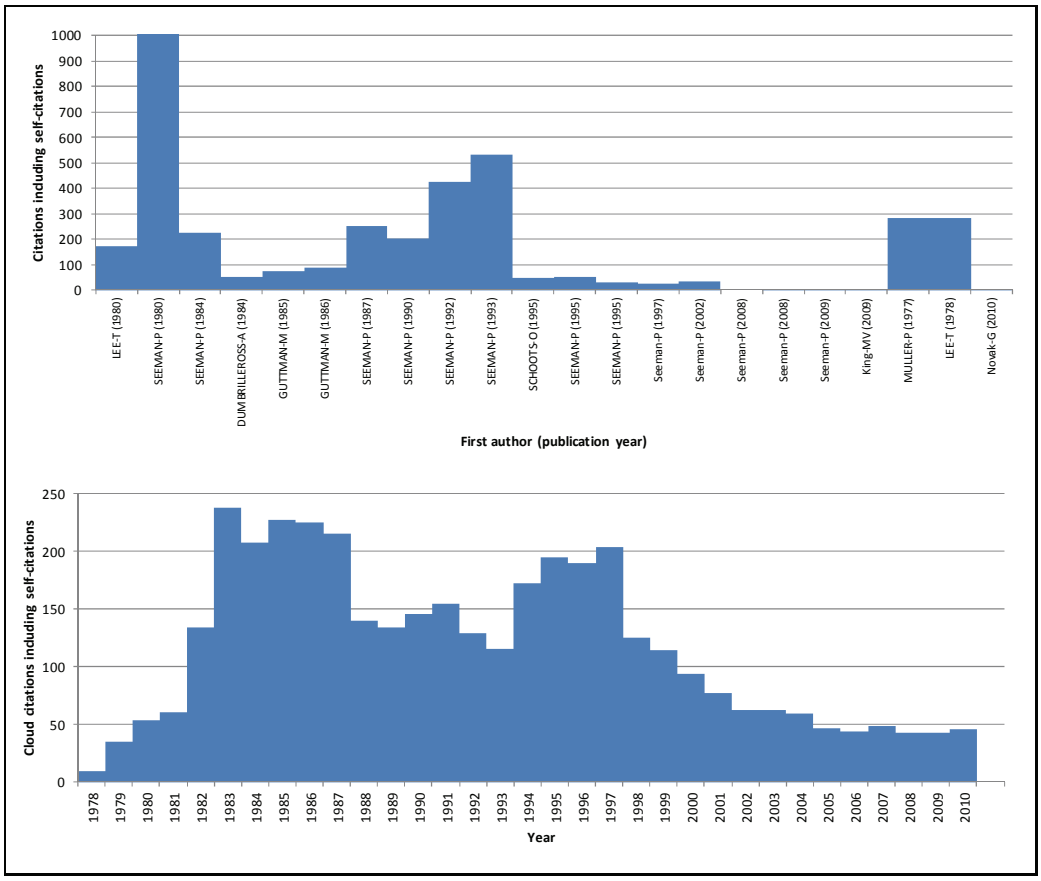
Knowledge

The main contribution of Seeman's wider research trail was to identify and reaffirm a link between dopamine D2 receptors and schizophrenia. Seeman's aggregate of research, published from the 1970s through to the present, has helped to provide a body of evidence on the relationship between antipsychotics and dopamine D2 receptors. His research into density of receptors and schizophrenia was part of the aggregate of work, helping to reaffirm the link between schizophrenia and dopamine. This link was also found at other labs in the 1970s (for example, Seeman & Lee, 1975; Creese, Burt et al., 1976; Seeman, Lee et al., 1976; Peroutka & Synder, 1980).

The specific contribution of this case study research to scientific knowledge has been less clear. While Seeman found some consistent evidence of a relationship between D2 receptor densities and schizophrenia, these findings were limited by the methodological and logistical challenges of post-mortem brain and animal model studies. The particular effect of schizophrenia on receptor density has continued to be questioned. Early PET studies showed conflicting results (Howes & Kapur, 2009). Research conducted by Farde and colleauges at the Karolinska Institute, Sweden, sought to measure D2 dopamine receptor densities using a different quantitative method and different ligand to Seeman; they could not confirm substantially elevated D2 dopamine receptor densities in the putamen or the caudate nucleus of drug-naive schizophrenics (Farde, Pauli et al., 1988; Farde, Nordstrom et al., 1992). Conflicting results were also published by Wong et al. (1985, 1986) using PET: in 1985, they reported no D2 dopamine receptor abnormalities were found in drug-naive schizophrenics; in 1986, a more sophisticated quantitative method found a two- to three-fold elevation of D2 dopamine receptor densities in the caudate nucleus. Studies considering differences in high- and low-affinity states of dopamine receptors have continued to add to the ambiguity around schizophrenia and the elevation of dopamine receptors. For example, animal models suggest the D2High state of the D2 receptor is elevated with psychosis, associated with behavioural dopamine supersensitivity; however, evidence on this in humans is not documented through human brain imaging data.

A bibliometric analysis of the papers produced from the research cloud is shown below.





Targeting future research

Effect on the researchers' careers

Seeman's research on dopamine and schizophrenia has continued to evolve throughout his career, with refined discoveries about the nature of receptors affected with antipsychotics and schizophrenia, and also new technologies and approaches. While he has continued to research and publish on receptor density, he also began, for example, to conduct experiments in the areas of molecular genetics,. In 1988 Bunzow and Van Tol isolated the DNA for the synthesis of the dopamine D2 receptor. This provided an isolated pure form of D2 that could be used in experimentation; similar possibilities arose for the D1, D3, D4 and D5 receptors between 1990 and 1991 as these were also cloned.

Throughout his career Seeman has sought to refine the dopamine hypothesis for schizophrenia. His objective remained to find a consistent cause of schizophrenia at the molecular level. Seeman's choice to focus his research solely the dopamine system limited the directions with which he took his research, but also helped him to make a very definite contribution to understanding a particular area. For example, while his research could not provide full clarity on the link between D2 receptor density and schizophrenia, it did help to refine understanding of some of the changes within the dopaminergic system with schizophrenia, other mental disorders, and treatment with neuroleptic drugs. In his recent work, Seeman and colleagues identified that the causes of human psychosis, including mutations, drugs such as amphetamines and LSD, birth injury and isolation syndrome result in elevated D2High receptors in rats (Seeman, Tallerico et al., 2002; King, Seeman

et al., 2009; Novak & Seeman, 2010). Potential to measure D2High receptors in humans is suggested with the use of radioactive PHNO and apomorphine-type compounds, but such studies are not yet published.

Other researchers involved in this research cloud moved in different directions afterwards: most were students or early career researchers at the time, or had peripheral roles (for example, providing expertise on particular disorders or facilitating access to brain tissues for the research). However, many of the collaborators with Seeman on this work, including the graduate students, did go on the make notable contributions to psychopharmacology research (for example, Gavin Reynolds). Seeman appears unique in his unilateral, consistent commitment to improving understanding dopamine receptors and the cause of schizophrenia.

Future work

The dopamine hypothesis for schizophrenia remains an enduring neurochemical hypothesis for schizophrenia, as well as one of the best explanations of the mechanisms of action of antipsychotic medications. This hypothesis rests on four pillars: that antipsychotic medications block D2 receptors; that dopaminergic agonists are psychotogenic; that imaging and related studies indicate changes in dopaminergic neurotransmission in schizophrenia (see, for example, Lyon et al., 2011); and finally, that genetic studies implicate genes related to dopamine in schizophrenia. The last of these pillars remains the weakest. This research cloud made a strong contribution to the first pillar, demonstrating that antipsychotic medications block D2 receptors.

More widely in the field, alongside this case study research, researchers sought to challenge, better understand and refine this hypothesis. In 1991, Davis, Kahn et al. (1991) published a reconceptualisation of the dopamine hypothesis of schizophrenia, which took into account findings up to that time, including: (i) lack of a universal elevation of dopamine metabolites in the cerebrospinal fluid or serum of patients with schizophrenia; (ii) findings that clozapine had a relatively low affinity for and occupancy at D2 receptors but was effective for patients with schizophrenia who were resistant to other drugs; (iii) inconsistent evidence in post-mortem brain and in early PET Studies on D2 receptors in schizophrenia (Howes & Kapur, 2009). However, there was still at the time uncertainty about links between dopamine abnormalities and clinical realities. Evidence relied on inferences from animal studies or other clinical conditions, as well as limited direct evidence for low dopamine levels in the frontal cortex and for elevated striatal dopaminergic function.

Research on receptor density was transformed with the introduction of newer, more advanced technologies, particularly PET and single photon emission computerised tomography (SPECT) from the mid-1980s. Imaging technology made it possible to test for elevation of dopamine receptors in drug-naive brains, which had not been a possible assumption when using post-mortem tissue. Neurochemical imaging of brains with schizophrenia could provide indirect indices of dopamine synthesis and release, and of synaptic dopamine levels. PET and SPECT studies have provided images of dopamine D2/3 receptors in schizophrenia. Considering the evidence from imaging studies, three meta-analyses conclude a modest (at most) elevation in striatal D2/3 receptor density in schizophrenia independent of antipsychotics analysis (Laruelle, 1998; Zakzanis & Hansen, 1998; Kestler, Walker et al., 2001; Howes & Kapur, 2009). A recent SPECT study,

looking at untreated first-episode patients, also finds a modest rise in D2 receptor binding in patients with first episode psychosis (Corripio, Escarti et al., 2011).[14]

The link between dopamine D2 receptors and schizophrenia has continued to be explored by the scientific community through the 1990s and 2000s; for example, Howes & Kapur (2009) estimate more than 6,700 articles and 18,000 citations on the topic of 'dopamine and schizophrenia' since 1991. In 2009, Howe & Kapur (2009) attempted to take stock of the evidence, and suggested further revised hypotheses to guide research going forward. They suggest that dopamine might be better linked to psychosis specifically rather than schizophrenia, and that it results through the interaction of multiple 'hits' with dysregulation primarily at the presynaptic dopaminergic control level.

Finally, as well as making a seminal contribution to the dopamine hypothesis of schizophrenia, Seeman's research has generated some wider interest in neuroscience research, being cited outside of pharmacology literature. One example of this was in the area of reward-related learning; from the late 1970s, the role of dopamine was also being discovered in this field (see, for example, Wise, Spindler et al., 1978) and Seeman's findings were discussed and cited in relation to it (Randaldi & Beninger, 1993; Beninger & Millar, 1998).

8.8 Interface B: Dissemination

Publication was the main channel used to disseminate findings from this research cloud. Seeman published each new finding on dopamine and schizophrenia throughout the progression of the research. Articles in peer-reviewed journals were the main mode of dissemination; Seeman would also publish letters to the editor and comment articles in scientific journals, actively putting forward his hypotheses and body of evidence on the linkages between dopamine receptors and schizophrenia (Seeman, Niznik et al., 1990; Seeman, 1992a).

In addition to this, researchers active in the field discussed progress face-to-face at conferences. For example, Seeman would attend the International Union of Basic and Clinical Pharmacology (IUPHAR)'s conference, held every four years (PS). Interactions at conferences helped to make labs more aware of international research aimed at addressing similar questions (IC). Seeman suggests that the tendency in the field was to be suspicious of competing labs and to restrict the sharing of information prior to publication. However, at times, researchers were open to sharing findings to help progress the field; for example, Seeman cited one instance where he openly shared his findings on dopamine D2 receptors and antipsychotics with Snyder; Seeman suggests that he was more interested in helping to progress the set up of the PET Unit in Baltimore to research dopamine receptors and schizophrenia, than in making advances against the competition (PS).

[14] Corripio, Escarti et al. (2011)'s study examined receptor density in 37 untreated patients with first-episode psychosis and 18 control subjects, using I^{123}-IBZM SPECT. The study found that patients who developed schiozphrenia showed higher D2 receptor binding than non-schizophrenia patients at first-episode psychosis. The study acknowledges some limitations: the investigators did not assess medication adherence through analysis of plasmatic levels, psychiatrists were not blind to baseline and follow-up clinical assessment, patient self-selection could introduce a bias, and finally the use of the frontal cortex as the control region.

8.9 Stage 4: Secondary outputs

None identified.

8.10 Stage 5: Applications

Though Seeman's research remained basic in nature, he maintained his final objective was to contribute to improved clinical treatment of schizophrenia, by improving understanding of its cause. Seeman defines his research as 'translational research', 'always with an… eye right down to the patient' and 'with treatment in mind' (PS). This interest in clinical research was supported by the constant influence of his wife, who was involved in the clinical side of mental disorders:

> Although I know the molecular basis of a lot of things, [Mary Seeman] knows how people feel and how people think. …She taught me the clinical relevance of what was going on. (PS)

Seeman suggests his research to establish the link between the receptor and the target for antipsychotics (the precursor to this research cloud) has been applied commercially, to inform screening tests for new neuroleptic drugs at pharmaceutical companies. A common target for neuroleptics could inform quick and automated screening tests on the potential for new drugs to be appropriate to treating the symptoms of schizophrenia. But the research cloud in question, examining receptor density, did not result in the same clarity of findings as the earlier work, due to methodological and logistical challenges surrounding the heterogeneity of the patients and their clinical histories, and the disorder.

Alongside his research, Seeman also aimed to have some influence on policy in Canada. He has actively lobbied for research funding and research policy in Canada; for example, in 1974 he published an article critiquing cuts to grant funding by the MRC of Canada. However, evidence of the potential influence of this lobbying on Canadian research policy has not been obtained.

8.11 Stage 6: Public engagement

None identified.

8.12 Stage 7: Final outcomes

As basic research, no clear linkages to final outcomes were identified. One reason for this could be that the trails from research outcomes, for example the development of new assays through to final outcomes on patients, are too diffuse to specify.

8.13 Table of payback

Payback category	Impacts from case study
Knowledge Production	• Seeman's wider research on dopamine receptors and antipsychotics has confirmed a common relationship between these receptors and

	neuroleptic treatments for schizophrenia. • This research cloud was unable to demonstrate with certainty a substantial increase in dopamine receptors with schizophrenia, independent of treatment. This was not largely resolved until the introduction of imaging studies (completed at other labs).
Research Targeting and Capacity Building	• Seeman's early research on dopamine receptors and schizophrenia helped to promote interest in schizophrenia and the dopaminergic system. • Setting up of PET units at John Hopkins University (Baltimore), and the Karolinska Institute (Stockholm) was influenced by research on molecular-level explanations of mental disorders (PS).
Informing Policy and Product Development	• Seeman's trail of research on dopamine receptors and antipsychotics has contributed to screening processes for antipsychotics. • D2 receptor occupancies identified with Seeman's work in the 1970s are used in drug development and in clinical treatment of patients with schizophrenia.
Health and Health Sector Benefits	• None identified.
Broader Social and Economic Benefits	• None identified.

8.14 Timeline

1967	Seeman takes up a research post at the University of Toronto
1967	Seeman begins to receive consistent grant funding from the Canadian Medical Research Council (MRC)
1970	Seeman begins to receive consistent funding from Ontario Mental Health Foundation
1974	First preparation of 3H Haloperidol with high specific activity to allow autoradiography (cited in Seeman, 1980)
1974	First preparation of +/- butaclamol to allow stereo spec auto radiography (cited in Seeman, 1980)
1976	Striking correlation of binding strength at D2 and therapeutic dose by Seeman's lab, similar findings published the same year by Snyder's lab at John Hopkins University
1977	Initial 20 schizophrenic brains accessed by Seeman's lab
1977	Seeman publishes on elevated D2 in schizophrenics
1980–1986	Seeman collects brain tissues for his research, acquiring tissues from tissue banks in Boston, Cambridge, Los Angeles, and Vienna

1978	Seeman's lab identifies D2 elevation in Parkinson's post-mortem brains but only for non-L-DOPA patients (Lee, Seeman et al., 1978)
1978	Identification of D2 elevation in Parkinson's patients with psychosis and neuroleptics. It is not clear which caused the elevation
1980	A formidable challenge was isolating the D2 receptor; found it could be solubilised by digitonin (Seeman, 1980)
1980	Seeman raises the question whether D2 elevation is due to neuroleptic administration. He also suggests looking at early stages of Huntington's disease for elevated D2 (when there are psychotic symptoms) (Seeman, 1980)
1980	Four types of dopamine binding sites are defined by differing sensitivities to dopamine and neuroleptics proposed (Seeman, 1980)
1980	Two affinities of D2 are identified
1985	Seeman discusses difficulties of measurement caused by two affinities of D1 and D2 receptors; not clear how this affects earlier data (Seeman, 1985; Seeman, 1987)
Mid-1980s	PET imaging is used to examine D2 receptors in living subjects
1986	Using PET, Wong et al. (1985, 1986) find a 2–3-fold elevation of D2 dopamine receptor densities in the caudate nucleus in drug-naive schizophrenic patients
1988, 1992	Using PET, Farde et al. (1988, 1993) do not find substantially elevated D2 dopamine receptor densities in the putamen or the caudate nucleus of drug-naive schizophrenics
1987	There remains considerable variation in in vivo PET measurements suggesting more work is needed (Seeman, 1987)
1988	Bunzow and Van Tol isolate the DNA for the synthesis of the dopamine D2 receptor in rat
1989	Remains unclear from early PET studies if D2 is elevated beyond adaptive response to treatment (Waddington, 1989)
Late 1980s	Dopamine hyperfunction is a key theory for schizophrenia but there remain critical unanswered questions (Waddington, 1989)
1990–1991	D1, D3, D4 and D5 receptors are cloned
1990	Seeman and Niznik publish a review of the evidence from post-mortem, PET and SPECT studies on dopamine receptors and transporters in Parkinson's Disease and schizophrenia; this suggests evidence shows a consistent elevation of D2 receptor density in brain putamen and caudate nucleus in schizophrenia

1991 Davis, Kahn et al., (1991) published a reconceptualisation of the dopamine hypothesis of schizophrenia, taking into account findings up to that time

Late 1990s – early 2000s
Imaging studies find only modest increases in receptor density (Laruelle, 1998; Zakzanis & Hansen, 1998; Kestler, Walker et al., 2001)

8.15 References

Beninger, R.J., & Millar, R. (1998). Dopamine D1-like receptors and reward-related incentive learning. *Neuroscience & Behavioral Reviews*, 22(2), 335–345.

Bird, E.D., Barnes, J., et al. (1977). Increased brain dopamine and reduced glutamic acid decarboxylase and choline acetyl transferase activity in schizophrenia and related psychoses. *The Lancet*, 310(8049), 1157–1159.

Bird, E.D., Spokes, E.G., et al. (1979a). Brain norepinephrine and dopamine in schizophrenia. *Science*, 204(4388), 93–94.

Bird, E.D., Spokes, E.G., et al. (1979b). Increased dopamine concentration in limbic areas of brain from patients dying with schizophrenia. *Brain: A Journal of Neurology*, 102(2), 347.

Corripio, I., Escarti, M.J., et al. (2011). Density of striatal D2 receptors in untreated first-episode psychoisis: an I123-IBZM SPECT study. *European Neuropyschopharmacology*, 21(11), 861–866.

Creese, I., Burt, D.R., et al. (1976). Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science*, 192(4238), 481.

Crow, T., Baker, H., et al. (1979). Monoamine mechanisms in chronic schizophrenia: post-mortem neurochemical findings. *British Journal of Psychiatry*, 134(3), 249–256.

Crow, T.J., Longden, A., et al. (1978). *Dopamine Turnover in Postmortem Brains in Schizophrenia*. Proceedings of the 7th International Congress for Pharmacology, Paris.

Davis, K.L., Kahn, R.S., et al. (1991). Dopamine in schizophrenia: a review and reconceptualization. *American Journal of Psychiatry*, 148(11), 1474–1486.

Dumbrille-Ross, A., & Seeman, P. (1984). Dopamine receptor elevation by cholecystokinin. *Peptides*, 5(6), 1207–1212.

Farde, L., Nordstrom, A.L., et al. (1992). Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine: relation to extrapyramidal side effects. *Archives of General Psychiatry*, 49(7), 538.

Farde, L., Pauli, S., et al. (1988). Stereoselective binding of 11C-raclopride in living human brain – a search for extrastriatal central D2-dopamine receptors by PET. *Psychopharmacology*, 94(4): 471-478.

Farley, I., Price, K., et al. (1977). Dopamine in the limbic regions of the human brain: normal and abnormal. *Advances in Biochemical Psychopharmacology*, 16, 57.

George, S., Watanabe, M., et al. (1985). The functional state of the dopamine receptor in the anterior pituitary is in the high affinity form. *Endocrinology*, 117(2), 690.

Guttman, M., & Seeman, P. (1986). Dopamine D2 receptor density in Parkinsonian brain is constant for duration of disease, age and duration of L-DOPA therapy. *Advances in Neurology*, 45, 51–57.

Guttman, M., & Seeman, P. (1985). L-DOPA reverses the elevated D2 dopamine receptor density in Parkinson's diseased striatum. *Journal of Neural Transmission*, 64(2), 93–103.

Guttman, M., Seeman, P., Bergeron, C., Riederer, P., Jellinger, K., & Tourtellotte, W.W. (1986). Dopamine D2 receptor density remains constant in treated Parkinson's disease. *Annals of Neurology*, 19(5), 487–492.

Howes, O.D., & Kapur, S., (2009). The dopamine hypothesis of schizophrenia: version III—the final common pathway. *Schizophrenia Bulletin*, 35(3), 549.

Kestler, L., Walker, E., et al. (2001). Dopamine receptors in the brains of schizophrenia patients: a meta-analysis of the findings. *Behavioural Pharmacology*, 12(5), 355.

King, M.V., Seeman, P., et al. (2009). Increased dopamine D(2)(high) receptors in rats reared in social isolation. *Synapse*, 63(6), 476–483.

Laruelle, M. (1998). Imaging dopamine transmission in schizophrenia. A review and meta-analysis. *The Quarterly Journal of Nuclear Medicine*, 42(3), 211.

Lee, T., & Seeman, P. (1980). Elevation of brain neuroleptic/dopamine receptors in schizophrenia. *American Journal of Psychiatry*, 137(2), 191–197.

Lee, T., Seeman, P., Tourtellotte, W.W., Farley, J., & Hornykeiwicz, I.J. (1978). Binding of 3H-neuroleptics and 3H-apomorphine in schizophrenic brains. *Nature*, 274, 897–900.

Lee, T., Seeman, P., et al. (1978). Receptor basis for dopaminergic supersensitivity in Parkinson's disease. *Nature*, 273(5657), 59–61.

Lyon, G.J., Abi-Dargham, A., et al. (2011). Presynaptic regulation of dopamine transmission in schiozphrenia. *Schiozphrenia Bulletin*, 37(1), 108–117.

Mackay, A.V.P., Iversen, L.L., et al. (1982). Increased brain dopamine and dopamine receptors in schizophrenia. *Archives of General Psychiatry*, 39(9), 991.

McGeer, P.L., & McGeer, E.G. (1977). Possible changes in striatal and limbic cholinergic systems in schizophrenia. *Archives of General Psychiatry*, 34(11), 1319.

Novak, G., & Seeman, P. (2010). Hyperactive mice show elevated D2High receptors, a model for schizophrenia: calcium/calmodulin-dependent kinase II alpha knockouts. *Synapse*, 64(10), 794–800.

Peroutka, S.J., & Synder, S., (1980). Relationship of neuroleptic drug effects at brain dopamine, serotonin, alpha-adrenergic, and histamine receptors to clinical potency. *American Journal of Psychiatry*, 137(12), 1518.

Randaldi, R., & Beninger, R.J. (1993). Dopamine D1 and D2 antagonists attenuate amphetamine-produced enhancement of responding for conditioned reward in rats. *Psychopharmacology*, 113, 110–118.

Schoots, O., Seeman, P., Guan, H.-C., Paterson, A., & Van Tol, H.H.M. (1995). Long-term haloperidol elevates dopamine D4 receptors by two-fold in rats. *European Journal of Pharmacology*, 289(1), 67–72.

Seeman, P. (2011). All roads to schizophrenia lead to dopamine supersensitivity and elevated dopamine D2High receptors. *CNS Neuroscience and Therapeutics*, 17(2), 118–132.

Seeman, P. (2008a). Dopamine D2High receptors moderately elevated by sertindole. *Synapse*, 62(5), 389–393.

Seeman, P. (2008b). Dopamine D2High receptors moderately elevated by bifeprunox and aripiprazole. *Synapse*, 62(12), 902–908.

Seeman, P. (2008c). Dopamine D2High receptors measured ex vivo are elevated in amphetamine-sensitized animals. *Synapse*, 63(3), 186–192.

Seeman, P. (1992a). Elevated D2 in schizophrenia: role of endogenous dopamine and cerebellum. Commentary on 'The current status of PET scanning with respect to schizophrenia'. *Neuropsychopharmacology*, 7(1), 55.

Seeman, P. (1992b). Dopamine receptor sequences. Therapeutic levels of neuroleptics occupy D2 receptors, clozapine occupies D4. *Neuropsychopharmacology*, 7(4), 261–84.

Seeman, P. (1987). Dopamine receptors and the dopamine hypothesis of schizophrenia. *Synapse*, 1(2), 133–152.

Seeman, P. (1980). Brain dopamine receptors. *Pharmacological Reviews*, 32(3), 229.

Seeman, P., & Lee, T. (1975). Antipsychotic drugs: direct correlation between clinical potency and presynaptic action on dopamine neurons. *Science*, 188(4194), 1217.

Seeman, P., & Niznik, H.B. (1990). Dopamine receptors and transporters in Parkinson's disease and schizophrenia. *FASEB Journal*, 4(10), 2737–2744.

Seeman, N., & Seeman, P. (2009). *Psychosis: Discovery of the Antipsychotic Receptor*. Toronto: SZ Publications.

Seeman, P., & Van Tol, H.H.M. (1995). Dopamine D4-like receptor elevation in schizophrenia: cloned D2 and D4 receptors cannot be discriminated by raclopride competition against [3H]nemonapride. *Journal of Neurochemistry*, 64(3), 1413–1415.

Seeman, P., Bzowej, N.H., et al. (1987a). Human brain dopamine receptors in children and aging adults. *Synapse* 1(5): 399–404.

Seeman, P., Bzowej, N.H., et al. (1987b). Human brain D1 and D2 dopamine receptors in schizophrenia, Alzheimer's, Parkinson's and Huntington's diseases. *Neuropsychopharmacology*, 1(1), 5–15.

Seeman, P., Chau-Wong, M., et al. (1975). Brain receptors for antipsychotic drugs and dopamine: direct binding assays. *Proceedings of the National Academy of Sciences*, 72(11), 4376.

Seeman, P., Guan, H.-C., Nobrega, J., Jiwa, D., Markstein, R., Balk, J.-H., Picetti, R., Borelli, E., & Van Tol, H.H.M. (1997). Dopamine D2-like sites in schizophrenia, but not in Huntington's, Alzheimer's or control brains, for [3H]benzquinoline. *Synapse*, 25(2), 137–146.

Seeman, P., Guan, H.-C., & Van Tol, H.H.M. (1995). Schizophrenia: elevation of dopamine D4-like sites, using [3H]nemonapride and [125I]epidepride. *European Journal of Pharmacology*, 286(2), R3–R5.

Seeman, P., Guan, H.-C., & Van Tol, H.H.M. (1993). Dopamine D4 receptors elevated in schizophrenia. *Nature*, 365(6445), 441–445.

Seeman, P., Lee, T., Bird, E.D., & Tourtellotte, W.W. (1980). Elevation of brain neuroleptic/dopamine receptors in schizophrenia. In Baxter, C., & Melnechuk, T. (eds.), *Perspectives in Schizophrenia Research*, New York: Raven Press, 195–202.

Seeman, P., Lee, T., et al. (1976). Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature*, 261(5562), 717–719.

Seeman, P., Niznik, H.B., et al. (1990). Elevation of dopamine D2 receptors in schizophrenia is underestimated by radioactive raclopride. *Archives of General Psychiatry*, 47(12), 1170.

Seeman, P., Tallerico, T., et al. (2002). Amphetamine-sensitized animals show a marked increase in dopamine D2 high receptors occupied by endogenous dopamine, even in the absence of acute challenges. *Synapse*, 46(4), 235–239.

Seeman, P., Ulpian, C., Bergeron, C., Riederer, P., Jellinger, K., Gabriel, E., Reynolds, G.P., & Tourtellotte, W.W. (1984). Bimodal distribution of dopamine receptor densities in brains of schizophrenics. *Science*, 225(4663), 728–731.

Van Rossum, J. (1966). The significance of dopamine-receptor blockade for the mechanism of action of neuroleptic drugs. *Archives internationales de pharmacodynamie et de therapie*, 160(2), 492.

Waddington, J.L. (1989). Sight and insight: Brain dopamine receptor occupancy by neuroleptics visualised in living schizophrenic patients by positron emission tomography. *British Journal of Psychiatry*.

Wise, R.A., Spindler, J., et al. (1978). Neuroleptic-induced 'anhedonia' in rats: pimozide blocks reward quality of food. *Science*, 21, 262–264.

Wong, D.F., Wagner, H.N., et al. (1985). Dopamine receptor binding of C-11-3-N-methylspiperone in the caudate in schizophrenia and bipolar disorder: a preliminary report. *Psychopharmacology Bulletin*, 21(3), 595.

Wong, D.F., Wagner, H.N., et al. (1986). Positron emission tomography reveals elevated D2 dopamine receptors in drug-naive schizophrenics. *Science*, 234(4783), 1558.

Wreggett, K.A., & Seeman, P. (1984). Agonist high-and low-affinity states of the D2-dopamine receptor in calf brain. Partial conversion by guanine nucleotide. *Molecular Pharmacology*, 25(1), 10.

Zakzanis, K.K., & Hansen, K.T. (1998). Dopamine D2 densities and the schizophrenic brain. *Schizophrenia Research*, 32(3), 201–206.

CHAPTER 9 Expressed emotion research in London, UK, Chandigarh, India and Aarhus, Denmark

This case study is based on the research that produced the paper:

Leff, J., Wig, N.N., Bedi, H., Menon, D.K., Kuipers, L, Korten, A., Ernberg, G., Day, R., Sartorius, N., & Jablensky, A. (1990). Relatives' expressed emotion and the course of schizophrenia in Chandigarh. A two-year follow-up of a first-contact sample. *British Journal of Psychiatry*, 156(3), 351–356.

Information was gathered from interviews with Elizabeth Kuipers, Julian Leff, Keerti Menon and Norman Sartorius, as well as desk-based research.

9.1 Summary

The target paper is part of the World Health Organization study on Determinants of Outcomes of Severe Mental Disorders (DOSMD), looking at relatives' expressed emotion and the effects on outcomes of patients with schizophrenia. The DOSMD followed on from the International Pilot Study of Schizophrenia (IPSS), testing the reliability of the IPSS findings on cross-country incidence and experience of schizophrenia through an epidemiological study of mental disorder in defined populations.

This research cloud was a discrete piece of work within the DOSMD study, specifically aimed at testing whether differences in relatives' expressed emotion could help explain variation in the course and outcomes of schizophrenia across cultures. The expressed emotion hypothesis was tested in two locations: Aarhus and Chandigarh. This work was conducted in the late 1970s with a two-year follow-up completed in early 1980, and is a 'nested study' within the wider epidemiological work. Patient samples included individuals aged 15–54 years who contacted a psychiatric service for the first time within a specified two-year period, and who could be classified as schizophrenic or suffering from paranoid or other psychotic states. Aarhus provided 28 patients, and Chandigarh some 78.

The study included researchers from the Psychiatry Unit at the Institute of Psychiatry (IOP), the WHO headquarters in Geneva, and the Aarhus and Chandigarh field centres (J. Leff, E. Kuipers and A. Ghosh from London; N.N. Wig, K. Menon and H. Bedi from Chandigarh; E. Strömgren, G. Thestrup and J. Achton Nielsen from Aarhus; and N. Sartorius, A. Jablensky, R. Day, G. Ernberg and A. Korten from the WHO).

The main conclusions of this study were that in Aarhus, Danish relatives were very similar to UK relatives in their mean score and the interrelationships of expressed emotion characteristics. However, the sample size was too small to come to any meaningful conclusion about potential differences with the UK. The sample size was further reduced as some patients' initial illness failed to improve during the first year and they were placed in sheltered accommodation; attrition prevented further meaningful analysis. In Chandigarh, there were noticeable differences in expressed emotion between rural and urban relatives. In addition, in Chandigarh the relapse rate at year two was 37 percent (22 out of 60). Expressed emotion measured only at times of crisis (as consistent with earlier research) had a significant association with predicted relapse.

The study had several novel contributions to the field methodologically and substantively. First, it provided evidence that an interview protocol based on tone and conversation could be translated and applied in a different language and culture, other than the one in which it was originally designed. Secondly, it suggested that there could be cross-cultural differences in the manifestation of expressed emotion among families and other carers between studies done in the UK, in Aarhus, and in rural and urban Chandigarh. The study found low levels of expressed emotion on average among city dwellers in Chandigarh (30 percent) versus the average in England, which was about 54 percent. Peasant farmers in Chandigarh had an even lower percentage with high levels of expressed emotion (8 percent). At the one-year follow-up no rural relatives were rated as high expressed emotion. Thirdly, the study suggested that expressed emotion did correspond with differences in outcomes of schizophrenia in India, similar to what had been found in the UK. Substantially more people in Chandigarh were not ill after two years; and substantially fewer relatives in Chandigarh had high expressed emotion compared to English relatives. Finally, one researcher involved suggested that this was one of the first studies in India (if not the first) to look at psychosocial factors associated with mental illness, in particular, acute psychosis. Prior to the WHO work, the first mental health survey in India had been undertaken in 1961.

This research provided value by helping to explain why cases of specific mental disorders might differ between countries and cultures. By looking at expressed emotion, it also had the potential to contribute to debate about the relevance and value of psychosocial approaches to understanding the course and outcomes of schizophrenia. In the UK, there was a growing interest in psychosocial approaches to understanding schizophrenia, despite a decline in interest in psychosocial aspects of schizophrenia in the US in the 1970. Expressed emotion was one strand of research pursued by those interested in psychosocial approaches; in the 1970s and 1980s, the relevance of expressed emotion to understanding schizophrenia was contested. From when the research was conducted in the late 1970s through to its publication in the late 1980s, there remained an ongoing divide in the field between those taking a more biological view of the course of schizophrenia (i.e., that expressed emotion was a result of the impact of the illness on the family, not an influencing factor on the course of the disorder), and those emphasising the psychological (i.e., arguing that expressed emotion altered the course of schizophrenia).

Collaboration was key to the implementation of this study. Both the research funding (shared between the WHO, the NIMH and participating field research centres) and the research activities (engaging researchers based in Geneva, London, Chandigarh and

Aarhus) were collaborative. None of the researchers involved chose to maintain a focus solely on expressed emotion studies following the completion of this research.

9.2 Introduction

9.2.1 Scientific background

Relative's expressed emotion (EE) is 'a measure of the family environment that is based on how the relatives of a psychiatric patient spontaneously talk about the patient' (Butzlaff & Hooley, 1998, 547). Expressed emotion is assessed among relatives and carers of patients during a semi-structured interview about the family member with the disorder. A summary rating is made based on the content and affective tone of the comments during the interview. Relatives are classified as high expressed emotion if they make a threshold number of critical comments, show signs of hostility or a marked emotional over-involvement (Vaughn & Leff, 1976b).

The **Camberwell Family Interview (CFI)** is a protocol and scale used to assess expressed emotion (e.g., warmth, hostility, critical comments) among carers and family members of those with mental disorders. The interview is conducted in private with the relatives, taped, and coded afterwards by a trained rater. Ratings are allocated on the number of critical remarks, based on content or tone, that indicate dislike or disapproval of some characteristic or behaviour of the patient. Studies using the CFI most often do not observe negative interactions between the family members and patients; they are based solely on how a family member or carer discusses and expresses feelings about the person with the mental disorder (see Vaughn & Leff, 1976b; Hooley, Rosen et al., 1995). There have been two studies of direct interaction between relatives and patients that have shown a close correspondence between ratings of the CFI and of videotaped direct interactions (see Strachan, Leff et al., 1986).

9.2.2 Researchers' background

The research was conducted as part of the World Health Organization (WHO)-coordinated Determinants of Outcomes of Severe Mental Disorder (DOSMD) study. The work that is the focus for this case study involved researchers from London (UK), Aarhus (Denmark) and Chandigarh (India). Implementing the study involved the following investigators: J. Leff, E. Kuipers and A. Ghosh from London; N.N. Wig, K. Menon and H. Bedi from Chandigarh; E. Strömgren, G. Thestrup and J. Achton Nielsen from Aarhus; and N. Sartorius, A. Jablensky, R. Day, G. Ernberg and A. Korten from the WHO – and involved in coordination, oversight and/or analysis of the study.

MRC Social Psychiatry Unit, Institute of Psychiatry, London, UK

Julian Leff was a researcher at the MRC Social Psychiatry Unit at the Institute of Psychiatry (IOP) in London, headed by John Wing, when this research took place. In 1968, Wing tasked Leff with designing and completing a trial of medication for schizophrenia, to study whether it was worth continuing patients on antipsychotics for their whole life. Leff agreed but also continued to pursue an interest in social psychiatry. When Christine Vaughn joined the unit in the 1970s as a PhD student, Leff and Vaughn collaborated on research into expressed emotion. This work was a precursor to and provided context for his work on expressed emotion and cross-cultural experiences of

schizophrenia in this research cloud. Leff is currently a Professor Emeritus in social psychiatry at the IOP and an honorary professor at University College London.

Elizabeth Kuipers joined the IOP in 1977. Initially, her research focus was family intervention in schizophrenia. For this research cloud, Kuipers trained researchers at the Chandigarh (Bedi and Menon) and Aarhus field centres in rating expressed emotion from the CFI. Kuipers currently is a Professor of Clinical Psychology and Head of the Department of Psychology at the IOP. Her research interests are now focused on cognitive models of schizophrenia and caregiving, as well as developing and evaluating family intervention and cognitive behavioural therapy (CBT) for psychosis.

A. Ghosh was a researcher at the IOP during the case study research. Ghosh had completed postgraduate studies at Chandigarh, before migrating to the UK in the 1970s and accepting a research position at the IOP. At the IOP Ghosh was trained in the CFI. His role in this research cloud was to ensure inter-rater reliability, checking consistency and validating the application of the CFI in Hindi by Bedi and Menon.

WHO Collaborating Centre for Research and Training in Mental Health, Postgraduate Institute of Medical Education and Research (PGI), Chandigarh, India

N.N. Wig was the chief collaborating investigator for the Chandigarh Field Research Centre from 1976–1980, based at the Postgraduate Institute of Medical Education & Research (PGI) Chandigarh. Wig was instrumental in shaping the direction of the research at the Chandigarh field study centre (KM). Wig was also Head of the Department of Psychiatry at PGI Chandigarh until 1980, upon which he took up the position of Professor and Head of Psychiatry Department at the All Indian Institute of Medical Sciences (AIIMS), New Delhi. From 1984 to 1990, Wig was also the appointed Regional Advisor, Mental Health at Alexandria, Egypt for the WHO. He is now retired and remains an Emeritus Professor at PGI Chandigarh.[15]

H. Bedi was a social scientist working with the WHO Collaborating Centre for Research and Training in Mental Health at PGI Chandigarh for this research. She conducted the CFI protocol the first time around with Menon, and also conducted the one- and two-year follow-up interviews. Bedi remained in research until 1981–1982. At present, she lives in Chandigarh with her family (NW).

D. Keerti Menon was a clinical psychologist with a temporary contract at the WHO Collaborating Centre, Chandigarh when this research was conducted. He carried out the investigation and interviews at Chandigarh with Bedi. After moving to the Indian Council of Medical Research in June 1981, he took up the position of Director of the National Institute for the Mentally Handicapped in 1984. Here, Menon continued to pursue an interest in the role of the carer and family members, but moved away from looking at individuals with schizophrenia to individuals with learning disabilities.

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[15] Those involved in the Chandigarh work for the DOSMD more widely included R.S. Murthy, K.P. Mangalwedhe, P. P. Behere, H. Kaur, A.K. Misra, S.K. Khandelwal, H.R. Phookun, E.N. Gupta, R.S. Lamba, C.B. Kare, R.K. Agarwal, V.K. Sharma, R.C. Jiloha, B.M. Tripathi and M. Khare. See Sartorius, Jablensky et al. (1986).

WHO International Pilot Study of Schizophrenia (IPSS) and DOSMD Headquarters, Geneva, Switzerland

Norman Sartorius became head of the WHO programme of epidemiology and social psychiatry soon after joining the WHO in 1967. He was the principal investigator for the International Pilot Study of Schizophrenia (IPSS) and the DOSMD. He became Director of the Division of Mental Health of the WHO in 1977, holding this position until 1993.

Assen Jablensky was a co-principal investigator for the DOSMD when the research cloud was conducted. From 1982–1987 Jablensky was also chair of the WHO Task Force developing the ICD-10 diagnostic criteria for mental disorders. In 1993 he moved to Australia, continuing research on epidemiology, genetics, classification of mental disorders and psychotic disorders. Jablensky currently is a Winthrop Professor at the University of Western Australia and Director of the Centre for Clinical Research in Neuropsychiatry (CCRN), Graylands Hospital.

G. Ernberg, R. Day and **A. Korten** were also involved in the research as part of the wider DOSMD team. **Ernberg** was a technical officer at the Division of Mental Health, WHO, in Geneva. **Day** was based at the WHO headquarters and at the Psychiatric Epidemiology Program, University of Pittsburgh, Pennsylvania. **Korten** was a researcher in medical statistics and epidemiology at the WHO in Geneva during the DOSMD. She returned to Australia in 1985 and took up a research post at the Australian National University.

Aarhus

E. Strömgren became the chief collaborating investigator at the Aarhus field research centre in 1966, holding this position during this research cloud. **Grethe Thestrup** and **Jørgen Achton Nielsen** were also involved in conducting research at Aarhus.[16]

9.3 Defining the research cloud

This research cloud was part of a wider WHO-coordinated study, the Determinants of Outcome of Severe Mental Disorder (DOSMD). The DOSMD followed on from the International Pilot Study of Schizophrenia (IPSS); the aim of the latter was to develop a basis for a subsequent, meaningful and internationally comparative epidemiological study of mental disorders. The DOSMD remains one of few studies designed to examine the incidence and course of schizophrenia in contrasting sociocultural contexts.

The researchers involved in the IPSS sought to establish whether it was possible to develop and implement a standardised psychiatric diagnosis, classification and statistics, as well as determine if there were comparable cases of mental disorders across populations. Among the findings of the IPSS was the suggestion that patients with schizophrenia in India and other developing countries faced better prognosis than from field centres in Europe and North America.

The DOSMD was designed to follow on from the IPSS, testing the reliability of the IPSS findings on cross-country incidence and experience of schizophrenia through an

[16] Others involved in the DOSMD at Aarhus but not authors on publications from this research cloud were M. Fischer, A. Bertelsen, P. Munk-Jørgensen and L. Sand-Stromgren.

epidemiological study of mental disorder in defined populations. The DOSMD was conducted in nine WHO field centres, using nine different languages. The DOSMD had an incidence sample of 1,017 patients with schizophrenia with first-in-lifetime contact with a helping agency as a result of psychotic symptoms across the centres.[17]

This research cloud was a discrete piece of work within the DOSMD study, specifically aimed at testing whether differences in relatives' expressed emotion (EE) could help explain variation in the course and outcomes of schizophrenia across cultures. The EE hypothesis was tested in two locations: Aarhus and Chandigarh.

The paper selected as the entry point to the research cloud was:

1. Leff, J., Wig, N.N., Bedi, H., Menon, D.K., Kuipers, L, Korten, A., Ernberg, G., Day, R., Sartorius, N., & Jablensky, A. (1990). Relatives' expressed emotion and the course of schizophrenia in Chandigarh. A two-year follow-up of a first-contact sample. *British Journal of Psychiatry*, 156(3), 351–356.

Other publications describing the findings of this research cloud include:

2. Leff, J., Wig, N.N., Ghosh, A., Bedi, H., Menon, D.K., Kuipers, L., Korten, A., Ernberg, G., Day, R., Sartorius, N., et al. (1987). Expressed emotion and schizophrenia in north India. III. Influence of relatives' expressed emotion on the course of schizophrenia in Chandigarh. *British Journal of Psychiatry*, 151, 166–173.
3. Wig, N.N., Menon, D.K., Bedi, H., Ghosh, A., Kuipers, L., Leff, J., Korten, A., Day, R., Sartorius, N., Ernberg, G., et al. (1987). Expressed emotion and schizophrenia in north India. I. Cross-cultural transfer of ratings of relatives' expressed emotion. *British Journal of Psychiatry*, 151, 156–160.
4. Wig, N.N., Menon, D.K., Bedi, H., Leff, J., Kuipers, L., Ghosh, A., Day, R., Korten, A., Ernberg, G., Sartorius, N., et al. (1987). Expressed emotion and schizophrenia in north India. II. Distribution of expressed emotion components among relatives of schizophrenic patients in Aarhus and Chandigarh. *British Journal of Psychiatry*, 151, 160–165. Erratum in: *British Journal of Psychiatry*, 151, 870.

9.4 Stage 0: Opportunity identification/research needs assessment

Inspiration

The decision to implement the DOSMD arose through the coming together of new publications, informal discussions and formal consultations. First, the decision was influenced by two publications on the methods and scope for epidemiology in mental disorders, respectively (Reid, 1960; Lin, Standley et al., 1962). At this time, informal

[17] The study included 1,379 patients initially, of which 78.2 percent completed the follow-up after two years. Cohorts were recruited over two years, through active case finding within defined geographical areas, aiming to intercept all new onsets at all kind of facilities (e.g., including primary care, traditional healers, religious shrines). The duration of untreated psychosis was less than one year for 85 percent of included cases; of these, 10 percent had been prescribed antipsychotic drugs prior to entry into the study (Jablensky & Sartorius (2008).

discussions took place about feasible approaches to cross-cultural psychiatric epidemiological research between M. Kramer, S.W. Greenhouse, M. Katz, T.Y. Lin, B. Pasamanick and J. Zubin (International Pilot Study of Schizophrenia, 1973), and consultations were held with research experts more widely (including with John Wing, head of the MRC Social Psychiatry Unit at the IOP). The culmination of this was a successful application for funding by a group from the WHO's Scientific Group to the National Institute of Mental Health (US), WHO and multiple WHO field research centres to conduct an international comparative study on the course and outcomes of schizophrenia.

By the mid-1970s, research, including that conducted through the IPSS and DOSMD, was suggesting that the course and outcomes of schizophrenia varied between countries (Adeoye Lambo, 1955; Rin & Lin, 1962; Jilek & Jilek-Aall, 1970; Murphy & Raman, 1971; Waxler, 1979); however, the reasons for this variation were not known. Within the context of the DOSMD, the coordinating body decided to explore specific hypotheses to seek an explanation. Differences in the level and nature of expressed emotion (EE) among carers of patients with schizophrenia was put forward as a possible reason for variation across cultures.

In the 1970s, a group of researchers in the UK, primarily at the MRC's Social Psychiatry Unit, London, were investigating the effect of the EE of carers on relapse of psychosis (Brown, 1959). Interest in the effect of EE had been sparked by key studies published at the Social Psychiatry Unit that showed relatives' EE to be a significant predictor of the progress and re-admission of men discharged from mental hospitals (Brown, Birley et al., 1972; Vaughn & Leff, 1976a; Vaughn & Leff, 1976b).

The MRC Social Psychiatry Unit was also a WHO collaborating field research centre at the time. This allowed for cross-fertilisation and sharing of ideas between researchers involved in the IPSS and DOSMD, and investigating EE. This crossover between individuals involved in the two areas of research helped in forming the idea for a sub-study within the DOSMD to examine whether EE was a contributing factor to international variation in the course and outcomes of schizophrenia.

Feasibility

The sub-study on EE was enabled through operating resources committed for the DOSMD. There was a central coordinating body to manage the study based in Geneva, supported by specific teams, instruments, and screening, translation, training and quality control procedures. Nine field research centres also participated: Aarhus, Agra, Cali, Ibadan, London, Moscow, Taipei, Washington and Prague.[18] These field study centres had committed patients, infrastructure and expertise for the DOSMD wider research

[18] The DOSMD set out specific criteria for selection of field study centres. To be eligible, centres were required to have a network of services that could detect a substantial proportion of likely cases of schizophrenia in the population, have available census data on the population, have low death and emigration rates, have a well-trained staff of psychiatrists, be able to set up reporting systems to inform psychiatrists of the potential cases of schizophrenia, and have a distinct local culture(s).

programme, who could be accessed for the sub-studies on potential explanations for cross-cultural variation (NS) (see also Jablensky & Sartorius, 2008).[19,20]

There were additional specific reasons that made the research question on EE particularly feasible for the DOSMD team. Brown and Rutter at the IOP had already developed an interview protocol that could be used to examine this (which was the basis for the CFI) (Brown & Rutter, 1966), and the protocol had been made more concise by Vaughn and Leff, also at the IOP (1976a; 1976b). Additionally, the researchers at the IOP who were involved also in the IPSS and DOSMD were among the early researchers applying this interview protocol, and examining the effects of EE on the course and outcome of patients with schizophrenia. The IOP was at the forefront of work on EE, in particular, Leff, Vaughn and Kuipers with Ruth Berkovitch, David Sturgeon and Rosemary Eberlein-Friess were involved in exploring research on EE of families and carers of individuals with schizophrenia.

Potential value

The DOSMD was designed to improve management of diseases through acquisition of morbidity statistics across countries. The research programme developed to contribute to this aim included studies designed to support standardisation of psychiatric diagnosis, classification and statistics, and as well as comparative research on specific mental disorders, to determine whether comparable cases could be identified across populations (Lin, Sartorius et al., 1973). This research could provide value by helping to explain why cases of specific mental disorders might differ between countries and cultures. By looking at EE, this research also had potential to contribute to the debate about the relevance and value of psychosocial approaches to understanding the course and outcomes of schizophrenia. In the UK, there was a growing interest in psychosocial approaches to understanding schizophrenia, despite a decline in interest in psychosocial aspects of schizophrenia in the US in the 1970s.[21] EE was one strand of research pursued by those interested in psychosocial approaches; in the 1970s and 1980s, the relevance of EE to understanding schizophrenia was contested. From when the research was conducted in the late 1970s through to its publication in the late 1980s, there remained an ongoing divide in the field between those taking a more biological view of the course of schizophrenia (i.e., that EE was a result of the impact of the illness on the family, not an influencing factor on the course of the disorder), and those emphasising the psychological (i.e., arguing that EE altered the course of schizophrenia). One area of contention was the relationship between EE and relapse: if high EE was a causal factor of relapse, or whether patients with very severe symptoms were more likely to both relapse and trouble their families.

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[19] Sub-studies were conducted within the first two years, each in one or two field study centres. Topics included stressful life events, job support and disability (NS), and expressed emotion (Sartorius, Jablensky et al. (1986).

[20] The one- and two-year follow-ups for the expressed emotion study were not completed in Aarhus, Denmark, due to a combination of challenges including high levels of attrition among the patient population (i.e., too few remained with their families to allow for follow-up at one and two years).

[21] For example, evidenced by a sharp decline in psychosocial articles in the *American Journal of Psychiatry* (JL).

During this time, a series of interventional studies found that reducing EE levels among family members led to a reduction in the likelihood of early psychiatric relapse among discharged patients (e.g., Falloon, Boyd et al., 1982; Leff, Kuipers et al., 1982; Leff, Kuipers et al., 1985; Hogarty, Anderson et al., 1986). Notably, Leff, Kuipers et al. (1982) published an important controlled trial arguing in favour of the causal effect of high expressed emotion on the course of schizophrenia, as well as the therapeutic effectiveness of social interventions combined with drug treatment. However, other interventional studies disagreed with these findings. In particular, MacMillan, Gold et al. (1986) found that after controlling for medication status and duration of illness, the relationships between high levels of EE and relapse in first-episode schizophrenics became insignificant. Research on EE internationally would provide additional evidence to help bring clarity to this debate.

9.5 Stage 1: Inputs to research

Money, researcher time, lab/office space and consumables

As specified above, operating costs for this research were covered through funding and other resources committed to the DOSMD. Funding for the DOSMD covered the cost of doing the research, including exchanges and visits between collaborating investigators, consultants, research support and clerks, and supplies, and was provided in equal parts by the WHO, the WHO Field Research Centres, and the National Institute of Mental Health in the US (Grant No. MH09239) (NS). All three funders as well as WHO management and leadership, investigators and collaborating institutions had input into how funding was spent. For example, the decisions about which sub-studies to support or which field research centres to include were made collaboratively (NS). Funders could also input into how their specific contributions were spent: NIMH specified that some of its funding should be set aside for annual meetings that brought together investigators from each of the participating field research centres. These meetings were usually week-long affairs, and were used to share experiences, progress and challenges, and to check on the inter-rater reliability of the investigators.

Investigator salaries were not covered through the general DOSMD funding; there were no direct financial benefits for investing time to DOSMD research (EK, NS). Field research centre investigators were paid by their institutions. The lack of DOSMD funding for investigators' time had implications for the researchers' motivation and scope to commit time to DOSMD research, including the EE study:

> It was nobody's main job. We weren't funded to do this specific study, we just happened to do it as well. So then it depends on personal interest and enthusiasm, and who's got the time. (EK)

To maintain investigator engagement in the research, the WHO coordinating body took on the task of motivating collaborating investigators:

> The strong motivation was of crucial importance. We then had to think about how to maintain this motivation and make sure people continued with the same spirit. (NS)

While it could be challenging to coordinate and engage dispersed and diverse researchers, one interviewee from the DOSMD headquarters suggests that they were able to successfully encourage sustained engagement and cooperation:

> It required a bit of skill to make [the collaboration] work, but it was perfectly possible. [The investigators] were people with good will and were good scientists also. It was quite possible to make them agree and proceed with the work. (NS)

Field research centres provided infrastructure, equipment and patient populations for the research. Three field research centres were involved in this study: a London centre based at the IOP and the Maudsley Hospital; a centre in Aarhus at the University of Aarhus, and a centre in Chandigarh, based at PGI Chandigarh. The fieldwork took place in Chandigarh and Aarhus (primarily the former). PGI Chandigarh was set up in 1962 (becoming an autonomous body in 1967) to provide high-quality patient care, and to provide postgraduate medical education and training to meet national requirements for medical teaching and for basic community-based research.[22] Research activities at PGI Chandigarh were supported by access to international research publications,[23] as well as a bilingual research staff (in English and Hindi; bilingualism was essential to the EE study as it depended heavily on language) (KM). The patient population for the fieldwork in Chandigarh came from the surrounding urban and rural communities, and were patients of PGI Chandigarh.

Expertise and techniques

Successfully implementing this research required investigators to conduct and assess CFI interviews held with carers of patients with schizophrenia in Chandigarh and Aarhus. The researchers at the WHO headquarters, and the London, Aarhus and Chandigarh field research centres had varying degrees of familiarity and experience in the CFI protocol. For example, Leff had experience conducting cross-cultural studies as well as implementing and assessing CFI interviews, whereas researchers based at Chandigarh and Aarhus had not previously worked with the EE schedule.[24] To achieve sufficient expertise across the research team in conducting and assessing the CFI, researchers at Aarhus and Chandigarh underwent training provided by researchers from the IOP. Training was first conducted in London; Kuipers followed this up with further training in Chandigarh, and also observed some interviews to check their implementation. Kuipers had the knowledge to take on this role, having been trained previously by Vaughn, who was among the original researchers to modify and shorten the CFI to be used for patients with schizophrenia (EK).

The CFI protocol also was not yet translated into Hindi or Danish; this created an additional challenge as it required researchers to have the expertise to translate the protocol across languages and cultures. Translating and checking the validity of the translation became one of the first stages of this research.

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[22] The urban environment at Chandigarh was unique in India. It was a planned city designed by Le Corbusier, with Phase One of the city built between 1951 and 1965. Leff suggests a substantial number of highly educated people were attracted to the city because of its social and cultural infrastructure, and also the postgraduate medical institute.

[23] For example, Menon would write a letter to the US National Institutes of Health with keywords of interest and within approximately two weeks he would receive printouts of relevant abstracts.

[24] Though not experienced in expressed emotion, there was some existing interest at the Chandigarh field centre in how this could be applied to looking at schizophrenia in India. Menon in particular had been interested in the findings of Leff & Vaughn (1976a, 1976b), and Brown, Birley and Wing (1972).

Collaborators

Collaboration was a key to implementation of this study. Both the research funding (shared between the WHO, the NIMH and participating field research centres) and the research activities (engaging researchers based in Geneva, London, Chandigarh and Aarhus) were collaborative.

Researchers were invited to participate in the EE study by the DOSMD coordinators (NS). Most of the selected researchers had particular expertise and/or were already involved in other DOSMD research. For example, Leff was seen as a logical key investigator for the study, as a result of his ongoing contacts with the wider WHO work and his experience in EE research (EK, NS).

Collaboration was strengthened by the commitment and interest of the researchers involved:

> They contributed their own time and effort in a very generous way. …They participated because on the one hand they were interested in the topic, but they were also interested in maintaining good relations with the rest of the crowd. It was really a very enthusiastic feeling. (NS)

Coordination and communication between dispersed researchers was important to effectively engaging them in the research. Effective coordination was provided through defined management structures and multiple lines for communication and engagement. The management and research process for the DOSMD was participatory and democratic (NS). Investigators would discuss the study at regular intervals, and also would vote on key decisions about how to conduct the work.

The design of communication arrangements used in the DOSMD drew on lessons learnt from the IPSS. This previous experience had affirmed the importance of multiple channels of communication for effective implementation of research across geographically and culturally disparate centres (International Pilot Study of Schizophrenia, 1973). Researchers communicated through material and written correspondence, visits by headquarters staff to the field research centres (several times per year), exchange of visits of collaborating investigators, and general meetings of investigators. Opportunities for face-to-face meetings (for example, the annual NIMH-funded meeting between investigators) were also particularly valuable to sharing progress, challenges and findings. Also, researchers from neighbouring field research centres would meet and discuss their work. Finally, collaborating researchers made specific visits for training and data validation. Kuipers and Leff both travelled to Chandigarh, and researchers from Aarhus and Chandigarh attended training in London.

There was also some external collaboration for the EE work. Leff collaborated with Fiona MacMillan to access unpublished data from the Northwick Park study; this allowed a comparison of those findings with the two-year follow-up data from Chandigarh (Leff, Wig et al., 1990) (JL).

9.6 Stage 2: Processes

The work took place in the late 1970s, with the two-year follow-up completed in the early 1980s. The EE interviews were implemented by research staff at the field study centres at

Chandigarh and Aarhus (Bedi, Menon, Achton Nielsen and Thestrup). Patient samples included individuals aged 15–54 years old who contacted a psychiatric service for the first time within a specified two-year period, and who could be classified as schizophrenic or suffering from paranoid or other psychotic states. Aarhus provided 28 patients, and Chandigarh some 78.

A condensed form of the Present State Examination was administered at each patient visit, and the CFI was administered with the family members. At initial contact, a clinical assessment and CFI was completed, at one-year follow-up a clinical assessment and CFI, and at two-year follow-up, a clinical assessment. Leff scrutinised Present State Examination records independently to assess if relapse had occurred; he was blind to the EE ratings of relatives.

During the research, several steps were taken to complete the study and validate the findings. These included: translation of the interview schedule, training of the participating researchers in implementing and analysing the interviews, and then cross-checking of the interviews for consistency and validity. Careful and reliable translation and implementation of the interview schedule into appropriate languages, while retaining its meaning and use, was a crucial first step in setting up the study. Following this, researchers then had to ensure inter-rater reliability between those implementing the interview, and with existing studies.

A few challenges emerged in translating the interview protocol and ensuring inter-rater reliability. For example, one challenge was cultural conventions around interviewing in Chandigarh:

> I think the only kind of issue that came up was… the relatively more hierarchical structure of Indian society. In Chandigarh, when you're interviewed by someone you [tend to] do as you're asked. …There was a bit of having to make sure that people were actually allowed to talk spontaneously and say what they thought. (EK)

The study incorporated several steps to address challenges. These were important for the internal coherence of the work, as well as its comparability with other studies in different cultures.

An independent assessor (Ghosh) was used to help ensure inter-rater reliability for the work in Chandigarh. Ghosh was bilingual in English and Hindi, and was trained at the IOP in the CFI by Christine Vaughn (JL). Ghosh came to the Chandigarh centre a few times to cross-check rater reliability.[25]

Training courses were also provided to further improve the reliability of the application of the interviews. Researchers from Aarhus and Chandigarh went to the IOP to be trained by Kuipers in conducting the CFI in 1977 (July/July/August). She provided trainees with 10 interviews to rate; their ratings were then compared to standard ratings. Later, Kuipers also travelled to Chandigarh from April to June 1978, and observed Bedi and Menon's interviews, in Hindi and in English, and in urban and rural settings.

[25] There were still some challenges in ratings of warmth: Ghosh was unable to rate warmth after the training, and as a result the accuracy of warmth ratings in the study remains uncertain. Ghosh's other ratings had good reliability (JL).

Finally, after the interviews were completed, Kuipers checked back translations of the interviews in Chandigarh (EK). This process of translating and back translating was used more widely across the WHO study to check reliability of translation.

9.7 Stage 3: Primary outputs

Knowledge

The preliminary conclusions from the wider DOSMD were published in 1986 (Sartorius, Jablensky et al., 1986). These findings aligned with the findings of the earlier IPSS, suggesting similar differences in outcomes of schizophrenia across countries: this study indicated schizophrenic illnesses were ubiquitous, with a similar incidence, as well as clinical features that were more similar than different across cultures (Jablensky, Sartorius et al., 1992). Also, it indicated that those with schizophrenia and related disorders in Europe and the US had less favourable outcomes than counterparts in Africa, Asia and Latin America countries) (International Pilot Study of Schizophrenia, 1973; Jablensky, Sartorius et al., 1992).

The main conclusions from the EE study specifically were:

- In Aarhus, Danish relatives were very similar to UK relatives in their mean score and the interrelationships of EE characteristics. However, the sample size was too small to come to any meaningful conclusion about potential differences with the UK. The sample size was further reduced as some patients' initial illness failed to improve during the first year and they were placed in sheltered accommodation; attrition prevented further meaningful analysis.
- In Chandigarh, there were noticeable differences in EE between rural and urban relatives. No rural relative was rated as having high expressed emotion at follow-up (one year) compared with 7 of 56 urban relatives. A highly significant reduction occurred in each of the components and in the EE index, affecting both negative and positive aspects of EE. Comments at year one suggested acceptance of positive and negative symptoms. This pattern was rarely encountered in research on Anglo-American families at initial assessment or follow-up.
- In Chandigarh, the relapse rate at year two was 37 percent (22 out of 60). EE measured only at times of crisis (as consistent with earlier research) had a significant association with predicted relapse. The only statistically significant difference in relapse rates was for hostility. The global EE index was significantly related to the one-year relapse rate but not for the two-year data. Hostility remained significantly associated with relapse at the two-year follow-up. Hostility was also the only negative component of EE that was as common as that found in British and Danish relatives (drawing on Northwick Park study data).

The study had several novel contributions to the field methodologically and substantively:

First, the study provided evidence that an interview protocol based on tone and conversation could be translated and applied in a different language and culture, other than the one in which it was originally designed (KM, EK). There were a few challenges in implementation (e.g. one rater could not assess warmth), but generally the interview was consistently applied and back translated. Specifically, this demonstrated the transferability

of the EE scales across languages and cultures (KM). Kuipers suggests that the study 'may have even been the first study of non-western participants… which showed that expressed emotion could move across cultures like that' (EK). This was particularly interesting because the EE work relied on judging tone and cultural expectations (EK).

Secondly, it suggested there could be cross-cultural differences in the manifestation of EE among families and other carers between studies done in the UK, in Aarhus, and in rural and urban Chandigarh. The study found low levels of EE on average among city dwellers in Chandigarh (30 percent) versus the average in England, which was about 54 percent. Peasant farmers in Chandigarh had an even lower percentage with high levels of expressed emotion (8 percent). At the one-year follow-up no rural relatives were rated as high expressed emotion. The findings also challenged a purely biological view of schizophrenia:

> The fact that expressed emotion has been a robust predictor of relapse, in a condition that was seen as entirely biological. This showed that it was susceptible to other influences. Now there's a more… nuanced view that there were all sorts of things going on. (EK)

One researcher involved suggests these findings helped legitimise family interventions to treat schizophrenia in different cultural contexts:

> I think what it's done is enabled people in other cultures to have a look at family intervention work and to involve families in treatments and try to improve outcomes in a more social way rather than just giving people medication. (EK)

Thirdly, the study suggested that EE did correspond with differences in outcomes of schizophrenia in India, similar to what had been found in the UK. Substantially more people in Chandigarh were not ill after two years; and substantially fewer relatives in Chandigarh had high EE compared to English relatives. The work in Chandigarh was compared to the first contact survey done by Leff and Vaughn (Vaughn & Leff, 1976a; Vaughn & Leff, 1976b). They found statistically that the difference in EE proportions entirely explained the outcome differences between England and Chandigarh. It attributed some of the better outcomes of schizophrenia in developing countries to low EE (Bhugra & McKenzie, 2003).

Finally, one researcher involved suggests this was one of the first studies in India (if not the first) to look at psychosocial factors associated with mental illness, in particular, acute psychosis. Prior to the WHO work, the first mental health survey in India had been undertaken in 1961.

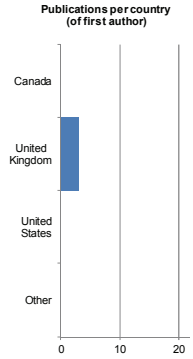
A bibliometric analysis of the papers produced from the research cloud is shown below.

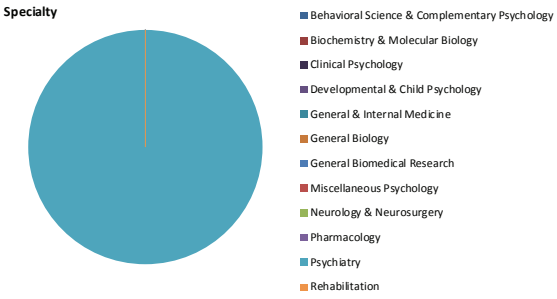
Research cloud:

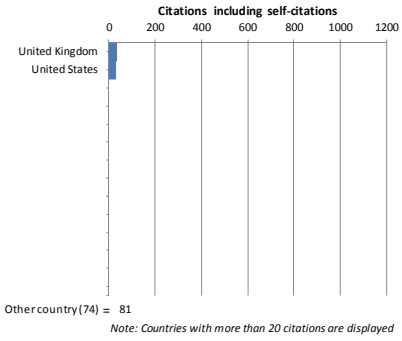
	Citations in:		% of total citations	Research level of cloud papers	
WoS Indexed papers: 3	**RCT:**	4	2%	Clinical **1:**	100%
Total citations of papers: 212	**Meta-analyses:**	2	1%	**2:**	0%
of which, self-citations: 0.9%	**Indexed practice guidelines:**	0	0%	**3:**	0%
Mean citations per paper: 71	**Review articles:**	31	15%	Basic **4:**	0%
Distinct cloud citations: 121					
Second-generation cloud citations: 4,182					
Third-generation cloud citations: 45,556					

Most highly cited article: Leff J, Wig NN, Ghosh A, Bedi H, Menon DK, Kuipers L, Korten A, Ernberg G, Day R, Sartorius N, et al (1987). Expressed emotion and schizophrenia in north India. III. Influence of relatives' expressed emotion on the course of schizophrenia in Chandigarh. Br J Psychiatry. 151:166-73

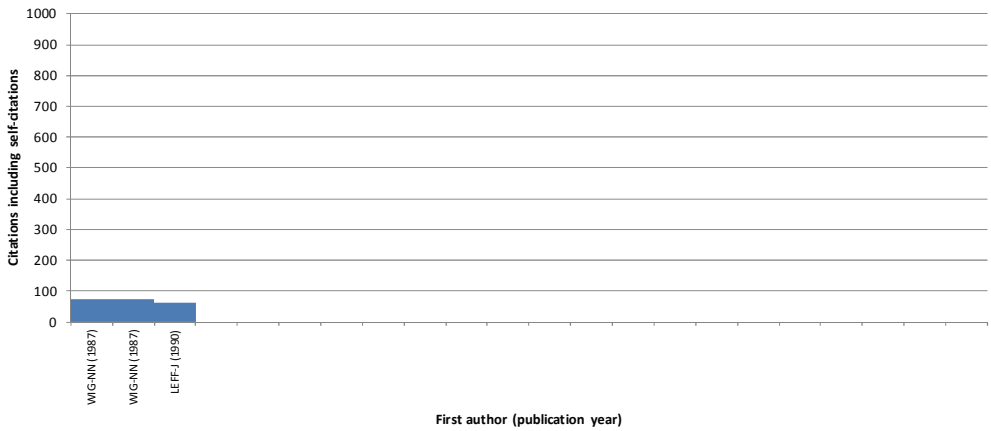
Times cited: 74

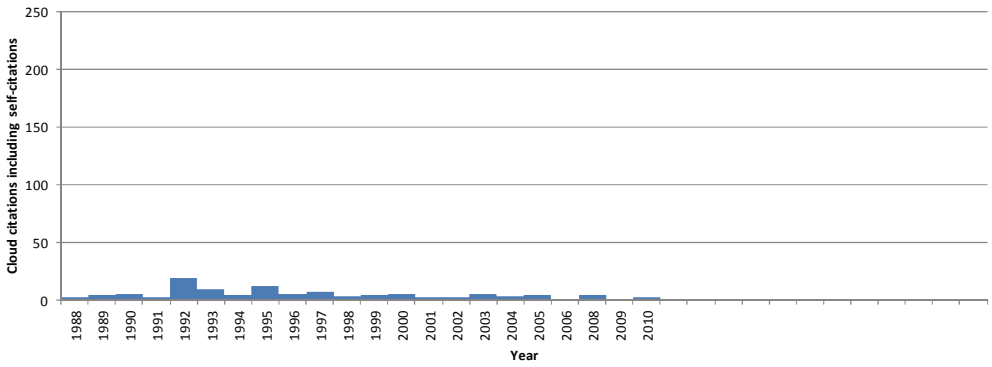






Note: Countries with more than 20 citations are displayed





Targeting future research

Effect on the researchers' careers

None of the researchers involved chose to maintain a focus solely on EE studies following the completion of this research. Leff's interests turned to a few related workstreams; primarily, he became involved in research around deinstitutionalisation in the UK and worked for 13 years with a team to investigate the implications of deinstitutionalisation for patients. Leff did retain a longer-term interest in cross-cultural studies, and the role of the family and carer in schizophrenia; he was involved in three randomised controlled trials on EE and outcomes of schizophrenia.[26] Leff also developed a line of research on ethnic minorities in the UK. This was in response to studies showing higher rates of schizophrenia among immigrants from the West Indies to the UK post-WWII. Leff used the WHO schedule for this work, in addition to a new schedule he developed, the Ethnic Identify Schedule.

Following this research, Kuipers led a small family intervention study for schizophrenia in 1982, which used EE as an outcome measure, and completed a follow-up study on family intervention with Leff and Lam. This led to a published manual of family intervention for schizophrenia (first published in 1992, with a second edition released in 2002; Kuipers, Kuipers et al., 2002). She looked at EE in staff carers compared to unpaid family carers, as well as at the relationship between the burden of care and EE. Kuipers completed subsequent work on the perception of critical comments by people with schizophrenia. Her family intervention work fuelled an interest in intervening with patients directly, and her research group began working on randomised trials of CBT for psychosis and on mechanisms of therapeutic change, in both family intervention and individual CBT for psychosis.

The researchers based in Chandigarh also shifted away from EE and schizophrenia. Menon left the Chandigarh field research centre in 1981, taking up a permanent contract with the Indian Council of Medical Research (ICMR) (KM). At ICMR, Menon became chief coordinator of research in Mental Health and was involved in allocation of research funding for non-communicable diseases. In 1984, Menon became the director of the national Institute for the Mentally Handicapped. In this role, Menon promoted research into the role of the family in learning disabilities and helped to develop training for parents (Peshawaria, Menon et al., 1994). The remaining researchers involved at Chandigarh appear not to have pursued EE or schizophrenia research much further. Bedi continued at the centre for a few years. She conducted the two-year follow-up interviews for the EE

[26] Additionally, following on from these, Leff was involved in developing community psychiatric nurse training packages.
This work considered EE and non-family carers. Leff was involved in developing the Thorn initiative programme, which focussed on working with community psychiatric nurses to help decrease levels of EE in their relationships (not directly tackling EE in staff–patient relationships). Themes within this programme include exploration of relative's perspective, psycho-education, problem solving, tackling criticism, challenging emotional over involvement, defusing other emotions (e.g., guilt, rejection), flexibility, recognising and detailing with the insoluble, persistence, working as co-therapists, handouts, role play ideas, scenarios, and overhead material (Willetts & Leff, 1997).

study at Chandigarh as Menon had left by this point. In the early 1982, however, she completely left research.

Future work

There have been a number of follow on studies from the wider IPSS and DOSMD, at 5-, 15- and 25- year intervals (Leff, Sartorius et al., 1992; Harrison, Hopper et al., 2001), continuing to involve researchers at Chandigarh. This included a third WHO study, incorporating data from another set of treated incidence cases groups from different catchment areas (the Assessment and Reduction of Psychiatry Disability; see Wiersma, Giel et al., 1996). In 1980, Vijoy Varma succeeded Wig as Head of Psychiatry at PGI Chandigarh. Varma continued to work on follow-up studies, using data from the DOSMD. While these studies did not continue the EE work, they did explore issues around cross-cultural differences in the course and outcomes of schizophrenia, and the potential influence of culture on this (Hopper & Wanderling, 2000; Mojtabai & Susser, 2000; Harrison, Hopper et al., 2001). Follow-up work to the sub-study on EE was not pursued by the WHO coordinating body or by the co-authors on this paper (JL, EK, NS); however, it was part of the wider DOSMD research that did continue to inspire further research to try to explain differences in the course and outcome of schizophrenia, suggested by the DOSMD, including in Chandigarh. Debate around the evidence for, and explanation of, potential cross-cultural differences in the course and outcome of schizophrenia has continued to inspire further study and controversy (Edgerton & Cohen, 1994; Cohen, Patel et al., 2008; Kleinman, 2008; Jablensky & Sartorius, 2008).

Future work in India: In India, as a follow-up to the DOSMD (albeit without the involvement of the researchers from the research cloud), the Indian Council of Medical Research (ICMR) launched a number of parallel studies to expand and validate the dataset from the IPSS and DOSMD. One parallel study, conducted at three centres in Lucknow, Madras and Vellore between October 1981 and October 1982, used an adapted version of the DOSMD schedule to examine specific factors associated with the course and outcome of schizophrenia (Shah, Parhee et al., 2005). The study done at the Lucknow centre examined relatives' EE and confirmed the findings from this research cloud, also concluding that critical comments, hostility, dissatisfaction and lack of warmth were significantly related to poor course and outcomes of schizophrenia.

Also, in Chandigarh specifically, the EE study and wider DOSMD work had an impact on capacity building: both researcher skills as well as the building of infrastructure for research.

Future work internationally: More widely, the model for cross-cultural research used and refined through the EE study has continued to be applied more widely. Researchers have continued to question and explore the evidence if outcomes do differ between 'developed' and 'developing' countries. In particular, one study tested for the effect of six potential sources of biases on cross-cultural differences; this study found that none of the potential biases could explain away differences in the course and outcome of schizophrenia (Hopper & Wanderling, 2000). One particular challenge that continues to inspire further research into cross-cultural differences in schizophrenia is work on Non-affective Acute Remitting Psychoses (NARP) (Susser, Varma et al., 1995; Hopper & Wanderling, 2000); this is a psychotic disorder misdiagnosed as schizophrenia that has a better prognosis (see Hopper

& Wanderling, 2000). Again, however, this research also does not seem to explain away differences in course and outcome across cultures.

Specific to EE, there has been further study into its affect on schizophrenia across countries and cultures. The field of research on family intervention had the potential to take on different directions and considerations of the family environment: for example, exploring differences in the course of schizophrenia for those living with extended versus nuclear families (El Islam, 1979; Birchwood, Cochran et al., 1992). However, such areas were not pursued to the same degree as EE. Since this research was published, future work has analysed relatives' EE and schizophrenia in different country and cultural contexts (Hashemi & Cochrane, 1999; Bhugra & McKenzie, 2003). Such studies have been conducted in the US (California), Australia and the UK, as well as in a number of middle-income countries and emerging economies, including Eygpt (Okasha, El Akabawi et al., 1994), Israel (Heresco-Levy, Greenberg et al., 1990), mainland China (Xiong, Phillips et al., 1994; Phillips & Xiong, 1995) and Japan (Mino, Tanaka et al., 1995). These studies seem to confirm the findings introduced by this research cloud, that 'different components of expressed emotion (emotional over-involvement, hostility and criticism) have different significance for families from different cultural backgrounds and had differential power in predicting schizophrenic outcomes' (Hashemi & Cochrane, 1999, 219).

Studies have also looked at specific subsets of the population in the US and UK, particularly Mexican Americans in California (Karno, Jenkins et al., 1987; Jenkins & Gaines, 1992), and Pakistani and Sikh Asian communities in the UK (Hashemi & Cochrane, 1999). These studies find that adjusting the scale can result in more significant relationships between EE and patient outcomes. For example, high EE did not predict relapse among Pakistani and Sikh groups when using the standard scale. It became a better predictor of relapse when raising the cut-off for emotional over-involvement (Hashemi & Cochrane, 1999; Bhugra & McKenzie, 2003). These differences reaffirm one of the initial hypotheses for this research cloud – that cultural and social factors could mediate how indicators of EE are understood and accepted, and also experienced by the individual (Bhugra & McKenzie, 2003).

Finally, since the research, EE has been applied to examining a wider range of disorders and illnesses (JL). EE studies have been completed on unipolar depression (Vaughn & Leff, 1976a; Hooley, Orley et al., 1986), bipolar disorder (Miklowitz, Goldstein et al., 1988), eating disorders (Szmukler, Eisler et al., 1985), dementia (Vitaliano, Becker et al., 1989), and diabetes mellitus (Koenigsberg, Klausner et al., 1993; Liakopoulou, Alifieraki et al., 2000).

9.8 Interface B: Dissemination

Though the sub-study on EE was implemented in the first two years of the DOSMD (the first CFI interviews were conducted in 1978) (EK), the main findings were not published until after the preliminary results for the DOSMD. The first paper on the study methodology and results was published in 1987, almost 10 years after it was conducted.

It took a number of years to draft and acquire investigators' approval for the results and publication. Some of this delay was linked to the collaborative nature of the work.

Investigators were required to review, discuss and approve the publication (NS). This resulted in a long process of consultation, with printed drafts shipped between the researchers. Additionally, some of the delay was procedural. There was an agreement between the Government of India and the WHO on data transfer, which had to be followed. Also, the WHO had its own process for publishing studies, to assess ownership of the study and its findings and their implications for policy (KM). One investigator posits this delay provides evidence of a trade-off between ensuring certainty of the findings, and timely publication of new ideas (KM).

The long process to approve publications had implications on opportunities to present the findings at conferences, seminars and other meetings. The terms of the WHO study contract prevented researchers from disseminating results prior to the publication (KM). Any presentation prior to the publication required permission from the WHO. For this study, researchers received permission to present to local researchers at the Indian Psychiatric Society to obtain their perspective on the work. Menon suggests the study was well received by this audience at the time.

During the review and publication process, researchers informally shared findings through a strong interpersonal network of researchers interested in psychosocial approaches to schizophrenia (JL). The researchers would share progress at conferences; for example, at the World Schizophrenia Fellowship in Christchurch (1997), Leff remembers discussing and debating the principles of family work with Ian Falloon and William McFarlane.

9.9 Stage 4: Secondary outputs

Competing reviews and aggregate analysis of EE interventional studies continued to be published through the 1980s to the 2000s. A few, including one by Kuipers (1979), concluded EE ratings were a predictive factor of outcomes for discharged patients with schizophrenia (Kuipers, 1979; Hooley, 1985; Bebbington & Kuipers, 1994; Hooley, Rosen et al., 1995; Butzlaff & Hooley, 1998). Hooley, Rosen et al. (1995) suggest that a few non-replication studies are expected, as the EE interview is only a moderately reliable measure of an imperfectly measured underlying construct; however, they argue this does not necessarily invalidate positive findings (Hooley, Rosen et al., 1995). More critical reviews of the link between EE and outcomes of schizophrenia argue that there is sufficient variation to challenge the significance of this association (Dulz & Hand, 1986; Parker, Johnston et al., 1988; Parker & Hadzi-Pavlovic, 1990).

Few secondary outputs (e.g., reviews, RCTs) directly cite this research cloud. In a few instances the cloud was cited as preliminary evidence on cross-cultural variation in styles of family intervention, or variation in the components of EE in an RCT (Finnema, Louwerens et al., 1996) or meta-analysis (Hopper & Wanderling, 2000).

9.10 Stage 5: Applications

EE studies have relevance to the application of family and carer interventions, to help treat outcomes of schizophrenia. Stress theories generally, including EE studies, help to justify psycho-educational approaches to treatment, seeking to improve relapse rates by altering

the family environment (Hooley & Gotlib, 2000). Proponents argue EE studies provided encouraging prospects for clinical treatment of schizophrenia (Butzlaff & Hooley, 1998).

EE studies, including this research cloud, can show the value of engaging relatives and carers in treatment programmes as a means to help improve outcomes for patients with schizophrenia. Both Leff and Kuipers have been at the forefront in family intervention research and implementation.[27] On the back of evidence on EE and family intervention, training courses have been developed to equip practitioners to provide treatment to carers (Gournay, 2000). Birley, Leff, Marks, Craig, Tarriar, Butterworth and colleagues from the IOP and from Manchester secured funding from the Sir Jules Thorn Charitable Trust to develop a training course for community psychiatric nurses – the Thorn Initiative. This was first based at the IOP and the University of Manchester, with the aim to provide evidence-based skills training for nurses (Gournay, 2000). Nursing staff were receptive to such initiatives, and it has since been expanded to trainees from clinical psychology, social work, occupational therapy and individuals in case management roles in the voluntary sector. Further training in family intervention has been rolled out as part of MSc programmes at the Universities of Manchester, Sheffield, Middlesex and Birmingham (Gournay, 2000).[28]

Additionally, initiatives have also been set up to assist carers and family members of patients with schizophrenia, alongside growing concerns about the burden on carers and family members in the 1970s (Arnhoff, 1975; Dincin, 1975). One such network in Reading, Berkshire, was set up by nurses trained through the Thorn Initiative, and was informed by Leff and Kuipers' work on family intervention (Sin, Moone et al., 2003). This network seeks to support carers of those with schizophrenia, to both address the potential for high EE, and reduce some of the burden placed on carers (Sin, Moone et al., 2005).

However, it is also important to note that while some suggest EE research generally encourages efforts to support carers of those with schizophrenia, others, particularly some carer and family groups in the US, continue to fear potential negative implications of EE research (EK). Some groups have criticised EE as contributing to the view that relatives might be responsible for poor outcomes of patients with schizophrenia (Lefley, 1992). In 1986, Gwynneth Hemmings, of the Schizophrenia Association of Great Britain, submitted a letter to the *British Journal of Psychiatry* critical of the effect of social intervention on participants. In other cases, charity and support groups have argued for greater support through family intervention; in 1998, J.B. Gardner of the National Schizophrenia Fellowship also wrote a letter to the *British Journal of Psychiatry* advocating the importance of care and provision of information to families of those with mental illness.

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[27] Separately, and unknown to Leff at the time, Falloon and colleagues in California were also developing a family intervention in the 1980s (Falloon et al., 1982). Fadden has also been very involved in expanding family intervention work in the UK (Fadden et al., 1987; Fadden, 1998, 2006).

[28] Additionally, one of the external reviewers notes that while nursing staff were enthusiastic about these initiatives, they found a challenge with sustained family intervention was that it could also be intensive in the time required to provide support, emotional toll, and difficulties in finding solutions.

Finally, use of family intervention as part of treatment for patients with schizophrenia has been supported through the inclusion of family intervention in the NICE guidelines in the UK and PORT guidelines in the US. The current NICE guidelines in the UK recommend the offer of 'family intervention to all families of people with schizophrenia who live with or are in close contact with the service user' (NICE, 2009, 9), in the acute phase or later; similarly, the PORT guidelines in the US recommend offering family intervention lasting a minimum of six to nine months, as it has been shown to reduce relapse and rehospitalisation rates (Dixon, Dickerson et al., 2010).

9.11 Stage 6: Public engagement

None identified.

9.12 Stage 7: Final outcomes

None identified.

9.13 Table of payback

Payback category	Impacts from case study
Knowledge Production	• Provided evidence of how an interview protocol based on tone and conversation could be translated and applied in a different language and culture, other than the one where it was originally designed. • Supported the view that cross-cultural differences in the manifestation of expressed emotion among families and other carers between studies done in the UK, in Aarhus, and in rural and urban Chandigarh. • Confirmed expressed emotion corresponded with differences in outcomes of schizophrenia in India, as had been found in the UK.
Research Targeting and Capacity Building	• Included training of researchers in India and Denmark in application of the CFI protocol. • Translated the CFI protocol into Hindi and Danish, to support further application and study of expressed emotion in these languages.
Informing Policy and Product Development	• Contributed to research into family interventions in schizophrenia (EE as an outcome measure of family functioning). Family intervention is now a recommended treatment for schizophrenia in UK government's NICE guidelines and US PORT guidelines.
Health and Health Sector Benefits	• Contributed to a justification for family intervention, and training programmes for carers of patients with schizophrenia (e.g. the Thorn Initiative; Meriden programme UK).
Broader Social and	• Helped to understand the importance of the caring role in schizophrenia and

Economic Benefits	the social and economic impact of care on wider family networks in different cultures.

9.14 Timeline

1966	Brown and Rutter develop and publish the CFI
1967	Sartorius becomes head of the WHO programme of epidemiology and social psychiatry after joining the WHO
1972	Brown, Birley and Wing publish their study finding that relatives' expressed emotion to be a significant predictor of on the progress and readmission of men discharged from mental hospitals
1976	Leff and Vaughn develop a concise form of the CFI, and publish a replication study of Brown, Birley and Wing (1972)
1976–1980	Wig holds the post of chief collaborating investigator for the Chandigarh WHO Field Research Centre
1977	Kuipers joins MRC social psychiatry unit at the Institute of Psychiatry, London
1977–1993	Sartorius is Director of the Division of Mental Health of the WHO
1978	The initial interviews for the expressed emotion study are conducted; one- and two-year follow-ups are completed in 1979 and 1980
1980	Menon leaves the Chandigarh field research centre for a permanent contract with the Indian Council of Medical Research (ICMR)
1980	Wig leaves Chandigarh and takes up the position of Professor and Head of Psychiatry Department at the All Indian Institute of Medical Sciences (AIIMS), New Delhi
1981/1982	Bedi leaves research
1986	The preliminary conclusions from the DOSMD are published
1987	The first results of the research cloud are published

9.15 References

Adeoye Lambo, T. (1955). The role of cultural factors in paranoid psychosis among the Yoruba tribe. *The British Journal of Psychiatry*, 101(423), 239–266.

Arnhoff, F.N. (1975). Social consequences of policy toward mental illness. *Science*, 188(4195), 1277–1281.

Bebbington, P., & Kuipers, L. (1994). The predictive utility of expressed emotion in schizophrenia: an aggregate analysis. *Psychological medicine*, 24(03), 707–718.

Bhugra, D., & McKenzie, K. (2003). Expressed emotion across cultures. *Advances in Psychiatric Treatment*, 9(5), 342–348.

Birchwood, M., Cochrane, R., et al. (1992). The influence of ethnicity and family structure on relapse in first-episode schizophrenia. A comparison of Asian, Afro-Caribbean, and white patients. *British Journal of Psychiatry*, 161, 783–790.

Brown, G.W. (1959). Experiences of discharged chronic schizophrenic mental hospital patients in various types of living group. *Millbank Memorial Fund Quarterly*, 37, 101–131.

Brown, G.W., Birley, J.L.T., et al. (1972). Influence of family life on the course of schizophrenic disorders: a replication. *British Journal of Psychiatry*, 121(562), 241–258.

Brown, G.W., & Rutter, M. (1966). The measurement of family activities and relationships: a methodological study. *Human Relations*, 19, 241–263.

Butzlaff, R.L., & Hooley, J.M. (1998). Expressed emotion and psychiatric relapse: a meta-analysis. *Archives of General Psychiatry*, 55(6), 547–552.

Cohen, A., Patel, V., et al. (2008). Questioning an Axiom: Better Prognosis for Schizophrenia in the Developing World? *Schizophrenia Bulletin*, 34(2), 229–244.

Dincin, J. (1975). Psychiatric rehabilitation. *Schizophrenia Bulletin*, 1(13), 131–147.

Dixon, L.B., Dickerson, F., et al. (2010). The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. *Schizophrenia Bulletin*, 36(1), 48–70.

Dulz, B., & Hand, I. (1986). Short-term relapse in young schizophrenics: can it be predicted and affected by family (CFI), patient, and treatment variables? An experimental study. In Goldstein et al. (eds.), *Treatment of Schizophrenia: Family Assessment and Intervention*, Springer, 59–75.

Edgerton, R.B., & Cohen, A. (1994). Culture and schizophrenia: the DOSMD challenge. *British Journal of Psychiatry*, 164(2), 222–231.

El-Islam, E.F. (1979). A better outlook for schizophrenics living in extended families. *British Journal of Psychiatry*, 135, 343–347.

Fadden, G., Bebbington, P., et al. (1987). The burden of care: the impact of functional psychiatric illness on the patient's family. *British Journal of Psychiatry*, 150(3), 285.

Fadden, G. (1998). Family intervention in psychosis. *Journal of Mental Health*, 7(2), 115–122.

Fadden, G. (2006). Training and disseminating family interventions for schizophrenia: developing family intervention skills with multi disciplinary groups. *Journal of Family Therapy*, 28(1), 23–38.

Falloon, I., Boyd, J., Mcgill, C., Williamson, M., Razani, J., Moss, H., & Gilderman, A. (1982). Family management in the prevention of exacerbations of schizophrenia. *New England Journal of Medicine,* 306(24), 1437–1440.

Finnema, E.J., Louwerens, J.W., et al. (1996). Expressed emotion on long-stay wards. *Journal of Advanced Nursing*, 24(3), 473–478.

Gardner, J.B. (1998). Correspondence: well-being in the families of people with schizophrenia. *British Journal of Psychiatry*, 172, 540–541.

Gournay, K. (2000). Role of the community psychiatric nurse in the management of schizophrenia. *Advances in Psychiatric Treatment*, 6(4), 243–249.

Harrison, G., Hopper, K., et al. (2001). Recovery from psychotic illness: a 15- and 25-year international follow-up study. *British Journal of Psychiatry*, 178, 506–517.

Hashemi, A.H., & Cochrane, R. (1999). Expressed emotion and schizophrenia: a review of studies across cultures. *International Review of Psychiatry*, 11(2–3), 219–224.

Hemmings, G. (1986). Correspondence: social interventions in the families of schizophrenics. *British Journal of Psychiatry*, 148, 332–334.

Heresco-Levy, U., Greenberg, D., et al. (1990). Family expressed emotion: concepts, dilemmas and the Israeli perspective. *Israel Journal of Psychiatry and Related Sciences*, 27(4), 205–215.

Hogarty, G.E., Anderson, C.M., et al. (1986). Family psychoeducation, social skills training, and maintenance chemotherapy in the aftercare treatment of schizophrenia I. One-year effects of a controlled study on relapse and expressed emotion. *Archives of General Psychiatry*, 43(7), 633–642.

Hooley, J.M. (1985). Expressed emotion: a review of the critical literature. *Clinical Psychology Review*, 5(2), 119–139.

Hooley, J.M., & Gotlib, I.H. (2000). A diathesis-stress conceptualization of expressed emotion and clinical outcome. *Applied and Preventive Psychology*, 9(3), 135–151.

Hooley, J.M., Orley, J., et al. (1986). Levels of expressed emotion and relapse in depressed patients. *British Journal of Psychiatry*, 148(6), 642–647.

Hooley, J.M., Rosen, L.R., et al. (1995). Expressed emotion: toward clarification of a critical construct. In Miller, G. (ed.), *The Behavioral High-Risk Paradigm in Psychopathology*, New York: Springer, 88–120.

Hopper, K., & Wanderling, J. (2000). Revisiting the developed versus developing country distinction in course and outcome in schizophrenia: results From ISoS, the WHO Collaborative Followup Project. *Schizophrenia Bulletin*, 26(4), 835–846.

International Pilot Study of Schizophrenia. (1973). *Report of the International Pilot Study of Schizophrenia Volume 1. Results of the Initial Evaluation Phase.* Geneva: World Health Organization.

Jablensky, A., & Sartorius, N. (2008). What did the WHO studies really find? *Schizophrenia Bulletin*, 34(2), 253–255.

Jablensky, A., Sartorius, N., et al. (1992). Schizophrenia: manifestations, incidence and course in different cultures: a World Health Organization ten-country study. *Psychological Medicine* 20, 1–97 (erratum in *Psychological Medicine* Monograph Supplement 1992).

Jilek, W.G., & Jilek-Aall, L. (1970). Transient psychoses in Africans. *Psychiatria Clinica*, 3, 337–364.

Kleinman, A. (2008). Commentary on Alex Cohen et al: Questioning an axiom: Better prognosis for schizophrenia in the developing world. *Schizophrenia Bulletin*, 34(2), 249–250.

Koenigsberg, H.W., Klausner, E., et al. (1993). Expressed emotion and glucose control in insulin-dependent diabetes mellitus. *American Journal of Psychiatry*, 150(7), 1114–1115.

Kuipers, E., Kuipers, L., et al. (2002). *Family Work for Schizophrenia: A Practical Guide*. Gaskell Press.

Kuipers, L. (1979). Expressed emotion: a review. *British Journal of Social & Clinical Psychology*, 18(2), 237–243.

Leff, J., Kuipers, L., Berkowitz, R., Eberlein-Vries, R., & Sturgeon, D. (1982). A controlled trial of social intervention in the families of schizophrenic patients. *British Journal of Psychiatry,* 141, 121–134.

Leff, J., Kuipers, L., Berkowitz, R., & Sturgeon, D. (1985). A controlled trial of social intervention in the families of schizophrenic patients: two year follow-up. *British Journal of Psychiatry,* 146, 594–600.

Leff, J., Sartorius, N., et al. (1992). The International Pilot Study of Schizophrenia: five-year follow-up findings. *Psychological Medicine*, 22(1), 131–145.

Leff, J., Wig, N.N., Bedi, H., Menon, D.K., Kuipers, L, Korten, A., Ernberg, G., Day, R., Sartorius, N., & Jablensky, A. (1990). Relatives' expressed emotion and the course of schizophrenia in Chandigarh. A two-year follow-up of a first-contact sample. *British Journal of Psychiatry*, 156(3), 351–356.

Leff, J., Wig, N.N., Ghosh, A., Bedi, H., Menon, D.K., Kuipers, L., Korten, A., Ernberg, G., Day, R., Sartorius, N., et al. (1987). Expressed emotion and schizophrenia in north India. III. Influence of relatives' expressed emotion on the course of schizophrenia in Chandigarh. *British Journal of Psychiatry*, 151, 166–173.

Lefley, H.P. (1992). Expressed emotion: conceptual, clinical, and social policy issues. *Psychiatric Services*, 43(6), 591–598.

Liakopoulou, M., Alifieraki, T., et al. (2000). Maternal expressed emotion and metabolic control of children and adolescents with diabetes mellitus. *Psychotherapy and Psychosomatics*, 70(2), 78–85.

Lin, T., Sartorius, N., et al. (1973). *Report of the International Pilot Study of Schizophrenia: Volume 1 Results of the Initial Evaluation Phase*. Geneva: World Health Organization.

Lin, T., Standley, C., et al. (1962). *The Scope of Epidemiology in Psychiatry*. Geneva: World Health Organization.

Macmillan, J.F., Gold, A., Crow, T.J., Johnson, A.L., & Johnstone, E.C. (1986). The Northwick Park study of schizophrenia. IV. Expressed emotion and relapse. *British Journal of Psychiatry*, 148, 133–143.

Miklowitz, D.J., Goldstein, M.J., et al. (1988). Family factors and the course of bipolar affective disorder. *Archives of General Psychiatry*, 45(3), 225–231.

Mino, Y., Tanaka, S., et al. (1995). Expressed emotion components in families of schizophrenic patients in Japan. *International Journal of Mental Health*, 24(2), 38–49.

Mojtabai, R., & Susser, E. (2000). Duration of remitting psychosis with acute onset. Implications for ICD-10. *British Journal of Psychiatry*, 176, 576–580.

Murphy, H., & Raman, A. (1971). The chronicity of schizophrenia in indigenous tropical peoples: results of a twelve-year follow-up survey in Mauritius. *British Journal of Psychiatry*, 118, 489–497.

National Institute for Health and Clinical Excellence. (2009). *Schizophrenia*. London: National Institute for Health and Clinical Excellence.

Okasha, A., El Akabawi, A.S., et al. (1994). Expressed emotion, perceived criticism, and relapse in depression: a replication in an Egyptian community. *American Journal of Psychiatry*, 151(7), 1001–1005.

Parker, G., & Hadzi-Pavlovic, D. (1990). Expressed emotion as a predictor of schizophrenic relapse: an analysis of aggregated data. *Psychological Medicine*, 20(4), 961–965.

Parker, G., Johnston, P., et al. (1988). Parental 'expressed emotion' as a predictor of schizophrenic relapse. *Archives of General Psychiatry*, 45(9): 806–813.

Peshawaria, R., Menon, D., et al. (1994). *For the Welfare of hte Mentally Retarded Persons in India: Directory of Parent Associations working for the Welfare of the Mentally Retarded Persons in India*. Manovikasnagar, Secunderabad: National Institute for the Mentally Handicapped.

Phillips, M.R., & Xiong, W. (1995). Expressed emotion in mainland China: Chinese families with schizophrenic patients. *International Journal of Mental Health*, 24(3), 54–75.

Reid, D.D. (1960). *Epidemiological Methods in the Study of Mental Disorders*. Geneva: World Health Organization.

Rin, H., & Lin, T.Y. (1962). Mental illness among Formosan aborigines as compared with the Chinese in Taiwan. *British Journal of Psychiatry*, 108(453), 134–146.

Sartorius, N., Jablensky, A., et al. (1986). Early manifestations and first-contact incidence of schizophrenia in different cultures. *Psychological Medicine*, 16(4), 909–928.

Shah, B., Parhee, R., et al. (2005). *Mental Health Research in India*. New Delhi: Division of Noncommunicable Diseases, Indian Council of Medical Research.

Sin, J., Moone, N., et al. (2005). Developing services for the carers of young adults with early onset psychosis – listening to their experiences and needs. *Journal of Psychiatric and Mental Health Nursing*, 12(5), 589–597.

Sin, J., Moone, N., et al. (2003). Incorporating psycho educational family and carers work into routine clinical practice. *Journal of Psychiatric and Mental Health Nursing*, 10(6), 730–734.

Strachan, A.M., Leff, J., et al. (1986). Emotional attitudes and direct communication in the families of schizophrenics: a cross-national replication. *British Journal of Psychiatry*, 149(3), 279–287.

Susser, E., Varma, V.K., et al. (1995). Delineation of acute and transient psychotic disorders in a developing country setting. *British Journal of Psychiatry*, 167(2), 216–219.

Szmukler, G.I., Eisler, I., et al. (1985). Anorexia nervosa, parental 'expressed emotion' and dropping out of treatment. British Journal of Psychiatry, 147(3), 265–271.

Vaughn, C., & Leff, J. (1976a). The influence of family and social factors on the course of psychiatric illness: A comparison of schizophrenic and depressed neurotic patients. *British Journal of Psychiatry*, 129, 125–137.

Vaughn, C., & Leff, J. (1976b). The measurement of expressed emotion in the families of psychatirc patients. *British Journal of Social and Clinical Psychology*, 15(2), 157–165.

Vitaliano, P.P., Becker, J., et al. (1989). Expressed emotion in spouse caregivers of patients with Alzheimer's disease. *Journal of Applied Social Sciences*, 13(1), 215–250.

Waxler, N.E. (1979). Is outcome for schizophrenia better in nonindustrial societies? The case of Sri Lanka. *Journal of Nervous and Mental Disease*, 167(3), 144–158.

Wiersma, D., Nienhuis, F.J., et al. (1996). Assessment of the need for care 15 years after onset of a Dutch cohort of schizophrenic patients and an international comparison. *Social Psychiatry and Psychiatric Epidemiology*, 31, 114–121.

Wig, N.N., Menon, D.K., Bedi, H., Ghosh, A., Kuipers, L., Leff, J., Korten, A., Day, R., Sartorius, N., Ernberg, G., et al. (1987). Expressed emotion and schizophrenia in north India. I. Cross-cultural transfer of ratings of relatives' expressed emotion. *British Journal of Psychiatry*, 151, 156–160.

Wig, N.N., Menon, D.K., Bedi, H., Leff, J., Kuipers, L., Ghosh, A., Day, R., Korten, A., Ernberg, G., Sartorius, N., et al. (1987). Expressed emotion and schizophrenia in north India. II. Distribution of expressed emotion components among relatives of schizophrenic patients in Aarhus and Chandigarh. *British Journal of Psychiatry*, 151, 160–165. Erratum in: *British Journal of Psychiatry*, 151, 870.

Willetts, L.E., & Leff, J. (1997). Expressed emotion and schizophrenia: the efficacy of a staff training programme. *Journal of Advanced Nursing*, 26(6), 1125–1133.

Xiong, W., Phillips, M.R., et al. (1994). Family-based intervention for schizophrenic patients in China. A randomised controlled trial. *British Journal of Psychiatry*, 165(2), 239–247.

CHAPTER 10 Northwick park study of outcomes following and characteristics prior to first schizophrenic episodes

This case study is based on research related to the following publication, which was selected using a bibliometric analysis:

Johnstone, E.C., Macmillan, J.F., Frith, C.D., Benn, D.K., & Crow, T.J. (1990). Further investigation of the predictors of outcome following first schizophrenic episodes. *British Journal of Psychiatry*, 157, 182–189.

Information was gathered from interviews with the lead author, Eve Johnstone, and Tim Crow, John Kane and Fiona MacMillan, as well as from desk-based research.

10.1 Summary

This case study focusses on first-episode schizophrenics, comparing outcomes for those who received neuroleptic treatment to those on placebo, as well as exploring their experiences prior to first treatment. A notable finding of the study is that the duration of untreated psychosis is correlated with worse patient outcomes. This finding, combined with the evidence compiled regarding the inadequacy of the treatment at, and prior to first admission, was influential in the development of early intervention services, though significant further research was also conducted by other groups following this initial discovery. MacMillan, one of the researchers on this study, was involved in an influential group in the West Midlands who pushed for the introduction of early intervention services into practice in the UK, and she considers that this study was very influential on her and others. The study took place at Northwick Park MRC clinical research centre and was entirely funded by the MRC through central funding to the clinical research centre. The researchers considered the environment at Northwick Park, where researchers did not need to devote time and energy to teaching or funding applications, to have had a significant impact on their ability to conduct this challenging study. Early intervention has led to important social benefits in terms of quality of care, and has also brought economic benefits in terms of cost reductions for the healthcare system. Health benefits are less clear, as the researchers who worked on this study suggest that the relationship between a longer period of untreated psychosis and worse outcomes might be a correlation rather than causal.

10.2 Introduction

10.2.1 Scientific background

At the time that this study was conducted, neuroleptic drugs had been trialled and were shown to take away psychotic experiences. However, initial use had been reactive rather than prophylactic. It was expected that in most cases, once treated, people were 'well' and wouldn't need continued medication – relapse wasn't expected. However, it soon became apparent that this wasn't always the case, so in some instances drugs began to be used prophylactically after multiple relapses. However, antipsychotics were not typically used prophylactically from the first episode, and this idea was controversial around the 1980s as it was expected that many people would not relapse, and there was concern about the possible neurological effects of the drugs. Therefore, this study aimed to build on previous studies that had shown that the continued use of neuroleptics prevented relapse, but for the first time looking at first episodes. The team expected that they would be able to identify a population that was unlikely to relapse and hence would not need to take neuroleptics, and thus provide some guidance on which cases required drugs as part of their treatment. They were not able to identify such a group but instead found that the duration of untreated illness (i.e., before starting drugs) was correlated with poorer outcomes in terms of relapse. This was a novel and significant finding, which was later confirmed by a number of studies by other groups. They also found that care provision was inadequate, particularly in terms of initial access to treatment, and that this was distressing for families and could potentially be damaging for society as untreated schizophrenia could lead to dangerous and criminal behaviour.

10.2.2 Researchers' background

Eve Johnstone was the corresponding author on selected paper. She qualified as a clinician in 1967, and took a diploma in Psychological Medicine in 1970. She worked initially as a Registrar, and later a Senior Registrar in Psychiatry in Glasgow, but following an interest in research, she became a lecturer in Psychological Medicine at the University of Glasgow. She had wanted to work on schizophrenia due to personal interest in the topic, but was advised against this by her superiors at that time, who suggested that 'it was an impossible task, and you would never get anywhere' (EJ). Johnstone did not agree, and when she was invited to work at the MRC centre at Northwick Park soon after it opened, she accepted this opportunity, and started work as a Senior Registrar in 1974. By the time the research in this case study was carried out, she had been promoted to Consultant, largely on the basis of some high-profile imaging work she had conducted.

Fiona MacMillan was originally hired as an SHO (Senior House Officer) at Northwick Park. She joined the project as a clinician and did a significant proportion of the work directly with patients in this project, along with Johnstone. This was her first research position and she completed her thesis on the basis of the research involved. MacMillan was not looking specifically for a research position when she applied for this role, and it is possible that if she had not come to Northwick Park, she would have stayed in purely clinical positions and not had a significant involvement in research. She was subsequently promoted to senior registrar and later went on to take research posts and was heavily involved in the Early Intervention movement in the West Midlands.

Chris Frith was an established researcher at the time the work took place. He was involved in the study and analysis of the results as a member of staff at Northwick Park.

Desmond Benn was a clinician working on the project as his first job in the UK.

Tim Crow was head of the mental health unit at Northwick Park. He brought the project team together, and was the PI on this project.

John Kane was based at a hospital in Long Island, New York, at the time this research was conducted. He was PI on a project a group of researchers were conducting there at the same time the Northwick Park study took place, also looking at drug intervention in first-episode schizophrenia.

Martin Humphreys was a lecturer in forensic psychiatry in Edinburgh in the early 1990s, when Eve Johnstone was Professor of Psychiatry and Head of Department there. She had taken a set of the data from the first episode study to Edinburgh and took the opportunity of Dr. Humphreys' interest in the work to have the aspects of offending behaviour of first-episode patients analysed by someone who specialised in offending behaviour and in the interface between psychiatry and the law. Humphreys went on to become Senior Lecturer in Psychiatry at Birmingham. It is likely that his involvement in this work helped him to obtain this post.

David Cunningham Owens worked at Northwick Park as a senior registrar and was later promoted to Consultant. He was there at the time of the first episodes study but was not involved in it as at that time. He later went to work in Edinburgh as Senior Lecturer and later Professor of Clinical Psychiatry. He shared the team's concerns about the way in which the Northwick Park study data was being presented and used to support early intervention. With time, the claims that early intervention affected the long-term outcome of schizophrenia (rather than producing a better quality of care for very distressed patients and families) lessened. In this context, Owens collaborated with Johnstone and others to reanalyse the Northwick Park data using more modern methods and drawing on his good knowledge of the psychopharmalogical literature and his longstanding knowledge of the details of the first episode study.

10.2.3 Institution background

The MRC Centre at Northwick Park was opened on 8 September 1970, with the aim being to provide an integrated site combining both the study and treatment of patients (Johnson et al., 2010). The planned costs of the hospital were over £10.5m, with this funding coming from the regional hospital board, and an additional £5.1m for the accompanying research centre, which came from the MRC (*BMJ*, 1970). The psychiatry unit did not open in the first instance, but formed part of the third and final stage of the development, which was completed in 1974 and brought the total number of research positions to 134 (Johnson et al., 2010), and the total number of beds at the hospital to 815, as well as providing full accident and emergency, outpatient, and diagnostic and treatment services (*BMJ*, 1969). The centre was directed initially by Professor Graham Bull, who appointed heads for each of the research areas within it. At the time of opening, it was suggested that the centre was the first of its kind internationally to simultaneously to serve as a community hospital and undertake a wide programme of research without any

commitment to teaching (*BMJ*, 1970). The centre was supported on an ongoing basis by the MRC.

The centre ultimately closed in 1994, with the main reason cited being the failure of the academic and clinical communities to integrate to the extent necessary. In a report to the MRC, the clinical research committee (1986) describe how efforts by the director (initially Graham Bull, later Chris Booth) to set up major research projects were hampered by his lack of influence over NHS appointments, and how the lack of postgraduate training also limited the centre's development. A witness reported to the House of Commons Select Committee on Science and Technology (2005) that 'there was a fundamental conflict between the hospital and the medical establishment and the MRC appointed staff'. This was confirmed by further evidence to the select committee from Professor Savill, an MRC council member, who states that 'the primary reason that Northwick Park failed was that it was science grafted into an unreceptive environment at a district general hospital'. The Clinical research committee report to the MRC (1986) concludes that as a national force in clinical research the CRC had been unsuccessful: 'The whole does not appear to be as great as the sum of its parts.' The extent to which this analysis applies to the psychiatry research unit is less clear, and indeed was disputed by the unit's director, Crow, in a letter to the *BMJ* in 1991 (Crow, 1991), providing citation evidence that in fact the unit made an impact out of proportion to its size, and indeed outperformed the intramural programme of the NIMH. It should also be stated that no formal assessment of the research performance of the centre was conducted before it was closed.

10.3 Defining the research cloud

This case study focuses on the research on first-episode schizophrenia conducted at Northwick Park Hospital in the late 1970s and 1980s. This research examined a group of 253 patients referred to Northwick Park Hospital from nine medical centres in North West London between 1 August 1979 and 2 February 1982. They were followed up for two years, or to the end of the study, whichever was earlier, and a series of papers were published spanning their experiences and outcomes. The case study also encompasses some later work conducted by the PI at Edinburgh University following up a few of the findings of the initial work at Northwick Park. This is included since it relates to the most significant outcomes of this study, and the study teams' viewpoints on them. A publications list spanning the research cloud is given below. The cloud looks at outcomes for patients following first-episode schizophrenia, covering both medical and wider outcomes, and for those taking neuroleptics by comparison to those taking a placebo. It also tracks their history prior to first admission, looking at the steps that led up to admission and their behaviour in the prodromal period.

1. Crow, T.J., Macmillan, J.F., Johnson, A.L., & Johnstone, E.C. (1986). The Northwick Park study of 1st episodes of schizophrenia. II. A randomized controlled trial of prophylactic neuroleptic treatment. *British Journal of Psychiatry*, 148, 120–127.
2. Johnstone, E.C., Crow, T.J., Johnson, A.L., & Macmillan, J.F. (1986). The Northwick Park study of first episodes of schizophrenia. I. Presentation of the

illness and problems relating to admission. *British Journal of Psychiatry*, 148, 115–20.

3. Johnstone, E.C., Crow, T.J., Macmillan, J.F., Owens, D.G.C., Bydder, G.M., & Steiner, R.E. (1986). A magnetic resonance study of early schizophrenia. *Journal of Neurology, Neurosurgery and Psychiatry*, 49, 136–139.
4. Macmillan, J.F., Crow, T.J., Johnson, A.L., & Johnstone, E.C. (1986). The Northwick Park study of 1st episodes of schizophrenia. III. Short-term outcome in trial entrants and trial eligible patients. *British Journal of Psychiatry*, 148, 128–133.
5. Macmillan, J.F., Gold, A., Crow, T.J., Johnson, A.L., & Johnstone, E.C. (1986). The Northwick Park study of schizophrenia. IV. Expressed emotion and relapse. *British Journal of Psychiatry*, 148, 133–143.
6. Johnstone, E.C., Macmillan, J.F., & Crow, T.J. (1987). The occurrence of organic disease of possible or probable aetiological significance in a population of 268 cases of first episode schizophrenia. *Psychological Medicine*, 17, 371–379.
7. Macmillan, J.F., Crow, T.J., Johnson, A.L., & Johnstone, E.C. (1987). Expressed emotion and relapse in first episodes of schizophrenia. *British Journal of Psychiatry*, 151, 320–323.
8. Johnstone, E.C., Macmillan, J.F., Frith, C.D., Benn, D.K., & Crow, T.J. (1990). Further investigation of the predictors of outcome following first schizophrenic episodes. *British Journal of Psychiatry*, 157, 182–189.
9. Humphreys, M.S., Johnstone, E.C., MacMillan, J.F., & Taylor, P.J. (1992). Dangerous behaviour preceding first admissions for schizophrenia. *British Journal of Psychiatry*, 161, 501–505.
10. Humphreys, M.S., Johnstone, E.C., & Macmillan, J.F. (1994). Offending among first episode schizophrenics. *Journal of Forensic Psychiatry*, 5, 51–61.
11. Geddes, J., Mercer, G., Frith, C.D., MacMillan, J.F., Owens, D.G., & Johnstone, E.C. (1994). Prediction of outcome following a first episode of schizophrenia. A follow-up study of Northwick Park first episode study subjects. *British Journal of Psychiatry*, 165, 664–668.
12. Owens, D.G., & Johnstone, E.C. (2006). Precursors and prodromata of schizophrenia: findings from the Edinburgh High Risk Study and their literature context. *Psychological Medicine*, 36, 1501–1514.
13. Owens, D.C., Johnstone, E.C., Miller, P., Macmillan, J.F., & Crow, T. (2010). Duration of untreated illness and outcome in schizophrenia: test of predictions in relation to relapse risk. *British Journal of Psychiatry*, 196, 296–301.

10.4 Stage 0: Opportunity identification/research needs assessment

Inspiration

Prior work that was particularly influential in the decision to conduct this study was conducted at NIMH in the US by Nina Schooler and Gerard Hogarty in the 1970s; this

demonstrated the importance of neuroleptics in preventing relapse (e.g., Hogarty et al., 1973; Hogarty & Ulrich, 1977; Hogarty et al., 1979). They had looked at all episode schizophrenia and found that on neuroleptics 31 percent of people would relapse between 2 and 12 months after treatment initiation, compared to 67 percent for those on placebo (Hogarty et al., 1979). Johnstone and Crow were interested to note that this meant there was a population of people who would not relapse, even without treatment. They were interested to see whether one could identify this group, as then you could avoid treating them unnecessarily. This led them to decide to focus on first episode cases, as they expected that this population may be larger, as there are some schizophrenics who only have one psychotic episode.

[What] we were looking for was this possibility that there was a population that were neuroleptic requiring and a population that was going to do fairly well anyway. (TC)

Also influential was the work of Gerry Klerman and colleagues, who did some research that showed that it was possible to see different profiles of improvement and equally different trajectories of relapse between a group on neuroleptics and one on placebo (Goldberg et al., 1965). Goldberg also looked at how different drugs may be better suited to different groups of patients depending on their behaviour and characteristics (Goldberg et al., 1966). This work was important as it meant that the team hoped it may be possible to distinguish a 'neuroleptic requiring' group, and equally a group who may do well without drug treatment.

Finally, another key external influence was a lecture given by Richard Peto at Northwick Park that Crow and Johnstone both attended. He discussed methods of design of clinical trials, describing how they should be designed to fit into the clinical practice; they should be kept simple; and should have a clear end point. The fit to clinical practice in particular enables a large study group to be assembled. They were impressed with his ideas, and wanted to apply his techniques to psychosis. Peto's ideas were influential in the way the study was put together, and even in the team's decision to try and attempt a study of this type, although they had done a few smaller trials previously.

Feasibility

This study came soon after the establishment of the MRC centre at Northwick Park Hospital. The centre, and the way it was set up, was crucial to the design and success of this study. Crow had been asked by the Director of the centre, Graham Bull, to join as head of the mental health research division on the basis of his previous work in Scotland and Manchester, and he was asked to put an appropriate team together. This level of flexibility allowed him to put together a complementary team that was a good fit for this study and for the other work at the department. He brought in Johnstone, who added clinical skills and experience to Crow's more academic background, and then just as this project started, MacMillan joined the team as a junior clinician on the project. She had clinical skills, but also excellent people skills, crucial in holding together the group of patients required for this work. He also invited Frith to join the department, and he also became involved in the study. The structure of the MRC enabled him not only to bring this team together, but keep them together – Crow received tenure upon joining Northwick Park, and Frith and Johnstone joined on the understanding that they would be awarded tenure within a few years, and indeed this was the case. The combination of

people, and the timing in bringing them together, made this work feasible at the point in time when academic interest in this area was developing. It also was important for the development of the idea for the study, which came primarily out of discussions between Johnstone and Crow.

As described, the establishment of the centre was important in enabling this study to happen. Also important was location. It was crucial that the team could assemble a large patient sample and track it over a series of years to obtain meaningful results. The location they were in made this possible.

We thought we could maybe do this. We knew we would need an awful lot of patients. But of course we were in an area where there was a high density of population – a relatively young population but not hopelessly unstable so that we had a hope of being able to hang on to them. (EJ)

As Johnstone describes, the northwest London location of the centre gave them access to a large population including a relatively high number of young people. However, unlike many areas where populations were largely transitory and hard to follow, this was a relatively stable population. This was partly due to affluence – many young people in the area could count on family support and were in stable housing. This meant it was more likely that the team would be able to do follow-ups over a number of years and successfully monitor the group of patients without considerable attrition. This realisation was a key influencing factor in the development of the study as it encouraged belief that such a challenging piece of work might be possible. In other more rural locations, or areas with transitory populations, doing the work effectively would have been very difficult, if not impossible.

The research environment at the MRC centre was also very important. The staff were entirely focussed on research – there were no teaching requirements as there would be in a university, and there was great flexibility about the extent of the clinical work that was done, although in fact most of the psychiatrists did a great deal as the confidence this engendered in the patients and general practitioners locally in the level of care they would provide made the studies possible. There was encouragement within the centre to take on challenging research projects that would have been difficult to conduct in other research environments. Also funding was relatively secure, and there was no need to apply for grants on an ongoing basis.

We worked at that time for the Medical Research Council. We were in circumstances where it was possible to spend a great deal of your time actually doing research projects. This really isn't the case usually… nobody works like that now because the academics all have to teach and stuff as well. But we didn't… we just did the research and the clinical work that we wanted to do and it was actually possible to work like that. We were greatly encouraged to do things that… would be of value that would be very difficult for people to achieve in other circumstances. (EJ)

Potential value

As described above, the team were hoping that they might be able to identify a population who would not relapse without medication. If they were able to do this, it would have a significant impact, as it would be possible to avoid treating this group unnecessarily. This

would have great potential value for those patients in terms of avoiding the side effects of medication, and would also reduce treatment costs for healthcare providers. Because the results of the study were unexpected, the key outcome of this work in identifying duration of untreated psychosis as being related to poorer outcomes was not part of the motivation for the study.

10.5 Stage 1: Inputs to research

Money, researcher time, lab/office space and consumables

All the funding for this study came from the MRC. The funding environment at the MRC centre was fairly unusual in that there was great flexibility to work on whichever areas were of interest and also reliability of funding over the long term. Researchers devised programmes and presented them to the MRC as a block programme of a series of proposed studies. Once accepted, they were peer reviewed by the MRC every four years, but provided the work was considered acceptable, the funding was continued. The reviewing committees had the power to recommend the expansion or discontinuation of programmes or sub-programmes through recommendations to the Director and reports to the council of the MRC. However, by this time the psychiatry unit had a strong reputation for clinical trials and so this project was not heavily scrutinised. Funding was adequate to support the study and no other funding was required (and indeed researchers were not permitted to apply to other funding sources).

This research environment was considered beneficial by those involved because it allowed them to pursue challenging studies – and in fact they were encouraged to do this, as outlined above – and because it freed up a lot of time that might otherwise have been spent on rolling funding applications. Similarly, there was no requirement for researchers to spend time on teaching as there would have been in a university environment. The clinical demands placed on staff were to some extent optimal, and flexible depending on the needs of the research programme. These were assessed by the standard methods of the time via the relevant boards and finally the MRC council. In fact, the clinical work that did take place often was crucial to, and formed part of the research work, as in this trial. All this meant that there was a significant amount of time available to simply focus on research. In this sense, time was a useful input in allowing the team to focus on this demanding study, which even so still required very long hours.

The consistency of funding also meant that the study could be carried out by a consistent set of staff, as outlined previously. This was important, as Johnstone and MacMillan in particular built up close relationships with participants in the study and their families, a significant factor in ensuring that follow-up took place over two years across the full patient group.

Expertise and techniques

The team brought together the necessary skills to conduct the research. Crow brought the research experience and the overview of the field as well as the seniority required. Frith and Johnstone had strong research reputations. Johnstone also brought experience of conducting clinical trials and significant clinical expertise. MacMillan brought clinical skills but equally importantly patience and strong interpersonal skills, which allowed her to engage with and maintain the group of patients

Samples/patients

It was difficult to recruit and maintain a group of patients of this size, and this was one of the main challenges in the successful completion of the study, and that made its findings influential. There were a number of factors that made this possible, including consistent long-term funding, and time to focus on research, as described above. Also important was the location in which the research was conducted. However, probably the most crucial input was the hard work and commitment to the work of the team involved, most notably Johnstone and MacMillan, who spent a significant amount of time and effort building the relationships required to maintain consistent involvement. It is important to note that they did not enforce participation in the study or compliance to drug regimens – if patients were not in a fit condition to make their own decisions they were not considered to be able to give consent to join the trial.

Collaborators

The key collaborators on this work were the 36 psychiatrists who referred/identified the candidate patients for participation in the study. This enabled the group of patients to be brought together and their enthusiasm for the work and participation was very important.

That was really quite rewarding that they were willing to do this. I don't know. I mean I suppose we were surprised at how well that went actually because we just called a meeting and people turned up. You know, we wrote to people and said 'Would you be interested in this?' And they came along and it seemed they wanted to do something. (TC)

They did not have collaborators at other academic institutions, as most of the work on this type of trial required day-to-day involvement on the ground engaging with the patients.

10.6 Stage 2: Processes

The methodology in itself was not particularly novel, consisting of a placebo-controlled trial of a drug with follow-up over a period of two years. As outlined previously, it was impressive that contact was maintained with a large group of patients over this length of time, which is notoriously difficult, particularly for patients suffering from schizophrenia. However, this was not in itself remarkable. There were, however, a few characteristics of the process that were significant. The first was the careful way in which the study was structured to fit into clinical practice, reflecting the influence of Peto in the study design. However, more critical was the use of first-episode schizophrenics as the focus of the study; this was one of the earliest studies to focus on the first episode. This was important for the study design but also crucial in terms of the unexpected study outcomes regarding duration of untreated illness. However, it was also important in marking out the first psychotic episode as being a crucial stage in the process of schizophrenia. At that time, the concept of schizophrenia being a developmental disease that followed a course across people's lives was not well established. It is now known that the age of onset of schizophrenia is a critical factor in the progression of the disease and likely outcomes, and this study, as one of the first to place this emphasis on the first episode, was important in the subsequent movement internationally to look at first episodes and subsequently to understand the arc of the condition through people's lives and the importance of this particular stage.

10.7 Stage 3: Primary outputs

Knowledge

As stated previously, what the team hoped to establish from this study was whether there was a population who fared well without the need for neuroleptic treatment, and if so, how you could identify them. They also expected that relapse rates without neuroleptic treatment would be lower for first episode cases than for later episodes. However, this did not prove to be the case. They found similar rates of relapse for those on placebo, but rates of relapse for those on treatment, though lower, were not as dramatically reduced as in the previous work by Hogarty et al. (1973). They concluded that use of neuroleptics was still a strong predictor of relapse. However, their most influential finding was that duration of untreated illness was also correlated with patient outcomes, and that facilities for initial admission were often inadequate. This led to a significant number of further studies in this area, as described in the following sections, and is the main reason that the publications relating to this research cloud are highly cited. The findings of the four core study papers are outlined below.

The first publication of the four core study publications (Johnstone et al., 1986a) considers the presentation of the illness at first episode admissions and problems relating to admission. The team found that in many cases illness had preceded admission by more than one year, and that this year of untreated illness had been characterised by behavioural disturbance and difficulties in gaining admission. The authors conclude that the existing arrangements for initiating management of schizophrenia were often unsatisfactory, causing distress to patients and their families. This is supported by two further papers in the cloud that describe behaviour prior to admission, showing that 16 percent of the group had committed an offence in the five years preceding admission, and though half of these had shown clear signs of psychiatric illness at the time, only a minority had been referred for psychiatric treatment (Humphreys et al., 1994), and that 52 of the 253 patients had exhibited dangerous behaviour threatening to the lives of others prior to admission (Humphreys et al., 1992). Despite evidence that this was motivated by psychotic symptoms in 23 of the cases, fewer than half of the patients were admitted as a direct result of their dangerous behaviour.

The second core study publication (Crow et al., 1986) describes the findings of the controlled drug trial. It was found that when on active medication, 46 percent of patients relapsed, whereas on placebo, 62 percent of patients relapsed, similar to the previous findings by Hogarty et al. (1973), though less marked. However, the more striking finding was that the most important determinant of relapse other than medication was the duration of untreated illness prior to starting neuroleptics. This was a novel finding, and combined with findings described in the previous paper around difficulties in accessing service, formed a significant plank of the early intervention movement that followed, as described in later sections. However, it should be noted that the study does state that no conclusion is drawn as to whether this finding reflected a difference in outcomes that could be prevented by early intervention, or whether this was actually related to patient characteristics, in that the extended duration before treatment initiation may be present more frequently in those who would have a poorer prognosis anyway. In discussion, the authors suggest that they felt this latter explanation was more likely even at the time and were sceptical about the attention this aspect of the study received. This is reflected in a

2006 paper (Cunningham Owens et al.) looking at 'high risk' candidates for schizophrenia. Reviewing the evidence, the authors conclude that it is quality of care considerations, rather than the evidence base about outcomes, that are addressed by early intervention. The Northwick Park data was re-investigated with this point in mind more recently in a publication that suggests the data supports the conjecture that those patients who have a longer duration of untreated illness are also those who are likely to have a worse prognosis in any case (Owens et al., 2010).

In the third publication in the series (MacMillan et al., 1986a), the authors look at the short-term outcomes for the patients. Subsequent papers look at outcomes at later follow-ups (Johnstone et al., 1990; Geddes et al., 1994), and in all cases the primary conclusion is that outcomes are very poor for many patients, whatever metrics are used. In the short term, they find that age, sex, ethnic origin, duration of admission, social withdrawal before admission and type of onset of illness are not significantly related to relapse rates (MacMillan et al., 1986). What the later follow-up does find is that wider outcomes related to, for example, employment, are actually slightly better for those on placebo than those on active medication, despite the worse outcome in terms of relapse among these patients (Johnstone et al., 1990). The authors speculate that this might be related to the impact of the medication on personal characteristics that are related to good outcome, such as social presence and competitiveness. A longer term follow-up also challenged the conventional view at that time that symptoms of depression are associated with better outcomes in schizophrenia, finding that time to first re-admission was shorter for those exhibiting feelings of depression upon first admission (Geddes et al., 1994).

In the final publication in this series (MacMillan et al., 1986b), the authors discuss the evidence regarding expressed emotion and its relation to relapse. Expressed emotion refers to attitudes towards and interactions with schizophrenic patients by their families. It was thought that characteristics such as 'critical comment' in interactions with the family, and 'social contact', meaning the level of contact between the family and the patient, could have significant impacts on the course of illness. However, here it was found that these two factors, which were the only expressed emotion factors that were measureable for this sample, were not related to outcome or response to medication. The authors conclude that expressed emotion is not significant, certainly in comparison to the importance of medication. This received some critical response, particularly from Mintz et al. (1987), who suggest that the findings and data are inconsistent. However, this is rebuffed in a later publication by the study team, in which they confirm and restate their findings (MacMillan et al., 1987).

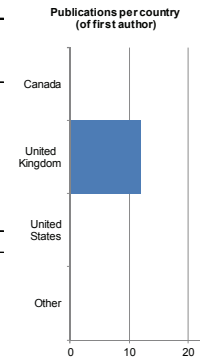
A bibliometric analysis of the papers produced from the research cloud is shown below.

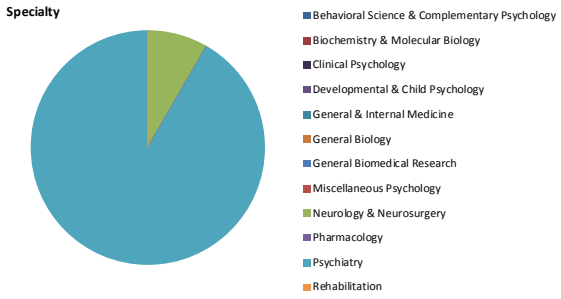
Research cloud:

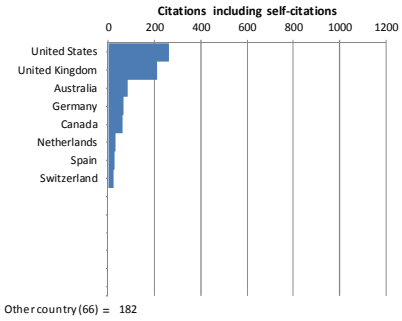
	Citations in:		**% of total citations**	**Research level of cloud papers**
WoS Indexed papers: 12	**RCT:**	57	5%	Clinical **1:** 92%
Total citations of papers: 1,149	**Meta-analyses:**	5	0%	**2:** 8%
of which, self-citations: 1.7%	**Indexed practice guidelines:**	4	0%	**3:** 0%
Mean citations per paper: 96	**Review articles:**	217	19%	Basic **4:** 0%
Distinct cloud citations: 856				
Second-generation cloud citations: 28,697				
Third-generation cloud citations: 320,189				

Most highly cited article: Crow TJ, Macmillan JF, Johnson AL, Johnstone EC. (1986). The Northwick Park Study of 1st episodes of schizophrenia. II A randomized controlled trial of prophylactic neuroleptic treatment. British Journal of Psychiatry 148, 120-127.

Times cited: 265

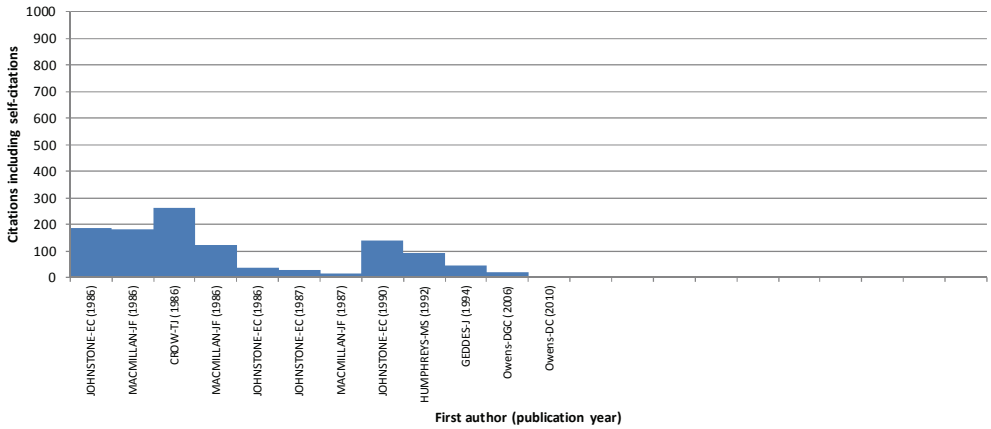


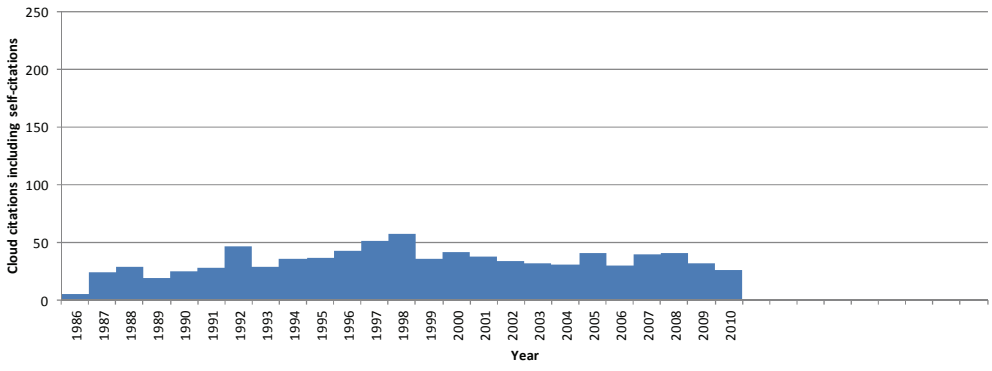




Other country (66) = 182

Note: Countries with more than 20 citations are displayed





Targeting future research

Effect on the researchers' careers

Benn joined Northwick Park as his first position in the UK after leaving South Africa. The project was the opportunity for his to get his first publication – he joined in 1987 – and he then went on to a Senior Registrar position in the Newcastle area. In establishing his reputation in the UK and providing an opportunity to move over it had a useful though not radical impact on his career.

Johnstone left Northwick Park in 1989, at which point it was starting to become clear that the centre was going to be closed. She was invited to take a position as Professor of Psychiatry and Head of Department of Psychiatry at the University of Edinburgh, and accepted this as a promotion, but also as a more secure position. It is likely that this study was among the work that led to this later position, but she had been involved in a range of other high-quality research, including a previous imaging study that was the first using a CT scanner in the field. This combination of high-profile and novel work led to her being given the position of Chair of the Neurosciences Board of the MRC from 1999–2002 as well as a range of other positions with the MRC and Royal College of Psychiatrists over the years. In her role at the MRC she was involved in a range of high-profile policy related work that was not closely related to her primary work in schizophrenia, including a report on autism and MMR and the Liverpool Alder Hey enquiry. She was awarded a CBE in 2002 for services to medicine, and was also awarded a Gildea Prize for research in schizophrenia in 1999, a Stanley Dean Award (American College of Psychiatrists) for research in schizophrenia in 2002 and the Lieber Prize for research in schizophrenia in 2006.

MacMillan was promoted from SHO to a Registrar post on the basis of the work she conducted in this study, so it did have an impact on her career. It also was her first foray into research and in that sense shaped her career significantly, as she wasn't necessarily seeking a research post at that time and could have easily pursued a purely clinical career. She completed her doctoral thesis on the basis of the research she conducted at Northwick Park, and her subsequent appointment as Lecturer in Edinburgh was almost entirely on the basis of the research work she had conducted there. Her experience with the families and some of the difficulties they faced in getting that first treatment also had an effect on her viewpoint and formed part of her decision to be involved in the early intervention movement and patient advocacy that became an important part of her later work. She went to Birmingham after Edinburgh as a Senior Lecturer, and later went into more clinical work in Staffordshire, where she is now a visiting professor at Staffordshire University. Her later work was more clinically focussed than that of Crow or Johnstone, but her involvement in this work along with her clinical experience of the challenges patients felt led to her being one of the founding members of IRIS, which was influential in the development of early intervention services in the UK and internationally. The role this played in the early intervention movement is also described in more detail in the early intervention case study.

Crow joined Northwick Park in 1974 and stayed there for 20 years. The position was a promotion to Head of Division from his job as Senior Lecturer in Manchester previously. Once the centre closed, he moved to Oxford as the Honorary Director of the SANE Prince

of Wales International Centre for Research on Schizophrenia and Depression. He has been awarded a series of academic distinctions including the Kurt Schenider award in 2005 and the Alexander Gralnick award of the American Psychiatric Foundation in 2000. He is an associate editor of the *British Journal of Psychiatry* and has edited a range of other journals. The extent to which any of these awards or prestigious positions has been the result of this specific piece of work is difficult to determine. More likely they are the result of the full stream of work at Northwick Park, where many studies, including this one, were high profile and highly cited.

Future work

Many members of the project team in this study have continued to work in schizophrenia research. Johnstone is conducting a large and ongoing cohort study in Scotland through the Edinburgh High Risk Study, which looks at adolescents with high genetic risk of developing schizophrenia. A lot of this work follows up on some of the issues around first episodes and characteristics and challenges in the prodromal period that were explored in the Northwick Park first episode study. Crow has also continued to work on topics in schizophrenia, although he has generally moved away from the clinical side of the work and focusses on imaging, genetics and neuropathology. MacMillan has continued to work in schizophrenia, including some further research, which it is unlikely she would have done if she had not come to Northwick Park and worked there as a researcher. However, clinical work has been a bigger focus in her career and she has tended to work with others on research rather than start her own research projects.

Although the team did continue to do some work in this area, much more significant is the quantity of work that has been conducted by others. This was the first study to demonstrate a relationship between duration of untreated psychosis and outcomes, and there has been a significant amount of further research in this area by a number of groups internationally. Searching for 'duration of untreated psychosis' on Web of Science yields 699 hits, all subsequent to this study. Several important later studies cite papers from this research cloud, for example, the work by Loebel et al. (1992) looking at duration of psychosis at Long Island Jewish-Hillside Medical Center, and the work by McGorry et al. (1996) at EPPIC (the Early Psychosis Prevention and Intervention Centre) in developing the system of early detection and optimal management of psychosis. These two papers in particular were cited 526 and 391 times respectively (according to Web of Science). However, attribution here is difficult. It is clear that this was the first study to produce this result, and partly because of the challenges in getting such a large group of first episode patients together, there were few competitor groups at the time who published similar results soon afterwards. One notable exception is the work of Rabiner et al. (1986) in the US, who were also conducting a study into first episodes of schizophrenia and published their one-year follow-up results later the same year. They did note that duration of illness was a factor in terms of prognosis, but did not measure this as duration before start of treatment, rather looking at duration of illness before baseline evaluation. The focus of the studies, and consequently their design, were a little different as explained by Kane at interview:

I think the Northwick Park study was more of what we would call now an effectiveness study in the sense that patients were discharged from hospital and they were followed by their doctors in the community. And there was not really tight control over their treatment

or how frequently they were seen. Whereas our study was what we would call an efficacy study where it was very tightly controlled, all of the patients were seen in the same clinic by the same doctors. They were assessed quite frequently to look for the emergence of symptoms. They were more consistently and more actively treated in a variety of ways. Some patients were also getting a form of psycho social treatment as well. And I think in the Northwick Park study it was as I said more of an effectiveness study. Patients were seen less often, they were seen by different people and I think that's probably what accounts for the higher relapse rates. (JK)

There is some argument that all studies looking at duration of untreated illness and in fact the whole early intervention movement is at least partly related to this work. However, it should be noted that there were other factors contributing to the interest in early intervention in psychosis that developed subsequently. An important influence was the relative failure of the promised revolution in neurobiology, as well as traditional and pharmacological treatments, which led people to look for other possible treatment approaches.

Although this was the first study to find a relationship between duration of untreated psychosis and outcomes, it is worth noting that this particular data set is not often included in the analysis of data in systematic reviews of the topic. For example, in the two relevant Cochrane reviews in this area, the study is referred to, but excluded from the analysis for methodological reasons, in one case because a range of different drugs was used, and results were not broken down by drug (Adams et al., 2009), and in the second case because no specific early intervention protocol was used (Marshall & Rathbone, 2011) – largely because the early intervention concept didn't exist at this time. This shows that although this study played an important role, other subsequent studies are also significant in the developments in clinical practice that resulted.

However, it is clear that the work was influential in developing others' thinking in this area, not only from the number of citations of the core papers (see

), but from the prominent position it takes in several reviews in the area (see, for example, Singh, 2007; McGlashan & Johannessen, 1996) and particular in the influential review by Wyatt (1991), which was considered crucial in cementing opinion on the subject and had an impact on many of the health service changes that followed. This is outlined in more detail in the next section. In the subsequent sections we will consider some of the wider impacts of this study in terms of the early intervention movement both in the UK and internationally, but it must always be taken into account that although this was perhaps the starting point for this to some extent, it was other research groups that continued the work in this area and were responsible for some of the more rigorous data that were used as evidence. Quantifying the extent to which this particular study was responsible for these changes is almost impossible, but in this case it is fair to conclude that the contribution was fairly significant.

Table 2. Citations for cloud publications in Web of Science

Cloud publication	Citations in Web of Science
Crow et al. (1986)	282

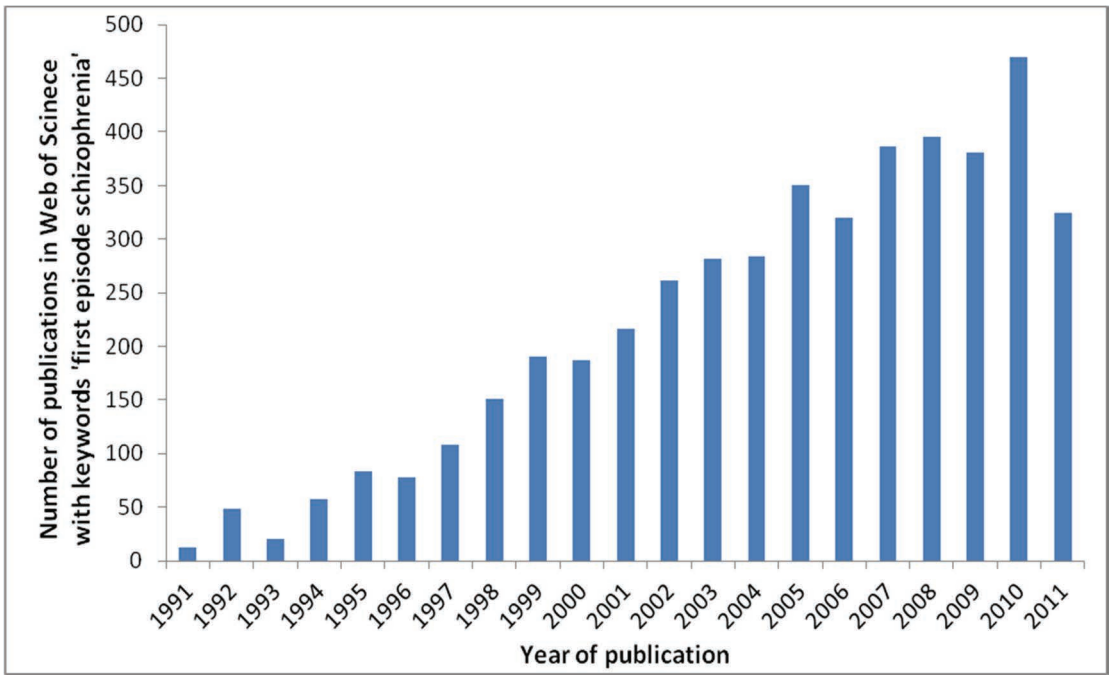
Johnstone et al. (1986a)	203
Johnstone et al. (1986b)	39
Macmillan et al. (1986a)	65
Macmillan et al. (1986b)	128
Johnstone et al. (1987)	32
Macmillan et al. (1987)	17
Johnstone et al. (1990)	147
Humphreys et al. (1992)	104
Humphreys et al. (1994)	Not in Web of Science
Geddes et al. (1994)	46
Cunningham Owens & Johnstone (2006)	23
Owens et al. (2010)	6

Another notable element of this study in terms of targeting of future research is the focus on first episodes. Although this certainly wasn't the first study to do this (e.g., Kane et al., 1982; Gift et al., 1981), it was part of a movement around that time to start to look at the course of progression of the disease, and to focus on this particular point as a moment of significance – now a widespread and important concept in the understanding of schizophrenia. Crow explained this at interview:

I think in the course of that we've sort of set a milestone for using first episodes – using the onset as a particular critical point in the disease. And that certainly has caught on… I think the concept was just beginning to be formulated in 1985, the idea of schizophrenia as a developmental disease. And that I think everybody subscribes to now and it's…. You know it's sort of a rather trivial concept it seems at first, but it's a very important concept because it means that you're dealing with something that is in development, built into the development of an individual. And there are crucial points and psychosis actually relates to one of those crucial points and the whole of psychosis relates to development in some aspect I think now. (TC)

Here, attribution is more questionable, as not only was this not the first study to look at first episodes, it was one of a reasonable number around this time to take that approach. However, it was perhaps one of the first in the UK, and given its high number of citations, it was an influential piece of work. Therefore, it perhaps played a role, as part of the wider literature, in developing this mode of thinking about the disease and in the greater consideration of the first episode as an important milestone. This is illustrated by **Error! Reference source not found.** below, which shows the number of publications in Web of Science with the key words 'first episode schizophrenia' by year. It is interesting to note that the papers from this study are not noted, and indeed the first time the key words 'first episode' are found is 1991.

Figure 2. Plot showing number of publications with key words 'first episode schizophrenia' by year



10.8 Interface B: Dissemination

Academic dissemination

Dissemination was via the standard routes, through journal publications and academic conferences and seminars. The authors felt that presenting results in a clear manner in high-quality academic journals was by far the most important way of disseminating the work.

I think they were mostly academic meetings you know standard academic meetings of ACNP and the CINP and things like that. And national societies. I mean I guess Eve must have talked a lot across to national societies and I have done as well over time. And we would've included these results along with others. You know our concept of what was, what was happening…. I don't think we did anything particularly to disseminate results. I mean I, I'm always impressed by the fact that journal articles get cited and other things don't get cited very much. It seems to me it's important that you put the thing into a journal in as clear a fashion as you can and with the commentary of referees. And that's what counts really. (TC)

10.9 Stage 4: Secondary outputs

There have been significant changes in policy regarding early intervention since the Northwick Park study was conducted, particularly in the UK. NICE guidance in 2002 noted that some early intervention approaches had been developed but that there wasn't sufficient evidence to recommend them. This was updated in 2009, recognising the growing evidence that the early intervention approaches can be beneficial. Current guidance recommends that early intervention services be provided at the first episode stage.

The Northwick Park study is not referred to in the latest guidance, but it does refer to many studies that cite Northwick Park themselves (e.g., McGorry, 1996). The Scottish Intercollegiate Guidelines Network guidance (1998) also recommends that early intervention should take place at the first episode stage and does not directly refer to the Northwick Park study, but Johnstone was involved in compiling this guidance. This is due to her wider reputation in mental health research, rather than any specific work on this study. As an influential piece of work, the Northwick Park study will form a part of this reputation, but it should be noted that Johnstone was involved in a number of high-profile studies, including a previous imaging study providing the first evidence of differences in structure in the brains of schizophrenics (Johnstone, 1976).

American Psychiatric Association guidance (2006) is more tentative, not giving significant mention to early intervention as a treatment strategy (it is placed in the section covering approaches that have a limited evidence base), but stating that it is important to treat as early as possible. The guidance refers to two studies from the research cloud (Johnstone et al., 1986a; Crow et al., 1986) in reference to levels of relapse on neuroleptic medication compared to placebo, and the average time from first presentation of symptoms and initial treatment.

Canadian Psychiatric Association guidance states that upon first episode, treatment should be initiated as soon as possible, noting that delay in treatment is related to worse outcomes (Canadian Psychiatric Association, 1999) The guidance does cite the publication by Crow et al. (1986), but not in relation to duration of untreated psychosis, rather on the figures relating to rates of relapse on medication in comparison to placebo.

In 2005 the International Early Psychosis Association published guidelines on early psychosis (International Early Psychosis Association Writing Group, 2005). They outline standards of care at first episode, including levels of access and approaches to treatment that should be used. The Northwick Park study is not directly referenced in this guidance.

More details on the existing guidance on early intervention can be found in the early intervention case study. However, what we can note here is that early intervention forms a part, although tentative in some cases, of clinical practice guidance internationally. But none of these guidelines includes the Northwick Park study as evidence for its inclusion. This is not surprising, as this initial study discovered the role of duration of untreated psychosis, and since this result was not expected, it is unlikely to provide the best test of approaches to minimise this. However, the work is referred to in several guidelines for the data provided on rates of relapse on and off neuroleptic medication, and, as outlined below in the applications section, one of the study team was significantly involved in the promotion of early intervention, particularly in the UK. Ultimately, the extent to which this study has influenced policy depends on the extent to which follow-on work in studying the importance of early treatment can be attributed to the Northwick Park findings.

The work has also been cited in a number of systematic reviews, including the Cochrane reviews on chlorpromazine as a neuroleptic (Adams et al., 2007) and on early intervention (2011) as described previously. One review cited as influential by Crow at interview, and in one of the later publications in the cloud, was that by Wyatt (1991). This review is suggested to be very influential in terms of healthcare policy, and Kane suggests it was

considered important largely because it was one of the first reviews covering duration of untreated psychosis, and because Wyatt was such a highly respected researcher. He reviewed 22 studies in total, including the Northwick Park study and concluded that a long duration of untreated psychosis was damaging and that early intervention could improve outcomes in the long term.

However, some of the other findings from the publications were not picked up, which in some cases was a little surprising to the authors. For example, Johnstone et al. (1990) finds that in terms of some measures of outcome, such as employment prospects, the patients on placebo performed better than those on neuroleptic medication, despite the greater risk of relapse, but this has not been subject to further investigation nor have the implications of this for policy and practice been considered further. Johnstone suggests this may be because the implications for policy are unclear and difficult to use.

So we were a wee bit surprised when we published the big paper that nobody paid any attention at all to this issue, that maybe there could be a bad side to having people on antipsychotic drugs. I remember I mentioned it when I was presenting the whole thing at the Institute of Psychiatry. I mentioned it and [a colleague] said, 'Well the work is beautiful but what are we to do? If you are saying that giving them drugs stops them from relapsing but maybe it is bad for them in other ways. They have to give people some sort of a message…'. He meant that you want to be able to formulate a policy that is clear, with no ifs, no buts. In reality of course it is a situation that is full of ifs and buts and maybes and we are not very sure. This is not actually awfully helpful from the point of view of Government at all. (EJ)

In terms of drug trials, it is also difficult to test for these types of outcomes in the time periods typically used in these types of tests, making it hard to design treatments that do not have negative implications for outcomes in this way.

If you are trialling new drugs, you know, you really are looking for something that is going to occur or not occur in four weeks flat. You cannot be putting people on new stuff for two years. They are not going to take it…. Of course not. Persuading them to stick any drug regime for two years is very difficult. But they are not going to take, if you say, 'Well we are not sure about this drug because it is just new.' They are quite willing, well they are often very willing for other people to take it. They want it to be tested. But whether they want it to be tested on themselves is sometimes another matter. (EJ)

10.10 Stage 5: Applications

Treatment of first episodes of psychosis, and in particular minimising the period of untreated illness, has been the standard for care in schizophrenia for many years now across all three study countries. According to McGorry (2002), 'the postulated benefit of reducing DUP has been one of several arguments used to justify the establishment of early intervention services in the United States, Canada, Australia, and several European countries'. Although the emphasis of the guidelines differs between countries, as outlined above, in all cases attempts to prevent long periods of untreated illness are in place. This is perhaps most marked in the UK, where, for example, the NHS has set specific targets for early intervention timelines. In England, under the National

Health Service Plan, 50 early intervention teams had been established, at a cost of £70m, by 2000. UK Mental Health Policy published in 2001 (Department of Health, 2001) set out a range of criteria recommended for early intervention care, including an aim to reduce the duration of untreated illness to less than three months.

In the UK in particular, there is a clear connection between this movement to reduce the period of untreated illness and the Northwick Park study. This is not just because of the study's role as the first to uncover the relationship between prognosis and duration of untreated psychosis, and it being featured on clinical guidelines as outlined above, but also because of the role played by MacMillan in the UK early intervention movement. She was one of the co-founders of the West Midlands IRIS (Initiative to Reduce the Impact of Schizophrenia) group and working with Max Birchwood from 1995 they developed an early intervention service in that area which formed a template for early intervention services that were later rolled out across the UK. The group were vocal campaigners for better first episode care, and were highly influential in terms of changes to policy and practice in the UK. This is evident in the UK Department of Health Mental Health Policy Implementation Guide (Department of Health, 2001), which acknowledges, amongst a limited list of eight, both Max Birchwood and IRIS for their contribution. The extent to which MacMillan's work in this particular study is important in these later achievements can be debated, but she was involved heavily in the work looking at the challenges people had faced in access to treatment, as published in the first of the core study papers (Macmillan et al., 1986a). She wrote her MD on the basis of this work, and in it included vignettes about every single patient and the difficulties they faced, which was a significant influence on her feelings about the inadequacy of care and the need for change within the healthcare system. At interview, she suggests that this had a significant impact on her thinking, and her clinical practice.

I think it was probably the greatest influence on my subsequent clinical approach. You have to remember I was in my mid 20s at this stage so I was often the same age as these clients and their parents weren't so different from my parents and their brothers and sisters weren't so different from mine…. I visited them in hospital, at home…. I probably had more clinical experience of early schizophrenia than anybody else. (JM)

Links to changes in practice in other countries are less clear. The study is cited by McGorry et al. (1996) in some of their work developing the EPPIC (the Early Psychosis Prevention and Intervention Centre) approach to early intervention in Australia, which was influential not only in laying the foundations for changes in practice in Australia, but also internationally as one of the first such schemes, being established in 1992. Application of early intervention approaches has been slower to take place in the US and Canada. In Canada, early intervention has been adopted but not in any consistent manner across the whole country, but rather on a more regional basis. Further discussion of developments and implementation in early intervention are described in the early intervention backwards-tracing case study. However, it is fair to say this has been a significant movement in the treatment of schizophrenia. This is evident in the statement by the World Health Organization in 2004, issued jointly with the International Early Psychosis Association. This international consensus statement outlines a five-year programme of action on early intervention for psychosis. It is worth noting that this is based upon the

UK Newcastle Early Psychosis Declaration (2002), which was conceived by the IRIS group, which included MacMillan.

10.11 Stage 6: Public engagement

None identified.

10.12 Stage 7: Final outcomes

It is clear that early intervention has been implemented internationally, and particularly in the UK. However, the extent to which the Northwick Park study has had an impact on wider public health and well-being depends on two factors: the extent to which the study influenced the early intervention movement, and the extent to which early intervention has improved health and wellbeing. The first of these is covered earlier, and remains to an extent subjective. The second also leaves some questions to be answered.

In terms of improving long-term outcomes of schizophrenics, the evidence remains weak, and indeed the final publication in the cloud concludes that the relationship between duration of untreated illness and prognosis is probably not causal. Certainly, the study authors are sceptical about any improvement in outcomes from early intervention.

Well the early intervention stuff I mean we thought that – it was put into legislation in England at an early stage. We thought it was put in on the basis of inadequate evidence. But we did find of course that one of the determinants of how they did two years' later was how long it had taken them to get into treatment in the first place. And the ones that had not got into treatment for more than a year did worse. That was seized upon relentlessly. We thought that we were almost flying a kite with the suggestion that maybe having a long period of untreated illness had some sort of malignant effect. Because I mean what the heck could it possibly be? But that was seized upon with tremendous fervour and has been advanced relentlessly in support of early intervention programmes. But of course we were never claiming and knew indeed that it was not the case that you needed to get on to treatment very quickly. The early intervention stuff to my mind, was over promoted. (EJ)

I think the important thing is that we stress that you can interpret this in two ways. You could think that it mattered whether people got on to treatment early, got detected early and admitted early but treated early did better. Or maybe a long delay in getting admitted meant that you were withdrawn and asocial and you were going to do worse anyway. And that's the importance of this paper here [Owens et al., 2010], because everybody has interpreted it in terms of the first interpretation and people get very excited about how important it is to treat people early but I don't think we know that. I don't think that's clear…. The alternative is that you're dealing with a spectrum of predispositions and some people are going to do badly and they are the ones who are asocial, who have the negative symptoms in particular. (TC)

Although benefits in terms of patient outcome might be uncertain, it is important to stress that this does not mean that the early intervention movement has not lead to improvements in quality of care. As outlined in MacMillan et al. (1986a), the provision of services in many places was inadequate and the distress caused to family and patients by

extended periods of untreated psychosis could be significant. Reductions in this distressing period by improved access to treatment and care, even if it does not improve outcomes, can have significant benefits to society, not just for the patients and their families, but in reducing dangerous and criminal behaviour that can characterise periods of psychosis in some cases, as outlined in work by Humphreys et al. (1992, 1994). Providing phase appropriate, structured care to individuals from the outset offers obvious benefits to patients and families even if it does not affect subsequent prognosis, and highlighting the inadequacies in the current system was another key role that this study played.

Also clear are the financial benefits of early intervention. Recent work by McCrone et al. (2010) suggests that in the UK, early intervention programmes could save up to £40m per year. This figure takes into account some of the wider societal costs of schizophrenia, including unemployment and suicide. However, this is a figure for the first few years, where effects are on both service use and employment. They expect that these savings would fall to around £20m per year in the longer term, where gains are from employment and reduced costs from suicide rather than reduced service costs. This is also described over the shorter term by Valmaggia et al. (2009), who demonstrate that the costs for early intervention using the OASIS (Outreach and Support in South London) approach compared to care as usual, although higher after 12 months, are lower after 24 months once employment is taken into account. In both cases, some of the wider societal costs relating to crime and dangerous or threatening behaviour in untreated psychosis as described in the work by the Northwick Park team are not taken into account. Also not included are the potential costs in terms of health and possibly also employment to family members of schizophrenics undergoing extended periods of untreated psychosis. Therefore, these are likely to be conservative estimates.

However, there may have been negative consequences also. At interview, both Johnstone and MacMillan, though recognising some of the benefits brought about by the increased focus on first episode schizophrenia, suggested, for example, that it may have taken resources from older patients.

I think it has been very influential. I think it has raised the profile of schizophrenia. I think it has changed people's perceptions of someone with schizophrenia as being 45 with funny trousers to somebody a lot younger. I think that's true but and I think it has to some degree, to some modest degree changed tactics. But what of course one finds is that while people are perhaps more interested in the very young people with early psychosis in the first four or five years, families say and certainly the Schizophrenia Fellowship says that resources from the more mature clients, the clients in their 40s and stuff have been further reduced. (FM)

There is a difference of opinion about this, because while some psychiatrists favour early intervention a lot of psychiatrists would say that there was truth in the idea – that they developed these early intervention services which are of doubtful value, except that of course they do provide care, at the expense of the rest of the service. Nobody is going to dispute the enhanced quality of care for distressed young people and their families. But that they have taken from elsewhere no extra money was provided. So they have taken services from the generality of the sick people who are all of other ages and perhaps less appealing and fed it into early intervention. You know, there is a controversy about it. (EJ)

10.13 Table of payback

Payback category	Impacts from case study
Knowledge Production	• First study to find that duration of untreated psychosis is associated with poorer outcomes. • Showed that access to treatment was often woefully inadequate. • Found that neuroleptic treatment was strongest predictor of outcome. • Did not find any noticeable effect of expressed emotion. • Evidence that on some wider outcomes particularly in terms of social functioning, patients perform better on placebo than on medication.
Research Targeting and Capacity Building	• Significant number of subsequent studies looked at duration of untreated psychosis. • Large number of studies subsequently looked at first episodes and the life course of schizophrenia. • MacMillan's first research position; she obtained her PhD on the basis of it and it was a significant influence on her future career trajectory. • One of a number of high-profile studies coming out of the work at Northwick Park that enhanced the reputation of Crow, Johnstone and Frith.
Informing Policy and Product Development	• The first evidence that duration of untreated psychosis might be significant, which combined with the evidence regarding treatment access was one of the main starting points for the move towards early intervention. • Cited in a number of Cochrane reviews; however, studies designed with the question of early intervention in mind tend to be used in these analyses and in guidelines rather than this 'discovery' study.
Health and Health Sector Benefits	• MacMillan played an important role in early intervention movement in West Midlands, which was critical in the implementation of early intervention in the UK; she attributed this significantly to the Northwick Park study and suggests it was a strong influence on others in the UK. • Health benefits of early intervention disputable, but benefits for families, quality of care, and economic benefits for health care system clearer. • Early intervention also important in Australia but connection less direct.
Broader Social and Economic Benefits	• Social benefits of early intervention services; improvements in quality of care benefiting both patients and families.

	• Evidence suggests significant economic benefits in savings in healthcare costs through early intervention. • Possible social benefits as untreated psychosis associated with crime and violent or dangerous behaviour. • Extent to which this attributable to study questionable as many other important people and studies involved; however, this was one of the key early studies that established early intervention as a topic of research interest, so benefits can be at least partly attributed to this work.

10.14 Timeline

1973	Publication of study into neuroleptic treatment by Hogarty et al.
1974	Northwick Park MRC centre opens; Crow joins as Head of Division; Johnstone joins from Glasgow
1976	MacMillan joins Northwick Park as SHO to Johnstone
1977	MacMillan promoted to Registrar
1979	Started to recruit the patients for the study; MacMillan works as a Clinical Scientist on the project
1982	Finished recruiting patients for the study; MacMillan leaves Northwick Park
1986	Core study results published in a series of four papers
1989	Johnstone leaves Northwick Park for Edinburgh
1991	Publication of Wyatt's influential review of early intervention
1992	EPPIC program for early intervention developed (Australia)
1994	Crow leaves Northwick Park for Oxford
1995	Birmingham Early Intervention Service established; IRIS established
2001	UK mental health policy implementation guide prioritises development of early intervention teams
2002	Early intervention mentioned in NICE guidance
2004	WHO/IEPA joint statement on early intervention published
2009	Updated NICE guidance notes evidence that early intervention is beneficial

10.15 References

American Psychiatric Association. (2006). *Practice Guidelines for the Treatment of Psychiatric Disorders: Compendium 2006*. Arlington, VA: American Psychiatric Association.

British Medical Journal. (1986). The future of clinical research in Britain. *British Medical Journal*, 292, 416–417.

British Medical Journal. (1970). Northwick Park Hospital And Clinical Research Centre. *British Medical Journal*, 3(5722), 576–580.

British Medical Journal. (1969). Hospital Topics: Northwick Park Hospital and Clinical Research Centre. *British Medical Journal*, 4(5675), 105.

Canadian Psychiatric Association. (1999). Canadian clinical practice guidelines for the treatment of schizophrenia. *Canadian Journal of Psychiatry*, 43(S2), 25S–40S.

Clinical Research Centre Committee. (1986). Report to the Medical Research Council on the CRC at Northwick Park. London: Medical Research Council.

Crow, T.J. (1991). Starting again with clinical research. *British Medical Journal*, 302, 530.

Crow, T.J., Macmillan, J.F., Johnson, A.L., & Johnstone, E.C. (1986). The Northwick Park study of 1st episodes of schizophrenia. II. A randomized controlled trial of prophylactic neuroleptic treatment. *British Journal of Psychiatry*, 148, 120–127.

Department of Health. (2001). *The Mental Health Policy Implementation Guide*. London: Department of Health.

Department of Health. (2000). *The NHS Plan: A Plan for Investment, a Plan for Reform*. London: Department of Health.

Geddes, J., Mercer, G., Frith, C.D., MacMillan, J.F., Owens, D.G., & Johnstone, E.C. (1994). Prediction of outcome following a first episode of schizophrenia. A follow-up study of Northwick Park first episode study subjects. *British Journal of Psychiatry*, 165, 664–668.

Gift, T.E., Strauss, J.S., Harder, D.W., Kokes, R.F., & Ritzler, B.A. (1981). Established chronicity of psychotic symptoms in first-admission schizophrenic patients. *American Journal of Psychiatry*, 138, 779–784.

Goldberg, S.C., Klerman, G.L., & Cole, J.O. (1966). Changes in schizophrenic psychopathology and ward behaviour as a function of phenothiazine treatment. *British Journal of Psychiatry*, 111, 120–133.

Goldberg, S.C., Mattsson, N., Cole, J.O., & Klerman, G.L. (1967). Prediction of improvement in schizophrenia under four phenothiazines. *Archives of General Psychiatry*, 16, 107–117.

Hogarty, G.E., & Baltimore, S.C. (1973). Drug and sociotherapy in the aftercare of schizophrenic patients: one-year relapse rates. *Archives of General Psychiatry,* 28, 54–64.

House of Commons Science and Technology Select Committee. (2005). Fourth report.

Humphreys, M.S., Johnstone, E.C., & Macmillan, J.F. (1994). Offending among first episode schizophrenics. *Journal of Forensic Psychiatry*, 5, 51–61.

Humphreys, M.S., Johnstone, E.C., MacMillan, J.F., & Taylor, P.J. (1992). Dangerous behaviour preceding first admissions for schizophrenia. *British Journal of Psychiatry*, 161, 501–505.

International Early Psychosis Association Writing Group (2005). International clinical practice guidelines for early psychosis. *British Journal of Psychiatry*, S8, S120–S124.

Johnson, M.H., Franklin, S.B., Cottingham, M., & Hopwood, N. (2010). Why the Medical Research Council refused Robert Edwards and Patrick Steptoe support for research on human conception in 1971. *Human Reproduction*, 25(9), 2157–2174.

Johnstone, E.C., Crow, T.J., Frith, C.D., Husband, J., & Kreel, L. (1976). Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *The Lancet*, 2(7992), 924–926.

Johnstone, E.C., Crow, T.J., Johnson, A.L., & Macmillan, J.F. (1986). The Northwick Park study of first episodes of schizophrenia. I. Presentation of the illness and problems relating to admission. *British Journal of Psychiatry*, 148, 115–20.

Johnstone, E.C., Crow, T.J., Macmillan, J.F., Owens, D.G.C., Bydder, G.M., & Steiner, R.E. (1986). A magnetic resonance study of early schizophrenia. *Journal of Neurology, Neurosurgery and Psychiatry*, 49, 136–139.

Johnstone, E.C., Macmillan, J.F., & Crow, T.J. (1987). The occurrence of organic disease of possible or probable aetiological significance in a population of 268 cases of first episode schizophrenia. *Psychological Medicine*, 17, 371–379.

Johnstone, E.C., Macmillan, J.F., Frith, C.D., Benn, D.K., & Crow, T.J. (1990). Further investigation of the predictors of outcome following first schizophrenic episodes. *British Journal of Psychiatry*, 157, 182–189.

Kane, J.M., Rifkin, A., Quitkin, F., Nayak, D., & Ramos-Lorenzi, J. (1982). Fluphenazine vs. placebo in patients with remitted acutre first-episode schizophrenia. *Archives of General Psychiatry*, 39, 70–73.

Loebel, A.D., Lieberman, J.A., Alvir, J.M., Mayerhoff, D.I., Geisler, S.H., & Szymanski, S.R. (1992). Duration of psychosis and outcome in first-episode psychosis. *American Journal of Psychiatry*, 149, 1183–1188.

Macmillan, J.F., Crow, T.J., Johnson, A.L., & Johnstone, E.C. (1987). Expressed emotion and relapse in first episodes of schizophrenia. *British Journal of Psychiatry*, 151, 320–323.

Macmillan, J.F., Crow, T.J., Johnson, A.L., & Johnstone, E.C. (1986). The Northwick Park study of 1st episodes of schizophrenia. III. Short-term outcome in trial entrants and trial eligible patients. *British Journal of Psychiatry*, 148, 128–133.

Macmillan, J.F., Gold, A., Crow, T.J., Johnson, A.L., & Johnstone, E.C. (1986). The Northwick Park study of schizophrenia. IV. Expressed emotion and relapse. *British Journal of Psychiatry*, 148, 133–143.

Marshall, M., Lewis, S., Lockwood, A., Drake, R., Jones, P., & Croudace, T. (2005). Association between duration of untreated psychosis and outcome in cohorts of first-episode patients. *Archives of General Psychiatry*, 62, 975–983.

McCrone, P., Park, A.-L., & Knapp, M. (2010). *Economic Evaluation of Early Intervention (EI) Services: Phase IV Report*. PSSRU Discussion Paper 274.

McGlashan, T.H. (1988). A selective review of recent North American long-term follow-up studies of schizophrenia. *Schizophrenia Bulletin*, 14(4), 515–542.

McGlashan, T.H., & Johannessen, J.O. (1996). Early detection and intervention with schizophrenia: rationale. *Schizophrenia Bulletin*, 22(2), 201–222.

McGorry, P.D., Edwards, J., Mihalopoulos, C., Harrigan, S.M., & Jackson, H.J. (1996). EPPIC: an evolving system of early detection and optimal management. *Schizophrenia Bulletin*, 22(2), 305–326.

McGorry, E.J. (2002). *Implementing Early Intervention in Psychosis: A Guide to Establishing Early Psychosis Services* (1st ed.). London: Martin Dunitz.

Mintz, J., Mintz, L., & Goldstein, M. (1987). Expressed emotion and relapse in first episodes of schizophrenia. A rejoinder to Macmillan et al. (1986). *British Journal of Psychiatry*, 151, 314–20.

National Institute for Health and Clinical Excellence. (2009). *Schizophrenia*. London: National Institute for Health and Clinical Excellence.

National Institute for Health and Clinical Excellence. (2002). *Schizophrenia*. London: National Institute for Health and Clinical Excellence.

Owens, D.G., & Johnstone, E.C. (2006). Precursors and prodromata of schizophrenia: findings from the Edinburgh High Risk Study and their literature context. *Psychological Medicine*, 36, 1501–1514.

Owens, D.C., Johnstone, E.C., Miller, P., Macmillan, J.F., & Crow, T. (2010). Duration of untreated illness and outcome in schizophrenia: test of predictions in relation to relapse risk. *British Journal of Psychiatry*, 196, 296–301.

Rabiner, C.J., Wegner, J.T., & Kane, J.M. (1986). Outcome study of first-episode psychosis I: relapse rates after 1 year. *American Journal of Psychiatry*, 143(9), 1155–1158.

Scottish Intercollegiate Guidelines Network. (1998). *Psychosocial Interventions in the Management of Schizophrenia: A National Clinical Guideline*. SIGN publication 30.

Singh, S.P. (2007). Outcome measures in early psychosis: relevance of duration of untreated psychosis. *British Journal of Psychiatry*, 191(S50), S58–S63.

Valmaggia, L.R., McCrone, P., Knapp, M., Wooley, J.B., Broome, M.R., Tabraham, P., Johns, L.C., Prescott, C., Bramon, E., Lappin, J., Power, P., & McGuire, P.K. (2009). Economic impact of early intervention in people at high risk of psychosis. *Journal of Psychological Medicine*, 39, 1617–1626.

Wyatt, R.J. (1991). Neuroleptics and the natural course of schizophrenia. *Schizophrenia Bulletin*, 17(2), 325–351.

CHAPTER 11 Low frontal glucose utilization in chronic schizophrenia: a replication study

This case study is based on the research that produced the paper:

Wolkin, A., Angrist, B., Wolf, A., Brodie, J., Wolkin, B., Jaeger, J., Cancro, R., & Rotrosen, J. (1988). Low frontal glucose utilization in chronic schizophrenia: a replication study. *American Journal of Psychiatry*, 145(2), 251–253.

Information was gathered from interviews with the lead author, Dr. Adam Wolkin, as well as desk-based research.

11.1 Summary

This research examines the underlying biological or brain mechanisms causing schizophrenia using positron emission tomography (PET) imaging, specifically assessing the metabolism of glucose in different regions of the brain. The work was conducted by Adam Wolkin, who became an Assistant Professor of Psychiatry in the School of Medicine at New York University (NYU) in 1984 after completing his residency at NYU in 1982. Wolkin was interested in exploring cerebral structural and functional abnormalities in schizophrenia. His research initially sought to understand the relationship of abnormalities in brain function with so-called positive symptoms using the new PET imaging technology.

At the time Wolkin completed his residency, NYU was forging a relationship with the Brookhaven National Laboratory, which was one of the few laboratories in the world at that time with radiochemistry expertise and a PET camera. The developing collaboration between NYU and Brookhaven provided Wolkin with an opportunity to extend preliminary work by his group and by others on the functioning of the schizophrenic brain using the new technology. Specifically, prior research had suggested frontal lobe dysfunction in schizophrenia. The PET methodology provided a new and powerful tool for imaging the entire brain and exploring these and other potential deficits. Wolkin and colleagues used this new neuroimaging technology to compare brain functioning in schizophrenia with normal controls. Using PET, they found that the frontal/posterior ratios of glucose metabolism were significantly lower in schizophrenic patients compared to controls, a finding that they subsequently replicated and reported again in the identified paper.

Moving forward, Wolkin and colleagues moved beyond the exploratory studies to more hypothesis-driven research addressing dopamine mechanisms in schizophrenia and the relationship of frontal lobe functional and structural abnormalities to psychiatric and neuropsychological deficits. In subsequent work they also they introduced the use of dopamine agonist- and antagonist-drug challenges with PET to further examine cerebral abnormalities in schizophrenia. Wolkin remains at the Veteran's Affairs (VA) Medical Center in New York. Nearly all of Wolkin's work has been funded through the VA Merit Review funding system

Although this case study research did not lead directly to clinical practice or applications, collectively with similar research and findings from other PET labs it led to a greater focus on frontal lobe deficits in the schizophrenic brain. This focus on frontal lobe deficits helped move the field towards further research in areas such as negative symptoms, neuropsychological deficits, and dopaminergic hyper- and hypo-function in schizophrenia, which in turn affected the clinical approach to treatment for schizophrenia. By linking hypofrontality to structural deficits and disconnection, this body of research increased understanding of the utility and importance of cognitive remediation and treatment targeting the amelioration of hypofrontality.

11.2 Introduction

11.2.1 Scientific background

This research examines the brain mechanisms underlying schizophrenia using PET imaging, specifically the metabolism of glucose in different regions of the brain, and characteristics of dopaminergic ligand binding. Imaging of cerebral metabolism became feasible in the 1970s with advances in both scanner technology and radiopharmaceutical synthesis. PET scanning provides a means for the direct, in vivo measurement of a broad array of cerebral processes, in this case glucose metabolism, which can be used to determine regional cerebral activity. During the 1980s, PET scanning was increasingly used to study the functioning of the brain, and in particular, to understand the pathophysiology of schizophrenia. Some early work by Ingvar and Buschbaum measured cerebral blood flow and found evidence of hypofrontality (Ingvar & Franen, 1974; Buschbaum et al., 1982). At the time of the research, several exploratory PET studies had been conducted at NYU that found lower rates of glucose metabolism in the frontal lobes of schizophrenic patients than in the posterior regions of the brain (Farkas et al., 1984; Wolkin et al., 1985). This lower frontal/posterior ratio of metabolic activity is known as hypofrontality, though it was not a consistent finding in patients with schizophrenia across all PET labs.

The identified paper describes a study using PET imaging experiments on a relatively small sample of subjects: 13 schizophrenic patients and 8 normal controls in which Wolkin and colleagues replicated their earlier 1985 finding of hypofrontality in a new cohort of patients with schizophrenia.

11.2.2 Researchers' background

Adam Wolkin spent his fourth year of psychiatry residency on an elective in schizophrenia research with a group at the New York VA Medical Center, headed by **John Rotrosen**, Chief of Psychiatry at the VA Medical Center and Professor of Psychiatry at NYU. Prior to moving to the VA, Rotrosen had been part of a research group at Bellevue Hospital/NYU

led by Sam Gershon, a pioneer in the field of psychopharmacology. When Gershon left NYU to become Professor and Chairman of the Department of Psychiatry at Wayne State University and Director of the Lafayette Clinic in New York, Rotrosen, and fellow schizophrenia researcher and NYU professor **Burt Angrist**, moved to the VA Medical Center. Rotrosen and Angrist became Wolkin's primary mentors.

Wolkin completed his psychiatry residency at NYU in 1982, and took a position at the VA Medical Center. At this time, NYU was forging a relationship with colleagues at Brookhaven National Laboratory in Upton, Long Island, who, under **Alfred Wolf** (Chair of the Department of Chemistry at Brookhaven), were leaders in the development of PET and related radiotracers. On the NYU side, **Jonathan Brodie**, Professor of Psychiatry, was a key member of this developing collaboration. Brodie also became a mentor for Wolkin. Overall, the collaboration between NYU and Brookhaven gave Wolkin a unique opportunity as a junior researcher to enter an exciting and nascent field. Wolkin's first paper using PET was published in 1985 (Wolkin et al., 1985).

Wolkin went on to conduct schizophrenia and imaging research at the VA for the next 20 years. Since 1998, Wolkin has also been the Associate Chief of Staff for Mental Health at the NY VA and Associate Professor at NYU Langone School of Medicine.

Rotrosen continues at NYU as Professor of Psychiatry and Director of the NYU Center of Excellence in Addiction. Angrist was active in schizophrenia research until his retirement in the mid 2000s. Brodie is currently Professor of Psychiatry at NYU and remains active in PET imaging.

11.3 Defining the research cloud

The research cloud for this study focuses on the work that Wolkin and colleagues conducted to examine the neurobiological basis of schizophrenia. Specifically, this research cloud examined the frontal lobe as an area of functional and neuropsychological deficits in the schizophrenic brain. The studies in this research cloud sought to understand the complex of abnormalities and behaviours that related hypofrontality to negative symptoms and possibly poor treatment outcomes.

The research cloud includes two papers published prior to the identified paper; both of these papers are cited by the identified paper. The remaining two papers in this cloud were published in 1992 and 1996. All shared many of the same co-authors as the target paper, including Angrist, Brodie, Wolf, and Rotrosen.

The publications included in the cloud for this case study are as follows:

1. *Farkas, T., Wolf, A.P., Jaeger, J., Brodie, J.D., Christman, D.R., & Fowler, J.S. (1984). Regional brain glucose metabolism in chronic schizophrenia. Archives of General Psychiatry*, 41(3), 293–300.
2. *Wolkin, A., Jaeger, J., Brodie, J.D., Wolf, A.P., Fowler, J., Rotrosen, J., Gomez-Mont, F., & Cancro, R.* (1985). Persistence of cerebral metabolic abnormalities in chronic schizophrenia as determined by positron emission tomography. *American Journal of Psychiatry,* 142(5), 564–571.

3. Wolkin, A., Angrist, B., Wolf, A., Brodie, J., Wolkin, B., Jaeger, J., Cancro, R., & Rotrosen, J. (1988). Low frontal glucose utilization in chronic schizophrenia: a replication study. *American Journal of Psychiatry*, 145(2), 251–253.
4. *Wolkin, A., Sanfilipo, M., Wolf, A.P., Angrist, B., Brodie, J.D., & Rotrosen, J.* (1992). Negative symptoms and hypofrontality in chronic schizophrenia. *Archives of General Psychiatry*, 49(12), 959–965.
5. *Wolkin, A., Sanfilipo, M., Duncan, E., Angrist, B., Wolf, A.P., Cooper, T.B., Brodie, J.D., Laska, E., & Rotrosen, J.P.* (1996). Blunted change in cerebral glucose utilization after haloperidol treatment in schizophrenic patients with prominent negative symptoms. *American Journal of Psychiatry*, 153(3), 346–354.

11.4 Stage 0: Opportunity identification/research needs assessment

Inspiration

Wolkin's early work examining the function of the schizophrenic brain using PET imaging was conducted in a nascent field and at a time when the hypothesis of dopaminergic hyperactivity in schizophrenia was predominant.

> At the time when we started our PET research, the dopamine hypothesis, derived in part from the CNS Stimulant model of schizophrenia to which Burt Angrist had contributed, was the pre-eminent model of the neurochemical basis of schizophrenia. This seemed an obvious starting point to utilize PET in order to study the underlying biological or brain mechanisms causing schizophrenia. (AW)

Originally, Wolkin's interest in schizophrenia was primarily around positive symptoms, such as hallucinations, delusions and illusions, reflecting the focus in the field on the relationship between putative hyper-dopaminergia and psychotic symptoms. At the same time, a major enticement of PET research was its unique strength for use as an exploratory technique that allowed imaging of the entire brain.

> We were intrigued by the idea of being able to visualize a living brain and to potentially identify the underpinnings for schizophrenia. It would take a while for the sophistication to grow in study design from these initial exploratory studies comparing human and schizophrenic brain functioning to more carefully designed and hypothesis-driven studies. (AW)

Feasibility

The introduction of PET imaging technology to examine the schizophrenic brain made this research cloud possible. Many in the research community were drawn to the opportunity to use the new techniques.

> As a young psychiatrist just out of residency and starting a research career, I knew I was interested in schizophrenia, but that was about it. There were a variety of projects and directions we were looking at [in the VA research group], one of which was brain imaging at Brookhaven National Laboratory. In that this was one of the few sites in the world at the time that had a PET camera, it was an extraordinary opportunity to do early investigation with PET. (AW)

Potential value

Among the potential benefits of this research was the ability to better understand abnormalities in brain function in schizophrenia, which, in turn might lead to improvements in the clinical treatment of schizophrenia.

11.5 Stage 1: Inputs to research

Money, researcher time, lab/office space and consumables

PET studies at NYU were supported through various individual and project programme grants at Brookhaven and NYU. Almost all of Wolkin's individual work was subsequently funded through VA Merit Review, the VA peer review funding system (similar to a NIH R01 grant). The identified paper came out in 1988 and along with prior work provided the basis for his first VA grant from 1988 to 1992. He continued to receive funding through the Merit Review programme until 2002.

PET studies were also supported in part by the pharmaceutical industry, which early on recognised the strength of PET in better understanding drug actions and characteristics in the living brain.

At the time, Brookhaven had extensive funding from the Department of Energy and multiple other funding agencies that supported the PET camera, related equipment and facilities. There was an extensive and unique infrastructure at Brookhaven to support collaborative studies with PET imaging. Aside from the scanner, this ranged from radiochemical development to post-imaging processing. Wolkin and others acknowledged these funding sources in the papers based on the research conducted with the PET scanner.

For an individual junior investigator such as Wolkin, these were labour-intensive studies. He had to recruit the patients, transport them to Long Island for their scans, and conduct image and data analysis. This in part constrained sample sizes.

Knowledge

The early work by Wolkin and others using PET in schizophrenia built on an existing literature at the time that suggested lower activity in the frontal lobe as compared to the posterior region in schizophrenic patients. There were also neuropsychological findings going back decades suggesting frontal lobe dysfunction deficits in schizophrenia.

> Starting with our first PET study, we found a pattern of decreased metabolism in the frontal part of the brain as compared to normal subjects. This was consistent with what had been reported in a preceding paper by Farkas, also coming out of the BNL/NYU collaboration. There had been similar report of hypofrontality using cruder brain imaging techniques before the time of PET. Together this gave as assurance that this was a real finding and something we wanted to continue to explore. And sure enough, it showed up in the 1985 paper. (AW)

Expertise and techniques

Wolkin's replication study reported in the identified paper built on the two exploratory studies that came out of the NYU-Brookhaven collaboration. NYU's Farkas and colleagues examined rates of glucose metabolism in the frontal and posterior regions of the brain in both schizophrenic patients and normal controls using a combination of PET imaging and CT scanning. Farkas found that schizophrenic patients had significantly lower

frontal/posterior ratios of glucose metabolism compared to controls (Farkas et al., 1984). In Wolkin's first study, he found a pattern of decreased metabolism in the frontal part of the brain in schizophrenic patients compared to normal controls (Wolkin et al., 1985). Through these exploratory studies, Wolkin developed experience in analysing the PET images that he then used in his subsequent work.

Collaborators

The collaboration with Brookhaven began before Wolkin finished his NYU residency and joined the VA research group, and primarily involved Alzheimer's disease, depression and schizophrenia. When Wolkin joined the VA research group, John Rotrosen encouraged him to work in this area. Much of his initial work and a large part of subsequent work was in collaboration with Brodie.

> This was a tremendous and critically needed collaboration since the field was really in its infancy. There were debates whether the deoxyglucose methods was even a valid index of brain activity, let alone how best to conduct image analysis. (AW)

The collaboration involved periodic conferences, meetings, data reviews and discussions. Papers were circulated among a group of scientists with different backgrounds, including the psychiatrists, clinical and laboratory staff, chemists, and those conducting the PET imaging, all of whom had their area of expertise but also had a general understanding of the current status of the field. This collaboration on the research results was a very formative process in terms of getting the feedback from a cadre of different types of scientists with different backgrounds.

11.6 Stage 2: Processes

The process to conduct this research, aside from clinical aspects, entailed synthesis of chemical compounds, operation of the PET camera, running the scanning procedure, procurement of raw PET data, and analytic computations, in this case to measure metabolism. Specifically, the scientists at Brookhaven synthesised the fluorodeoxyglucose compound that was the basis for imaging cerebral metabolism. The Brookhaven researchers also refined the modelling techniques to calculate the rate of glucose metabolism.

11.7 Stage 3: Primary Outputs

Knowledge

The results of the replication study described in the target paper found, using PET imaging, that the frontal/posterior ratios of glucose metabolism were significantly lower in schizophrenic patients compared to controls. A number of other PET investigators, most notably Monte Buchsbaum, were also strong proponents of hypofrontality in schizophrenia. However, other sites were unable to replicate this finding. As a result, an intense debate in the literature emerged along with various hypotheses to explain the basis for the different findings. For example, at the University of Pennsylvania in PET work led by Raquel Gur, hypofrontality was not found and instead the group were strong proponents of temporal lobe hyperactivity (for which there was also strong support in neuropsychiatric literature).

> …A number of sites also found this so-called hypofrontality, and a number of sites did not. This became somewhat of a mini-controversy in the field and led to various hypotheses concerning these differences. (AW)

The critiques of Wolkin's findings focussed on his patient population. Some researchers questioned whether Wolkin's results were a medication effect, because they were studying veterans who were not first-episode patients and had been previously taking antipsychotic medications. To partially address this concern, Wolkin studied patients who were off antipsychotic medicine at the time of their PET scan. Others questioned whether the observed hypofrontality in Wolkin's research reflected chronicity of illness, since the veteran patients tended to have had their illness for several decades.

This paper was highly cited at the time partly because of the debate over the different findings across research sites and partly because it was a relatively narrow field. The study was initially recognised because it used a novel methodology to provide one of the early lines of evidence of hypofrontality in schizophrenia, despite a small sample size.

> It was serendipitous that the population of patients whom we studied at the VA had both robust positive and negative symptoms. As a result, we were able to pick up a strong signal for hypofrontality even in very small samples sizes. It's rather unusual to have such strong statistical findings with an N of only a dozen or so subjects. (AW)

The 1992 paper began to examine the association between negative symptoms and frontal lobe abnormalities in patients with schizophrenia and found a close relationship in a specific area of the frontal lobe. Subsequent papers by Wolkin using PET imaging in schizophrenia examined the effect of haloperidol treatment on cerebral metabolism; the effects of acute stimulant challenge; and the relationship between hypofrontality, white matter frontal lobe structural deficits, and negative symptoms.

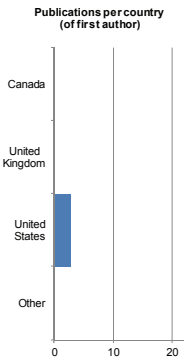
A bibliometric analysis of the papers produced from the research cloud is shown below.

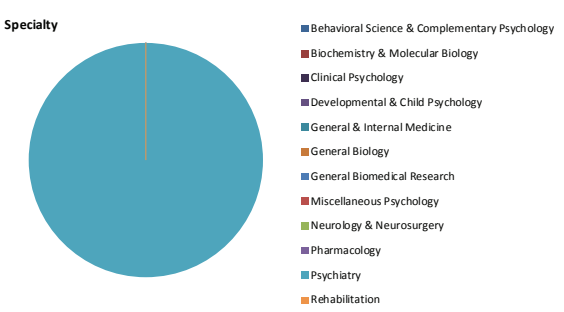
Research cloud:

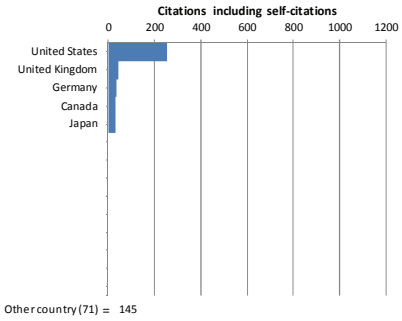
	Citations in:		**% of total citations**	**Research level of cloud papers**
WoS Indexed papers: 3	**RCT:**	14	3%	Clinical **1:** 100%
Total citations of papers: 518	**Meta-analyses:**	4	1%	**2:** 0%
of which, self-citations: 1.4%	**Indexed practice guidelines:**	0	0%	**3:** 0%
Mean citations per paper: 173	**Review articles:**	115	22%	Basic **4:** 0%
Distinct cloud citations: 486				
Second-generation cloud citations: 17,691				
Third-generation cloud citations: 231,028				

Most highly cited article: Wolkin A, Sanfilipo M, Wolf AP, Angrist B, Brodie JD, Rotrosen J (1992). Negative symptoms and hypofrontality in chronic schizophrenia. Archives of general psychiatry. 49(12):959-65.

Times cited: 247

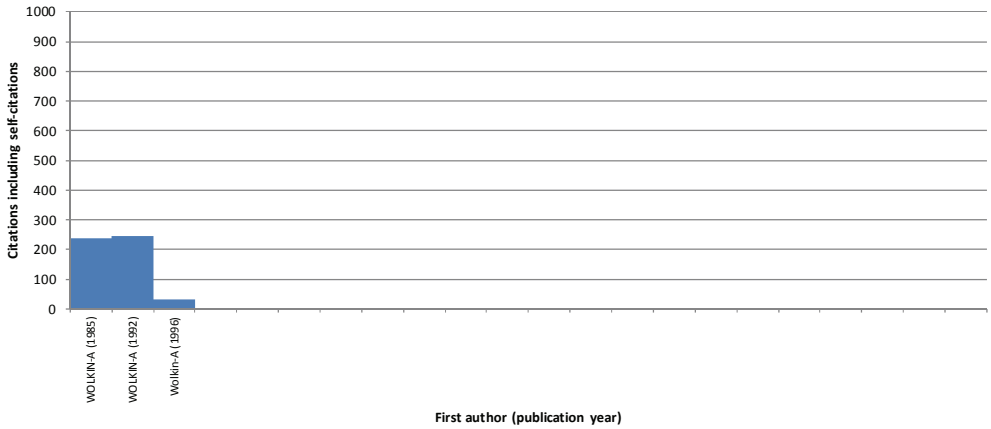


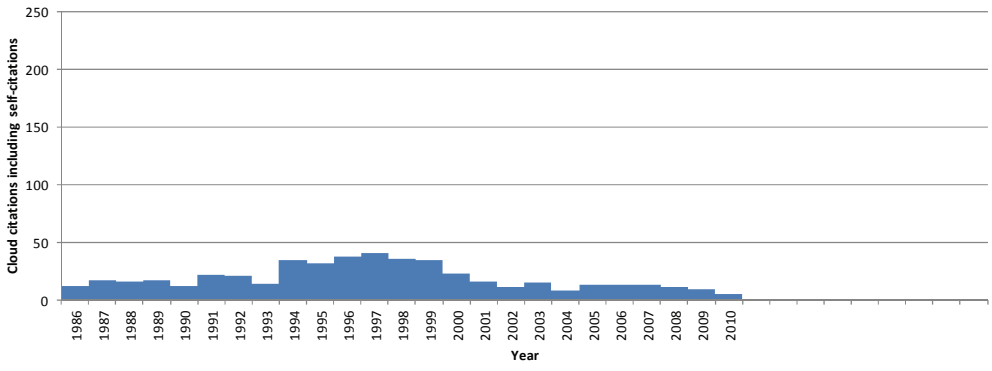




Other country (71) = 145

Note: Countries with more than 20 citations are displayed





Targeting Future Research

Effect on the researchers' careers

The initial formulation of the collaboration between Brookhaven and NYU, in which Brodie and Rotrosen were active, offered Wolkin an opportunity to become involved in schizophrenia research. This helped focus his research interests when he was embarking on his research career at the VA. Using PET imaging, Wolkin, along with several others, produced data to indicate that an area that had been suspected of being abnormal in schizophrenia was in fact so. With the study described in the identified paper, Wolkin began to develop a track record in this area. In subsequent work, his interest expanded to exploring negative symptoms and possible functional and structural abnormalities in the brain. Ultimately, this exposure shaped his subsequent research activities for 25 years.

> My original interest and what attracted me to schizophrenia were so-called positive symptoms – hallucinations, delusions, illusions. And, at that time, these were the symptoms at the core of the dopamine hypothesis of schizophrenia and related amphetamine model, so that piqued my interest all the more in terms of what might be found with PET. I had less of an interest conceptually in what became known as negative symptoms. However, as we continued to look at relations between brain function and symptoms, it became increasingly apparent, at least in our population, that this is where the most salient findings were – the correlations between these frontal lobe deficits and negative symptoms. (AW)

The early collaboration between NYU and Brookhaven led to the development of other careers as well. Judy Jaeger was a neuropsychologist who was involved in cognitive remediation had a very successful career that followed from having done much of the early work with PET. Michael Sanfilipo was Wolkin's research assistant, and he went on to medical school and then a psychiatry residency before joining the faculty at the University of Miami. His involvement as a research assistant in the PET imaging studies at NYU shaped his subsequent research interests.

A number of researchers who started out in PET imaging and schizophrenia realised that it would probably be an easier tool to use in substance abuse. For example, Nora Volkow, who was a resident at NYU and part of the informal group that was active in the Brookhaven collaboration, became interested in the study of substance abuse. She has had an extremely successful imaging career in this field and now is the Director of the National Institute of Drug Abuse (NIDA) at the National Institute of Health.

Future work

From this replication study, Wolkin and colleagues moved on to more hypothesis-driven research around the neurochemical basis of schizophrenia dopamine mechanisms. Meanwhile, other PET research groups were able to generate larger sample sizes and demonstrate hypofrontality in less chronic and medication-free populations. These papers became compelling in establishing prefrontal lobe dysfunction in schizophrenia. Nonetheless, the replication study reported in the identified paper was also a primary impetus for further studies with PET imaging.

> In the early days of brain imaging, there was of course very little data and very few reports suggesting any clear-cut abnormality. We, along with several others, reported data that the prefrontal cortex – an area long suspected of being abnormal in schizophrenia was a focal point of the pathophysiology in schizophrenia. However, by the end of the first decade of

> work, the initial work we did was fortunately superseded by other studies that were able to eliminate some of the ambiguity and confounds with which we were confronted – such as long term medication effects, relation to stage of illness, and so on. (AW)

The field also moved forward with a focus on using PET technology to examine metabolic rates during functional activation of the brain. Wolkin's exploratory studies had been done in the so-called resting state, with patients awake during the scan but otherwise not engaged in any particular cognitive activity. Subsequently, other researchers began to conduct similar PET studies but during specific cognitive tasks – initially as an attempt to have a more uniform mental set during scanning, and later with the realisation that this served as a way of activating or inhibiting brain circuits.

> At the outset, the approach was – let's take a picture of your brain in its 'usual' state. And then researchers began to suggest that the resting state was quite variable, what was one schizophrenic patient thinking / 'doing' while lying in the camera as opposed to another? There's potentially too much variability. So the idea was one needed to structure the activity. (AW)

The work in this research cloud used a new technique to demonstrate some ways in which schizophrenic brains were not 'working' the same as those in a control group. This led to questions about the resulting cognitive and behavioural deficits. With the movement away from the resting state came the recognition that functional imaging could be particularly powerful in assessing brain activation during a particular cognitive task. Pre-eminent work in this area was led by Daniel Weinberger. In his laboratory at NIMH, Weinberger used xenon inhalation to image the brain during tasks that were presumed to specifically activate the prefrontal cortex (i.e. the Wisconsin Card Sort). In the ensuing decades, this has become the predominant paradigm for study of brain activity, especially using functional MRI.

11.8 Interface B: Dissemination

The primary method of dissemination was through publication in mainstream psychiatric journals. There was attention and excitement associated with the studies because of the novelty of the PET technology. Wolkin presented the findings at scientific meetings and imaging symposia.

While the advent of brain imaging was also noted in the mainstream press, there is little evidence of public engagement with this particular research in hypofrontality.

11.9 Stage 4: Secondary outputs

Early on, as review papers came out, this replication study was cited in the accumulating body of evidence supporting hypofrontality, including:

1. Weinberger, D.R., & Berman, K.F. (1988). Speculation on the meaning of cerebral metabolic hypofrontality in schizophrenia. *Schizophrenia Bulletin*, 14(2), 157–168.
2. Buchsbaum, M.S. (1990). The frontal lobes, basal ganglia, and temporal lobes as sites for schizophrenia. *Schizophrenia Bulletin*, 16(3), 379–389.

3. Wiesel, F. (1989). Positron emission tomography in psychiatry. *Psychiatric Developments*, 1, 19–47.
4. Sedvall, G. (1992). The current status of PET scanning with respect to schizophrenia. *Neuropsychopharmacology*, 7(1), 41–54.

The field remained relatively small for some time because of the scarcity of PET scanners, but subsequently expanded markedly with the advent of functional MRI, which is much more accessible. The small sample in Wolkin's study precluded its inclusion in later meta-analyses.

11.10 Stage 5: Applications

None identified.

11.11 Stage 6: Public engagement

None identified.

11.12 Stage 7: Final Outcomes

None identified.

11.13 Table of payback

Payback category	Impacts from case study
Knowledge Production	• Demonstrated utility of PET in brain imaging in schizophrenia as viable research approach. • Demonstrated that the frontal/posterior ratios of glucose metabolism were significantly lower in schizophrenic patients compared to controls.
Research Targeting and Capacity Building	• Enabled Wolkin to obtain VA Merit Review funding to continue this line of inquiry. • Beneficial to other researchers who learned to use PET imaging to conduct studies of brain functioning in schizophrenia and other neuropsychiatric disorders.
Informing Policy and Product Development	• None identified.
Health and Health Sector Benefits	• None identified.
Broader Social and Economic Benefits	• None identified.

11.14 Timeline

1982	Wolkin completes Psychiatry Research Residency at NYU and Bellevue Hospital
1982	Wolkin joins the psychiatry department at NYU School of Medicine, the staff at New York VA Medical Center, and visiting staff at Brookhaven National Laboratory
1984	Exploratory study results published by Farkas
1985	Wolkin publishes his first PET report on hypofrontality
1988	Replication study results published by Wolkin; Wolkin receives his first Merit Review funding from the VA

11.15 References

Buchsbaum, M.S. (1990). The frontal lobes, basal ganglia, and temporal lobes as sites for schizophrenia. *Schizophrenia Bulletin*, 16(3), 379–389.

Buchsbaum, M.S., Ingvar, D.H., Kessler, R., Waters, R.N., Cappelletti, J., van Kammen, D.P., King, C., Johnson, J.L., Manning, R.G., Flynn, R.W., Mann, L.S., Bunney, W.E., & Sokoloff, S. (1982). Cerebral glucography with positron tomography: use in normal subjects and in patients with schizophrenia. *Archives of General Psychiatry*, 39(3), 251–259.

Farkas, T., Wolf, A.P., Jaeger, J., Brodie, J.D., Christman, D.R., & Fowler, J.S. (1984). Regional brain glucose metabolism in chronic schizophrenia. Archives of General Psychiatry, 41(3), 293–300.

Ingvar, D.H., & Franzén, G. (1974). Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. *Acta Psychiatrica Scandinavica*, 50, 425–462.

Sedvall, G. (1992). The current status of PET scanning with respect to schizophrenia. *Neuropsychopharmacology*, 7(1), 41–54.

Weinberger, D.R., & Berman, K.F. (1988). Speculation on the meaning of cerebral metabolic hypofrontality in schizophrenia. *Schizophrenia Bulletin*, 14(2), 157–168.

Wiesel, F. (1989). Positron emission tomography in psychiatry. *Psychiatric Developments*, 1, 19–47.

Wolkin, A., Jaeger, J., Brodie, J.D., Wolf, A.P., Fowler, J., Rotrosen, J., Gomez-Mont, F., & Cancro, R. (1985). Persistence of cerebral metabolic abnormalities in chronic schizophrenia as determined by positron emission tomography. *American Journal of Psychiatry,* 142(5), 564–571.

Wolkin, A., Angrist, B., Wolf, A., Brodie, J., Wolkin, B., Jaeger, J., Cancro, R., & Rotrosen, J. (1988). Low frontal glucose utilization in chronic schizophrenia: a replication study. *American Journal of Psychiatry*, 145(2), 251–253.

Wolkin, A., Sanfilipo, M., Wolf, A.P., Angrist, B., Brodie, J.D., & Rotrosen, J. (1992). Negative symptoms and hypofrontality in chronic schizophrenia. *Archives of General Psychiatry*, 49(12), 959–965.

Wolkin, A., Sanfilipo, M., Duncan, E., Angrist, B., Wolf, A.P., Cooper, T.B., Brodie, J.D., Laska, E., & Rotrosen, J.P. **(1996).** Blunted change in cerebral glucose utilization after haloperidol treatment in schizophrenic patients with prominent negative symptoms. *American Journal of Psychiatry*, 153(3), 346–354.

CHAPTER 12

Using childhood home movies of adult schizophrenia patients to investigate the development of physical and behavioural abnormalities

This case study is based on research related to the following publication, which was selected using a bibliometric analysis:

Walker, E.F., & Lewine, R.J. (1990). Prediction of adult-onset schizophrenia from childhood home movies of the patients. *American Journal of Psychiatry*, 147(8), 1052–1056.

Information was gathered from interviews with the lead author, Elaine Walker, as well as Richard Lewine, Craig Neumann, Vijal Mittal and Norman Watt, as well as desk-based research.

12.1 Summary

This case study focusses on work conducted by Elaine Walker and colleagues at Emory University, Atlanta, looking at childhood home movies of adult schizophrenia patients. This was a novel method for examining case histories of adult schizophrenics, developed by Walker. Her relationship with the National Alliance for the Mentally Ill enabled access to the home videos. The study showed that there were noticeable behavioural and neuromotor abnormalities from a very young age for those children who developed schizophrenia in adulthood, which was the first direct observational evidence of abnormalities in such young pre-schizophrenics. This evidence, and the novel methodology, was compelling and led to considerable media attention and interest in these results at the time, which accounts for the high level of citation, particularly of the first proof of concept paper.

12.2 Introduction

12.2.1 Scientific background

The origins of schizophrenia are not well understood. It is now evident that there is some genetic element, but otherwise causes and origins remain unexplained. At the time this work was conducted, a number of ideas had been suggested regarding the origins of the

condition, and to some extent the prevailing views on this differed between countries. In the US, one strong concept had been the idea first postulated by Fromm-Reichmann (1948) that treatment by the family, and in particular the mother, was a significant factor in the onset of schizophrenia – the concept is known as the 'schizophrenogenic' mother. A wide variety of other concepts were under consideration, for example some had postulated that schizophrenia might be caused by a virus (e.g., Tyrell et al., 1979). One concept that was gaining some credibility at the time was the idea that there may be neurodevelopmental origins for the condition, and that these might be present from an early age. Clearly, this would be in strong contradistinction to the 'schizophrenogenic' family concept. However, given that schizophrenia typically does not present until late adolescence or later, this was difficult to investigate.

At the time this work was conducted, there had been some studies indicating that vulnerability to schizophrenia may be present at an early stage, and perhaps even birth, in many patients (Fish, 1977; Feinberg, 1982; Weinberger 1987). However, there were no hard data as the evidence relied on retrospective studies and review of medical records. Researchers had started to look at groups at high risk for schizophrenia (on the basis of family history of the condition) but that work was still developing, and it was evident that there were significant limitations on what could be achieved using retrospective methods. This home movie study was one of the first to show hard evidence of abnormalities in behaviour and also neuromotor abnormalities at a very young age, even if only in a limited sample. This formed part of the evidence that neurodevelopmental origins are likely to be a significant factor in schizophrenia.

12.2.2 Researchers' background

Elaine Walker started work on this study soon after arriving at Emory University in 1986 as associate professor in the Department of Psychology. Previously she had been working as an associate professor at Cornell University. She received her BA in Psychology from Washington University in 1974, and her PhD in Psychology from the University of Missouri in 1979. She was PI for this project, and the source of the idea for the study. Walker had originally started working on research in childhood development, but had developed a significant interest in schizophrenia research through her work with Sarnoff Mednick at the University of Southern California prior to joining Cornell. By the time she arrived at Emory, she had already worked on the early stages of schizophrenia, and published several papers on behavioural and neuromotor abnormalities, as well as having been involved in several large-scale patient studies.

Richard Lewine was involved in the work on this study as a rater of the home movies. This work was a natural extension of his existing interests in early schizophrenia, and Lewine is still working in schizophrenia research.

Craig Neumann was a post-doc working on this study, and has subsequently continued to work in research in this area at the University of North Texas.

Vijay Mittal was a graduate, and later a postgraduate student at Emory working with Walker. Mittal had always had an interest in schizophrenia research, and had previously worked at UCLA with a group that collaborated with Walker. He specifically applied to Emory for graduate school in order to work with her as he was interested continuing the research he had already started in the field. He developed an interest in movement

abnormalities through his work at Emory and has continued to conduct research in this field to the present.

Norman Watt was a researcher also conducting work in early schizophrenia in the 1980s and subsequently. He was a competitor, but also at times a collaborator of Walker's, and more notably collaborated on an ongoing basis with Mednick, her mentor at the University of Southern California.

12.2.3 Institution background

Walker had a joint appointment in the Departments of Psychiatry and Psychology when she came to Emory in 1986. This research was carried out in the psychology department. Collaborators on the project included researchers from the Departments of Psychiatry (Lewine) and Neurology. A variety of research areas were being pursued by the 25 faculty staff in the psychology department: cognitive psychology, basic neuroscience, and research on depression and psychotic disorders.

12.3 Defining the research cloud

The research cloud for this study focuses on the work that Walker and colleagues conducted using home movies from the childhood of adult schizophrenics to investigate a number of behavioural precursors of schizophrenia. This research was designed to examine the underlying neuromotor abnormalities in children who later develop schizophrenia. This defines a clear set of publications as the researchers worked on this for a limited period, and then moved on to other topics having established all they felt could be using this approach. The publications included in the cloud for this case study are as follows:

1. Walker, E.F., & Lewine, R.J. (1990). Prediction of adult-onset schizophrenia from childhood home movies of the patients. *American Journal of Psychiatry*, 147(8), 1052–1056.
2. Litter, J., & Walker, E. (1993). Interpersonal-behaviour of preschizophrenic children – a study of home-movies. *Child Psychiatry and Human Development,* 23(4), 283–295.
3. Walker, E.F., Grimes, K.E., Davis, D.M., & Smith, A.J. (1993). Childhood precursors of schizophrenia – facial expressions of emotion. *American Journal of Psychiatry*, 150(11), 1654–1660.
4. Walker, E.F., Savoie, T., & Davis, D. (1994). Neuromotor precursors of schizophrenia. *Schizophrenia Bulletin*, 20(3), 441–451.
5. Grimes, K., & Walker, E.F. (1994). Childhood emotional expressions, educational-attainment and age at onset of illness in schizophrenia. *Journal of Abnormal Psychology*, 103(4), 784–790.
6. Walker, E. (1994). Developmentally moderated expressions of the neuropathology underlying schizophrenia. *Schizophrenia Bulletin*, 20, 453–480.
7. Walker, E. Lewine, R.J., & Neumann, C. (1996). Childhood behavioral characteristics and adult brain morphology in schizophrenia patients. *Schizophrenia Research*, 22, 93–101.

12.4 Stage 0: Opportunity identification/research needs assessment

Inspiration

Walker was interested in investigating when and how neurological soft signs related to schizophrenia arise in individuals. Walker's initial idea had been to use photographs of schizophrenics as infants to see if they could observe distinctive characteristics and abnormalities in their faces. They hoped to gather the photographs from local mental health advocacy groups. However, in discussion with a representative from NAMI (National Alliance for the Mentally Ill) it was suggested that home movies might be available for the study.

The original idea of using photographs came to Walker during a conference in discussion with a colleague.

> I [was] sitting next to a colleague at a conference during a presentation on minor physical anomalies and neuromotor abnormalities in schizophrenia, adult schizophrenia patients and saying, we really need to get a better idea of when those originate and I think I said to him, I'm going to ask my colleague at NAMI whether she thinks we could get enough infant and young childhood photographs to study those things. (EW)

Feasibility

As described above, the idea to use home movies instead of photographs came from discussion with NAMI, who also conducted a survey on behalf of the researchers to try and establish whether sufficient videos would be available. From the survey, it soon became apparent that there would be sufficient data available and that the study would be feasible. Thus, Walker's relationship with NAMI was essential both in developing the idea for the study, establishing feasibility, and putting the study sample together.

The existing relationship between Walker and Lewine also contributed to the feasibility of this project. Walker and Lewine already knew each other before they arrived at Emory as they were part of an NIMH consortium of researchers looking at High Risk for Schizophrenia as post-docs, and this pre-existing relationship and shared interest made them natural collaborators.

> Well I think part of the history of that goes back to NIMH's effort to support a number of post-docs who would be researching what was then called High Risk for Schizophrenia. There was a consortium of mentors and Elaine and I were two of the mentees. She was at Cornell at the time, I was at UMass, and the intent of the programme was to sensitise and train a fairly large group of young researchers to become involved in high-risk research which translated into how early we can identify people who are going to develop the disorder. That was part of the background. And then she and I ended up at Emory quite by accident together, so part of it was serendipity and the combination of our shared post-doctoral training and contact and collaboration earlier, plus our being on the same campus, led to our collaboration in that study. (RL)

Potential value

Walker and colleagues were aware that existing methods to look at childhood signals in patients that later developed schizophrenia were inadequate, relying on retrospective secondary data sources. This novel method offered the possibility to directly observe these characteristics in a way that had not been previously possible.

12.5 Stage 1: Inputs to research

Money, researcher time, lab/office space and consumables

There were three main funding inputs to this study, all from the National Institute of Mental Health (NIMH):

- R03 'Developmental precursors of schizophrenia' (1988–1990)
- R01 'Neurodevelopmental and socioemotional antecedents of schizophrenia' (1990–1995)
- K02 'Childhood precursors and clinical outcomes in schizophrenia' (initially 1990–1995, later extended to 2001).

The total for the first two grants was around $150,000, and the K02 award was for a little more than this. For the R01, there was a site visit by NIMH prior to commencing the study. Such site visits were not always conducted, but they also were not unusual at the time. From Walker's perspective, NIMH conducted the site visit for her study because the approach was novel. No changes were made in the methodology proposed after the site visit. Walker suggests that it was not difficult to obtain the funding. A summary of the deliberations of the review committee was provided to applicants for federal research grants. The reviews emphasized the novelty of the approach and ideas.

Walker also notes that the funding provided was quite small, and not much money was required, especially for an initial study.

> This was a very inexpensive little study to do because it just was a matter of getting a lot of colleagues here at Emory to sit down and feeding them lunch and watching films. (EW)

More money was needed for the frame-by frame analysis as this was more time consuming, but the study still was relatively inexpensive. Walker thought it was important to note that you can do something useful without spending a lot of money, given that most studies in recent times, in her opinion, seem to be very costly.

Knowledge

Walker collaborated with Lewine on a number of studies, including this one. As noted above, they already knew each other and shared an interest in the early stages of the development of schizophrenia; however Walker led this work. She had previously done a post-doc with Sarnoff Mednick, who was one of the first to use the genetic high-risk method, conducting longitudinal studies of the children of schizophrenic parents. Walker's work on that research had looked at early childhood medical and other records collected. At Cornell, she had started to do some work on neurological soft signs, which are subtle, unusual movements or facial or limb characteristics that are associated with exposure to pre-natal problems and cause neural developmental abnormalities, but this work was on adult patients. This childhood home move study, which was initiated after she moved to Emory, used a mix of these experiences and knowledge.

Another input was the experience and knowledge of others at Emory University, including a paediatric neurologist, a developmental specialist, and some other researchers in the field of schizophrenia. In particular, the paediatric neurologist Nicholas Krawieki provided input on the way neurological exams are conducted on children and infants and the inferences that one can draw about some movement abnormalities with respect to brain

abnormalities. This was helpful both in putting together an effective project and in getting the project funded, as, according to Walker, he was involved in the NIMH site visit.

Samples/patients

As described in the previous section, the existing and ongoing relationship the study team had with NAMI was crucial not only in developing the methodology for the study but also in getting the home movies from families necessary to conduct the study. Once NAMI had made these links to the families, the families themselves were also an important source of information, with many of them providing large quantities of material about childhood behaviour.

> So we then, in addition to collecting childhood home movies, collected extensive data from parents on the individuals' development, their siblings, their siblings' development, family history of mental illness. The parents were all very eager to cooperate and in many cases, sent us boxes of material on their child. (EW)

Walker notes that her location in Atlanta with access to a large population also made this and other studies more feasible.

> One of the advantages of coming to Emory, compared to Cornell University in Ithaca, New York, where I was, is the fact that Emory is in Atlanta, a large metropolitan community which made it more likely that I could conduct some of the research that I was interested in doing which required a larger population. (EW)

Collaborators

Although Walker had networks of collaborators that were important for much of the other work she was involved in, all of the work for this study was conducted at Emory and there were no important external collaborators. However, there was useful input to the study from the well-regarded neurobiology group that exists at Emory, in particular from the neurologist Mahlon Delong, who is an expert in Parkinson's disease and had mapped out some of neural circuits that are involved in the movement disorders in that disease. Walker drew on this work and in discussion with Mahlon was able to speculate on what the neural circuitry might be given the movement abnormalities seen in the home movies and what had been reported in the schizophrenia literature more widely.

12.6 Stage 2: Processes

One of the most notable things about this work was the novel methodology. The idea of using childhood home movies of adult schizophrenics to investigate abnormalities in behaviour and movement at an early age was completely novel. For this reason, the study attracted much interest. It was an interesting approach as previous attempts to investigate the childhood of adult schizophrenics had relied on retrospective reporting or medical records where available, which often provided somewhat inadequate information. This approach, though still case-control retrospective, does allow direct observation of childhood behaviour.

> So we were very excited about [the study] because even though there were some suggestive studies that vulnerability was probably present in many patients at birth, we really didn't have any hard data on that because we had to rely on retrospective reports and medical records. So for example, studies that involved interviewing parents and asking them to tell

> us about their adult child with schizophrenia when they were an infant, did you notice anything unusual? Some studies were able to get medical records, but those weren't very adequate, those really weren't very helpful because most paediatricians when they do baby visits conclude the baby is well, and if parents say things like, well you know, he seems to be a little slow or there's something odd, the standard paediatric response – for good reason, I think – is there's so much variability among children and how fast they progress and so on, don't worry. So it turns out that there were significant limitations to what you could do with actual medical records from infancy, even if you could obtain them. So what we realized is that this home movie approach was going to give us an opportunity to look directly at behaviour and motor development, without any filters, without the bias of retrospective reporting. (EW)

The methodology consisted of using a standardised procedure for coding facial expressions of emotions using frame-by-frame analysis and a modified version of pre-existing paediatric neural motor rating scales. The researchers also used data from parents about the development of the schizophrenic children and their siblings and the relevant family history of illness.

The approach used a control group of patients with major affective disorder (which covers mental illnesses that have a mood-related component, such as bipolar disorder) and a further comparison group of individuals with no mental disorder. However, the key focus of the study was to make a comparison between the patient and his or her healthy sibling in order to control for differences in contextual factors, the timing of the video, and family size, dynamics, and other factors.

> We took that approach because parents differ, families differ in the context in which they make films of their children, so for some families it tends to be a higher concentration of family events and the family is larger so there's more opportunity for social interaction among the children. In other cases, if the family is smaller or has less social activities, the contexts are somewhat different. So by utilizing same sex, nearest in age siblings with healthy adult outcomes as our comparison group, we had a greater opportunity for controlling for context. (EW)

12.7 Stage 3: Primary outputs

Knowledge

One of the key outcomes of the study was the evidence that there were detectable abnormalities in childhood that were evident well before the onset of clinical schizophrenia. It also showed that these abnormalities were evident early, even shortly after birth in some cases. Furthermore, the work helped to identify certain brain regions that were implicated in this abnormal behaviour.

The first publication, Walker & Lewine (1990), was effectively a proof of concept paper that showed that it was possible to reliably identify a pre-schizophrenic child in comparison to their healthy sibling, indicating that there are differences in behaviour present at this early age. It was first time that these differences in behaviour were directly shown to be present in the first eight years of life, and the paper also set out the novel methodology used, providing the basis for the subsequent studies. This paper was highly cited, according to Walker, because it was the first to demonstrate that there were

abnormalities in development that could be detected long before the onset of the clinical syndrome.

This was followed by two publications in 1993 that outlined the findings from the more detailed frame-by-frame analysis of the videos. In Litter & Walker (1993), the interpersonal behaviour of the children is analysed in two age groups: 5–7 years and 8–10 years. They found that the pre-schizophrenic children displayed more frequent negative emotions in the younger age group, but that this difference was not evident in the older age group. This was the first direct evidence of developmental problems in children younger than 11 years of age who would go on to develop schizophrenia. Similarly, Walker et al. (1993) found evidence of emotional vulnerability in young pre-schizophrenic children in an analysis of facial expressions, again with increased negative emotions in the pre-schizophrenic children compared to the sibling comparison group.

Two papers in 1994 then went on to explore neurological differences. Walker et al. (1994a) found that there were higher rates of neuromotor abnormalities in the pre-schizophrenic children, as well as poorer motor skills. They also noted that the neuromotor abnormalities occurred primarily on the left hand side of the body, and that they were most marked in the first two years of life. This paper starts to consider the implications of these findings for the developmental origins of schizophrenia. However, according to Walker, the most important publication coming out of this study was Walker (1994b), which explores the underlying neuropathology evidenced by this work in more detail.

> This paper was dealing with potential underlying mechanisms and in particular, addressing the question of where the abnormality might be in the brain and the conclusion was… it was likely in a brain region called the striatum that is involved in multiple neural circuits that connect sub-cortical with cortical regions of the brain that govern higher cognitive processes. In addition, that paper addressed the question of why would we be seeing them in infancy but then less so, why would they become less apparent as the child got older and why would what might originally be a brain abnormality that was manifested as abnormalities in movement later on be one that is manifested in the illness we call schizophrenia. So that paper deals with the neuroscience of that and the neurodevelopment. That I think subsequently has been the chief contribution of that study, it was spawned a lot more targeted research, focussing on those regions of the brain, the striatum and that neural circuitry and the results have shown that, indeed, there are abnormalities in the neurotransmitter dopamine in that region of the brain. So the findings have been consistent with the model that you'd infer based on what we saw in the infant movement. (EW)

Also in 1994, a paper was published looking at the connection between childhood emotional expressions, educational attainment and age of onset of schizophrenia (Grimes & Walker, 1994). They found that facial expressions were not associated with level of educational achievement, but were linked to age of onset. Increased levels of negative emotion in late childhood and adolescence were associated with a later onset of illness, which is in contrast to what might have been expected from the prior literature.

The final publication in the cloud, Walker et al. (1996), continued in this vein, looking at childhood behavioural characteristics in relation to adult brain morphology of the same subjects. They found that early neuromotor defects and high levels of negative emotions were linked with certain brain characteristics in adulthood. They also found more complex

relationships between brain morphology and ratings of behaviour problem dimensions. The results suggest that behaviour problems that are 'externalised' or dis-inhibited, such as delinquent behaviour, are associated with more brain abnormality. By contrast, 'internalised' problems, such as withdrawal and anxiety are linked to less brain abnormality. The paper also discusses what this implies in terms of the developmental origins of schizophrenia.

Overall, the study is important as it provided the most direct evidence to date of childhood abnormalities in schizophrenia, which are evident from a very young age, long before onset of the clinical syndrome, and also because it goes on to link this to brain morphology and the possible origins of schizophrenia. It was also important in demonstrating that movement abnormalities were an intrinsic part of the condition, rather than solely a side effect of medication.

> Prior to this study, again, what we knew about neurological abnormalities in schizophrenia was based on just adult diagnosed patients who had been treated with medication, so the abnormalities could have been a side effect of the medication, not many people argued they were, in fact sometimes they are. But these findings put that notion to rest, that any motor or neurological abnormalities were just due to the side effects of antipsychotic medication. (EW)

As outlined previously, the study authors were also anxious to show that family interaction was not a causal factor in the development of schizophrenia. Although this is not explicitly stated in the publications, direct evidence is provided to show that indicators of abnormality are present at very young ages. This does not eliminate the possibility of family interaction affecting outcomes, as it may still aggravate a genetic disposition, for example. However, it does show that the condition is evident from a very early age, virtually from birth.

> It provided some of the first objective data indicating that something is awry shortly after birth, at least in some patients. We couldn't generalize that this was the case with all patients but at least in some patients. (EW)

Of course, this does not preclude the impact of environmental factors in the translation of risk factors or vulnerabilities to diagnosable illness.

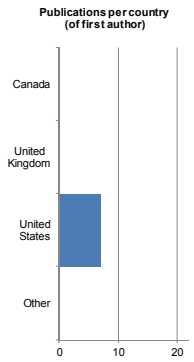
A bibliometric analysis of the papers produced from the research cloud is shown below.

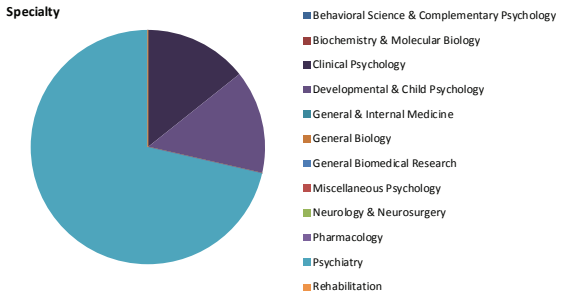
Research cloud:

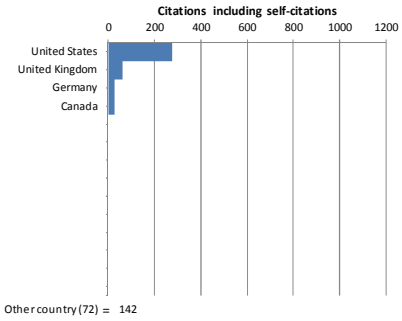
	Citations in:		**% of total citations**	**Research level of cloud papers**
WoS Indexed papers: 7	**RCT:**	4	1%	Clinical **1:** 86%
Total citations of papers: 582	**Meta-analyses:**	0	0%	**2:** 0%
of which, self-citations: 2.7%	**Indexed practice guidelines:**	0	0%	**3:** 0%
Mean citations per paper: 83	**Review articles:**	167	29%	Basic **4:** 0%
Distinct cloud citations: 450				
Second-generation cloud citations: 20,050				
Third-generation cloud citations: 240,623				

Most highly cited article: Walker EF, Savoie T, Davis D. Neuromotor precursors of schizophrenia. Schizophrenia Bulletin 20(3):441-451 1994

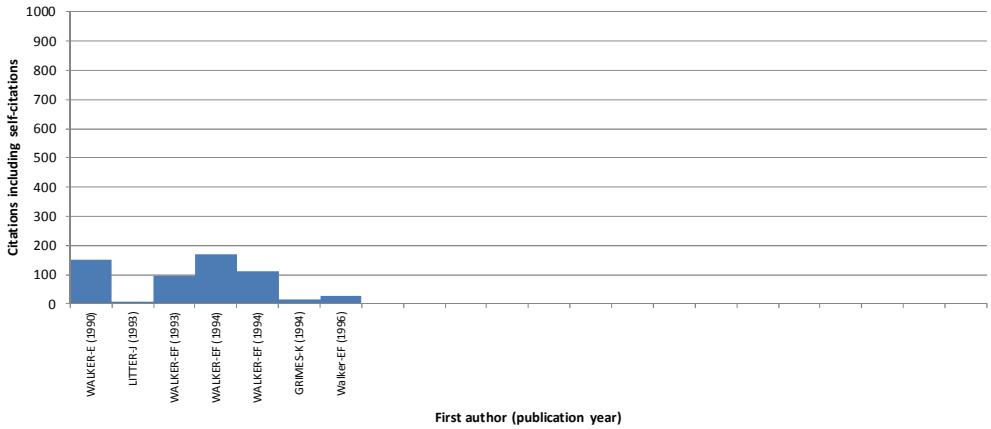
Times cited: 170

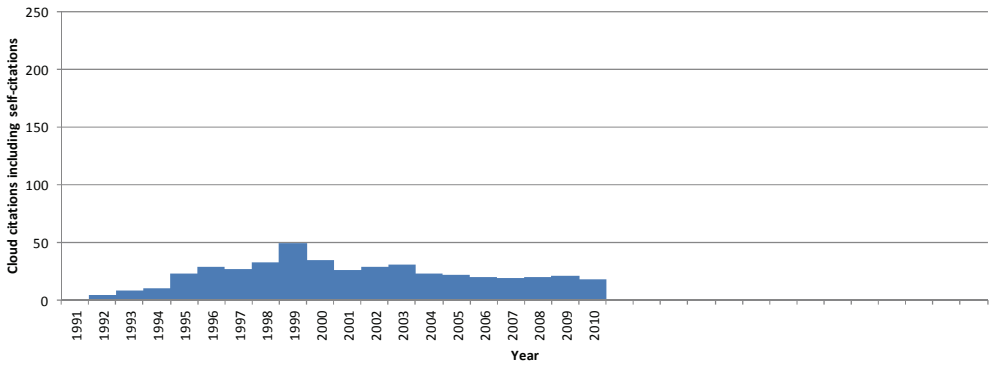






Note: Countries with more than 20 citations are displayed





Targeting future research

Effect on the researchers' careers

Walker identifies two main ways that this work had an impact on the careers of the researchers involved. First, there were a number of people who were involved in the project in the early stages that later went on to clinical careers that utilised the skills and expertise that were developed through this work. Walker gave an example of this at interview, referring to a graduate student who was involved in the work at the time, Dana Davis.

> There's a woman named Dana Davis who is a practitioner here in Atlanta whose specialty is early neurodevelopmental abnormalities and disorders, diagnosis and treatment in children and she's one of the few people in the area who conducts assessments of infants and children. (EW)

The second way in which the work influenced the careers of the researchers involved was when the researchers used the qualifications, skills, or experience from this project in their future work. For example, Craig Neumann was a post-doc at the time of this work and is an author on one of the papers. He is now a professor at the University of Texas and does research on early indicators of risk for mental disorders in youth, which follows from the initial grounding and experience gained in this work. He also continued to collaborate with Walker after leaving Emory, so the development of that relationship was also important in his later career. Similarly, Vijay Mittal was a graduate student working with Walker and has continued to work on movement abnormalities in schizophrenia, frequently in collaboration with Walker, since leaving Emory. He is now Assistant Professor at the Department of Psychology and Neuroscience at the University of Colorado.

Walker also suggests that the work might have had some impact on her career in terms of funding and status, given the highly cited publications, and its high profile in the media. For example, she was awarded the Samuel Candler Dobbs Endowed Chair in Psychology in 1994, probably in part due to this work. Lewine also suggests that it was a positive influence on his career and supported his later work on brain imaging and early indicators for schizophrenia.

Finally, it is also interesting, as noted by Mittal at interview, that Walker's background was in psychology. She didn't have any formal neurological training, but despite this, she went on to conduct work in neuroscience. This was unusual at that time, but is more commonplace in research now. Mittal suggests she was one of the first people to do this, and that it 'inspired a lot of people' to conduct interdisciplinary research.

Future work

Walker and others at Emory did maintain an interest in premorbid schizophrenia research, but their interest moved to later stages such as the prodromal period, as a natural extension of the findings from this work.

> The findings raised the question of how these abnormalities in the brain that might subserve what we observed in the infant films changed over time with development to become a clinical disorder in adolescence or early adulthood. So that really drew my interest into shifting the focus to adolescence and young adulthood because we know that some of these same neural circuits are undergoing significant change during that period and there are also some interesting changes in neurological function and the manifestation

> of certain neurological disorders during adolescence. So my research remained premorbid development but kind of moved forward through the life course into adolescence to look more closely at not only motor functions during that period and how they change in clinical at-risk adolescence but also the underlying brain mechanisms. (EW)

At that time, there were a number of other researchers in the United States who were looking at the adolescent premorbid period in schizophrenia. Walker explains that her work and the work of others in this area was significant and led the NIMH to set up a consortium to fund large multisite studies. Walker still works with this multisite group, the North American Prodrome Longitudinal Study consortium.

In terms of the work on movement and motor abnormalities, that did continue at Emory University though not in the case of infants after this study. Walker and her colleagues continued to look at these issues in adult patients, particularly in the case of first-episode schizophrenics and pre-schizophrenic adolescents. Mittal suggests that this work had an important impact in terms of demonstrating that the movements were not solely the result of medication, and that this has also spawned some further research, both by Mittal himself, and by other groups.

> Prior to Elaine's study no-one had really looked at the movements in this way. One reason was that the field largely assumed that the movements were a by-product of antipsychotic medication…. All the schizophrenic patients that had been taking these medications for a long time started to show Parkinson's-like movements. And so everyone kind of ignored all movements all together. But Elaine found that movements were in these children who obviously weren't taking medications for several decades. And so it really opened up the idea that the movements actually are present in an abnormal state as part of the actual pathophysiology of the illness. (VM)

There were a number of other groups working on issues related to pre-schizophrenic children at that time. In fact, there were regular communications between these groups in the United States, with two meetings annually. One example of this was the earlier work of Norman Watt, who looked at school and teachers records (Watt, 1972). Like the home movies, this method was close to an independent observation since the teachers did not have any prior knowledge of the future development of these students. Another person who was working in a similar area around that time was Barbara Cornblatt in New York, who was conducting a study looking at 'high risk' children who were considered to have a strong likelihood of later schizophrenia. She also found some movement abnormalities (Dworkin et al., 1993). She has continued working on these issues subsequently and developed this much further in terms of potential interventions. Lewine described her work as follows:

> As I understand what Barbara has been doing in New York is identifying kids that are at high risk because of these attentional disturbances… the RAP [Recognition and Prevention] Project…. Barbara Cornblatt was a very long-standing, well-established schizophrenia researcher, in my mind she has been the one who has actually tried to do intervention or who has done interventions based on this early high-risk research identifying precursors of schizophrenia. (RL)

Other groups identified by the team as working in a similar area around that time (and subsequently) included the group at UCLA, including Keith Nuechterlein and Michael Green (a former gradute student of Walker) (e.g., Asarnow et al., 2002); Jason Schiffman

(a former student of Walker) and colleagues at the University of Hawaii (e.g., Schiffman et al., 2004); and a group led by Norman Garmezy in Minnesota (Garmezy et al., 1974).

In terms of the methodology, the use of home videos to explore behavioural characteristics has been used more widely, most particularly in the field of autism, where researchers are attempting to identify very early signs of the condition, even within the first month of life, using this technique. This work started in the 1970s and Walker suggests that it has been very effective since then, as home video technology has developed substantially and now includes sound, which greatly expands the opportunities for understanding unusual behavioural phenomena compared to the types of videos that were used in this study. Since autism can be diagnosed much earlier (typically at 36 months), the quality of video available for pre-diagnosis subjects is much higher than for schizophrenia. Some of this work in autism cites Walker and colleagues (Baranek, 1999; Teitelbaum et al., 1998).

Overall, although the work seemed important and exciting at the time, it has not had the impact on future research in schizophrenia as one might have expected. Lewine suggested that the logistical challenges along with the small sample size deterred people from replicating this approach, despite the interesting results that had come out of it. To replicate with large sample sizes would be quite costly.

> I think, sadly, what happened is that it was startlingly interesting at the time, but that the logistics and cost of replicating it probably simply discouraged people from taking it further… Among my more research-oriented friends, they were fairly negative about the small sample size and the ultimate inability to really get fine-tuned assessments. So you know, I've got neuropsychology friends or colleagues who said, 'Okay, it's great, you can tell me that the person was a little cognitively different, but I want to know exactly how.' And so I think that group of people wanted in vivo, prospective assessments of a rigorous sort. Whereas the videos just can't give you that. (RL)

Another reason was that the work was superseded by technology. As MRI and PET scanners became more prevalent, this approach seemed less relevant and useful. Lewine also explained that there were some further issues relating to the applicability of the approach as a diagnostic tool.

> I can give you two divergent views on [the study]. One, at the time it seemed like we were actually discovering things. It was very exciting, it was a different perspective, it was information that was untainted, or information collected untainted by the knowledge of the future outcome. So all of that was very encouraging. It led I think many of us to believe that we would be able to actually identify very early people with the disorder or who were to develop disorder. The longer term view… is that it also is susceptible to a common logic fallacy, post hoc ergo propter hoc, which is to say because many of these kids as adults became schizophrenic, we assumed that the things that came before were the [primary] causes. And I think that's a logical error that has led us somewhat astray. The other problem is that we have actually very little data on all children who might be somewhat deviant, say, in motor development. If we took the entire population of kids who were slow at motor development, they would not have a higher rate of schizophrenia than the general population, so there are some logical problems and data collection problems that I think had not been solved yet. But it was very exciting at the time. We actually thought we were going to find the cause of schizophrenia. (RL)

12.8 Interface B: Dissemination

Academic dissemination

Academic dissemination was through the standard means, such as publications and conferences, including the regular biannual meetings described above.

Wider dissemination

Before the study, Walker already had a relationship with NAMI, but this work strengthened that relationship. She continued to give talks at meetings and run educational programs for families, probably at a slightly higher rate.

More widely, this work received a fairly significant amount of media attention. In fact, Walker found this somewhat challenging to deal with, as she was worried about potentially simplistic and misleading notions about the research that might be propagated. For example, she was concerned that the study might be misinterpreted in some cases as concluding that schizophrenia could be predicted just by observing children. The media attention included reviews on national public radio and in the *New York Times* and local newspapers, and coverage in science magazines and NAMI publications. This level of attention led to many people contacting Walker about the work with misguided notions about what the findings might mean.

> In terms of the media attention and so on, which again I really tried to downplay because it got a little out of hand. I started having, for example, adoption agencies contact me, asking me if I would do assessments of infants, so they could tell the adoptive parents whether or not they would develop schizophrenia. (EW)

Walker did not actively pursue this media attention, nor did the university on her behalf, as she requested. The media became aware of the work via talks she gave at professional meetings. She speculates that the media attention resulted from the appeal of the notion that you could make predictions about the future,

> The idea that you could predict a future adult outcome by looking at an infant's behaviour, it is generally interesting to people, whether the adult outcome you're studying is criminality or schizophrenia or cancer, the idea that the clues to vulnerability might be detectable so early in life is just fascinating to people. (EW)

12.9 Stage 4: Secondary outputs

Some of the research on movement abnormalities that stemmed in part from this study has subsequently developed towards possible downstream application, largely for use as some form of biomarker for early detection of the onset of schizophrenia, though none of these have reached the application stage as yet. Mittal described one such potential application he has developed through his ongoing work on this area.

> We're working with several pieces of software that track handwriting. We have a handwriting analysis programme called NeuroScript (Caligiuri and Teulings), with which we ask adolescent participants to write a sentence on a computerized tablet. Using this software, we can actually analyse the velocity and jerkiness of character strokes, and pick up some of the same dyskinetic movements detectable by clinically observer-based measures. If we find something… for example if those adolescents who show marked deficits in frontal-subcortical circuit white matter growth and eventually develop psychosis

> had certain characteristics in their handwriting prior to this… that has a direct translational application, the software is something that could be more readily accessible and this type of assessment could be more widely disseminated. (VM)

Discussion is underway regarding the inclusion of motor abnormalities in the DSM criteria for schizophrenia. Walker recently published a letter (Mittal & Walker, 2010) arguing that although this is an important area of research it should not be included in diagnosis, partly in response to a publication by another group with the opposite viewpoint (van Harten & Tenback, 2009). As a result of her work in this research cloud looking at neuromotor abnormalities in schizophrenia, and her subsequent work in the same area, Walker is engaged in and has an important voice in this debate. Walker explained her viewpoint on this issue at interview.

> Not all patients with schizophrenia manifest, at least visually detectable movement abnormalities and it would be redefining the syndrome in a way that we might not want to do yet, learning about aetiology especially if there are distinct aetiological subtypes and if the group with more pronounced motor abnormalities have a different kind of brain abnormality, we need to be able to learn that and we won't if we change the diagnostic criteria now. (EW)

It is not yet clear what the outcome of these discussions will be, but it is clear that Walker will have an influence on the decisionmaking process.

Overall, the applicability of this approach is likely to be limited to a sub-group of schizophrenia patients, since not all exhibit these neuromotor abnormalities, and indeed as a predictor of future disease in children, it is unlikely to be effective since many children who will not go on to develop schizophrenia will exhibit such abnormalities, and similarly many children who do go on to develop schizophrenia will not exhibit them. This reflects the heterogeneity of the development of schizophrenia, and the challenges in relating childhood behaviours and symptoms to the behaviours once the disease has manifested from adolescence onwards.

This work does not appear to be included on any clinical guidelines or Cochrane systematic reviews.

12.10 Stage 5: Applications

Walker suggests that perhaps one of the main ways in which this work had an impact on practice was in that it was part of a body of evidence at the time that finally put to rest the notion that families and mothers in particular were responsible for schizophrenia in their children.

> Certainly I think a big clinical or practice implication is that the results of this study put to rest some of the old schizophrenogenic notions. Every place I went when I was speaking and the articles that were published on the research and the popular press, there was inevitably some comment like 'it appears that these children have a vulnerability that parents are not creating' or 'it appears that it's not what parents are doing, but something in the brain that's not working that even shows up when the child is born…'. Could we measure that effect on practice? I'm not sure, I only know that at the time that we were doing the study, most of the families told us that when they first took their child in for treatment, and that was usually in the teens, early twenties, that questions about how they

> reared the child were at the forefront of what they were asked. How did you discipline the child, did you actually want the child, did you convey that to the child, did he or she know that they were loved? And that was just at the time, that was commonplace, so these were families who had kids who were being diagnosed in the 60s, 70s, some in the 80s but they were still getting that. But you just don't hear that anymore in any reputable clinical setting, which is great. (EW)

Of course, the study by Walker and colleagues was only part of a wider body of evidence coming together at that time that led to these changes in attitude in clinical practice. However, by providing evidence of behavioural abnormalities at such a young age, Walker suggests that it was, perhaps 'the final straw' in terms of attitudes and practice in the United States.

> Not only was it saying, look, these patients that we're calling schizophrenia patients have these neurological abnormalities, it's saying they're present long before the parents could have done anything to create this illness. (EW)

Also important was the level of media attention that this study gained, which was important in changing attitudes. Walker feels that this study in particular might have obtained more attention than other concurrent studies, such as work looking at childhood clinical records or school records, because it had such an intriguing and easy to understand methodology. Certainly, many families felt that her work and the way in which it was presented were important in driving this practice change, and she has often received thanks from families of schizophrenics through her work with NAMI.

As a result of the high media interest, there has also been some interest in application of the research in ways that were not appropriate. For example, Walker was contacted by a company that wanted her to help them develop, patent and market an assessment tool to predict schizophrenia development in children, something that she would find inappropriate even if this approach were sufficiently developed to have real diagnostic utility, which, as described in the previous section, is unlikely given the heterogeneity of the condition.

12.11 Stage 6: Public engagement

None identified.

12.12 Stage 7: Final outcomes

It is difficult to determine the final outcomes from this work as there are significant questions around attribution. It is clear that at this time there were changing attitudes regarding notions of schizophrenagenic environments, which had implications in alleviating distress in families and developing effective treatment. However, it is not clear what the role of Walker's research was in these changing attitudes. It is likely that the change would have taken place regardless of Walker's work, though perhaps more slowly, given the media attention the study received. If the work does end up influencing the DSM criteria such that motor abnormalities are included in diagnosis, then this may also have an impact on diagnosis and treatment and hence health and wellbeing. However, this

has not taken place as yet, and even if it does occur, questions around attribution and contribution will remain.

12.13 Table of payback

Payback category	Impacts from case study
Knowledge Production	• First direct evidence of behavioural abnormalities in young pre-schizophrenic children. • Provided evidence that movement abnormalities in schizophrenia are not solely the result of medication.
Research Targeting and Capacity Building	• Provided training to several early career researchers. • High-profile study that enhanced the reputation of Walker and Lewine. • Walker continued to work in this area for some time. • Played a small role in the shift towards work focussing on the brain rather than psychosocial factors. • Influence on later studies that looked at movement abnormalities as an intrinsic part of schizophrenia, rather than just a side effect of medication.
Informing Policy and Product Development	• None clearly observed as yet, although neuromotor abnormalities are being considered for inclusion in the DSM criteria for schizophrenia. If so, this work will have made a contribution to that change.
Health and Health Sector Benefits	• No clear health benefits observed.
Broader Social and Economic Benefits	• No clear benefit as yet. • Small part of the shift in attitudes away from the concept of schizophrenagenic families, which may have had positive social benefits for families of schizophrenic patients.

12.14 Timeline

1986	Walker arrives at Emory; Lewine arrives at Emory
1988	R03 grant related to this work awarded by NIMH
1990	First 'proof of concept' study published (Walker & Lewine, 1990); R01 and K02 grants awarded by NIMH for the continuation of this work
1994	Publication of the underlying neurology published in Schizophrenia Bulletin (Walker, 1994); Walker awarded the Samuel Candler Dobbs Endowed Chair in Psychology
1996	Final publication in the cloud published

2002	Lewine leaves Emory
2009	van Harten and Tenback argue that motor abnormalities should be included in the DSM for schizophrenia
2010	Mittal and Walker respond in disagreement to van Harten and Tenback

12.15 References

Asarnow, R.F., Nuechterlein, K.H., Subotnik, K.L., Fogelson, D.L., Torquato, R.D., Payne, D.L., Asamen, J., Mintz, J., & Guthrie, D. (2002). Neurocognitive impairments in nonpsychotic parents of children with schizophrenia and attention-deficit/hyperactivity disorder: the University of California, Los Angeles Family Study. *Archives of General Psychiatry*, 59(11), 1053–1060.

Baranek, G.T. (1999). Autism during infancy: a retrospective video analysis of sensory-motor and social behaviors at 9–12 months of age. *Journal of Autism and Developmental Disorders*, 29(3), 213–24.

Dworkin, R.H., Cornblatt, B.A., Friedmann, R., Kaplansky, L.M., Lewis, J.A., Rinaldi, A., Shilliday, C., & Erlenmeyer-Kimling, L. (1993). Childhood precursors of Affective vs. Social Deficits in Adolescents at Risk for Schizophrenia. *Schizophrenia Bulletin*, 19(3), 563–577.

Feinberg, I. (1982). Schizophrenia: Caused by a fault in programmed synaptic elimination during adolescence? *Journal of Psychiatric Research*, 17, 319–334.

Fish, B. (1977). Neurologic antecedents of schizophrenia in children: Evidence for an inherited, congenital neurointegrative defecit. *Archive of General Psychiatry*, 34, 1297–1313.

Fromm-Reichmann, F. (1948). Notes on the development of treatment of schizophrenics by psychoanalysis and psychotherapy. *Psychiatry*, 11, 263–273.

Garmezy, N., & Streitman, S. (1974). Children at risk: the search for the antecedents of schizophrenia: I. Conceptual models and research methods. *Schizophrenia Bulletin*, 1(8), 14–90.

Grimes, K., & Walker, E.F. (1994). Childhood emotional expressions, educational-attainment and age at onset of illness in schizophrenia. *Journal of Abnormal Psychology*, 103(4), 784–790.

Litter, J., & Walker, E. (1993). Interpersonal-behaviour of preschizophrenic children – a study of home-movies. *Child Psychiatry and Human Development,* 23(4), 283–295.

Massie, H.N. (1975). The early natural history of childhood psychosis. *Journal of the American Academy of Child Psychiatry*, 14, 683–707.

Massie, H.N. (1977). Patterns of mother-infant behaviour and subsequent childhood psychosis. *Child Psychiatry and Human Development*, 7, 211–230.

Mittal, V.A., & Walker, E.F. (2010). Movement abnormalities and schizophrenia in DSM-V. *Psychological Medicine,* 40(9), 1581–1583.

Schiffman, J., Walker, E., Ekstrom, M., Schulsinger, F., Sorensen, H., & Mednick, S. (2004). Childhood videotaped social and neuromotor precursors of schizophrenia: a prospective investigation. *American Journal of Psychiatry*, 161, 2021–2027.

Teitelbaum, P., Teitelbaum, O., Nye, J., Fryman, J., & Maurer, R.G. (1998). Movement analysis in infancy may be useful for early diagnosis of autism. *Proceedings of the National Academy of Sciences of the United States of America*, 95(23), 13982–13987.

Tyrell, D.A.J., Parry, R.P., Crow, T.J., Johnstone, E.C., & Ferrier, I.N. (1979). Possible virus in schizophrenia and some neurological disorders. *The Lancet*, 313(8121), 839–841.

Van Harten, P.N., Tenback, D.E. (2009). Movement disorders should be a criterion for schizophrenia in DSM-V. *Psychological Medicine*, 39(10), 1754–1755.

Walker, E.F., & Lewine, R.J. (1990). Prediction of adult-onset schizophrenia from childhood home movies of the patients. *American Journal of Psychiatry*, 147(8), 1052–1056.

Walker, E.F., Grimes, K.E., Davis, D.M., & Smith, A.J. (1993). Childhood precursors of schizophrenia – facial expressions of emotion. *American Journal of Psychiatry*, 150(11), 1654–1660.

Walker, E.F., Savoie, T., & Davis, D. (1994). Neuromotor precursors of schizophrenia. *Schizophrenia Bulletin*, 20(3), 441–451.

Walker, E.F. (1994). Developmentally moderated expressions of the neuropathology underlying schizophrenia. *Schizophrenia Bulletin*, 20, 453–480.

Walker, E.F., Lewine, R.J., & Neumann, C. (1996). Childhood behavioral characteristics and adult brain morphology in schizophrenia patients. *Schizophrenia Research*, 22, 93–101.

Watt, N.F. (1972). Longitudinal changes in the social behavior of children hospitalized for schizophrenia as adults. *Journal of Nervous and Mental Disease*, 155(1), 42–54.

Weinberger, D. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Archives of General Psychiatry*, 44, 660–670.

CHAPTER 13 Verapamil in the treatment of chronic schizophrenia

This case study is based on the research that produced the paper:

Tourjman, S.V., Bloom, D.M., & Nair, N.P.V. (1987). Verapamil in the treatment of chronic schizophrenia. *Psychopharmacology Bulletin*, 23(1), 227–229.

Information was gathered from interviews with N.P. Vasavan Nair, Smadar Valerie Tourjman and David Bloom, as well as from desk-based research.

13.1 Summary

This case study covers the work done at the Douglas Hospital (Quebec, Canada) research centre to look at the role of calcium in schizophrenia and investigate the potential use of calcium channel blockers in the treatment of chronic schizophrenia. This research stemmed from studies by other groups showing that antipsychotics and calcium channel blockers share some properties and that verapamil was effective in treating some mood disorders, in particular mania in bipolar disorder. The team carried out a trial of verapamil as an add-on to haloperidol with one treatment-resistant patient, the success of which led to a larger follow-on trial. This second trial demonstrated an improvement in chronic symptoms, although fewer than half of the patients were judged to have clinically responded. No follow-up work was carried out at the Douglas, initially because the necessary funding was not available from industry sources, but also due to conflicting findings in other studies, the existence of other potentially fruitful lines of research, and the arrival of more effective treatments (in the form of new second-generation antipsychotics) that would likely have made redundant any clinical product that might have been developed. However, the research may have been beneficial in helping the team to pursue combined clinical and research careers, and Bloom has commented that the experience of working with patients in the case study research and other similar studies certainly enabled him to take better care of patients in his clinical work.

13.1.1 Introduction

Scientific background

Calcium channel blockers (CCBs), of which verapamil is one example, are compounds that act on voltage-gated calcium channels, preventing the entry of calcium to the cell. They are long established as a treatment for cardiovascular conditions including hypertension,

angina pectoris and arrhythmias (Triggle, 2007). However, different classes of CCB act on different receptor sites. Although most classes primarily affect vascular smooth muscle and cardiac muscle, the papaverine class, which includes verapamil, act on a site that is widely distributed in the brain, particularly in the hippocampus and cortex (Quirion et al., 1985).

The idea that calcium might have a significant role in the aetiology of mental disorders came from evidence indicating that changes in calcium levels were associated with changes in clinical features common in depression, bipolar disorder and schizophrenia (eg. Carman & Wyatt, 1979; Lishman, 1978). Initial therapeutic interest focussed on affective disorders, and in particular bipolar: several case reports and trials were published during the early 1980s suggesting that verapamil (which was one of the earliest CCBs available) was effective in treating mania (eg. Dubovsky et al., 1982; Giannini et al., 1984).

It was also discovered in the early 1980s that one particular class of antipsychotic drugs (diphenylbutylpiperidines), in addition to acting at dopamine receptors, are also potent CCBs, raising the possibility that this particular action may account for some of the drugs' effectiveness at alleviating negative symptoms of schizophrenia (Gould et al., 1983).

13.1.2 Researchers' backgrounds

N.P. Vasavan Nair went to the Douglas Hospital in 1972 to work with Dr. Heinz Lehmann, the clinician responsible for the introduction of chlorpromazine (the first antipsychotic) to North America. Lehmann retired three years after Nair's arrival. Nair had trained at Guy's Hospital (London, UK) with Dr. Stafford Clark, who helped shape his subsequent career path. Nair commented:

> He told me when I joined that in psychiatry there aren't many cures and at some point you have to tell patients 'I don't know what else to do'. If you don't want to say that, you have to get into research, so you'll always have something to do.' That's how I got into research. (VN)

At the time of the case study research, Nair was Director of the Research Centre and was Tourjman's research supervisor.

Smadar Valerie Tourjman, at the time of the case study research, was developing a combined clinical and research career and was a Resident at the Douglas Hospital for one year. During her training she did all but two of her optional stages in clinical research, meaning that her final two years were half research, half clinical work, a profile that was very unusual at the time.

David Bloom started at the Douglas Hospital in 1981 as a resident and was Tourjman's clinical supervisor during the case study research.

13.1.3 Institution background

When Heinz Lehmann retired from the Douglas, the hospital was left with little in the way of research infrastructure. After around a year, a committee of three experts was set up to recommend how research should proceed at the hospital, and in late 1978 they proposed the establishment of a separate research entity to provide a focussed way forward. At the time, the Fonds de Recherche Santé Québec (FRSQ) was planning to set up hospital-based research centres to consolidate and promote clinical research, and so Nair proposed that the Douglas become one of these centres for psychiatry, combining basic and clinical research in a hospital setting. By this point Nair was building a successful career combining

clinical practice and research, and ensuring the clinical applicability of even basic research was very important to him:

> It has to be clinician driven because all these questions come up because you are dealing with patients every day. So you need groups which include clinicians and basic neuroscientists. (VN)

The application process was competitive, and funding was provided on a yearly basis on condition that the centre was able to obtain other grants from accredited funding agencies, but the hospital's application was successful. The research centre was established and Nair became its director in 1979. He was provided with a small budget and any grants won by the centre were then matched by the FRSQ. Shortly after opening, Canada's first brain bank was set up at the research centre by Dr. Samarthji Lal, and Dr. Rémi Quirion was recruited as a basic scientist. At that time the centre had no administrative staff, so Nair was doing everything himself. Building up the centre meant borrowing money and the hospital got into debt supporting its development (eventually the Hospital Board fundraised to cover this), but by the time Nair left as Director in 1995, a critical mass of researchers had been established and annual income was around CAD$6 million.

13.2 Defining the research cloud

This case study focusses on the research team's work investigating the role of calcium in schizophrenia and looking at the potential use of verapamil as an add-on treatment for the condition. The research cloud produced two publications:

1. Bloom, D.M., Tourjman, S.V., & Nair, N.P.V. (1987). Verapamil in refractory schizophrenia – a case-report. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 11(2–3), 185–188.
2. Tourjman, S.V., Bloom, D.M., & Nair, N.P.V. (1987). Verapamil in the treatment of chronic schizophrenia. *Psychopharmacology Bulletin*, 23(1), 227–229.

13.3 Stage 0: Opportunity identification/research needs assessment

Inspiration

Tourjman had read some of the early work on the potential role of calcium in mood disorders, and was very interested in the idea that it might be possible to explain the switch between manic and depressive episodes through a single, unidirectional movement of calcium. With Bloom, she considered that intervention in chronic schizophrenia should be a focus for study, and she had an interest in studies comparing or combining current drugs in its treatment. This is an area that tends to be of little commercial interest to pharmaceutical companies, possibly because of the difficulties in designing and conducting this research with patients who often don't respond to treatment, but also because of the limited applicability of any findings. This kind of research is often poorly funded as a result (Tourjman interview).

When Tourjman arrived at the research centre there was not a project for her to work on. Although there had been no prior research at the Douglas using verapamil, Nair had become aware of a growing literature on the potential role of calcium in mental disorders.

Bloom suggested that Tourjman conduct a trial of verapamil, so she carried out a literature review (unpublished) and wrote up a protocol for a study that could be completed within her one-year placement.

As discussed above, evidence of a role for CCBs in mood disorders and the finding that diphenylbutylpiperidines also act on calcium channels suggested a potential therapeutic role for CCBs in treating schizophrenia. Diphenylbutylpiperidines are structurally similar to verapamil and functionally bind to the same site as verapamil (Pickar et al., 1987). Having noted the similarity between verapamil and the antipsychotic pimozide (a diphenylbutylpiperidine), Nair and Bloom decided that it may be worth trying verapamil alongside a standard antipsychotic. Quirion et al. (1985) had also demonstrated that verapamil is more active in the brain than other CCBs, making it a promising candidate to study.

Nair and Bloom had just completed similar work using cholecystokinin (CCK), another compound that they had been optimistic would be of therapeutic value. This turned out to be a dead-end for schizophrenia treatment, as initially promising results in open studies were not confirmed in a double-blind, placebo-controlled trial. There were also changes in the production of the compound the team was using: the positive results were obtained with CCK-33, but the supplier stopped producing it and replaced it with a synthetic version, CCK-8, which did not appear to be as effective. The team's findings were then taken up by researchers looking at panic disorder, but this also ultimately led to nothing.

Feasibilty

Bloom recalled that verapamil was the only commercially available CCB in Canada at the time, but another important factor in choosing to look at it was the fact that it had already been approved as a medication. The research centre, in its early stages, did not have the resources to go through the necessary safety trials to demonstrate the suitability of a new compound for use in patients.

The research team also drew on the expertise of two basic scientists at the research centre (who were not named on publications from the case study research): Rémi Quirion and Paul Wood. They were able to confirm the team's suspicions that calcium channel blockers might have a potential role in treating the symptoms of schizophrenia.

The case study research took place at a time when industry and academia were both active in the development of new drugs for treating schizophrenia, something that resulted in the research centre testing a number of compounds. This was also just prior to the last wave of deinstitutionalisation in Canada, a movement that saw the hospital shrink from 1100 beds in 1981 to around 240 now (Bloom interview). Larger hospital populations made it relatively easy to recruit trial participants and maintain contact with them.

Potential value

The team looked at the effects of verapamil in patients who showed limited response to standard antipsychotic medications, and so progress towards an effective treatment could have had a substantial impact on health outcomes.

13.4 Stage 1: Inputs to research

Money, researcher time, lab/office space and consumables

At the time of the case study research, the research centre was still in its early stages and was building up its reputation on the back of internal funding for small projects. A scientific committee at the hospital reviewed proposed studies and made recommendations to the management committee, which then prioritised studies according to the funding available. The case study research was funded through a combination of this basic funding from the hospital and surplus money from clinical trials. The research centre had conducted a number of studies for the pharmaceutical industry in the early 1980s, including a trial of a variant of clozapine for Sandoz, another with haloperidol decanoate and a number of studies of antidepressants. Nair commented that using the surplus from this contract research was one way of carrying out studies that industry had no interest in.

Bloom commented that it was important to have this internal funding available to attract basic scientists to the research centre. This was not necessary for psychiatrists, as they would often work based on sessional fees (i.e. billing so many hours per week of medical time to research). This arrangement would no longer be possible today, but at the time less attention was paid to how clinicians' time was spent.

> We ended up putting the fees that we would have gotten from the pharmaceutical industry – that in a certain sense should have gone to pay us – into the pot to try and build up the research centre. Now of course that's impossible to do, but in those days that was how it worked. (DB)

Verapamil was one of the first calcium channel blockers and, as mentioned above, was at the time the only one commercially available in Canada (Bloom interview). The drug's patent expired shortly after the case study research, in July 1986 (Suh et al., 2000), although just before this the manufacturer released a new extended release version which saw sales increase dramatically, approaching revenues of US$500 million in 1990 (Office of Technology Assessment, 1993).

Knowledge

As discussed previously, there was some suggestion in the early 1980s of a therapeutic role for CCBs in mood disorders. The combination of this evidence, the known calcium channel blocking properties of diphenylbutylpiperidines, and the confirmation by basic scientists at the Douglas that the team's suspicions were feasible, formed the foundations of the case study research.

Expertise and techniques

Tourjman was a resident (R2) at the time and was splitting the year between research and a chronic care rotation. Nair and Bloom were both clinicians and researchers, something that Tourjman was also aspiring to in her career.

Although not part of the core research team or included as authors on the papers that came from the research cloud, the input of two basic scientists at the Douglas, Rémi Quirion and Paul Wood, was essential in validating the approach and confirming Nair's suspicions that calcium channel blockers could potentially be effective in alleviating the symptoms of schizophrenia.

Similarly, the team also drew on the expertise of George Schwartz, a Research Associate who was a clinical psychologist. He worked a lot on clinical trials, and so was very involved in the trial planning, analysis and statistics with Nair.

Samples/patients

The Douglas Hospital's large inpatient population at the time helped the team complete the study within Tourjman's brief research rotation. The Douglas had a long tradition of clinical research that began in the 1950s when Heinz Lehmann was at the hospital. A number of clinicians also held academic positions at the university. Clinicians were generally happy to recommend their patients to the team for research projects and were happy for the extra attention that their patients got from participating in a study.

Although the larger hospital populations prior to the culmination of the deinstitutionalisation movement meant that clinical trials at the time tended to be conducted on inpatient populations, most of these were carried out on general wards. However, the Douglas was able to admit patients specifically for research studies because it had a dedicated inpatient research unit.

> The Douglas was unique at that time, in that we did have an inpatient research centre, we did have the nucleus of the small basic science group, we had also the nucleus at the time of the psychosocial research group in addition to the clinical research group. But no [other] places that I am aware of in Canada had a research unit to which one could admit patients. (DB)

Collaborators

Collaboration between basic and clinical researchers was one of the key principles underlying the setting up of the research centre. Nair commented:

> You need groups which include clinicians and basic neuroscientists…. There was no basic science lab at that time, so we had to build a lab and recruit a basic scientist to work with. That was the first thing we did. The first basic scientist didn't work out because we found out he was technically good but he was not able to cross boundaries… to direct clinical research you need to step outside your box. (VN)

At the time of the verapamil research it was not easy for the research centre to collaborate with other groups externally as they had not established a reputation in the field. Even at McGill University, with which the Douglas Hospital is affiliated and where several of the clinicians also held academic posts, it was very difficult to build collaboration with basic scientists. Nair commented that the centre had to build up its own expertise and facilities in order to have something to offer collaborators.

13.5 Stage 2: Processes

Tourjman drew up the protocol under the guidance of Bloom, with the aim of completing the study within the time of her residency. Such short-term research rotations are no longer possible due to the increased time it now takes to plan and obtain the necessary approvals for clinical trials (Bloom interview). The research had dual aims of understanding the mechanism by which antipsychotics operate and investigating potential treatment options for chronic refractory schizophrenia (Tourjman interview).

> I think it was mostly understanding the mechanism of action but at the same time it was also to see if there was something that could be done for this population of patients who are refractory, chronic schizophrenics and where we had gone to the end of the line with the agents that were already there. (ST)

The team initially tried verapamil in a very difficult to treat patient, as an add-on drug given alongside haloperidol (a first-generation antipsychotic). They subsequently set up a larger (open-label, uncontrolled) trial of 12 patients. The sample size was not determined by statistical considerations, but instead by the availability of resources and the need to complete the study in a reasonable period of time. As Bloom was just starting his clinical practice, he had a role in recruiting the patients and conducting assessments.

Bloom commented on the importance of understanding patients' subjective experience of different medications and took verapamil himself to learn what it was actually like. He started trying the medications being given to patients through participating in other projects at the research centre, and even today still takes every medication he prescribes to fully understands its effects.

> That was part of the legacy of the research centre as well. We would sign consents to be the normal subjects in this or that study of our research centre colleagues…. It was an education to go to work with a tricyclic antidepressant in your body and to see what it was like for patients who have to take them and had no alternative in those days. It was quite good to do that as a clinician I think. Very few clinicians have the opportunity to have that – but we had the opportunity at the Douglas Centre. (DB)

Tourjman doubted that the verapamil trial would have been published had it not shown the drug to be effective, as in clinical research there tends to be little interest in negative findings. She commented that:

> In terms of career paths, it's much easier to do research that just increases understanding than to do research that has actual application. (ST)

Tourjman sees this trend as a loss to the field, in that questions addressing gaps in the knowledge base, if posed correctly, are interesting whatever their outcome. In addition to this, the fact that there are always existing treatments of some form means that new treatments have to not just be effective, but be superior to those already in use. The difficulty in finding suitably large patient populations to demonstrate such effectiveness can often mean that this kind of research goes no further than initial exploratory studies.

13.6 Stage 3: Primary outputs

Knowledge

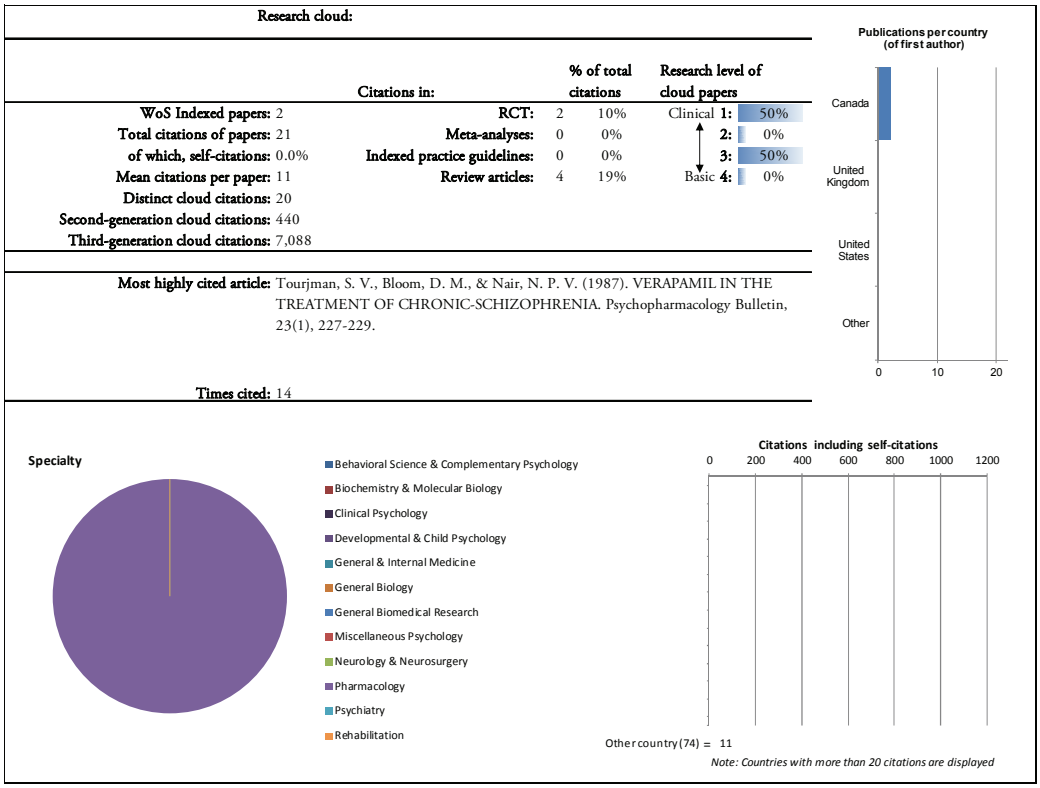
As mentioned above, the case study research was carried out in two parts, each of which produced a publication. The first reported on the case of a single treatment-resistant patient, who after failing to respond to high-dose neuroleptics, both alone and with concomitant diazepam or reserpine, was given verapamil as an add-on to haloperidol (Bloom et al., 1987). The patient made a substantial improvement in terms of clinical symptoms and score on the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962), and the team concluded that verapamil warranted further investigation in a larger sample.

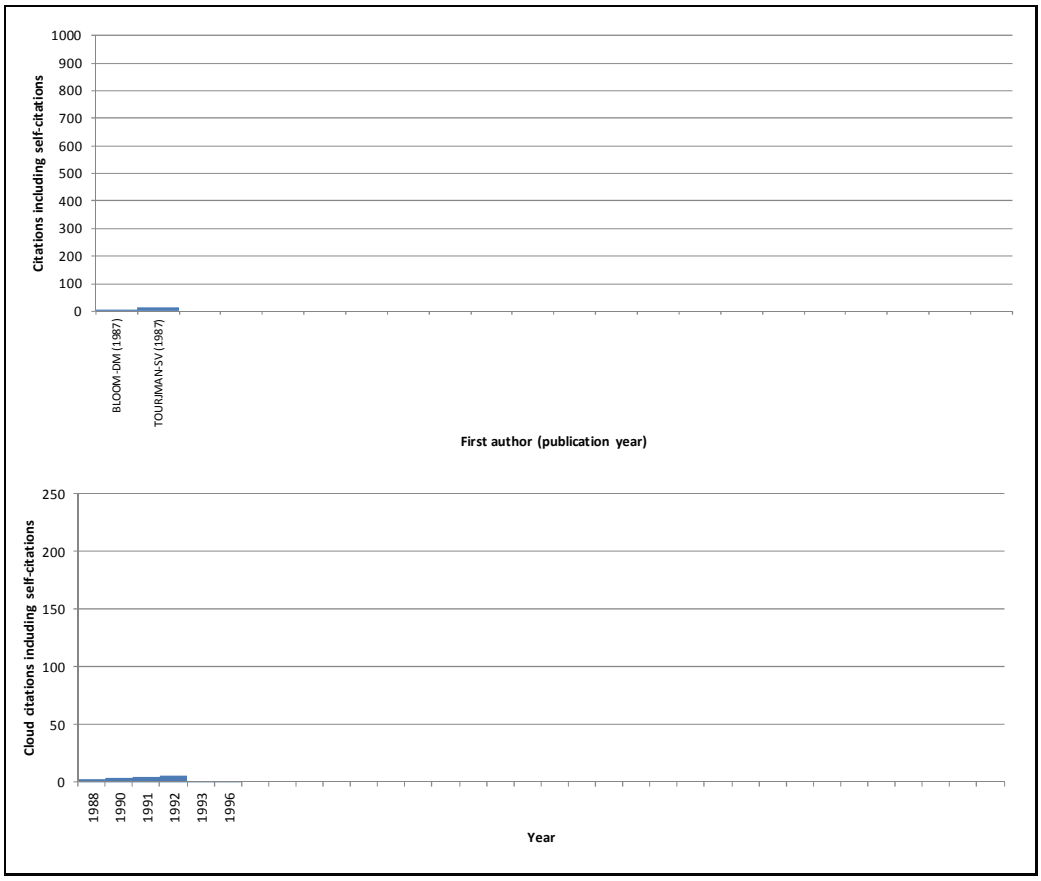
The second paper described the results of an open-label, uncontrolled study of 12 patients who had shown limited response to standard neuroleptic treatment (Tourjman et al., 1987). Outcomes measured using the BPRS and the Nurses' Observation Scale for Inpatient Evaluation (Honigfeld & Klett, 1965) showed statistically significant improvement in at least some factors, although only five of the 12 patients were judged clinically to have responded.

From their findings the team suggested that verapamil and the antipsychotics may have acted synergistically through a calcium channel blocking mechanism to reduce dopamine neurotransmission, a suggestion in line with the idea originally put forward by Gould et al. (1983). They also proposed further investigation of other CCBs, such as nifedipine and flunarazine, which had actually looked more promising than verapamil in early studies using animal models.

The 12 patient study has been cited 14 times as of November 2011 (Thomson Reuters). The majority of these articles either further investigate a potential role for CCBs in the treatment of schizophrenia (in particular, nifedipine) or cite the team's work as part of a wider review on, for example, treatment-resistant schizophrenia or the effects of CCBs.

A bibliometric analysis of the papers produced from the research cloud is shown below.





Targeting future research

Effect on the researchers' careers

All three of the researchers involved continued to pursue research alongside their clinical careers. As Tourjman commented:

> Our work as clinician researchers should be to further understanding but also the application of that understanding to treatment. I think a lot of people are doing research of various levels of, I would say, interest but certainly of very little clinical applicability. I think there's really, truly a need for people to look at treatment options and how does one apply knowledge to producing treatment options. (ST)

At the time of the verapamil work, Bloom was learning how to conduct clinical trials through an apprenticeship that took a number of years. This led to his involvement in many multicentre clinical trials with the same small group of Canadian investigators:

> The pharmaceutical industry was looking for centres and people that had the capacity to do multicentre trials…. Although Canada is quite a large country geographically, it is quite a small country, especially with respect to treatment for schizophrenia…. It was the same investigators, study after study, in Canada that were doing these multicentre studies with Risperidone or Quetiapine or Remoxipride, or what have you. As the new medicines came forward, we would be involved in studies. So it was a great introduction to the world of clinical research. (DB)

Bloom and Nair both remain at the Douglas Hospital today. Nair, whom Tourjman describes as one of the rare examples of someone who has achieved a true fusion of research

and clinical practice, went on to be the first director of the Department of Psychiatry before focussing more recently on treatments for Alzheimer's disease.

Following Tourjman's residency at the research centre, she completed another joint clinical-research year and a year as Chief Resident, before winning a fellowship in genetics funded by the Canadian Psychiatric Research Foundation (1989–1990). This allowed her to maintain a more academic profile than many of her peers. When she then applied for an academic position in her institution there seemed to be no openings, so she went to work at the Louis-H. Lafontaine Hospital in Montreal with a colleague who was similarly aiming to combine clinical work and research. At this point the half research, half clinical arrangement worked well for Tourjman, as she was starting a family and did not think she could shoulder the leadership of a research clinic.

When Tourjman returned from maternity leave, her colleague had left to work solely as a clinician (due to the pressures of trying to do research as well) and there was no longer a clinic at the hospital. She set out to establish a new research clinic, but this did not materialise. She eventually changed hospitals to join a researcher with a team in mood disorder research. However, the researcher she moved to work with stopped his research activity shortly after she arrived due to the completion of a project, and ultimately Tourjman returned to Louis-H. Lafontaine Hospital in 2009, where she is now Director of Clinical Research.

This experience demonstrated to Tourjman the extent to which clinical research structures tend to be dependent on one person:

> And so as soon as that single individual either is short of a project or is no longer there… the whole thing just crumbles and there's nothing in the institution. And I think that underlines the fragility of having research that is not fused with the clinical structure. (ST)

Tourjman commented that, knowing what she does now about the difficulties of establishing and maintaining this kind of career, she should have had a mentor from the start and would have applied immediately for an FRSQ clinician research programme.

Future work – in psychiatry

No follow-up work was carried out by the team at the Douglas. As the second part of the case study research was an open study with no control group, the next stage would have been to conduct a double-blind controlled trial. A protocol was prepared for this kind of study and the team consulted a statistician who determined that a sample of 60 patients would be needed to demonstrate efficacy. Nair suggested that at the time this would have cost around CAD$300,000, and although the team approached several pharmaceutical companies, they found little interest. They then approached the hospital's board, but as the research centre was still in its early days, were faced with the choice between running this one clinical trial or using the money to further develop the centre in other ways.

The absence of substantial follow-on work and difficulty in securing funding seem to be due to two main issues: a lack of confidence in the results and no real commercial incentive to try to develop a drug.

A number of other studies published around the time of the case study research reported conflicting findings on the effectiveness of verapamil in schizophrenia. For example, although Bartko et al. (1991) supported the findings of the case study research by

demonstrating the effective use of verapamil as an adjunct to standard neuroleptics, other studies prior to this had found no therapeutic effect of verapamil in treatment-resistant schizophrenia patients (Grebb et al., 1986; Pickar et al., 1987; Schepelern & Køster, 1987).

It was also not clear at this point whether all CCBs would have equivalent activity. A number of studies had published conflicting findings with respect to drugs other than verapamil and a distinction was beginning to emerge in the literature between those effective in schizophrenia and those not. This meant that it would have been necessary to conduct a comparison study of the various compounds, something that would generally not be in the interests of pharmaceutical companies (as discussed previously).

Bloom explained that the team may also have been slightly hesitant to invest in follow-up work due to lessons learnt from previous research they had carried out at the Douglas, including the immediately preceding work on cholecystokinin in schizophrenia:

> One of the things that I saw in some of the research studies that we had done – not only with verapamil, but with other molecules that we had worked with – is that they lost their efficacy with time. So there might have been more of a placebo component than we thought in the first two or three months of treatment… [the earlier work on cholecystokinin] was still a good education for me about placebo response in schizophrenia. The patients did get better for a certain time. (DB)

In relation to obtaining funding from elsewhere for a follow-on study, Bloom commented that the results needed to be a bit more clear cut to secure the interest of industry:

> There would have been [interest] had there been a little bit more meat around the bones I think. If the results had been a bit more promising, had there been a few more patients that we could have reported on; or another group could have reported on. (DB)

Nair did look at the possibility of obtaining funding from the Medical Research Council or FRSQ, as these funders were of increasing importance in the research centre's work, but the work on CCBs in schizophrenia was not considered to be a candidate likely to be successful in the highly competitive funding processes of these agencies, particularly given that the research centre was still in the early stages of its development and with the commencement of trials of second-generation antipsychotics.

Tourjman added that the work with verapamil could not have gone much further because the only realistic funding source was industry and it was clear that the research was not going to produce a marketable product. Shortly after the case study research was published the drug came off patent, limiting its commercial value – had this not been the case there may have been some interest from companies in funding a follow-up (Tourjman interview).

There were also other lines of research to pursue in the research centre. It was around the time that second-generation antipsychotics were being developed and tested, and the research centre was involved in a large multicentre Astra Pharmaceuticals study across Canada, the first of several in which they worked with various other research groups (Chouinard et al., 1993; Lapierre et al., 1992; Lapierre et al., 1990).

Bloom commented that this was a promising area to pursue, as at the time second-generation antipsychotics appeared much more effective than any drugs available previously:

> These medicines clearly worked, so at that point there was no impetus to look at add-ons. The whole idea of looking at the add-on strategy in the 1980s was that the treatment landscape was so bleak in schizophrenia at that time. (DB)

Bloom also recalled few other labs in Canada conducting add-on studies in schizophrenia at the time. The facilities for conducting such research, and in particular the existence of a dedicated inpatient research unit at the Douglas were unique in Canada.

According to Tourjman, the bulk of the work on CCBs in mood disorders also petered out around the end of the 1980s, and although she has heard some discussion of similar compounds at (non-clinical) conferences, she has seen nothing trickle down to the clinical knowledge base.

Although there has been relatively little work overall on the role of CCBs in psychiatric disorders, there are still a small number of studies being carried out. A recent review summarised the evidence base for the role of L-type calcium channels, concluding that converging evidence in animal and human models justified further investigation in mood disorders, substance abuse and Parkinson's disease (Casamassima et al., 2010). The authors commented that few studies so far have used adequately sized homogeneous samples, while also noting the need for genetic, pharmacogenetic and physiologic research to refine apparent genetic associations, better elucidate the role of different subunits and isoforms of calcium channels, and to provide new pharmacologic insights.

In treatment of schizophrenia specifically, there appears to have been little recent work, but a Cochrane review published in 2004 (Soares-Weiser & Rathbone, 2004) and subsequently updated (Essali et al., 2011) explored the use of CCBs in treating tardive dyskinesia caused by antipsychotic medication. However, neither of these reviews was able to include any of the trials identified due to a lack of robust methods, the authors therefore concluding that the effects of CCBs in neuroleptic-induced tardive dyskinesia remain unknown.

13.7 Interface B: Dissemination

Only two publications came from the research cloud, but the team was relatively active in attending conferences. Bloom presented a paper on the case study research at the prestigious New Clinical Drug Evaluation Unit annual meeting (NCDEU), sponsored by NIMH at the time, where he presented alongside Jeffrey Lieberman in a session chaired by Nina Schooler.

13.8 Stage 4: Secondary outputs

Tourjman described the case study research as always being intended as more of an intellectual exploration than something that would be likely to have a patentable outcome, as even if CCBs were found to be effective in schizophrenia, many other existing medications, despite primarily targeting other mechanisms, were also potent CCBs. In fact,

antipsychotics themselves often have a more powerful calcium-blocking property than that of verapamil. Demonstrating the effectiveness of verapamil would, however, show proof of concept for the role of calcium.

13.9 Stage 5: Applications

None identified.

13.10 Stage 6: Public engagement

None identified.

13.11 Stage 7: Final outcomes

Although the findings of the case study research have not led to clinical use, Bloom commented that simply being involved in research has enabled him to take better care of patients in the clinical side of his work:

> It gave me an insight into the humanity of the patients a bit more…. The medicines we had in those days, the first generation antipsychotic medicines, were quite terrible medicines. When we were doing placebo studies, we were able to take patients off their medicine and 'wash them out'. It was in those days, those wash out days, that we would see the patients come alive. So the so-called dull, negative, burnt out patients who had been ill for years were in fact not dull, burnt out patients, but people who could regain some of their affect, regain some of their interactive ability that clearly had been blunted by the first generation antipsychotic medicines – which were over used. So there is a pivotal point in my development as a clinician and a human being in terms of humane treatment of people, making sure that I didn't over medicate people. (DB)

According to Bloom, it was both dosage and the drugs themselves that affected people in this way:

> At that point there was still no good appreciation of patient variability – you know, everybody gets dose X, in the same way we give antibiotics nowadays…. But there was also very little appreciation of what the subjective feeling of taking the medicines was… if they are a little bit duller or a little bit slowed down, well that was part of the illness too… that was part of the price to pay to be well with these medications. (DB)

13.12 Other observations

Drug development and clinical trials

Current concerns over reduction in industry funding of drug development have led to the provision of seed money to initiate collaboration with industry. Such funding, if available at the time of the verapamil work, would have allowed for a much larger study (Nair interview).

Although Bloom became involved in many clinical trials in Canada after this work, he commented that it would now be much harder to follow this path. In the mid-1990s the philosophy of clinical equipoise emerged strongly in Canada, that is, the idea that all

patients should have an equal opportunity to receive something that is equally effective. Bloom explained that this more or less stopped placebo-controlled trials in Canada. He also commented that the increasing stringency around the format and procedure of clinical trials has limited opportunities:

> They are quite cumbersome trials. You can only recruit a certain number of patients per centre because it is so difficult to do. You need hundreds of centres to get something done and the only people that can do that sort of thing are big companies…. It is just almost unfathomable now what it takes to pull off the study. (DB)

Tourjman added that most psychopharmacological research is now done in China, Eastern Europe and Africa, and although western countries benefit from the results, they are not benefiting from the investment and jobs that existed in the past. She does work with industry herself, but commented that pharmaceutical companies have a lot to gain from working with academics. She remarked that pharmacological research is subsidised by government funding in Canada, but that despite this, such research is not competitive with the cheaper options available in other countries.

Challenges of combining research and clinical work

Much of Tourjman's career has focussed on building up links between clinical work and research and she and Nair both talked about the challenges this presents, both at the individual level and in the research system more widely. Tourjman highlighted the emphasis placed on publication in the academic world:

> The way the academic world is structured is that you succeed by your publications and how often you've been cited…. So there is a tension between being able to actually have clinical experience which allows you to generate clinically pertinent questions and being in the academic mode where you're just thinking about how many publications you'll produce. And when you actually look at many of the people who produce many publications, and you look at how many publications they produce, how many patients can they really be seeing? How many really, truly, innovative questions can they generate if they're not seeing patients and if they're not there really on the terrain exploring what clinical pathology is? (ST)

Tourjman had always wanted to pursue a combined research/clinical career, but commented on the difficulty in particular of getting back into research and obtaining funding following a break, for example, to have children. She suggested that the implications of following such a career path, and in particular of trying to compete for funding with full-time researchers, are a significant barrier to many:

> Essentially, you're giving of yourself and of your family's future to this kind of endeavour and that's not really rewarded or acknowledged…. You have to want it and you have to want to sacrifice a great deal to do that. And, you know, I think it's okay for some people to have that mission but you can't base a whole development programme on Mother Theresas. (ST)

The importance of having a strong publication record may also limit or shape the clinical questions that can be addressed in some instances:

> It means that if you're primarily a clinician you're starting at a disadvantage and you always have to ally yourself with someone else, which means you have to subordinate your question to the academician's theme. So it means that no purely clinician-generated question can be asked, no matter how well the protocol is written, no matter how feasible

> the project is… I think we've created a climate where we're looking for quantity rather than quality and we're looking for quick answers rather than having programmes that enable innovative work to be done… we've become an industry of publication rather than an industry of ideas, and the reality is that most people have perhaps one or two good ideas in their life – they don't have 300 or 600 or some of those amazing CVs that you read. (ST)

As mentioned previously, without the backing of the Douglas Hospital and the initial internal funding available to attract basic scientists and build the research centre's reputation, it would not have been possible to establish a successful clinical research centre at the hospital. Tourjman has faced similar challenges in her current position as Director of Clinical Research at Louis-H. Lafontaine Hospital. She highlighted two main barriers to fostering academic–clinical collaboration. Firstly, clinical research is often slow and challenging, making it difficult to generate the volume of publications needed to maintain funding. This can result in the research diverging from what is actually being done clinically. Secondly, many clinical researchers need 'clean' cases of a disorder for their research. However, those patients who are admitted to the hospital have always initially seen a GP and not responded to treatment, making them unsuitable participants for many research studies.

13.13 Table of payback

Payback category	Impacts from case study
Knowledge Production	• Two publications demonstrating the effectiveness of verapamil as an adjunct to standard antipsychotics in treatment-resistant schizophrenia patients.
Research Targeting and Capacity Building	• Helped Tourjman build her research profile and along with other research at the time helped the team pursue combined clinical and research careers.
Informing Policy and Product Development	• None identified.
Health and Health Sector Benefits	• Being involved in this research and other studies enabled Bloom to better understand and take care of patients in his clinical work.
Broader Social and Economic Benefits	• None identified.

13.14 Timeline

1972	Nair arrives at the Douglas Hospital
1979	The Douglas Hospital Research Centre is established and Nair is made its director

1980	Dr. Samarthji Lal sets up Canada's first brain bank
1981	Bloom starts work at the Douglas Hospital
1985–1986	Tourjman at the Douglas Hospital as a Resident
1986	Patent on verapamil expires
1986	The hospital launches a five-year fundraising campaign for the research centre
1987	The two papers describing the findings of the case study research are published
1991	Tourjman starts work at Louis-H. Lafontaine Hospital
1995	Rémi Quirion takes over from Nair as centre director, by which point annual income has been built up to around CAD$6 million
2007	Tourjman moves to Notre-Dame Hospital
2009	Tourjman returns to Louis-H. Lafontaine Hospital as Director of Clinical Research

13.15 References

Bartko, G., Horvath, S., Zador, G., & Frecska, E. (1991). Effects of adjunctive verapamil administration in chronic schizophrenic patients. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 15(3), 343–349.

Bloom, D.M., Tourjman, S.V., & Nair, N.P.V. (1987). Verapamil in refractory schizophrenia – a case-report. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 11(2–3), 185–188.

Carman, J.S., & Wyatt, R.J. (1979). Calcium: bivalent cation in the bivalent psychoses. *Biol Psychiatry*, 14(2), 295–336.

Casamassima, F., Hay, A.C., Benedetti, A., Lattanzi, L., Cassano, G.B., & Perlis, R.H. (2010). L-type calcium channels and psychiatric disorders: a brief review. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 153B(8), 1373–1390.

Chouinard, G., Jones, B., Remington, G., Bloom, D., Addington, D., Macewan, G.W., et al. (1993). A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic-schizophrenic patients. *Journal of Clinical Psychopharmacology*, 13(1), 25–40.

Dubovsky, S., Franks, R., Lifschitz, M., & Coen, P. (1982). Effectiveness of verapamil in the treatment of a manic patient. *American Journal of Psychiatry*, 139(4), 502–504.

Essali, A., Deirawan, H., Soares-Weiser, K., & Adams Clive, E. (2011). *Calcium Channel Blockers for Neuroleptic-Induced Tardive Dyskinesia*. Cochrane Database of Systematic Reviews.

Giannini, A., Houser, W. Jr, Loiselle, R., Giannini, M., & Price, W. (1984). Antimanic effects of verapamil. *American Journal of Psychiatry*, 141(12), 1602–1603.

Gould, R.J., Murphy, K.M., Reynolds, I.J., & Snyder, S.H. (1983). Antischizophrenic drugs of the diphenylbutylpiperidine type act as calcium channel antagonists. *Proceedings of the National Academy of Sciences*, 80(16), 5122–5125.

Grebb, J.A., Shelton, R.C., Taylor, E.H., & Bigelow, L.B. (1986). A negative, double-blind, placebo-controlled, clinical trial of verapamil in chronic schizophrenia. *Biological Psychiatry*, 21(7), 691–694.

Honigfeld, G., & Klett, C.J. (1965). The nurses' observation scale for inpatient evaluation. A new scale for measuring improvement in chronic schizophrenia. *Journal of Clinical Psychology*, 21(1), 65–71.

Lapierre, Y.D., Ancill, R., Awad, G., Bakish, D., Beaudry, P., Bloom, D., et al. (1992). A dose-finding study with remoxipride in the acute treatment of schizophrenic-patients. *Journal of Psychiatry & Neuroscience*, 17(4), 134–&.

Lapierre, Y.D., Nair, N.P.V., Chouinard, G., Awad, A.G., Saxena, B., Jones, B., et al. (1990). A controlled dose-ranging study of remoxipride and haloperidol in schizophrenia – a Canadian multicenter trial. *Acta Psychiatrica Scandinavica, 82*, 72–77.

Lishman, W.A. (1978). *Organic Psychiatry: The Psychological Consequences of Cerebral Disorder*. Oxford: Blackwell Scientific.

Office of Technology Assessment. (1993). *Pharmaceutical R&D: Costs, Risks, and Rewards*. Washington, DC: United States Congress, Office of Technology Assessment.

Overall, J.E., & Gorham, D.R. (1962). The Brief Psychiatric Rating Scale. *Psychological Reports*, 10, 799–812.

Pickar, D., Wolkowitz, O.M., Doran, A.R., Labarca, R., Roy, A., Breier, A., et al. (1987). Clinical and biochemical effects of verapamil administration to schizophrenic patients. *Archives of General Psychiatry*, 44(2), 113–118.

Quirion, R., Lal, S., Nair, N.P.V., Stratford, J.G., Ford, R.M., & Olivier, A. (1985). Comparative autoradiographic distribution of calcium channel antagonist binding sites for 1,4-dihydropyridine and phenylalkylamine in rat, guinea pig and human brain. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 9(5-6), 643–649.

Schepelern, S., & Køster, A. (1987). Verapamil in treatment of severe schizophrenia. *Acta Psychiatrica Scandinavica*, 75(5), 557–558.

Soares-Weiser, K., & Rathbone, J. (2004). *Calcium Channel Blockers for Neuroleptic-Induced Tardive Dyskinesia*. Cochrane Database of Systematic Reviews.

Suh, D.C., Manning, W.G. Jr., Schondelmeyer, S., & Hadsall, R.S. (2000). Effect of multiple-source entry on price competition after patent expiration in the pharmaceutical industry. *Health Services Research*, 35(2), 529–547.

Thomson Reuters. Web of Science. As of 10 September 2013: http://thomsonreuters.com/web-of-science/

Tourjman, S.V., Bloom, D.M., & Nair, N.P.V. (1987). Verapamil in the treatment of chronic schizophrenia. *Psychopharmacology Bulletin*, 23(1), 227–229.

Triggle, D.J. (2007). Calcium channel antagonists: clinical uses – past, present and future. *Biochemical Pharmacology*, 74(1), 1–9.

CHAPTER 14 The effects of neuroleptics on lateralisation in schizophrenic patients

This case study is based on the research cloud that produced the paper:

Tomer, R., & Flor-Henry, P. (1989). Neuroleptics Reverse Attention Asymmetries in Schizophrenic Patients. *Biological Psychiatry*, 25, 852–860.

Information was gathered from interviews with Rachel Tomer and Pierre Flor-Henry, as well as desk-based research.

14.1 Summary

This case study summarises work done to understand dopamine asymmetry in the brain. The main output of this research cloud was to show that there are asymmetries in the brain that are reversed by neuroleptic treatment. Specifically, the work was looking at the hypothesis that schizophrenia may be characterised by left hemisphere hyperarousal, and that neuroleptics can have an effect on this asymmetry. The studies that make up the research cloud show that asymmetry is reversed after one dose of neuroleptic treatment and, moreover, that this suggests that lateralisation of the dopaminergic system is not due to hyperarousal of the left hemisphere, but rather a more general dynamic imbalance. The research was considered to be very basic by the researchers with little to no clinical application. Few final outcomes or categories were identified; however, very few (if any) researchers have considered the interaction between laterality and neuroleptics as Tomer and Flor-Henry have done.

14.2 Introduction

Scientific background

This research is based on observations that were first made in the late 1960s (Flor-Henry, 1969), and subsequently studied by many others, that there are lateralisation effects in psychopathology. The topic of lateralisation in the brain is extremely broad and it would be impossible to cover all of it here; however, it is important to understand the basic concepts and implications in order to understand this case study. Lateralisation effects mean that there are different effects on each side of the brain that are caused either by structural or neurochemical mechanisms, like the dopaminergic system. For example, greater visual or aural accuracy on one side of the body versus the other is a lateralisation effect. This is also known as 'asymmetry'. The physical effects of lateralisation can often be

confusing to understand. This is because of a general feature of the way the brain controls movement in the body, something called 'contralateral influence'. Essentially, each hemisphere of the brain controls the space on the opposite side of the body – the right hemisphere deals with the left hemispace and vice versa. This means that the observable effect of something happening in the right hemisphere of the brain would be on the left side of the body. Thus, when we discuss lateralisation effects, it can be confusing to differentiate between the chemical effects in the brain, and the manifestations of those effects in physical or mental acuity.

While the first observations of asymmetry were made in patients with epilepsy, subsequent work has gone on to show that the dopaminergic system itself is asymmetrical in all individuals, regardless of whether the patient is mentally ill. The question then becomes one of the implications of this lateralisation. In particular, it had been noted that left hemisphere hyperarousal, where it had been hypothesised there may be greater dopamine production and hence a more 'aroused' state of the nervous system, was common in patients with schizophrenia and may even be a characterisation of the disease. Hyperarousal on one side of the brain is usually accompanied by hypoarousal on the other side and because of the contralateral effects of the brain, hyperarousal on one side of the brain often results in preferential physical 'orienting' to the opposite side. Indeed several studies, including one by Tomer (Mintz et al., 1982) had suggested that schizophrenic patients showed rightward lateral eye movements (LEM), quite literally shifts in gaze toward the right side. LEM are studied because they indicate asymmetry in cognitive activity, so when areas of the left hemisphere are hyperaroused, eye movements to the right are observed. However, all of these studies were done with patients who were medicated and some studies of unmedicated patient groups suggested there might not be consistent LEM movements, rightwards or leftwards. This led to the authors, and Tomer in particular, asking the question whether the effect of hyperarousal as indicated by LEM was one that was a result of the disease, or the result of neuroleptic medication. The question is an important one because it could have had implications for how the effects of neuroleptics were understood on the dopaminergic brain, and potentially for understanding the pathophysiology of schizophrenia. Thus, while Flor-Henry's early work introduced the concept of asymmetry and lateralisation, it was Tomer who introduced the idea that there could a neuroleptic interaction in this that was significant.

14.2.1 **Researcher's backgrounds**

Rachel Tomer was a post-doc of Pierre Flor-Henry's at the time the first studies in this research cloud were conducted. She had done her PhD work in Israel under Michael Myslobodosky. Myslobodosky was familiar with the work of Pierre Flor-Henry and, in particular, his seminal study on asymmetry in epileptic patients. Tomer's PhD was focussed around the research question: is the pathophysiology of schizophrenia lateralised? She was trained as a psychobiologist and electrophysiologist and one of the findings of her PhD was that it appeared that the medication schizophrenic patients were taking caused asymmetry in the brain. For her post-doc she wanted to do some follow-up work on this finding, in particular studying patients who were not on medication and exploring lateralisation effects in the brain.

> So I wanted to follow it up and see if I could test patients who were not on any medications and see if they were lateralised or not. And then follow them up when they're

> on medication and see if then, they then became lateralised and that would give us an answer to the question whether the lateralisation that most studies at the time reported was an artefact of the medication or a real thing. (Tomer, 2011)

Pierre Flor-Henry was a clinical researcher at the University of Alberta and Director of Admissions at the Clinical Diagnostics and Research Centre at the Alberta Hospital Edmonton at the time the initial studies in this research cloud were published. He was a well-established figure in the field and had published two seminal papers on lateralisation in the brain (Flor-Henry, 1969, 1976) by the time of this research cloud. Flor-Henry obtained his MD from the University of Edinburgh in 1966 and he did his work on lateralisation in psychotic epileptic patients while at the Maudsley Hospital in London from 1963–1968. In the 1970s he moved to Alberta and began clinical practice at Alberta Hospital Edmonton. In 1976 he became a Clinical Professor in the Department of Psychiatry at the University of Alberta. In 1977 he became the Clinical Director of Adult Psychiatry at the Alberta Hospital and in 1993 he became Clinical Director of the Clinical Diagnostics and Research Centre.

Flor-Henry described the main focus of his clinical research career as understanding laterality in psychopathology, and more specifically, laterality in schizophrenia. Similarly, Tomer describes her research career as focussing on the question 'what are the implications of lateralisation for dopaminergic neurotransmission in the brain?'

14.3 Defining the research cloud

There is one overarching research cloud related to this paper that shaped the entire career of Rachel Tomer and addresses the question: what are the implications of lateralisation in the dopaminergic brain? This work spans both Tomer and Flor-Henry's work with schizophrenia patients, but also the other mental health disorders that both went on to study. For the purposes of this case study, though, the research cloud is most clearly defined as looking at the effects of neuroleptics on dopaminergic lateralisation in patients with schizophrenia.

There were three important inputs to the research cloud that looked at dopaminergic lateralisation and asymmetry in the brain of patients with psychosis:

1. Flor-Henry, P. (1969). Psychosis and temporal lobe epilepsy: a controlled investigation. *Epilepsia,* 10**,** 363–395.
2. Flor-Henry, P. (1976). Lateralized temporal-limb dysfunction and psychopathology. *Annals of the New York Academy of Sciences,* 280**,** 777–795.
3. Tomer, R., Mintz, M., Levi, A., & Myslobodsky, M.S. (1979). Reactive gaze laterality in schizophrenic patients. *Biological Psychology,* 9**,** 115–127.

While these papers all lead to the identification of lateralisation and asymmetry in the brains of schizophrenic patients, the following papers form the research cloud that is specifically looking at the effects of neuroleptics on asymmetry and lateralisation of the dopaminergic system. The original paper that was used to identify the research cloud is listed first; all others are listed in chronological order. There are several papers that come before the 1989 paper which can be considered to be part of the research cloud, making the 1989 paper perhaps less of an initiating paper for the cloud and more of a paper that

sits at its heart, both temporally and research-wise. The papers from 1982–1987 were published while Tomer was a PhD student. The three papers published from 1989–1990 were the result of Tomer's post-doc work. The final two papers were conducted by Flor-Henry and a colleague at the University of Alberta and can be considered to be follow-on studies.

4. Tomer, R., & Flor-Henry, P. (1989). Neuroleptics Reverse Attention Asymmetries in Schizophrenic Patients. *Biological Psychiatry*, 25, 852–860.
5. Mintz, M., Tomer, R., & Myslobodsky, M.S. (1982). Neuroleptic-induced lateral asymmetry of visual evoked potentials in schizophrenia. *Biological Psychiatry,* 17, 815–828.
6. Tomer, R., Mintz, M., & Myslobodsky, M.S. (1982). Left hemisphere hyperactivity in schizophrenia: abnormality inherent to psychosis or neuroleptic side-effects? *Psychopharmacology*, 77, 168–170.
7. Tomer, R., Mintz, M., Kempler, S., & Sigal, M. (1987). Lateralized neuroleptic-induced side effects are associated with asymmetric visual evoked potentials. *Psychiatry Research,* 22, 311–318.
8. Tomer, R. (1989). Asymmetrical effects of neuroleptics on psychotic patients' performance of a tactile discrimination task. *Journal of Nervous and Mental Disease,* 177, 699–700.
9. Tomer, R. (1990). Neuroleptic effects on interhemispheric and intrahemispheric performance of tactile discrimination tasks by schizophrenic patients. *Psychiatry Research,* 32, 289–296.

Follow on studies drawing on the research cloud:

10. Purdon, S.E., Flor-Henry, P., Waldie, B.D., Woodward, N.D., & Reed, B.D. (2000). Asymmetrical olfactory acuity and neuroleptic treatment in schizophrenia. *Schizophrenia Research,* 41**,** 162–163.
11. Purdon, S.E., Woodward, N.D., & Flor-Henry, P. (2001). Asymmetrical hand force persistence and neuroleptic treatment in schizophrenia. *Journal of the International Neuropsychological Society,* 7**,** 606–614.

14.4 Stage 0: Opportunity identification/research needs assessment

Inspiration

The inspiration for this research cloud came from both the 'productive collision' of Flor-Henry and Tomer and from the general interest in asymmetry in the field at the time. When Tomer was doing her post-doc and the initial study in the research cloud (Tomer & Flor-Henry, 1989a), asymmetry was a very popular area of research.

> There's these fashions, they're questions that are very dominant and then they disappear and then they re-emerge. And that was – the period when I was a student asymmetry was very popular and there were a lot of studies about asymmetry. And the model and Pierre's model which was really, really brilliant I thought really nice was very popular and there was a lot of studies in psychopathology not just schizophrenia but because his model also says that affective disorders will have more active right hemisphere. So it was about all psychopathology in general…. (Tomer, 2011)

Flor-Henry was a well-known researcher and a major figure in lateralisation of schizophrenia. Tomer was introduced to Flor-Henry at a conference in London by her PhD supervisor, Michael Myslobodsky. Myslobodosky himself had been very influenced by the work of Flor-Henry and had been in touch with him ever since emigrating from Russia to Israel and setting up a research laboratory there (Flor-Henry, 2011). As Tomer recalled,

> I met him at a conference… in London in fact and I talked to him about it. And I said that I was interested in testing unmedicated schizophrenics but it was impossible to do that in Israel. And he said 'Oh come to Edmonton and I'll give you as many as you like.' So we started talking about how I could go there and he found out that there was a way to write a research grant and get it hopefully funded. So I did and it got funded and I packed my bags and went to Edmonton. (Tomer, 2011)

Flor-Henry also recalled that though Tomer didn't work on exactly similar issues as he was working on, their partnership was broadly in the same theoretical realm.

> I wasn't working on what she found. But I was working on brain analysis of schizophrenia, which involved a particular interest in lateralised hemispheric aspects. So this is why she came here. (Flor-Henry, 2011)

Feasibility

The main aspects that made the research cloud feasible were existing knowledge in the field and the availability of resources to do the work in Edmonton.

The existing knowledge rested upon Flor-Henry's work dating back to the mid-1960s. At that time, Flor-Henry was working at the Maudsley Hospital in London with the epileptic unit. He was therefore dealing with epileptic patients with psychiatric comorbidities. At the time it struck him that although epilepsy and psychiatry had been well discussed in the European literature from the 19th century up until that point, no one had ever done a systematic study and comparison of epileptic psychosis and epileptic patients without psychosis. He undertook this study using the Maudsley archives and in 1969 published a paper that showed for the first time that epilepsies of the left hemisphere were prone to schizophrenic psychosis and epilepsies of the right hemisphere were prone to manic depressive psychosis (Flor-Henry, 1969). The importance of the work is illustrated by its heavy citation rate. The work caused 'quite a stir' at the time and seems to have triggered an intense interest in further neuroscience research into lateralisation dimensions in psychiatry – 'before that, it didn't exist' (Flor-Henry, 2011).

A few years later, in 1976, Flor-Henry published further work on lateralisation suggesting that left hemispheral hyperarousal may characterise schizophrenia (Flor-Henry, 1976). Additional work in the field throughout the 1970s and into the 1980s continued to point to lateral effects in the brains of schizophrenic patients. In particular, Tomer and colleagues contributed to work showing that lateral eye movements (LEM) are indicative of differential hemispheric activity in the human brain. Tomer and colleagues applied the LEM research techniques to schizophrenic patients and showed that they tended to have rightward LEM (Tomer et al., 1979). This supported other work that had been done and was based on earlier work by Kinsbourne (1970) which had shown that LEM was a measure that reflected asymmetry in the direction of attention. Rightward LEM would

suggest predominant orienting towards the right hemispace, which would be supportive of the hypothesised left-sided hyperarousal in schizophrenic patients.

In addition to the work of Flor-Henry in the field, there were many other groups exploring lateralisation around the time. It is difficult to articulate the exact contributions of each: it is likely that Tomer and Flor-Henry drew on the work of Gur and Gur (Gur & Gur, 1974; Gur & Gur, 1975), Gruzelier (Gruzelier & Doig, 1996; Gruzelier, 1999), Reynolds (Reynolds, 1983), Bracha (Bracha, 1989) and Posner and Early (Posner et al., 1988) among many others studying lateralisation at the time.

However, Tomer noticed that many of these studies had been done on medicated patients. In fact, re-analysis of data published by Tomer and colleagues (Mintz et al., 1982) used EEGs to test the hypothesis that neuroleptic medication restored symmetry in the brain by addressing hemispheric dopamine imbalances. However, the study actually showed that rightward LEM predominated in a group of patients on medication, but that there was no dominant LEM in the group of unmedicated patients (Tomer et al., 1982). Tomer commented in the paper at the time:

> The present study indicates that the findings reported in the literature (including a report from our laboratory) may have been considerably confounded by the neuroleptic medication. (Tomer et al., 1982, 169)

She goes on to say that the findings had implications for the assumption that schizophrenia is simply due to hyperarousal in the left hemisphere and that neuroleptics simply rebalance this state. The neurolpetics they had used in the earlier study were piperazine derivatives that act in the direction of increasing left hemisphere activity. Thus, a neuroleptic that led to further hyperarousal would actually seem to disprove the hypothesis that the effect of medication is to rebalance the activity between the two hemispheres. This led Tomer to consider whether the asymmetry difference was based on the effect of neuroleptics, or whether it was inherent to the disease itself.

The resources were not available in Israel for Tomer to do the research, because she could not get access to unmedicated schizophrenic patients, but it seems that Flor-Henry's knowledge, expertise and standing in the field was the main driver for why she went to Edmonton to work with him.

14.5 Stage 1: Inputs to research

Money, researcher time, lab/office space and consumables

Tomer was supported through an Alberta Medical Research Heritage Foundation post-doctoral fellowship (now Alberta Innovates – Health Solutions). Flor-Henry identified the foundation, Tomer wrote the application in about three days. It was very generous funding, but limited in some important ways. Initially it was for one year, but by the end of that year she needed more time, so Flor-Henry suggested she ask for an extension. With the data she had she wrote to them and they approved an extension of two years.

The funding of the fellowship seemed to be important to the success of the research as it was very generous and flexible. The generosity of the fellowship meant Tomer was able to live comfortably and did not have to worry about funding for her research projects. She claimed that she had friends in the US at the time who had to make do with about half the

money she did. The second factor was that the terms of the fellowship were written so that the money was to be used to 'educate and improve the research skills of the Fellow.' Importantly, research funding could not benefit the institution. She wasn't allowed to buy any new equipment that would remain with the institution, but she could buy books, materials, attend conferences, courses, meetings, etc., as long as they benefitted her.

> And that was wonderful because I did go to many conferences. I went to all the biological psychiatry meetings, I went to neuropsychology meetings. I went to this school – really I mean and that was good not just because I learned a lot of stuff but because I met people, because I could present my research, get feedback on it, discuss it with people. See how other people worked. That was great in that sense, that was a really nice Fellowship. (Tomer, 2011)

Though funding was readily available for Tomer and she was able to attend conferences, courses and access other materials and resources needed to further her education, there was no electroencephalogram (EEG) machine that had an averager. An averager is used to average the recording of the electrical signals in the brain and, in Tomer's case, was essential to her ability to use EEG technology to look at evoked potentials in the brain. Though the hospital had an EEG machine that she thought would suit her needs when she wrote the proposal for her post-doc, when she arrived at the hospital, she realised the averaging equipment did not have the functionality needed for her experiments. Though the averager was a small piece of equipment that was not very expensive, the funding agency was very strict in their interpretation of the grant rules and they refused to let her purchase the device.

> But I understood that because they said – the person that I was talking to explained to me he said 'We don't want the hospital encouraging people to come just as a means of getting finance to buy equipment or things that they want. We want this to be for the Fellow.' So they wouldn't make an exception. (Tomer, 2011)

Overall, though, Tomer felt she had everything she needed. As outlined above, the funding for the post-doc was very generous and she was able to travel to conferences, purchase materials and have access to the patient population that was required of her study. She commented that:

> I mean people don't realise that but it's the best thing to be is a post-doc because you have all the opportunities and none of the responsibilities of an independent researcher. (Tomer, 2011)

Knowledge

Tomer had worked with schizophrenic patients during her Master's and doctoral research, but the initial interest in working with that patient group had been fairly serendipitous. The lab she was working in already had some studies with schizophrenic patients and so it was a readily available patient population that she started off working with. Flor-Henry had a long-time interest in working with this patient population, so both of them had appropriate knowledge on that front. They also both had worked on lateralisation and different ways of measuring of its effects, although as we will see below, Tomer needed to adopt a new approach to the research upon arriving in Alberta.

Expertise and techniques

Originally, Tomer's intent was to look at the transfer of information from one side of the brain to the other. To do that she would need an EEG machine, but there wasn't one in Alberta that met her needs, so she had to think quickly on her feet to develop a new research idea. She had previously been working with rats and her studies had been showing that there was an orientation difference which you could observe after giving the rats an amphetamine injection that stimulated dopamine production. The rats would turn consistently in one direction after this injection. Tomer had been doing this research and had in the back of her mind that this orientation observed in rats was due to dopamine asymmetry, so when she needed to come up with a new research idea she decided that she'd look for attention asymmetry in schizophrenic patients because it brought the two ideas together.

> So that's how I combined that with a… So I thought that must be dopamine and that [the behaviour] must be somehow indexing dopamine asymmetry and I wanted to see asymmetry of Dopamine so I thought 'That's what I'll look for in…' So that was my idea and I'm really – I was really pleased with it because that was the first, my first independent work. (Tomer, 2011)

However, this type of experiment required a whole new research approach. Tomer recalled that her PhD supervisor had once told her that 'if you have a good idea, you should be able to find a way to test it using pencil and paper' (Tomer, 2012). So she quite literally set out looking for a measurement that was much simpler to carry out. This required her to study neuropsychology methods and she spent a month in the library reading up on this field. She was trained in electrophysiology and psychobiology, so she knew very little about this field. One day she came upon the Mesulam Cancellation Test (described below): it was a test that only required a pencil and paper to do and it ended up forming the basis of the research method.

Samples/patients

There was also a readily available patient population at the hospital and this was in large part due to the position of Flor-Henry as a director of admissions.

> And Pierre was extremely helpful because he was the Director of Admissions and he gave an instruction to all the psychiatrists and everybody that when a patient comes in and he's psychotic or she's psychotic not to give them any medication until Dr Tomer sees them. (Tomer, 2011)

Collaborators

There were no collaborators on the original studies that Tomer conducted as a post-doc in Alberta under the supervision of Flor-Henry. However, in later years, after Tomer left Alberta, Flor-Henry collaborated with Scott Purdon. Prior to her work in Alberta, Tomer also collaborated with Mintz and Myslobodosky at Tel Aviv University. These studies, as detailed above, were important inputs to the research cloud.

14.6 Stage 2: Processes

There were several methodologies used in this research cloud, but all of them were used to test hypotheses about attention asymmetries in schizophrenic patients.

In the 1982 study by Tomer, Mintz and Myslobodsky (Mintz et al., 1982), electrophysiological techniques were used to test the hypothesis that neuroleptic treatment suppresses left hemisphere hyperarousal and therefore restores hemispheric dopamine balance. Nine non-medicated and 29 medicated schizophrenic patients were tested and the results compared with 34 normal controls. It was found that medicated patients had enhanced visual evoked potentials over the right hemisphere as a function of dosage, while the opposite effect was seen in drug-free patients. This suggested both that there was asymmetry in schizophrenic patients and that balance between the hemispheres was not restored in medicated patients.

In a follow-up study with the same patient group (Tomer et al., 1982), Tomer and colleagues tested a similar hypothesis about left hemisphere hyperarousal using the lateral eye movement technique, but in this case they more explicitly sought to identify the drug-sensitive component of the LEM. In order to compare the direction of reflective LEMs in drug-free and treated schizophrenic patients, electro-oculograms (EOG) were recorded for each patient in response to a series of different questions. EOGs are a way of measuring the way the eye is moving. It was found that though there were not significant differences between medicated and non-medicated patients in their patterns of asymmetry, there were differences between medicated patients depending on the type of neuroleptic they received. This finding not only suggested that the effects of earlier asymmetry studies, including the one described above, may have been confounded by the effect of neuroleptics, it also suggested that the 're-balancing' hypothesis of the effect of neuroleptics was oversimplified. In other words, neuroleptics were not restoring full balance to the brain, but rather were introducing a new kind of asymmetry.

In 1987, Tomer and colleagues published a study (Tomer et al., 1987) that again looked at the hypothesis that asymmetry of eye movements is associated with the lateralized appearance of neuroleptic-induced parkinsonism or tardive dyskinesia in schizophrenic patients. Again, electrophysiological techniques were used to determine the nature of the asymmetry and correlate this with neuroleptic-induced side effects. They found that lateralized drug-induced side effects were associated with asymmetries, which again was in agreement with previous studies showing neuroleptic medication induced different effects on different sides of the body.

The original target paper was published in 1989. Here, Tomer no longer had access to the electrophysiology machines she needed and so a different research process was used. She focussed on looking at the differences in unmedicated and medicated patients and the effect that neuroleptics could have on asymmetries in the brain, specifically attention asymmetries as indicated by asymmetries in visual search. In the first paper (Tomer & Flor-Henry, 1989b), 29 acutely psychotic patients were included in the study. These patients were tested immediately after hospital admission and before neuroleptic treatment had been administered. They were then retested after a period of treatment with medication.

The test used was a simple attention task called the Mesulam Cancellation Test (Weintraub & Mesulam, 1985). There were two test forms, one consisting of a randomly distributed array of 60 letters and the other a similarly random array of 60 symbols. A form was placed in front of the participant and they were asked to circle all of the instances of a

specific letter or symbol. The results were then analysed to determine whether neuroleptic medication had an effect on attentional asymmetry. They found that though performance on the test did not improve after medication, there was a significant effect of medication on attentional asymmetry: patients made more omissions in the right hemispace when unmedicated, showing support for the left hemisphere dysfunction hypothesis, but the direction of omissions was reversed when patients were medicated and more omissions were made in the left hemispace. Moreover, that this effect appeared after just one single dose of medication.

In a follow-up study, Tomer looked for a similar pattern of asymmetrical dysfunction in schizophrenic patients and the effect of neuroleptic medication using a tactile discrimination task (Tomer, 1989). Here, nine acutely psychotic patients were tested for their ability to discriminate a tactile shape. The patient was asked to determine whether two shapes were the same or different when placed in the left or the right hand. Here, all patients made errors in the first unmedicated testing session and improvement on the second session was not significant. However, the identification of shapes by the right hand improved considerably after medication, whereas the performance of the left hand remained the same or declined after medication. This again shows that neuroleptic medication may improve performance in the left hemisphere.

The final paper in the research cloud was published in 1990 and was a more detailed study than those previously described. This study was designed to examine the hypothesis that treatment with neuroleptic agents contributes to the observed failure of schizophrenic patients to transfer information between the two hemispheres. In comparison to the previous study, which was designed to show that asymmetrical effects could be determined by tactile discrimination, this study was designed specifically to test the transfer of information between the two hemispheres. The methodology was designed so that patients received one of two tactile shapes in either of their hands and then after five seconds of handling it the second shape was presented either to the same hand or to a different hand (RR, LL, RL and LR patterns were used).

Tomer believed that one of the reasons the 1989 paper on attention asymmetries, the first paper in the research conducted at the University of Alberta, was highly cited was due to the extreme care she took with the methodology and the significance and clarity of the findings as a result. Initially she had over 100 patients, but in the end only 30 patients made it into the final analysis because she was so careful about following them to make sure their diagnoses were really schizophrenia and that the medication was monitored carefully and included in the analysis. In particular, never being medicated was incredibly important to the study.

> And the reason that I was so insistent on getting patients who had never had any antipsychotic medication was because I was working with rats before. And I saw that for rats if you give them a single dose of a Haloperidol it changes their Dopamine system irreversibly, irreversibly for…. I mean we didn't keep them alive for years but for a period of several months. (Tomer, 2011)

This care paid off as it meant her findings were very clean and showed a very clear effect of neuroleptics on reversing attention asymmetries.

14.7 Stage 3: Primary outputs

Knowledge

The main output of this research cloud was to show that schizophrenic patients display asymmetries in spatial attention that are reversed by neuroleptic treatment. Both papers published in 1982 show that neuroleptics have an effect on lateralisation as reflected in psychophysiological measures, however the second paper (Tomer et al., 1982) looks specifically at lateralised eye movements and shows that different types of neuroleptics have differential effects on asymmetry. The 1987 paper again showed that electrophysiologically measured asymmetries reflect the drug-induced development of lateralized side effects, such as tardive dyskinesia. Though the main focus of the papers was on the reversals in attention asymmetries due to neuroleptics, there is some extrapolation that can be made, suggesting this asymmetry is a result of dopaminergic imbalances. However, this was not directly explored or proven by the research.

The 1989 paper in *Biological Psychiatry* showed very clearly that attention asymmetry was reversed in schizophrenic patients after treatment with neuroleptics. Prior to treatment, patients showed inattention to the right hemispace, and after treatment the asymmetry of their visual search was reversed, showing inattention to the left side. Moreover, the paper showed that just one dose of neuroleptics was sufficient to reverse attention from one side of the brain to the other.

The findings raised questions about the simplistic hypothesis that left hemisphere hyperarousal characterises schizophrenia. This is because hyperarousal of one hemisphere is accompanied by inattention to the opposite side. Therefore, if the hypothesis that left hemisphere hyperarousal characterises schizophrenia, you would have expected inattention to the right hemispace in unmedicated patients. Instead, the opposite was clearly shown. This is consistent with studies showing left hemisphere dysfunction, but not necessarily left hemisphere *hyper*arousal as inattention is characterised by *hypo*functioning of dopaminergic systems. Tomer and Flor-Henry therefore hypothesise that instead of schizophrenia reflecting a static hyperdopaminergic state, it may instead reflect a failure of dopaminergic regulation. Tomer commented that at the time they wrote the paper, she thought that schizophrenia was perhaps just a dopamine problem where there was too much dopamine in one side of the brain and too little dopamine in the other. She now recognises it's more complex.

> When I started working on it I had this naïve idea that schizophrenia is an illness of too much dopamine. …So I was thinking if what we have is – before they're medicated when they have too much dopamine they're neglecting the right side that means that there is perhaps too much dopamine in one hemisphere and not the other. There is an imbalance. And the medication affects more the hemisphere where there is less dopamine and that's why it produces this reversal of asymmetry. …Since then we've learned that it's – schizophrenia is much more complicated than that. It's a dysregulation so in some areas of the brain there is too much and in some areas of the brain there is too little. So it's probably more complex then that. (Tomer, 2011)

Because the methodology of the paper was so clear, though, the authors were able to make very clear conclusions about what might be happening with regards to attentional asymmetry, and hence, dopaminergic regulation. In other words, they knew that this was a real phenomenon they were observing, just not how it was happening.

In addition to the asymmetry findings, the other contribution to knowledge was a methodological one: how one could test asymmetry using a very simple pencil and paper test. At the time this surprised even the creator of the Mesulam Cancellation Test. He initially didn't think there was anything that would come of Tomer's paper, but he was pleasantly surprised by the results and subsequently asked Tomer to come to Boston to give a talk about it. She was not aware, though, of him going on to use her method in a similar way to her as he studied neurological patients and eye-tracking, not schizophrenia, but Mesulam did cite Tomer's paper in the future as an example of its application in different contexts.

The two papers that followed from this 1989 paper were the only other two outputs from Tomer's time as a post-doc (Tomer, 1989, 1990), and arguably from this research cloud. These papers looked at whether asymmetries in processing of information could be determined by using tactile discrimination tests. Tomer found that there was a failure of the two sides of the brain of medicated schizophrenic patients to integrate tactile information. In this study she also showed that interhemispheric dysfunction studies in schizophrenia are methodologically robust. This was an important finding as serious methodological criticisms had been raised in earlier studies about the conclusions drawn from them.

What is perhaps of most interest in this study, though, is the finding that patients did not perform significantly better on the crossed information processing tasks once medicated. However, they did perform better once medicated on the intrahemispheric processing task where the object was placed in the right hand both times. This is evidence of improvement in left hemispheric processing as was seen in the visual processing task study published the year before. The study also found that interhemispheric impairment is independent of the left hemispheric deficit in dopaminergic systems. Drawing on findings published around the same time, Tomer suggested that treatment with neuroleptics may normalise dopamine-related left hemispheric pathophysiology of schizophrenia, but this treatment did not appear to affect callosal dysfunction, that is, dysfunction in the band of white matter that connects the two hemispheres of the brain. In other words, neuroleptics were helping to treat asymmetry, but they could not help improve the way the brain coordinated information between the two hemispheres. This type of dysfunction represents a development pathology that is perhaps irreversible and would not respond to pharmacological treatment.

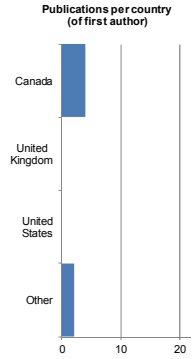
A bibliometric analysis of the papers produced from the research cloud is shown below.

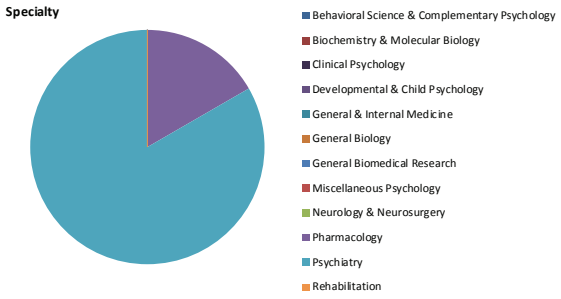
Research cloud:

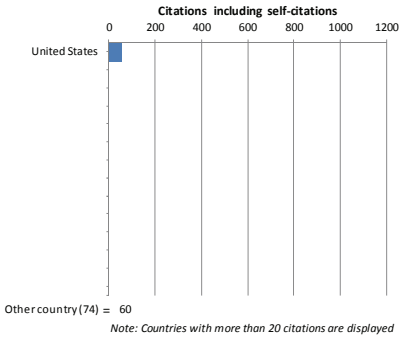
	Citations in:		% of total citations	Research level of cloud papers
WoS Indexed papers: 6	**RCT:**	2	1%	Clinical **1:** 50%
Total citations of papers: 139	**Meta-analyses:**	2	1%	**2:** 33%
of which, self-citations: 2.2%	**Indexed practice guidelines:**	0	0%	**3:** 17%
Mean citations per paper: 23	**Review articles:**	23	17%	Basic **4:** 0%
Distinct cloud citations: 113				
Second-generation cloud citations: 3,915				
Third-generation cloud citations: 91,088				

Most highly cited article: Tomer, R and Flor-Henry, P. 1989. 'Neuroleptics Reverse Attention Asymmetries in Schizophrenic Patients'. Biological Psychiatry 25: 852-860.

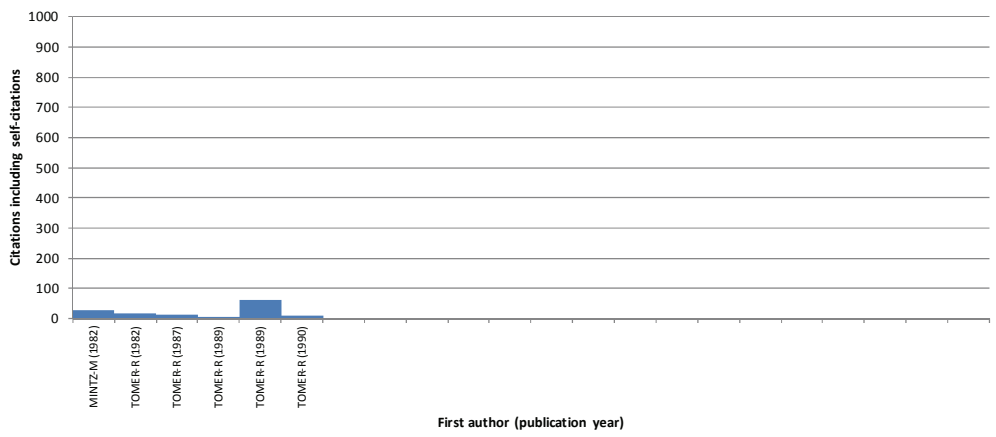
Times cited: 62

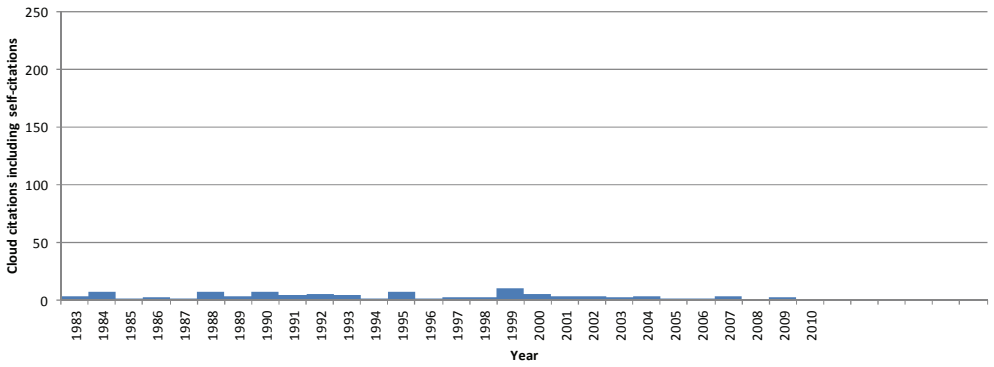






Note: Countries with more than 20 citations are displayed





Targeting future research

Effect on the researchers' careers

Tomer did not go on working in schizophrenia, though she looked at asymmetry in Parkinson's patients and has contributed to work in the area of dopamine asymmetry in the brain. One of the reasons Tomer moved on is that she thought it was too early in the research field to explore the kind of effects she was interested in. In other words, there was still too much to know about the pathophysiology of the disease before getting to a point where one could understand the causes or implications of dopamine asymmetry.

> It was too complicated and I didn't think that at the level that I was interested in which is understanding the basic brain processes that underlie the behaviour, it was too soon…. We needed to look at symptoms not at syndromes. And we needed to look at pathologies where we at least knew what was wrong in the brain. (Tomer, 2011)

So, instead of changing her questions about the role of dopamine asymmetry in the brain, Tomer changed the patient population she was working with.

> So I changed the patients that I was working with, not the questions, the patients. And I decided to work with patients with Parkinson's disease because we know what the pathophysiology of Parkinson is, unlike schizophrenia at the time. (Tomer, 2011)

Therefore, for the rest of her career Tomer has continued to look at individual differences in the behavioural implications of dopamine asymmetry.

> But it's a continuum so I think that looking at psychopathology and looking at healthy individuals is really just looking at different points on the continuum…. So this is the basic question. And the little, you know the little tiny area that I'm looking at is what's the contribution of dopamine asymmetry to these individual differences? Is dopamine asymmetry important to behaviour? Yes it is. How is it important? What is it important for? How does it explain some of the differences in behaviour that we see? (Tomer, 2011)

Flor-Henry has continued to study asymmetries in the brain and in particular the implications of gender in hemispheric asymmetries, as well as right-handedness and left-handedness. These were all ideas he developed in the early 1980s, but has only been able to test in recent years.

Future work – in psychiatry

Tomer did not feel that the research cloud had many practical implications for clinical practice. She felt she was asking basic science questions about dopamine asymmetry that would not have any implications for treatment. Rather, the research was helping to elucidate the way basic biology in the brain was working.

> I don't think that it has very many practical implications for treatment. I mean you don't – the attentional asymmetry that they show is not huge and it's not anything that you'd want to treat. …But theoretically it was very interesting because it opened a whole series of questions as to first of all, is the attention system lateralized? What's the role of dopamine in the modulation of attention? …How come the medication reverses it? What does it do? All sorts of questions. (Tomer, 2011)

Flor-Henry agreed, stating that the findings are 'difficult to translate into clinical practice' (Flor-Henry, 2011). Tomer did try to do a paper looking at negative symptoms versus positive symptoms of schizophrenia and the effects of asymmetry on them, which would help her essentially to understand the severity of the illness and whether this had any

correlations to lateralisation effects. But in order to do this research she would have had to do this with outpatients and that was much more difficult. She ended up collecting the data, but never being able to publish.

Tomer did, though, emphasise that the findings from the research on asymmetries were a significant inspiration for the research conducted over the rest of her career (see, in particular, Maril et al., 2007; Tomer, 2008).

> However, these findings were the inspiration for extensive research about asymmetries of dopamine in the healthy brain (as well as in other pathologies) and I continued to study the role of dopamine in modulating attention and orienting asymmetries in patients. (Tomer, 2012)

In 2000 and 2001 Flor-Henry published a paper with colleagues at the University of Alberta on asymmetrical hand force persistence and olfactory acuity in schizophrenics before and after neuroleptic treatment (Purdon & Flor-Henry, 2000; Purdon et al., 2001). The hand force study used a new technique for measuring hand force persistence, while the olfactory acuity study was novel in that while olfactory identification impairment was documented in schizophrenics, olfactory acuity had been previously neglected in the literature. The olfactory study showed an impairment in left nostril functioning that was again consistent with Tomer's earlier findings of inattention to the hypoaroused hemisphere. After treatment the advantage of the right nostril shifted to an advantage of the left nostril, again replicating Tomer's finding of a shift in asymmetry after neuroleptic treatment.

The hand force persistence study also showed impaired right-hand force persistence in the unmedicated sample and a reversal in this asymmetry after treatment. These findings provide further support for a primary left hemisphere cerebral involvement in schizophrenia and suggest that the paradoxical improvement of motor skill may relate to the substantial number of patients treated with second-generation neuroleptic medications (which were the ones tested in the study), which may have advantages in left hemisphere physiology.

In addition to the work of Flor-Henry and Tomer that arose from the original research cloud, others in the field were advancing knowledge around the subtle pathology of schizophrenia. Janice Stevens and Tim Crow are just two researchers who were all developing ideas alongside Flor-Henry about laterality in relation to epilepsy, which had influences on understanding of similar effects in schizophrenia (see, for example, Stevens, 1978; Crow, 1989, 2009). This work has resulted in a more complex view of brain asymmetry in schizophrenia, including in terms of developmental origins.

14.8 Interface B: Dissemination

Academic

Tomer did make efforts to connect with different research groups studying asymmetry at the time. She went to St. Louis to talk with researchers there and spent time in New York. She attended as many conferences as she could and tried to get many people to read her manuscripts. She was funded to do this travelling.

Flor-Henry also regularly goes to conferences to disseminate his work and felt this was an important way of disseminating findings in the field.

14.9 Stage 4: Secondary outputs

Tomer did not feel like the research had many practical applications and the secondary outputs did not extend beyond informing future research. However, Tomer did consider that the study had made an important impression on the way she approached research and the way she taught her students about working with patients. She realised during the course of the research in this cloud that it was critically important to have a strong understanding of the patient population one was working with before proceeding with any research.

> I don't know, I don't know of any case where a clinician actually changed their practice because of anything that I've told them. I don't think that happened but if it did I'm not aware of it. But I know that I learn a lot from them and I really think that it's important and I think that having spent those years in the hospital and not in a university I'm very happy about that. Because that has really made a fundamental change to my research in the sense that it made me think about things differently…. I tell all my students all the time because this has taught me that what they say in textbooks is one thing and what you see in the Lab is one thing. And what's real life is patients look different and you need to see – if you're interested in psychopathology or if you're interested in neurology. If you're interested in behaviour you need to see the real patients not just learn about them from the books. (Tomer, 2011)

Thus, though Tomer recognised that there was not a great academic output from her research, she felt it was a productive three years because of the wider impacts it had on her approach to the way she conducts her work today.

> And so in that respect… my post-doc with Pierre wasn't very productive in the conventional way, you know if you look at how many papers did you get? In these three years I only got out three papers so that's not a lot, definitely not in today's standards. …I'm very happy that I went to the hospital and that I spent all the time looking at patients and listening to patients and talking to clinicians. And learning – because I feel that I know what I'm talking about and I – and it's changed the way as I said that I think about the patients and I know that you need to think about the pathology in a broader sense. You have to look at the behaviour. (Tomer, 2011)

14.10 Stage 5: Applications

There was no evidence of any applications resulting from the research in this cloud.

14.11 Stage 6: Public engagement

None identified.

14.12 Stage 7: Final outcomes

The final outcomes of this study seem to be limited to knowledge production about the effects of asymmetry on attention in schizophrenic patients and the effects of neuroleptic treatment on this asymmetry. Looking back, it is interesting to note that the questions raised by Tomer and Flor-Henry about the mechanisms behind attentional asymmetry and the effects of neuroleptics on it have not been systematically studied and are still extant.

14.13 Table of payback

Payback category	Impacts from case study
Knowledge Production	• Evidence for attentional asymmetry in the brain. • Methodological innovation in evaluating attentional asymmetry. • Clear results showing reversal of attentional asymmetry after neuroleptic treatment. • Support for Flor-Henry's hypotheses of asymmetry going back to the 1960s.
Research Targeting and Capacity Building	• Contributed to Tomer's research career in dopamine asymmetry. • Importance of appreciating the patient disease.
Informing Policy and Product Development	• None identified.
Health and Health Sector Benefits	• None identified.
Broader Social and Economic Benefits	• None identified.

14.14 Timeline

1963–1968	Flor-Henry works at Maudsley and publishes research on lateralisation in epileptic patients
1970s	Flor-Henry moves to Alberta to work at Alberta Hospital Edmonton
1976	Flor-Henry becomes Clinical Professor in the Department of Psychiatry at the University of Alberta
1977	Flor-Henry becomes the Clinical Director of Adult Psychiatry at Alberta Hospital Edmonton
1979–1986	Tomer does her PhD work in Israel at Tel Aviv University
1987	Tomer comes to Alberta for her post-doc
1989	Tomer publishes her findings on lateralisation
1990	Tomer moves to Florida for a second post-doc

1995 Tomer returns to Israel for an academic post at Haifa University

14.15 References

Bracha, H.S. (1989). Is there a right hemi-hyper-dopaminergic psychosis? *Schizophrenia Research,* 2**,** 317–324.

Crow, T.J. (2009). A theory of the origin of cerebral asymmetry: epigenetic variation superimposed on a fixed right-shift. *Laterality: Asymmetries of Body, Brain and Cognition,* 15**,** 289–303.

Crow, T.J., Ball, J., Bloom, S.R., et al. (1989). Schizophrenia as an anomaly of development of cerebral asymmetry: A postmortem study and a proposal concerning the genetic basis of the disease. *Archives Of General Psychiatry,* 46(12)**,** 1145–1150.

Flor-Henry, P. (1976). Lateralized temporal-limb dysfunction and psychopathology. *Annals of the New York Academy of Sciences,* 280**,** 777–795.

Flor-Henry, P. (1969). Psychosis and temporal lobe epilepsy: a controlled investigation. *Epilepsia,* 10**,** 363–395.

Flor-Henry, P. (2011). *RE: Personal interview with Pierre Flor-Henry.* Communication with Pollitt, A., & Diepeveen, S.

Gruzelier, J.H. (1999). Functional neuropsychophysiological asymmetry in schizophrenia. *Schizophrenia Bulletin,* 25**,** 91–120.

Gruzelier, J.H., & Doig, A. (1996). The Factorial Structure of Schizotypy. *Schizophrenia Bulletin,* 22**,** 621–634.

Gur, R.C. & Gur, R.E. (1974). Handedness, sex, and eyedness as moderating variables in the relation between hypnotic susceptibility and functional brain asymmetry. *Journal of Abnormal Psychology,* 83**,** 635–643.

Gur, R.E. & Gur, R.C. (1975). Defense mechanisms, psychosomatic symptomatology, and conjugate lateral eye movements. *Journal of Consulting and Clinical Psychology,* 43**,** 416–420.

Kinsbourne, M. (1970). The cerebral basis of lateral asymmetries in attention. *Acta Psychologica,* 33, 193–201.

Maril, S., Hermesh, H., Gross-Isseroff, R., & Tomer, R. (2007). Spatial attention and neural asymmetry in obsessive-compulsive disorder. *Psychiatry Research,* 153**,** 189–193.

Mintz, M., Tomer, R., & Myslobodsky, M.S. (1982). Neuroleptic-induced lateral asymmetry of visual evoked potentials in schizophrenia. *Biological Psychiatry,* 17, 815–828.

Posner, M.I., Early, T.S., Reiman, E., Pardo, P.J., Dhawan, M. (1988). Asymmetries in hemispheric control of attention in schizophrenia. *Archives Of General Psychiatry,* 45**,** 814–821.

Purdon, S.E., & Flor-Henry, P. (2000). Asymmetrical olfactory acuity and neuroleptic treatment in schizophrenia. *Schizophrenia research,* 44**,** 221–232.

Purdon, S.E., Flor-Henry, P., Waldie, B.D., Woodward, N.D., & Reed, B.D. (2000). Asymmetrical olfactory acuity and neuroleptic treatment in schizophrenia. *Schizophrenia Research,* 41**,** 162–163.

Purdon, S.E., Woodward, N.D., & Flor-Henry, P. (2001). Asymmetrical hand force persistence and neuroleptic treatment in schizophrenia. *Journal of the International Neuropsychological Society,* 7**,** 606–614.

Reynolds, G.P. (1983). Increased concentrations and lateral asymmetry of amygdala dopamine in schizophrenia. *Nature,* 305**,** 527–529.

Stevens, J. (1978). Disturbances of ocular movements and blinking in schizophrenia. *Journal of Neurology, Neurosurgery, and Psychiatry,* 41**,** 1024–1030.

Tomer, R. (1989). Asymmetrical effects of neuroleptics on psychotic patients' performance of a tactile discrimination task. *Journal of Nervous and Mental Disease,* 177, 699–700.

Tomer, R. (1990). Neuroleptic effects on interhemispheric and intrahemispheric performance of tactile discrimination tasks by schizophrenic patients. *Psychiatry Research,* 32, 289–296.

Tomer, R. (2008). Attentional bias as trait: Correlations with novelty seeking. *Neuropsychologia,* 46**,** 2064–2070.

Tomer, R. (2011). *RE: Personal interview with Rachel Tomer.* Communication with Morgan Jones, M., & Pollitt, A.

Tomer, R. (2012). *RE: Personal email communication with R Tomer.* Communication with Morgan Jones, M.

Tomer, R., & Flor-Henry, P. (1989). Neuroleptics Reverse Attention Asymmetries in Schizophrenic Patients. *Biological Psychiatry*, 25, 852–860.

Tomer, R., Mintz, M., Kempler, S., & Sigal, M. (1987). Lateralized neuroleptic-induced side effects are associated with asymmetric visual evoked potentials. *Psychiatry Research,* 22, 311–318.

Tomer, R., Mintz, M., Levi, A., & Myslobodsky, M.S. (1979). Reactive gaze laterality in schizophrenic patients. *Biological Psychology,* 9**,** 115–127.

Tomer, R., Mintz, M., & Myslobodsky, M.S. (1982). Left hemisphere hyperactivity in schizophrenia: abnormality inherent to psychosis or neuroleptic side-effects? *Psychopharmacology*, 77, 168–170.

Weintraub, S., & Mesulam, M. (1985). Mental state assessment of young and elderly adults in behavioural neurology. In Mesulam, M. (ed.), *Principles of Behavioural Neurology*, Philadelphia: F.A. Davis.

CHAPTER 15 Specific and non-specific effects of educational intervention

This case study is based on the research that produced the paper:

Smith, J.V., & Birchwood, M.J. (1987). Specific and non-specific effects of educational intervention with families living with a schizophrenic relative. *British Journal of Psychiatry*, 150, 645–652.

Information was gathered from interviews with Jo Smith, Max Birchwood, Fiona MacMillan and Grainne Fadden, as well as from desk-based research.

15.1 Summary

Jo Smith and Max Birchwood conducted research in the 1980s looking at the role of education in psychosocial family interventions and the effect on family knowledge retention and improved patient outcomes. They did their work at a time when there was a growing interest in the role of the family in schizophrenia outcomes, and in particular the effect of families that might have high 'expressed emotions' on patient outcomes. However, unlike many others in the field, Smith and Birchwood queried the utility of the idea of expressed emotion and instead focussed on the ways family coping could be improved through education. Their studies were designed to examine the efficacy of family education alone by observing both specific (knowledge acquisition) and non-specific (stress reduction and attitude change) effects, both immediately following the educational intervention and after a six-month follow-up. They found that knowledge provision in itself was significant, whereas the manner in which it was provided was less so. Non-specific effects were less likely to be maintained at six months follow-up, but relatives did report a reduced sense of burden. Their studies contributed to the evidence base for the effectiveness of family interventions, which are recommended by NICE guidelines and form a part of many mental health services in the UK. The research also brought Smith and Birchwood together and cemented their working relationship, which was subsequently crucial to catalysing a broader coalition of support and advocacy for fundamental policy developments for mental health services in the UK, in particular in the establishment of early intervention services throughout England.

15.2 Introduction

15.2.1 Scientific background

At the time of this study many researchers were turning their attention to the role of the family in the development of schizophrenic illness, and in particular whether family-based interventions could play a role in reducing relapse rates and improving the nature of the illness in the individual. In particular, the concept of expressed emotion (EE) was gaining ground.[29] Expressed emotion was based on the premise that families who were highly emotionally involved, and expressing high criticism or rejection of their relatives with schizophrenia, were a factor in triggering relapse for that relative. In other words, it was thought that high expressed emotion families had a negative impact on patient outcomes. Therefore, many began studying the effect of family intervention in the progression of schizophrenia. In addition, many of these family interventions studies focussed on classifying families by their EE status, either as 'high' or 'low' EE. Birchwood and Smith, though, were concerned that with this growing area of research there was a lack of awareness and responsiveness to families' specific needs, particularly in respect of providing basic information about the illness. They were therefore interested in the needs of families and were especially concerned about the problems associated with the EE concept – particularly its potential pejorative implications (blaming families for illness) and concerns that 'low EE' families' needs would be neglected if 'high EE' was used as the only selection criterion for family intervention.

Against this broader backdrop, the research cloud discussed in this case study looked at the role of family education in family interventions, noting that in studies to date this had been unclear and could perhaps provide a way of bridging the needs of families and the individual, regardless of EE state. The research cloud also was concerned with developing interventions to respond to the needs of families, regardless of their EE status, in a very individualised manner which best served families and individuals.

15.2.2 Researcher backgrounds

Max Birchwood was finishing his PhD and was a newly appointed senior clinical psychologist when **Jo Smith** joined him as a trainee psychologist at the University of Birmingham in 1982. At the same time, Smith began a Master's degree in psychology at the University of Birmingham with Birchwood as her adviser, and the two began working together in the area of needs and interventions for families with schizophrenia. In addition to being based at the University of Birmingham, both Smith and Birchwood worked as clinical researchers with patients at All Saints Hospital in North Birmingham.

After completing her Master's degree, Smith went on to undertake her PhD part time in psychology at the University of Birmingham, and while she was also employed full time by the West Birmingham and Bromsgrove/Redditch Health Authority. The research published in the target paper was based in part on her Master's research, but also contributed to her PhD research. She was awarded her PhD through paper publications, including the target paper. Thus, Smith's PhD research was based upon her clinical work with patients at All Saints and built upon her Master's thesis research and the PhD research of Birchwood.

[29] This work is discussed in further detail in another Mental Health Retrosight case study.

Birchwood was the senior clinical researcher working on the study and the intellectual lead for the research. At the time of the paper publication, Birchwood was a senior academic working at the University of Birmingham and a clinician working at All Saints Hospital in Birmingham. Birchwood established the Early Intervention Service in Birmingham in the 1990s.

Fiona MacMillan was a clinician from Northwick Park, and was the lead clinical researcher in an influential early intervention study conducted in the early 1980s, often referred to as the Northwick Park study. She came to work in the Academic Unit at All Saints Hospital, Birmingham as an Honorary Consultant in February 1984 and stayed until August 1994. While at All Saints, MacMillan met Birchwood and the two began discussing their ideas and experiences with early intervention patients. From 1990 to the time she left, Macmillan was integrally involved in the implementation of family education and early intervention services in the Archer Unit at All Saints and worked closely with Birchwood and Smith during this time. She was not an author on the majority of the papers in the research cloud, but was involved in clinical work with Smith and Birchwood, and with later policy advocacy for early intervention services.

Grainne Fadden worked with Ian Falloon on one of the first early intervention services in the UK in Buckinghamshire. Both she and Falloon developed the behavioural family therapy model, which was an evidence-based approach to helping families of those with severe mental health difficulties to develop the understanding and skills to cope with the difficulties they faced.

15.3 Defining the research cloud

This case study covers research carried out in the West Midlands in the UK in the 1980s. It was part of a wider effort to develop a service model for needs-based family interventions, in particular investigating the effects of psychosocial education for families living with schizophrenic relatives.

The papers that define the research cloud include:

1. Smith, J.V., & Birchwood, M.J. (1990). Relatives and patients as partners in the management of schizophrenia: the development of a service model. *British Journal of Psychiatry*, 156, 654–660.[30]
2. Smith, J.V., Birchwood, M.J., & Cochrane, R. (1992). Specific and non-specific effects of educational intervention for families living with schizophrenia. A comparison of three methods. *British Journal of Psychiatry*, 160, 806–814.
3. Smith, J.V., & Birchwood, M.J. (1987). Specific and non-specific effects of educational intervention with families living with a schizophrenic relative. *British Journal of Psychiatry*, 150, 645–652.
4. Birchwood, M.J., & Smith, J.V. (1987) Expressed emotion and first episodes of schizophrenia. *British Journal of Psychiatry*, 152, 859–860.

[30] Birchwood described this paper as the core of the research cloud.

5. Birchwood, M.J., Smith, J.V., MacMillan, F., et al. (1989). Predicting relapse in schizophrenia: the development and implementation of an early signs monitoring system using patients and families as observers. *Psychological Medicine*, 19, 649–656.
6. Birchwood, M.J., Smith, J.V., Cochrane, R., Wetton, S., & Copestake, S. (1990). The Social Functioning Scale: the development and validation of a new scale of social adjustment for use in family intervention programmes with schizophrenic patients. *British Journal of Psychiatry*, 157, 853–859.
7. Sidley, G., Smith, J.V., & Howells, K. (1991). Is it ever too late to learn? Information provision to relatives of long-term schizophrenia sufferers. *Behavioural Psychotherapy*, 19: 305–320.
8. Smith, J.V., Birchwood, M.J., Cochrane, R., & George, S. (1993). The needs of high and low expressed emotion families: a normative approach. *Social Psychiatry and Psychiatric Epidemiology*, 28(1), 11–16.
9. Smith, J.V., Birchwood, M.J., & Haddrell, A. (1992). Informing people with schizophrenia about their illness: the effect of residual symptoms. *Journal of Mental Health*, 1, 61–70.

15.4 Stage 0: Opportunity identification/research needs assessment

Inspiration

The inspiration for this research lay in the development of the field of family intervention studies, the socio-political climate for mental health services, and the desire of the researchers to build upon and expand the conceptual work of Birchwood (first summarised in his PhD) and the practical work of Smith during her Master's degree. Each of these will be discussed in turn.

First, at the time of this study, researchers were beginning to focus on the role of families in the development of schizophrenia and related symptoms in individuals. There was increasing experimental evidence that psychosocial treatments, in particular those that involved working with families, could have a positive effect on patient outcomes. There were six main studies that had reported at that time (Falloon et al., 1982; Goldstein et al., 1978; Kottgen et al., 1984; Leff et al., 1982; Leff et al., 1985; Tarrier et al., 1988), all of which shared certain elements in common (Schooler et al., 1989), including enlistment of the family in a positive clinical alliance; education about schizophrenia; teaching of both communication and problem-solving skills; and encouragement for families to expand the social networks of themselves and the patient. To a certain extent, the researchers built on each other's work in different ways.

> That was the state of where things were at, because we were all doing that work. But it was fairly new and developing at that time, in terms of working with families. (Smith, 2011)

There was a particular interest in the role of family in affecting the course of the illness, especially around the work of Leff and colleagues on the theory of 'expressed emotion' (EE), that is, the ways in which families act out their emotions in their relationships with each other and the patient. They argued that a highly emotional state of families of people

with schizophrenia could contribute to, or even trigger, a relapse (Leff & Vaughn, 1985). While this approach to identifying families and trying to intervene caught on with many researchers, it was also problematic in that 'a lot of families took great exception to that… the way it was interpreted' (Birchwood, 2011).

Therefore, as a part of building a family intervention approach that reflected this thinking, Smith and Birchwood focussed on the educational component of family intervention. They were inspired to look at this because they felt it was a component that had been largely ignored as an aspect of family intervention studies up until that point. Thus, instead of focussing on how the intervention worked and was structured, they looked at how different aspects of the intervention itself, such as education, affected families and patients. Smith joined Birchwood a few years after he completed his PhD and Birchwood encouraged her to develop the educational component for her Master's research. With Birchwood's guidance, Smith wrote the *Understanding Schizophrenia* series of four booklets, which was to become the core of the educational intervention studies undertaken in this research cloud. Therefore, together the two of them built on ideas outlined in Birchwood's PhD thesis (Birchwood, 1983) and practically applied in Smith's Master's thesis, to develop a family educational intervention that rejected classifying families based on their EE state, and instead focussed on delivering a needs-based, individualised intervention that allowed for the education of families and individuals together.

Feasibility

The research cloud drew primarily on the expertise of Birchwood and Smith and this was a key aspect of the feasibility of the study. Birchwood was the more experienced researcher at the time the research was conducted, having worked with a population of patients in the Birmingham area. He was acutely aware of the challenges and difficulties facing them and their families. Smith had gained experience and practical knowledge during her Master's work, particularly in the piloting of the *Understanding Schizophrenia* series. Later on, Macmillan was to play a role in developing and implementing the family intervention service model for families and young people experiencing a first episode at the Archer Unit of All Saints Hospital. Though not directly involved in the research cloud, her expertise in building the unit was crucial to ensuring that the research cloud could happen, as it helped to establish a core patient population Smith and Birchwood could draw on, as well as an informal network of support.

In addition, to the knowledge of the researchers, the resources they were able to draw on contributed to making the research cloud feasible. In particular, the booklets that Smith wrote and piloted during her Master's research formed the basis of the educational intervention that was used with the families. More importantly, though, it was a foundation upon which she and Birchwood applied for more funding to develop interventions to respond to the needs of families. This was the real heart of the research cloud and what distinguished Birchwood and Smith's work from others.

Finally, the research was conducted while both Smith and Birchwood were working as clinical researchers at All Saints Hospital, Birmingham, and were also affiliated with the University of Birmingham. Smith described the academic research unit at All Saints at the time as providing a stimulating research environment in which to work, and importantly one that enabled her to do her clinical work and research work side-by-side. It was also

clear how the work might benefit the population of patients she was working with and how the clinical work and research could be brought together.

> It was a real hotbed of people, who were clinicians who were interested in research, or had joint academic roles. And that was partly why I was able to do my PhD because of the academic unit in All Saints there was a culture which saw clinicians doing research as being acceptable well more than acceptable was actually encouraged. In other settings there's often this dichotomy – you're either a clinician or you're a researcher. (Smith, 2011)

Moreover, the group of clinical psychologists at All Saints were all interested in psychosis. Looking back, one individual who worked there commented that Birchwood and Smith were 'fantastically unusual' in their interest in psychosis (Macmillan, 2011). At the time people were moving towards understanding schizophrenia as a biological disorder, not a psychological one. It therefore wasn't accepted that psychologists could work with families and patients with psychosis, particularly on an inpatient basis.

> We were laughed out of court then by a large number of people, at our brazen cheek as psychologists coming to suggest that in a biological disorder there might be some psychological influences. (Smith, 2011)

Potential value

The researchers had a broader concern with the community care movement and trying to develop a community-based care model. It was argued that with the closing of mental health hospitals and the subsequent movement of many patients back into communities, more mental health service resources would need to be redirected at clinicians and support for families. This raised a host of questions around appropriate models, feasibility, resourcing, understanding, and the integration of different service models. The research Birchwood and Smith were conducting could add value to future plans in this area.

In addition, the focus of Birchwood's PhD (Birchwood, 1983) work was also on the needs of families, and in particular understanding whether families could be a factor in triggering relapse. However, he came at the problem from a different perspective, arguing that EE is not a fixed or static state 'like height or weight' (Birchwood, 2011), but instead something that was changeable and part of the adaptation process a family goes through. From this followed the argument that families have their own needs in terms of learning how to deal with and understand the challenges they will face with their schizophrenic relative. In other words, families needed support in coping with their relative and a large part of this was educating them about the disease.

Finally, undercurrents of a shift from a biological to a psychological understanding were important for the family intervention work more broadly because they emphasised the role that psychosocial interventions could have as therapeutic interventions to improve outcomes for individuals.

15.5 Stage 1: Inputs to research

Money, researcher time, lab/office space and consumables

Smith was doing a PhD at the time the development of the family intervention work was occurring and most of the papers in the research cloud were being published. Though her

PhD funding was covered by the government, she was fully employed on a Locally Organised Research Scheme (LORS) grant supported by the West Birmingham Health Authority. The research grant was to do clinical psychology work at All Saints Hospital. There was also a grant from the Mental Health Foundation to support the work. The combined funds supported Smith's full-time salary, the cost of a full-time research assistant and administrative support. The work that the educational research was based on was part of Smith's Master's degree, and so did not require any specific funding. However, the work she conducted during her Master's degree allowed them to secure the family intervention grants and was subsequently written up as a formal paper as part of her clinical PhD work.

At a certain point during the study, Birchwood received funding from a local health promotion grant to develop some of the educational materials into a video, which also contributed to the research published in the 1993 paper (Smith et al., 1993).

Time was not a real issue for Smith and Birchwood while they did the research. They were based in an academic unit at All Saints Hospital and so they had time and space to do the research. In addition, because Smith was doing her PhD part time and was a full-time clinician with All Saints Hospital, the research and the clinical work fitted together very well. There also didn't seem to be significant issues with timing and research funding, although both Smith and Birchwood mentioned they were always searching for new funding sources.

Knowledge, expertise and techniques

As discussed above, both Birchwood and Smith had developed research knowledge and clinical expertise going back to the beginning of the 1980s and building in particular on the work of Birchwood's PhD thesis and Smith's piloting of educational booklets for her Master's thesis.

The approach of understanding and identifying the needs of families and developing interventions around them was a feature of Smith and Birchwood's research, as was their focus on psychosocial education as a feature of family interventions. In particular, they were one of the first groups to specifically focus on this aspect of family interventions. They built on this paper in subsequent years, developing different approaches to education in family interventions and testing them against each other.

In addition, because they were in a position of both running a service and doing research on it, this afforded them the ability to be rigorous while continuing to learn about what worked and what did nott work.

> It was developmental because we were trying to respond to the needs that were arising…. But because we were evaluating it, it was done under research conditions. (Smith, 2011)

Samples/patients

Patients and families were identified either because they came into All Saints Hospital in Birmingham, or came into contact with the Community Mental Health teams in West Birmingham who dealt with outpatients. The catchment area from which the patient population was drawn was in the heart of Birmingham and included a lot of patients who were in and out of psychiatric care – a 'revolving door', so to speak. This contributed a ready patient population for the intervention research.

Collaborators

There were no collaborators on the psycho-educational family intervention study; the work was mainly carried out by Smith and Birchwood. Macmillan was a later collaborator in the development and implementation of a needs-based family intervention service at the Archer Unit at All Saints Hospital, particularly for young people in the first episode. This service eventually became the Birmingham Early Intervention Service.

15.6 Stage 2: Processes

Two main studies by Smith and Birchwood examined the effect of education in family interventions by observing the specific (knowledge gains) and non-specific (reduction in anxiety, fear, stress, distress and patient disturbance levels) effects of education in family-based psychosocial interventions.

In the first study, published in 1987, half the families received educational booklets by post (the postal condition), while the other half received the same information, but for this set of families (the group condition) the delivery of the information was done in a group setting. In the group condition, families received the information through oral presentations with audiovisual aids. In addition, family participation and discussion was encouraged. Both groups received homework exercises designed to maximise information retention and encourage application of knowledge to their own situations. All family members were assessed before, immediately following, and six months after the intervention. The assessment instrument was a six-part, paper-based questionnaire that assessed knowledge acquisition, beliefs about schizophrenia and treatment, levels of worry and 'fear', levels of patient disturbance, levels of stress, and extent of family distress.

The second study was published in 1993 and was a follow-up designed to replicate and further develop the service model of educational family interventions presented in the 1987 paper. It compared the effects of different mechanisms of delivering the educational information, together with different modes of giving homework assignments. There were three different educational delivery mechanisms tested:

- One-third of families received only written materials.
- One-third received written materials together with a video presentation of the information.
- One-third received written information as well as group-based education.

The video component was introduced to see whether this could overcome the limitations of written information provision. The new homework modes were designed to encourage relatives to apply the information to their own circumstances. Half of the families across all three information groups were required to complete homework exercises, while the other half was only provided with information in one of the three forms. As before, families were assessed before, immediately after and six months after the intervention for their relative levels of: knowledge acquisition; beliefs and expectations; stress; distress; patient disturbance; and social function of the patient.

Other papers included in the research cloud drew on these two studies of educational interventions. One that slightly differed in its process was the study described in Smith et

al. (1992). This paper drew on the same set of educational materials the other two studies did (the booklets developed by Smith during her Masters work), but instead of delivering material to families, it was delivered directly to the schizophrenic patient. The patients included those with residual symptoms of schizophrenia, and those with no symptoms. The effect of this education was monitored for its impact on variables including information assimilation, insight, and attitude to medication and compliance. Significant knowledge gains were made in all groups, although individuals in the residual symptom group seemed to absorb less information about their symptoms.

15.7 Stage 3: Primary outputs

Knowledge

The findings of the research cloud demonstrated clear benefits in knowledge acquisition from the provision of education. However, the nature of these benefits, and the relationship to the conditions under which the education was delivered, varied.

The 1987 study found that knowledge acquisition by both groups was significantly improved from baseline and was maintained at follow-up after the intervention. Relatives in the group therapy cohort gained significantly more knowledge than relatives in the cohort who only received the information by post. The difference in knowledge acquisition for both cohorts remained after six months. However, the only non-knowledge based improvement that the researchers observed in both groups was a reduced feeling of burden after the education, and at six months follow-up. There were no differences in either group between baseline and follow-up that indicated a change in the belief in effectiveness of treatment. Fear scores were significantly reduced at six-month follow-up for families in the group that received information by mail, however a similar reduction in fear was not seen in families who received the information in the group setting. Stress effects within the family were significantly reduced from baseline across both groups after the educational intervention, however these reductions were not seen after six months. Levels of family-reported patient disturbance were not reduced post-education, nor at follow-up.

All of these results suggest that education in itself did significantly impact knowledge acquisition across both groups, but the differences in delivery of information did not lead to significantly different impact on non-specific effects in either group. In fact, at six-month follow-up only the specific effects of education, the knowledge acquisition, remained; all non-specific effects had effectively disappeared (with the exception of reduction in fear in the postal group). Though effects on knowledge acquisition and information retention were more significant for group relatives, the finding that knowledge acquisition effects were still retained in the postal group was encouraging and suggests that education itself is an important component of a family intervention. As the authors point out,

> In fact, the value of education would not seem to lie solely in knowledge acquisition, per se…. What may be important is the subjective effect of being or feeling more knowledgeable rather than the degree of improvement in knowledge itself. (Smith & Birchwood, 1987, 650).

Smith also noted that although there was not a huge difference between the two groups, this was not disappointing because it was the information itself that was the breakthrough of the intervention.

> …For families it was like a breath of fresh air because it covered things that often weren't covered…. They weren't getting any family support or information so, at last, they had some information. (Smith, 2011)

While the 1987 paper established that education was an important part of family intervention, the study published in 1993 looked at the efficacy of three different methods of delivering educational interventions to families living with a schizophrenic relative. Efficacy was studied in relation to the improvements seen in understanding of the illness and promotion of patient and family well-being. The study was slightly hampered in that 32 patients (out of a total study cohort of 134) did not return the six-month follow-up questionnaire, and therefore the data were analysed in terms of 'immediate benefit' and 'maintenance of gains' at six months.

In this study, relatives receiving the educational intervention in the group setting acquired more information than relatives in the postal or video group; however the differences in knowledge gains across groups were not observed at six-month follow-up. Across all groups, knowledge gains were significant immediately following the intervention, with 73 percent of relatives possessing relatively 'sophisticated' knowledge about schizophrenia (compared with only 17 percent possessing this level of knowledge prior to the intervention). Moreover, these improvements in knowledge remained at six months. Significant improvements were also seen in beliefs about the family's role in treatment and reductions in stress were reported. There were also significant benefits in social competence of the patient, which were maintained after six months. However these were not always seen immediately after the intervention. Interestingly, the improvements in social functioning were not correlated with knowledge acquisition by the families, even though knowledge acquisition was correlated with improvements in other non-specific effects.

When the educational intervention was given directly to individuals with schizophrenia, similarly positive outcomes about knowledge acquisition were seen across both individuals with residual symptoms of schizophrenia and those with no symptoms. Knowledge gains were most significant for those individuals with no symptoms, particularly knowledge about the symptoms of schizophrenia itself. However, medication compliance did not increase for either group. In addition, though the improvements in knowledge gain were important and showed that education can be beneficial to individuals with schizophrenia, there was a concern that the sample was not random and those participating were 'self-selected', as they had higher baseline knowledge scores than those who did not participate and thus may have been more open to knowledge gains.

Overall, all the studies in the research cloud reinforced the idea of 'information content as the important medium of change' (Smith et al., 1993, 812). The authors believed they had validated the idea that it was important to develop interventions that begin from the needs of families and patients, and that could be based on education to address those needs. Moreover, in the views of the authors, the studies provided important evidence that supported the idea that the family wasn't to blame in contributing to the progression of schizophrenia. In other words, the work of Birchwood and Smith began to lay a

foundation for a rejection of the EE concept and gave further support to their arguments for a needs-based approach to intervention more broadly. When asked why he thought the paper was highly cited, Birchwood reflected this thinking:

> I think [the reason we were highly cited] was that [the rejection of EE] was particularly important. And also probably because the intervention was actually quite simple. And it's something that a lot of services could easily do because the family interventions that were developing at the time were quite complicated. And we were interested in the extent to which you could know what are the benefits of a simple relatively un-intrusive relatively benign kind of intervention where you're not suggesting anyone is to blame for anything. (Birchwood, 2011)

As we have seen, during the 1980s Birchwood and Smith conducted several research studies, all of which centred around how to develop a needs-based intervention for families and relatives of patients with schizophrenia. Educational interventions like the ones described in the papers in the research cloud sat at the core of their model. In a paper published in 1990, they summarise their approach and philosophy to family intervention and the elements they thought a service model should have (Smith & Birchwood, 1990). Birchwood referred to the paper as a 'call to arms' for family intervention models, which they though should include the following elements:

- Fostering an ethos of 'informed partnership' where families, relatives and patients feel like they are all actively engaged in identifying each other's needs and planning interventions accordingly, and together.
- Education and training of 'front-line' service professionals so they are better able to identify and articulate the needs of families and provide appropriate information about schizophrenia.
- Development of interventions that are flexible and tailored to the needs of the individual and his family.

The family service model they outline was developed throughout the 1980s and was established in 1984 at All Saints Hospital in Birmingham. It is described in further detail below. Overall, one can see that education and the interactions with the families and relatives were central to effective service delivery. Thus, the work published in the original target paper (which led us into this cloud) is crucial to understanding how this information was delivered and the effects that it had on families. This ultimately led Birchwood and Smith to conclude that their family service model was effective as a psychosocial intervention.

A bibliometric analysis of the papers produced from the research cloud is shown below.

Research cloud:

		Citations in:		% of total citations	Research level of cloud papers	
WoS Indexed papers:	6	**RCT:**	43	9%	Clinical **1:**	83%
Total citations of papers:	455	**Meta-analyses:**	4	1%	**2:**	0%
of which, self-citations:	2.6%	**Indexed practice guidelines:**	1	0%	**3:**	0%
Mean citations per paper:	76	**Review articles:**	49	11%	Basic **4:**	0%
Distinct cloud citations:	429					
Second-generation cloud citations:	8,603					
Third-generation cloud citations:	66,932					

Most highly cited article: Birchwood M, Smith J, Cochrane R, Wetton S and Copestake S (1990) The Social Functioning Scale: The Development and Validation of a New Scale of Social Adjustment For Use In Family Intervention Programmes with Schizophrenic Patients. British Journal of Psychiatry, 157: 853

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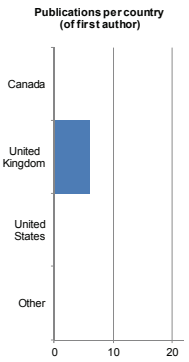
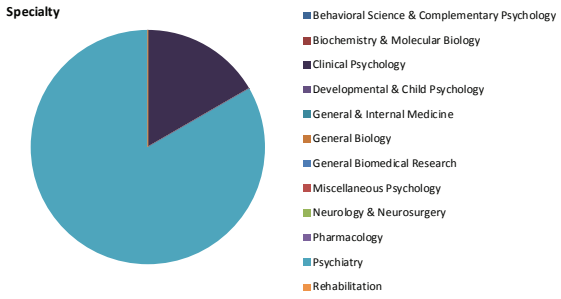
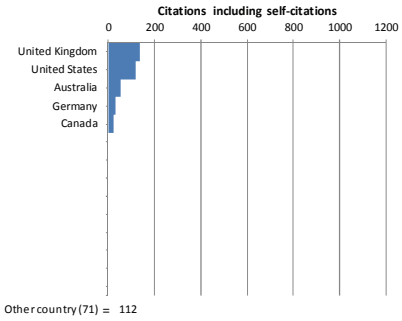
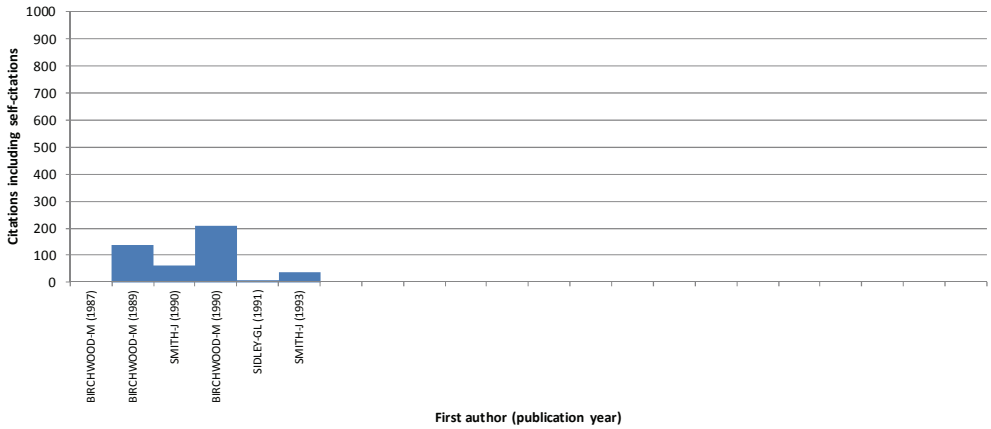


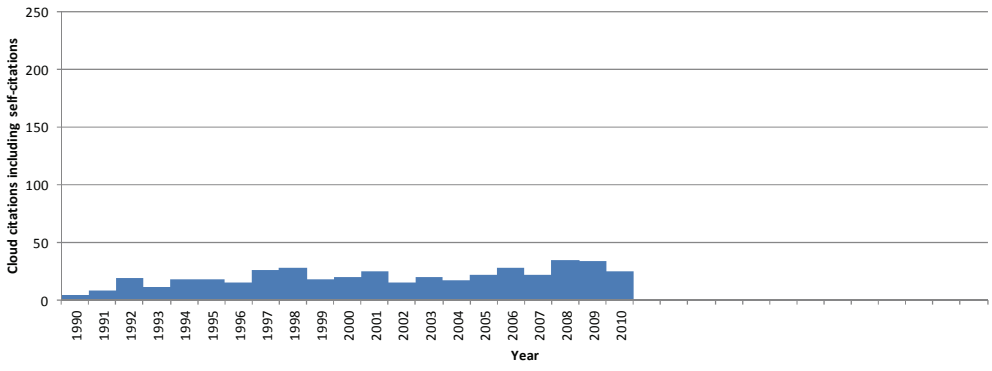




Other country (71) = 112

Note: Countries with more than 20 citations are displayed





Targeting future research

Effect on the researchers' careers

This research was important to both researchers' subsequent careers. It established them as leaders in the development of family interventions, and in particular in the development of a needs-based approach to family intervention.

Smith left All Saints in 1988, while this study was ongoing, for a clinical role in a health authority with no research unit. However, she continued to be involved in research because she enjoyed it, knew its value and because she and Birchwood had just received a grant from the Department of Health to research early signs of relapse and how family interventions might help avert relapse. Throughout the rest of her career Smith has continued to be an 'academic' clinician. She commented:

> It's interesting the influence that has had on me because I have spent the last few years straddling the research/clinical gap and here they probably see me as an academic clinician. So I tend to lead on service evaluation, and those kinds of things, and always have. I also constantly alert my colleagues to latest research evidence to keep them informed. A lot of the work I have done for which I have an international reputation has been in translating research into practice. (Smith, 2011)

Smith also seemed to be influenced not only in how she approached her clinical work, but also in her appreciation of how to bring research to clinicians who can subsequently use it to help patients. This is a theme that strongly emerges from her subsequent work and activities.

Birchwood was already on an upward career path at the time of the research, but it certainly contributed to establishing his reputation in the field. He went on to develop the first early intervention service for the UK in Birmingham and published work with a subsequent PhD student on the fluidity of expressed emotion. He was a co-author with Smith on the early signs work and, with Smith and other colleagues including MacMillan, went on to be a leading national figure in the campaign to introduce early intervention, and mental health services more broadly, to the national policy agenda.

Future work

After the educational intervention research projects, both Smith and Birchwood went on to develop family intervention services, albeit in different areas of the country as Smith had left Birmingham in 1988. Smith was still working on her PhD during this time though, so maintained her research links with Birchwood and Birmingham and the two continued to work together and collaborate on research and other initiatives throughout their careers.

While the work on family education was ongoing, Smith and Birchwood also began researching the early signs of relapse and the role family interventions could play in averting relapse. They published a paper with Macmillan in 1989 entitled 'Predicting relapse in schizophrenia: the development and implementation of an early signs monitoring system using patients and families as observers' (Birchwood et al., 1989). Though clearly tied to the original research cloud in respect of the role of education in family intervention, this piece of research in essence was a separate but complementary cloud.

Many subsequent papers were published in this area, leading Smith to become an 'internationally recognised expert' in the field (Smith, 2011). The 1989 paper is still cited today and 'set an international gold standard scale' for predictors of relapse (Smith, 2011). It also led to the publication of a manual that was written for predicting relapse and is used in mental health services today (Smith, 2001). In light of this work, the original *Understanding Schizophrenia* booklet series was rewritten by Birchwood as the *Understanding Psychosis* series, which had more of an emphasis on early psychosis and early intervention. These were then rewritten again as the *Back on Your Feet* booklet, which is used widely in the NHS today and can clearly be traced directly back to the original work done by Smith in the early 1980s. Another researcher working in the field commented that she thought their early signs work was the most important contribution Smith and Birchwood made to the field, more so than their contributions to the evidence base for family intervention. She saw the latter as important, but not necessarily central to their contributions to the field.

> I think the main influence was probably around relapse prevention and early psychosis. I mean the educational bit in itself we know isn't enough to change skills and change behaviour in the family so the kind of comprehensive models that looked at – that whole area of skilling up people such as the Falloon model and the Leff model are those that have the greatest impact. So it's broader than the educational bit. So if I was to say in relation to the family bit what was the biggest influence of Max and Jo's work it was probably around relapse prevention. (Fadden, 2011)

Even before the early signs work and subsequent booklets, Birchwood and Smith's research was already having an influence on other areas of the field and knowledge production. MacMillan, one of the main clinicians involved in the Northwick Park study of first episode schizophrenia, has said she used Birchwood's work in many different ways throughout that study (Macmillan, 2011). In fact, Birchwood and MacMillan went on to establish a family intervention service – which would later host the Birmingham Early Intervention Service (see below) – run out the Archer Centre at All Saints Hospital and which incorporated many components of psycho-educational and needs-based approaches to family intervention.

The Archer Centre was opened in late 1990 as a Specialist Rehabilitation Centre providing intervention programmes for people suffering from long-term mental health illnesses and symptoms of schizophrenia and manic depression. It included a recovery programme for patients recovering from acute psychosis, individual sessions in learning how to control symptoms of psychosis, family education, support and intervention programmes and sessions, maintenance and monitoring services with a dedicated medical and nursing staff to provide long-term drug therapies, individual and group sessions in daily living skills and social networking, and employment and preparation training. The Centre also had a teaching, research and evaluation component, the latter supported by a grant from the West Midlands Regional Health Authority. Patients were referred to the Archer Centre from Northern Birmingham Community Mental Health Teams and then accepted into the centre after an assessment by a multidisciplinary health team.

In addition to Birchwood's work at the Archer Centre, Smith set up an innovative team in Bromsgrove and Redditch Health Authority that involved integrating social services staff into a core team of health and social care workers to offer a range of health and social care

support, including addressing housing, welfare benefits and the employment needs of individuals with schizophrenia and their families. Though the team was based in a rehabilitation service, it was a novel joint care approach and drew on Smith's experience from family intervention research. It also involved an evaluation component, which meant that Smith was able to conduct both research and clinical work on the team's effectiveness.

> We established a very different team called the rehabilitation resource team. We had lots of international interest as this was one of the first genuine joint health and social care teams. It was an initiative where we successfully bid for joint funding to employ both health and social care staff within the same team. (Smith, 2011)

In the mid-1990s, Birchwood, Smith and MacMillan also began to become more involved in developing and researching early intervention services, particularly for young people. They were influenced by the work of Patrick McGorry in Australia and others in the UK and internationally who all came together both at key conferences and serendipitous meetings during the early 1990s.[31] All three were heavily involved in national campaigns to establish early intervention as a core component of developing mental health services (see below). However, MacMillan left Birmingham in 1994, prior to the early intervention service being established.

Birchwood also continued to research expressed emotion and in 2005 he published a paper with another of his PhD students, Paul Patterson, on the fluidity of EE (Patterson et al., 2005). Birchwood considered this paper to arise directly from the educational intervention work (Birchwood, 2011).

Along with other colleagues they worked with in the Archer Centre, in particular Professor Sadhidharan another clinician (Macmillan, 2012), Smith and Birchwood also contributed to making the West Midlands a leading place for innovative mental health services. Another colleague in the field, who was a proponent of a different type of family intervention model – behavioural family therapy rather than a needs-based approach, but still a believer in the core concept of engaging families – commented:

> At the time the North Birmingham Mental Health Trust was very innovative in terms of developing functional mental health services; so whole concepts of home treatment, crisis, care, assertive outreach. So having functionalised teams really developed from the Birmingham Service – they were developed here and then taken on nationally. (Fadden, 2011)

15.8 Interface B: Dissemination

Academic dissemination

Smith and Birchwood both recognised the importance of dissemination and they did it naturally as a part of their research projects. At first they did this in traditional ways through papers and conference publications, but at an early stage they also began to disseminate their work using more novel methods.

> And it's actually my belief that a lot of the influence that the work had was actually as much to do with the presentations and some of the training that we did nationally and

[31] See the early intervention backwards tracing case study in this report for further details.

> internationally as much as the papers themselves. Because the word of mouth is very important, adding to the perceived impact of it. (Birchwood, 2011)

In a sense, the *Understanding Schizophrenia* booklet series that formed the core of the educational intervention was one way of disseminating research directly to patients and families. This booklet series was turned into a video for the second study of this research cloud (Birchwood et al., 1992), but was also used as the basis of a BBC documentary called 'Zero Options'. This documentary in part arose from the research Birchwood and Smith were doing, since they involved the university's TV and film unit in the filming of the research video and the video unit had links with the BBC. They were also interviewed for their early signs of relapse work on the BBC programme 'Science Now'.

> So that was quite interesting because, I think psychological research had a bit of public appeal as well, because I remember we did quite a number of things around which were all quite novel, including getting involved with media. (Smith, 2011)

Smith points out that funding bodies did not always have specific requirements regarding research dissemination, but they always did it anyway. In fact, dissemination ended up being a core part of the work she did running the national early intervention programme (described in more detail below) and as part of the advocacy campaign to get the programme established. Smith realised that an important part of getting early intervention services adopted into policy was in providing a solid evidence base.

> We were selling a concept where there wasn't necessarily a robust evidence base when we first started selling it. And that was one of the criticisms, where people were saying, 'Well how come it's in policy and how come you've got services around something that [doesn't have an evidence base]?' It did have an evidence base [though] but not a robust one. (Smith, 2011)

In order to make sure that evidence was provided, they did several things to try and collect data from researchers around the country (described in more detail below). In order to disseminate this information during, and after, the national programme was established, they set up dedicated dissemination networks with regional leads.

> People would alert us to research. And we would, in turn, alert the field and get it out, we could get it out to regional leads, who would get it out to the field within the same day. (Smith, 2011)

In addition to this, Smith generally recognised the importance of communicating research in ways that made it easily translatable into practical, clinical knowledge. In discussing her work to date, it is clear that for Smith, the ideas about marrying practical application of knowledge and research still run strong.

> It was very much in terms of practical applications of research and how we use it to change practice. Again even with the information booklets for families, [the question] is how you take a [piece of] knowledge about diagnosis or an understanding of something and how you then make it accessible and understandable to users and families. (Smith, 2011)

Smith also recognised the importance and value of ensuring clinical staff were involved in the communication and dissemination of research findings, not just researchers. This was because it helped to ensure that research was grounded in practice.

> And I was quite keen to represent the clinical field, to make sure that some conference symposia were clinically focussed, with clinical staff attending. So I would purposely put in clinically based symposia, where we would look at the practical application of research evidence into clinical practice. (Smith, 2011)

Wider engagement

In addition to academic and clinical dissemination of their work, Smith and Birchwood also sought to engage with the wider public. They were founding members of the Initiative to Reduce the Impact of Schizophrenia (IRIS) and they also worked with Rethink, an advocacy group whose mission is to help everyone affected by mental illness to have a better life. IRIS is described in more detail below, but both organisations were advocacy groups that aimed to mobilise the mental health community from the top down and from the bottom up. Smith described the first stages of the partnerships between IRIS and Rethink in the following way:

> So the partnership with Rethink was started that fostered relationships which we harnessed and worked with throughout our work in the family service. We would feed families into National Schizophrenia Fellowship. We also would use some of their resources like their caring and coping manual which is a very, very good publication. They would sample some of our families for some of their work when collecting evidence of certain things they were looking at whether it be about medication and side effects or whatever. …Then subsequently we worked with them as allies when trying to lobby for the needs of first episode families. The difficulty you have when you try to lobby government is if you're working in the orthodoxy, it can be difficult sometimes to challenge existing practice because sometimes you can be told to shut up because you're in the orthodoxy, whereas Rethink were able to openly voice the same concerns without prejudice as they were not in the orthodoxy. (Smith, 2011)

15.9 Stage 4: Secondary outputs

Secondary outputs from the research cloud are those that arose out of the knowledge produced and have the potential to be adopted more widely in clinical practice – and there were many from Birchwood and Smith's work. One secondary output from the research cloud is its citation in clinical guidelines. The 1987 paper is cited in NICE clinical guidelines, but is not used as a citation for evidence of the efficacy of the study in psycho-education. However, a 1987 paper by Birchwood and Smith on EE and first-episode psychosis is cited in the 2001 DH Mental Health Implementation Guide as further reading evidence about first episodes.

Additional secondary outputs arose from Smith and Birchwood's collective further work in areas related to family psycho-educational intervention and their subsequent impact on national policy. This is most pronounced in influencing the publication of the national mental health strategy in 1999 in the UK. This arose from Birchwood and Smith's involvement in the mid-1990s with a future DH policymaker, Antony Sheehan. Sheehan had been regional mental health lead in the West Midlands, as well as a manager at All Saints Hospital, so he knew Birchwood and Smith very well. He was involved in some of the early IRIS campaign work and was exposed to their thinking about early intervention services in particular. According to Smith, Sheehan and another regional NHS figure, John Mahoney, moved jobs in the mid-1990s to work for the Department of Health for

England as joint national mental health leads and from there had a major influence on mental health strategy development in 1999.

> So they went to the Department of Health and then influenced the new mental health strategy [the national service framework, 1999]. That was where early intervention first appeared in 1999, and was the first mention of it. So that was directly from Antony and John's influence. …Then suddenly Max, myself, Fiona, David all found ourselves on a Department of Health task force where we were working with civil servants and politicians in terms of focus around early intervention… and the rest is history really. (Smith, 2011)

Alongside this, Birchwood, Smith and MacMillan formed and became centrally involved in a campaign called the Initiative to Reduce the Impact of Schizophrenia (IRIS), which aimed to develop and support the adoption of early intervention services into national mental health services. IRIS focusses on developing and supporting the implementation of early intervention programmes within England's National Health Service. It was initiated by a small group of clinicians and academics in the Birmingham area, including Smith, Birchwood and Macmillan, but was primarily motivated and driven by the passion of a local general practitioner, Dr David Shiers, whose daughter Mary had schizophrenia. The relationships that they were then able to build on through the IRIS group were a direct result of those established in the early educational intervention work.

> The relationships that were established with Rethink (formerly the National Schizophrenia Fellowship), initially in the West Midlands, was around that specific – non-specific effects stuff, because I actually went out to quite a number of National Schizophrenia Fellowship groups in Birmingham and Solihull. We formed a partnership with them. (Smith, 2011)

It could be said, then, that they catalysed advocacy efforts by bringing together a critical mass of researchers in the West Midlands who then were able to influence policy across the country. Shiers and Smith in particular were central to this movement, eventually leading the National Early Intervention Development Programme at the Department of Health for England. Interestingly, their efforts and those of IRIS more generally have subsequently been studied as an example of social movement.

Another important component of the early intervention policy campaign was the attempt to establish and build a robust evidence base for policymaking. In the early stages of the IRIS campaign, Smith spent significant time trying to get people to share and disseminate their information. She focussed her efforts particularly in trying to get access to information early (that is, prior to publication) in order to inform policy development and make the case for early intervention services at a national level. Therefore, their approach to the policy campaign was three-fold: getting access information, getting competitors to work together; and developing a cost-benefit argument drawing on the expertise of Martin Knapp and others at the London School of Economics (see, for example, McCrone & Knapp, 2007).

> So what we tried to do was look at how we could get access to information, without trying to compromise people's publication prospects. [We wanted to get] information out to the field or to policymakers or use information in advance of publication. And that required asking researchers to perhaps be less precious about that. And [we were] trying to appeal,

> too, for the greater good rather than their personal narcissism about having paper published. (Smith, 2011)
>
> And initially, when we were trying to produce early intervention research, we were trying to get essentially, what were research competitors, to think about combining efforts and data sets. So we were actually working against both personality and the culture. And again, we tried to use, values and principles to try and get people to rise above their personal narcissism. And we had some real coups where people who had been known to be very precious about sharing their research ideas, or working with others, where we successfully managed to engage them. (Smith, 2011)

15.10 Stage 5: Applications

The broader work of Smith and Birchwood, which started with the psycho-educational research cloud, contributed to some changes in clinical practice.

First, the Family Centre for Advice, Resources and Education was established at All Saints Hospital and was informed in part by the research in the cloud and the broader philosophy of a needs-based approach to family intervention of Birchwood and Smith. The centre had the remit of developing and evaluating interventions for individuals diagnosed with schizophrenia and their families. There was a focus on integrating and delivering these interventions in the context of mainstream psychiatric treatment services. In other words, the challenges inherent in standard psychiatric services were a key factor in shaping the types of family service interventions that could be implemented and the judgement of success given external limitations. The model had six key components (as described in Smith & Birchwood, 1990):

1. Active engagement of families at multiple entry points
2. Needs-led intervention
3. Ethos of 'informed partnership'
4. Integration with community agencies and psychiatric services
5. Training of 'front-line' professionals
6. Quality assurance.

Secondly, the results of the research cloud have been used in practice throughout the West Midlands and likely further afield. The *Back on Your Feet* manual is used in mental health clinical services and this traces directly back to the original booklets written by Smith. More broadly, the fundamental idea about providing families with information and educating them about schizophrenia is something that is at the core of many services today, but both pointed out that it was unusual in the 1980s. Smith reflected on the reaction of some clinicians to her booklets:

> That was an interesting process in terms of people's reactions to some of the things that were in those booklets. Like I remember a Doctor commenting… 'You can't tell people about side effects you'll worry them, they'll come off it.' [and] I was saying 'But how are people going to make informed choices about medication? Isn't one of the outcomes going to be that if you give people medication and they get side effects that aren't anticipated that actually they'll stop the medication anyway?' So [the clinicians were] censoring information in an incredible way in terms of seeing people like as if they were

> blank slates on which you could just add certain selective bits of information. (Smith, 2011)

Birchwood also pointed out that even though 'it now looks very basic and very simple' the idea of the research wasn't back then and, in fact, 'it was regarded as quite a strange thing to do' (Birchwood, 2011). In addition, Smith went on to establish the Worcestershire Early Intervention Service in January 2003. This was originally based in Worcester city serving the County of Worcestershire and was the sixth early intervention service established in the UK. Smith told us it has subsequently been recognised nationally and internationally as an exemplary EI service (Smith, 2012).

Thirdly, though the papers from the original cloud may not be specifically cited in clinical guidelines uptake in practice throughout the West Midlands and, subsequently internationally, what does seem to have happened is that family intervention and education is now a key guideline in the development of early intervention services and information.

> Family intervention is seen as integral. It was one of the key guidelines. Family education and family support were seen as a key element of family intervention. It was also included in the early intervention policy implementation guide. It is also included in core EI training curricula so the model does not vary around the country. (Smith, 2011)

> Here in the West Midlands EI service, staff have been trained in behavioural family therapy from the Meriden programme.[32] In my EI service we have three family intervention trainers who train staff from the whole of the county not just EI. Family intervention is seen as a core skill. It's in your core induction training to work in the service. (Smith, 2011)

In addition, family intervention models are a part of many mental health services and are a key component of the current NICE guidelines on schizophrenia. 'They (Birchwood and Smith) started the wave' (Macmillan, 2011). In eyes of one of their former colleagues, the more one knows about different family intervention approaches, 'the more the Max collaborative approach (between patients and families) wins out' (Macmillan, 2011).

Moreover, the impact of subsequent research by Birchwood and Smith in the area of developing early intervention services is apparent. A 2003 paper by Birchwood is published in the NICE guidelines (Birchwood, 2003) about the pathways to emotional dysfunction in early episode psychosis. Birchwood is also cited in the NICE guidelines for his randomised clinical trial of cognitive behavioural therapy (CBT). Currently, Birchwood is a lead PI for a national clinical trial evaluation of early intervention services, called SUPER EDEN, which is the follow-up to an initial evaluation of the delivery and effectiveness of early intervention services entitled EDEN.[33] Finally, a reviewer of this case study pointed out that their family intervention service in Cardiff ('STEP') was heavily influenced by Birchwood and Smith's work, as detailed in a review by Hughes in an article in the *Journal of Mental Health* (Hughes, 1996).

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[32] See, for example, Fadden & Heelis (2011). The Meriden West Midlands Family Programme: lessons learned over ten years. *Journal of Mental Health*, 20(1), 79–88.

[33] For a full description, see the backwards-tracing case study on early intervention.

15.11 Stage 6: Public engagement

None identified.

15.12 Stage 7: Final outcomes

The most significant impact from this research seems to be in the researchers' advocacy in getting mental health services higher up the national policy agenda in the UK. Specifically, Birchwood and Smith were central to getting early intervention services established in the UK and embedded in health services across the country. Though the research in the cloud only contributed to this, the role of Smith and Birchwood as advocates and leaders in the field was clearly critical. In addition, the work described in this research cloud brought Smith and Birchwood together and firmly established their working relationship and reputation in the field. This relationship, as we have seen, was critical for later policy developments in mental health and early intervention services.

Health economic data from NICE clinical guidelines state that providing family intervention costs £2,680 per person. The reduction in the rates of relapse in people with schizophrenia during treatment with family intervention in addition to standard care resulted in cost savings equalling £5,314 per person. Thus, family intervention resulted in an overall net saving of £2,634 per person with schizophrenia. (NICE, 2011). Considering, then, that Smith and Birchwood's research contributed to the body of evidence supporting family intervention, we can say that the research cloud led to economic savings, as well as improved patient outcomes. Though the current NICE guidelines did not find strong efficacy or economic data supporting early intervention services, they recognise the potential for them to contribute to improved patient outcomes and recommend early intervention services are offered to all people with a first episode or first presentation of psychosis.

Their research also has contributed to the growing body of work pointing to the importance of family intervention in addressing psychosis and improving family outcomes. Moreover, it has provided evidence for the importance of giving information and education to families, something that may seem obvious today, but was not when the research was published.

15.13 Table of payback

Payback category	Impacts from case study
Knowledge Production	• Evidence for specific and non-specific effects of education as part of family interventions. • Family intervention can have an impact on patient outcomes. • Contributed to the development of a service model for families that was implemented in Birmingham and, in some form, in other services in the West Midlands. • Early signs of relapse.

	• Evidence against the expressed emotion concept.
Research Targeting and Capacity Building	• Smith gained her PhD on the basis of the research. • Subsequent PhD students of Birchwood's helped to continue the research, particularly Paul Patterson. • Smith continued to play a role as an evidence broker in her local trust, encouraging clinicians and nurses to keep up to date with the latest research. • Both Smith and Birchwood went on to study the early signs of relapse and the role of families in preventing relapse. MacMillan contributed to this research as well.
Informing Policy and Product Development	• Through their local advocacy in the West Midlands, they came into a position where they were able to influence national policy for mental health, particularly for early intervention services. • The concept of family intervention is fully ingrained in mental health policy guidance. The needs-based model of Birchwood and Smith may not be used everywhere, but it is certainly a component and one approach of many being used.
Health and Health Sector Benefits	• Patients and families benefit from family intervention, improved social skills for patients and other non-specific effects. Health benefits are less clear, but wider benefits for the health system seem to be evident.
Broader Social and Economic Benefits	• Health economic work published in the NICE guidelines estimates that family intervention resulted in a cost savings of £2,634 per person with schizophrenia. • Social benefits for families receiving needs-based interventions. • Social benefits for families receiving early intervention services. • Public benefits in improved understanding of schizophrenia from public outreach and 'social movement' aspects of early intervention campaign.

15.14 Timeline

1980	Birchwood completes his PhD
1982	Smith begins her Master's; she writes and pilots *Understanding Schizophrenia* booklets
1984	Smith completes her MSC thesis
1984	Smith begins her PhD thesis focussing on the needs of families; Birchwood and Smith receive funding from Locally Organised Research Scheme (LORS) and is employed by West Birmingham Health Authority to examine the educational intervention and develop the family service model

1987	Smith publishes the original paper on specific and non-specific effects of educational interventions; MacMillan joins All Saints team.
1988	Smith leaves to go to work for Bromsgrove and Redditch Health Authority; Birchwood and Smith receive grant from the DH to look at early signs of relapse, Smith continues to work on this research and her PhD with Birchwood
1989	Early signs monitoring scale published
1990	Smith and Birchwood publish 'call to arms' paper on a needs-based family intervention service model
1992	Smith and Birchwood publish final paper of the educational research cloud
1994	MacMillan leaves Birmingham
1995	IRIS is founded and campaigning work for early intervention services, and mental health services more broadly begins
1999	Mental Health Strategy for England published, Birchwood and Smith papers cited
2002	National Early Intervention Programme is approved; NIMHE creates national programme, launched in 2004
2004	NIMHE creates the National Early Intervention Development Programme; Smith appointed Joint National Early Intervention Programme lead in a part time job share with Dr. David Shiers
2004	Birchwood leads EDEN project

15.15 References

Birchwood, M. (2011). *RE: Telephone interview with Max Birchwood.* Communication with Morgan Jones, M.

Birchwood, M. (2003). Pathways to emotional dysfunction in first-episode psychosis. *British Journal of Psychiatry,* 182**,** 373–375.

Birchwood, M. (1983). *Family Coping Behaviour and the Course of Schizophrenia.* PhD, University of Birmingham.

Birchwood, M.J., & Smith, J.V. (1987) Expressed emotion and first episodes of schizophrenia. *British Journal of Psychiatry*, 152, 859–860.

Birchwood, M.J., Smith, J.V., Cochrane, R., Wetton, S., & Copestake, S. (1990). The Social Functioning Scale: the development and validation of a new scale of social adjustment for use in family intervention programmes with schizophrenic patients. *British Journal of Psychiatry*, 157, 853–859.

Birchwood, M.J., Smith, J.V., MacMillan, F., et al. (1989). Predicting relapse in schizophrenia: the development and implementation of an early signs monitoring system using patients and families as observers. *Psychological Medicine*, 19, 649–656.

Fadden, G. (2011). *RE: Telephone interview with Grainne Fadden.* Communication with Morgan Jones, M.

Falloon, I., Boyd, J., Mcgill, C., Williamson, M., Razani, J., Moss, H., & Gilderman, A. (1982). Family management in the prevention of exacerbations of schizophrenia. *New England Journal of Medicine,* 306(24), 1437–1440.

Goldstein, M., Rodnick, E., Evans, J., May, P., & Steinberg, M. (1978). Drug and family therapy in the aftercare of acute schizophrenics. *Archives Of General Psychiatry,* 35, 1169–1177.

Hughes, I. (1996). Developing a family intervention service for serious mental illness: clinical observations and experiences. *Journal of Mental Health,* 5**,** 145–160.

Kottgen, C., Sonnichsen, I., Mollenhauer, K., & Jurth, R. (1984). Group therapy with the families of schizophrenic patients: results of the Hamburg Camberwell-family interview study III. *International Journal of Family Psychiatry,* 5(1), 83–94.

Leff, J., Kuipers, L., Berkowitz, R., & Sturgeon, D. (1985). A controlled trial of social intervention in the families of schizophrenic patients: two year follow-up. *British Journal of Psychiatry,* 146, 594–600.

Leff, J., Kuipers, L., Berkowitz, R., Eberlein-Vries, R., & Sturgeon, D. (1982). A controlled trial of social intervention in the families of schizophrenic patients. *British Journal of Psychiatry,* 141, 121–134.

Leff, J. & Vaughn, C. (1985). *Expressed Emotion in Families. Its Significance for Mental Illness.* New York: Guilford.

Macmillan, F. (2012). *RE: Email communication* Communication with Morgan Jones, M.

Macmillan, F. (2011). *RE: Telephone interview with Fiona Macmillan.* Communication with Morgan Jones, M., & Guthrie, S.

McCrone, P., & Knapp, M. (2007). Economic evaluation of early intervention services. *British Journal of Psychiatry,* 191**,** S19–S22.

Patterson, P., Birchwood, M., & Cochrane, R. (2005). Expressed emotion as an adaptation to loss. *British Journal of Psychiatry,* 187**,** S59–S64.

Schooler, N.R., Keith, S.J., Severe, J.B., & Matthews, S. (1989). Acute treatment response and short term outcome in schizophrenia: first results of the NIMH treatment strategies in schizophrenia study. Treatment Strategies in Schizophrenia Collaborative Study Group. *Psychopharmacology Bulletin*, 25(3), 331–335.

Sidley, G., Smith, J.V., & Howells, K. (1991). Is it ever too late to learn? Information provision to relatives of long-term schizophrenia sufferers. *Behavioural Psychotherapy*, 19: 305–320.

Smith, J.V. (2012). *RE: Email communication.* Communication with Morgan Jones, M.

Smith, J.V. (2011). *RE: Personal interview with Jo Smith.* Communication with Morgan Jones, M., & Guthrie, S.

Smith, J.V. (2001). Early signs self management training manual for individuals with psychosis. Worcester, UK: Worcestershire Community & Mental Health NHS Trust.

Smith, J.V., & Birchwood, M.J. (1990). Relatives and patients as partners in the management of schizophrenia: the development of a service model. *British Journal of Psychiatry*, 156, 654–660.

Smith, J.V., & Birchwood, M.J. (1987). Specific and non-specific effects of educational intervention with families living with a schizophrenic relative. *British Journal of Psychiatry*, 150, 645–652.

Smith, J.V., Birchwood, M.J., & Cochrane, R. (1992). Specific and non-specific effects of educational intervention for families living with schizophrenia. A comparison of three methods. *British Journal of Psychiatry*, 160, 806–814.

Smith, J.V., Birchwood, M.J., Cochrane, R., & George, S. (1993). The needs of high and low expressed emotion families: a normative approach. *Social Psychiatry and Psychiatric Epidemiology*, 28(1), 11–16.

Smith, J.V., Birchwood, M.J., & Haddrell, A. (1992). Informing people with schizophrenia about their illness: the effect of residual symptoms. *Journal of Mental Health*, 1, 61–70.

Tarrier, N., Barrowclough, C., Vaughn, C., Bamrah, J.S., Porceddu, K., Watts, S., & Freeman, H. (1988). The community management of schizophrenia. A controlled trial of a behavioural intervention with families to reduce relapse. *British Journal of Psychiatry,* 153, 532–542.

CHAPTER 16 Psychiatric morbidity of a long stay hospital population with chronic schizophrenia and implications for future community care

This case study is based on the research that produced the following initially selected paper:

Curson, D.A., Patel, M., Liddle, P.F., & Barnes, T.R.E. (1988). Psychiatric morbidity of a long stay hospital population with chronic schizophrenia and implications for future community care. *British Medical Journal*, 297(6652), 819–822.

Information was gathered from interviews with David Curson and Thomas Barnes, as well as from desk-based research.

16.1 Summary

This case study focusses on work conducted in the late 1980s and early 1990s to characterise the relationship between depression and negative symptoms in schizophrenia in a long-stay hospital population. The research team was brought together primarily through personal connections, and the main research question emerged from the experience of the team as clinicians working with patients with established schizophrenia. In describing the incidence and nature of depression in this patient population, the research added to the growing body of evidence suggesting that depressive symptoms are a core part of schizophrenia, rather than a side effect of medication or a reaction following a psychotic episode. This work was cited in the DSM-IV Sourcebook, and as part of an accumulation of evidence is likely to have helped shape thinking about the way comorbid depression in schizophrenia is managed. In the context of widespread hospital closures and an increasing emphasis on community care, the team also demonstrated the level of psychiatric morbidity in a long-stay population, highlighting the need for appropriate, comprehensive, community-based support to be provided. Follow-on work from the team continued to look at negative symptoms, the effects of institutionalism, social behaviour, and the subjective experience of depression in schizophrenia.

16.2 Introduction

16.2.1 Scientific background

The case study research focused on gaining a better understanding of depressive symptoms in schizophrenia, but was also very relevant in highlighting the needs of people with chronic schizophrenia at a time when the way that care was provided was changing dramatically.

It had long been recognised that depressive symptoms were prevalent in people with schizophrenia (e.g. Bleuler, 1950), most commonly in the acute phase of the disorder (Knights & Hirsch, 1981). However, a number of different explanations had been proposed to explain the relationship between schizophrenia and depression.

In the 1970s and early 1980s, one strongly held view was that depressive features in schizophrenia occurred as a result of antipsychotic medication, either directly (e.g. de Alarcon & Carney, 1969; Floru et al., 1975) or as a component of well-documented parkinsonian side-effects (e.g. Van Putten & May, 1978). Others proposed the concept of 'post-psychotic depression' (e.g. McGlashan & Carpenter, 1976), suggesting that depression occurs only immediately following a psychotic episode, as the person recovers from it.

Furthermore, there was no clear distinction between depression and some of the negative symptoms common in schizophrenia, such as lack of energy and social withdrawal.

The psychiatry field more generally was characterised at the time by a strong political pressure to discharge people from mental hospitals and instead introduce a system of community care. The programme of mental hospital closures that began in the 1960s (see Ministry of Health, 1962) had gathered pace, but there had been little systematic assessment of the needs of chronic patients as they returned to the community.

> There were major questions about whether community care was adequately funded and resourced. Were the services there to support these people moving into the community from the long-stay hospitals? Was there adequate, suitable accommodation? There was a chronic lack, and there always has been, of suitable community care facilities for people with psychotic illness. (TB)

Although the 1975 white paper 'Better services for the mentally ill' emphasised the need for comprehensive local services to be in place before hospitals could close, it was published at a time of recession and the level of expenditure required proved unfeasible. A Social Services Select Committee report in 1985 highlighted the lack of investment in community-care provisions:

> A decent community-based service for mentally ill or mentally handicapped people cannot be provided at the same overall cost as present services. The proposition that community care should be cost neutral is untenable…. Any fool can close a long-stay hospital: it takes more time and trouble to do it properly and compassionately. (House of Commons Social Services Committee, 1985).

Around the time that the case study research was published, an attempt at addressing this funding issue was made by the Griffiths report on community care (Griffiths, 1988) and a follow-up white paper 'Caring for people' (Department of Health, 1989). These paved the way for grants for local authorities to purchase services from the private sector, changes which came into effect through the NHS and Community Care Act 1990.

16.2.2 Researchers' backgrounds

After qualifying in medicine in 1970 and as a psychiatrist in 1976, **David Curson** took up a Senior Registrar position at Guy's Hospital in London. In 1978, Guy's and the Maudsley were trying to set up an exchange programme (as the Maudsley did not have enough patients for its clinical trainees). Curson was approached and hoped to go to the Maudsley's Social Psychiatry Research Unit to work on a research MD, but in the meantime was offered a consultant psychiatrist post at St Andrew's Hospital in Northampton. He chose to go into clinical practice over academia, but compromised by returning to Guy's one day a week as an honorary lecturer and spending that time doing research unpaid. Curson describes his interest as being in 'madness', and at an early stage in his career he noted that many schizophrenia symptoms resembled those of organic psychoses (i.e. psychosis as a result of another condition with a known biological substrate), suggesting that an organic cause and brain dysfunction may underlie schizophrenia.

Thomas Barnes began his training in psychiatry at Guy's, before becoming a Senior Wellcome Research Fellow at the University of Cambridge Clinical School, returning to London to work as a Lecturer at St. George's Medical School and subsequently appointed as a Senior Lecturer at Charing Cross and Westminster Medical School. Throughout his career he has had an interest in rational prescribing in psychiatry, and in particular in schizophrenia. His earliest work was in tardive dyskinesia, a side effect of antipsychotic medication. He then described the subjective and objective features of another antipsychotic side effect, akathisia (a condition characterised by 'inner restlessness' and a constant urge to be moving), and developed the Barnes Akathisia Rating Scale.

Peter Liddle completed his PhD in physics before switching to medicine and qualifying as a psychiatrist. He worked at Oxford University on delineating sub-syndromes of schizophrenia based on the statistical clustering of symptoms. This work drew the attention of Barnes and led to Liddle moving to Charing Cross as a lecturer.

Steven Hirsch was Professor of Psychiatry and head of department at Charing Cross and Westminster Medical School/Imperial College, London, between 1975 and 2002. He carried out the original MRC fluphenazine trial, subsequently followed-up by Curson and Barnes.

Meena Patel was a psychiatric registrar at Horton Hospital at the time of the research.

16.3 Defining the research cloud

The central focus of the case study research was characterizing the relationship between depression and schizophrenia in a long-stay hospital population.

The publications from the research cloud are as follows:

1. Curson, D.A., Patel, M., Liddle, P.F., & Barnes, T.R.E. (1988). Psychiatric morbidity of a long stay hospital population with chronic schizophrenia and implications for future community care. *British Medical Journal*, 297(6652), 819–822.

2. Barnes, T.R.E., Curson, D.A., Liddle, P.F., & Patel, M. (1989). The nature and prevalence of depression in chronic schizophrenic in-patients. *British Journal of Psychiatry*, 154, 486–491.
3. Hirsch, S.R., Jolley, A.G., Barnes, T.R.E., Liddle, P.F., Curson, D.A., Patel, A., et al. (1989). Dysphoric and depressive symptoms in chronic schizophrenia. *Schizophrenia Research*, 2(3), 259–264.
4. Barnes, T.R.E., Liddle, P.F., Curson, D.A., & Patel, M. (1989). Negative symptoms, tardive-dyskinesia and depression in chronic-schizophrenia. *British Journal of Psychiatry*, 155(7), 99–103.
5. Hirsch, S.R., Jolley, A.G., & Barnes, T.R.E. (1990). Are depressive symptoms part of the schizophrenic syndrome? In DeLisi, L.E. (ed.), *Depression in Schizophrenia*, Washington DC: American Psychiatric Press.
6. Liddle, P.F., Barnes, T.R.E., Curson, D.A., & Patel, M. (1993). Depression and the experience of psychological deficits in schizophrenia. *Acta Psychiatrica Scandinavica*, 88(4), 243–247.
7. Barnes, T.R.E., & McPhillips, M.A. (1995). How to distinguish between the neuroleptic-induced deficit syndrome, depression and disease-related negative symptoms in schizophrenia. *International Clinical Psychopharmacology*, 10, 115–122.

16.4 Stage 0: Opportunity identification/research needs assessment

Inspiration

The core of the research team was brought together primarily through personal connections. Curson stressed the importance of being able to work with a talented and extremely motivated team.

> It's having talented people who are interested and are motivated and you all get on well together… and that's what it was, we had a great time. (DC)

Curson and Barnes had both trained at Guy's Hospital Medical School and had carried out an earlier project together: the seven-year follow-up to the MRC fluphenazine placebo trial (Curson et al., 1985a; Curson et al., 1985b; Curson et al., 1985c). The original MRC study (Hirsch et al., 1973) had been the first ever placebo-controlled trial of long-term depot antipsychotics in outpatients with schizophrenia and had been based at St. Olave's Hospital in Bermondsey, London. As Curson was a Senior Registrar at this same hospital, when encouraged to take on a research project he decided to conduct a follow-up to investigate the long-term outcomes for the same group of patients. Steven Hirsch was also involved in this follow-up project, both because of his role in the original trial, and because he was head of department at Charing Cross. Curson commented that they received a lot of encouragement to complete this work from Douglas Bennett at the Maudsley, as well as the editor of the *British Journal of Psychiatry* (who was also a schizophrenia researcher). During the research there was a great deal of interest in what the results might show, and they were published as a series of three *British Journal of Psychiatry* articles in 1985.

One of the findings of the seven-year follow-up study that was particularly relevant to the case study research was that depression was present in a subgroup of patients and that this did not seem to occur as a side effect of medication (Curson et al., 1985b). Curson and Barnes maintained an interest in social behaviour and depression in schizophrenia following this work.

The seven-year follow-up study also made use of the Social Behaviour Assessment Scale (SBAS; Platt et al., 1980), a tool developed by Steve Platt, who was a medical sociologist at Charing Cross before moving to Edinburgh. Barnes and Curson used the SBAS in a clinical trial comparing a depot (fluphenazine) and oral (pimozide) antipsychotic for relapse prevention (Barnes et al., 1983), reflecting their interest in social behaviour and the importance of this for functioning in the community.

Both Barnes and Curson noted that their experience in seeing patients was important in forming research ideas. Many of these patients were at Horton Hospital in Epsom, which housed an academic unit of the Charing Cross and Westminster Medical School department of psychiatry. The hospital, which was due to close in the next few years, had a large long-stay population and was considered (borrowing Professor John Wing's term) as something of a 'living laboratory' by Curson. However, little was known systematically at the time about the level of symptomatology of the long-stay patients.

At the time the case study research began, Barnes was spending half of his time doing research and half doing clinical work, a balance that was not always easy to maintain. He was appointed to both Horton Hospital and the Gordon Hospital in Victoria, and was responsible for a new tertiary referral unit for people with treatment-resistant schizophrenia and two long-stay wards, as well as outpatient clinics and inpatients at the Gordon. The insights Barnes gained from working with both long-stay and community patients were critical for informing his research career, but the arrangement did result in a demanding workload (Barnes interview). It was through working with the long-stay population at Horton Hospital that Barnes and Liddle initially came up with the idea to look at the nature of depression in people with schizophrenia, building on the team's interests and previous work.

Around the same time, Tim Crow had revived interest in the concept of negative symptoms of schizophrenia (e.g. Crow, 1985), features that could often resemble the symptoms of depression, and the team became very interested in how to go about assessing them in a long-stay hospital population. Similar assessments of patients with chronic schizophrenia were being conducted at the Shenley Hospital in Hertfordshire (Cunningham Owens & Johnstone, 1980), at multiple sites in Scotland (McCreadie et al., 1983) and at the Friern Hospital in London (Leff et al., 1988).

In addition to growing awareness of depression in schizophrenia and a revival of interest in negative symptoms, there was also a realisation at the time that as mental hospitals closed, more needed to be known about the needs of patients who would in future be living in the community.

Feasibility

Curson's role at St. Andrew's Hospital entitled him to an 'away day' to pursue his own work. This arrangement was part of the standard contract at the hospital to compensate for

not having junior medical staff. While all of the other consultants devoted their free day to private practice, Curson chose to spend his doing research, because of both his own personal motivation and because when he started at St. Andrew's he was still part-way through conducting the seven-year follow-up study.

> My lifetime compromise was because I couldn't be a full time academic – I did it 20 percent of the time for free. (DC)

Hirsch and Barnes then suggested that, because of their shared interest in schizophrenia research, Curson spend his away day working at Charing Cross and Horton Hospitals, rather than at Guy's.

As a senior lecturer at Charing Cross and Westminster Medical School, Barnes was able to bring in a lecturer to assist him. He had heard Peter Liddle talk about his work on the statistical clustering of schizophrenia symptoms into 'sub-syndromes' and so invited him to move to Charing Cross, one aim being to carry out similar studies on a different patient sample.

Potential value

As discussed above, the research took place at a time when many mental hospitals were closing and a greater emphasis was being placed on community care. In this context of patients being moved out into communities where there might be a lack of comprehensive support, the team recognised that depression in chronic schizophrenia was likely to become an even more important issue, and that their research might be able to help highlight the nature and level of care needed by long-stay patients.

Additionally, from a purely methodological perspective, with fewer large populations of long-stay inpatients, there would in future be few opportunities to carry out large surveys of people with chronic schizophrenia (this was not something that was necessarily a factor in the research team's planning of this work, but it was an important factor in a later published study on institutionalism and schizophrenia, described below).

16.5 Stage 1: Inputs to research

Money, researcher time, lab/office space and consumables

The team had freedom to choose the topic of their research, and did not need to apply for any funding. As Barnes was appointed as a clinical academic, half his time was allocated to research and teaching, while his appointment at Horton Hospital meant that the necessary patient population was readily accessible. Peter Liddle was in a similar position. Curson volunteered his time one day a week on account of being entitled to an 'away day' while at St. Andrew's Hospital. Once ethical approval had been obtained, the team was able to go ahead with the work straight away.

As mentioned above, the team benefited from the 'living laboratory' that was the Horton Hospital long-stay population. The case study researchers were based in the academic unit at the hospital and participated in academic afternoons once a week. This opportunity to present and discuss their research with other staff in the hospital helped build a good working relationship with, for example, the nursing staff, whose cooperation and support was essential in being able to conduct some of the research.

Knowledge

The team's clinical knowledge of managing people with established schizophrenia was important in identifying the research topic and questions.

Expertise and techniques

Expertise in conducting assessments using particular measures of symptoms and functioning was crucial in collecting the vast quantity of data the research needed. Curson and Barnes had both been trained in conducting the Present State Examination (PSE; Wing et al., 1974), and Curson spent eight years training others in it, so they were also able to train other members of the team.

Liddle had initially been a physicist, but after obtaining his PhD began training as a doctor and psychiatrist (during which time he worked with Tim Crow on a study of age disorientation in schizophrenia). He was also a good statistician, and prior to joining the team was working on the statistical clustering of schizophrenia symptoms and investigating whether these clusters could define sub-syndromes of the disorder.

Curson suggested that Barnes' growing reputation in the field meant that a lot of people were keen to work with the team.

Samples/patients

The sample consisted of 194 patients with a diagnosis of schizophrenia on the Horton Hospital's eleven non-psychogeriatric, long-stay wards. Traditionally, the majority of the hospital's intake had come from central London, with many having drifted into London from other areas of the UK.

16.6 Stage 2: Processes

There was no systematic record of the level of symptomatology in patients on the long-stay wards at Horton Hospital. The first stage of the case study research was, therefore, to assess the sample through examining medical records and interviewing every patient. These interviews, which were conducted by Curson and Patel, were based around the Comprehensive Psychopathological Rating Scale (CPRS; Åsberg et al., 1978), which was selected primarily because it incorporates a depression subscale sensitive to change, known as the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979). Unlike many other scales in use at the time, it had a clearly defined seven-point scale for the assessment of symptom severity. The more commonly used scale at the time was the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962), but although the standard version did include a severity scale, there were no clear accompanying descriptors and it relied to some extent on subjective interpretation of symptoms by the rater. Additionally, the BPRS represented some items at a fairly abstract, behavioural level, whereas the research team had a clear idea of the specific mental state phenomena they wanted to assess.

As the team intended to investigate the relationship between depression and schizophrenia (Barnes et al., 1989a), they added an assessment of depressed mood (item 23, depressed mood as a symptom) from the Present State Examination (PSE; Wing et al., 1974) as a 'probe question' in order to identify a depressed subgroup. The item has a high threshold for rating the symptom of depressed mood as present to even a moderate degree. These

'item 23 positive' patients were then age-matched with 'item 23 negative' patients. The MADRS from the CPRS was used to elaborate the presence or absence of a depressive syndrome, while the remaining CPRS items allowed for the elaboration of a full range of psychiatric symptoms and any relationships between them or other factors. To determine whether these symptoms were related either to negative symptoms of schizophrenia or to the effects of neuroleptic medication, these patients and the age-matched control group were blindly assessed by Barnes and Liddle on the Scale for Assessment of Negative Symptoms (SANS; Andreasen, 1982), which the team modified to include a specific rating for anhedonia (an inability to experience pleasure from enjoyable activities), the Beck Depression Inventory (Beck et al., 1961), the Extrapyramidal Rating Scale (EPRS; Simpson et al., 1970) to assess parkinsonism, and rating scales for tardive dyskinesia (Barnes & Trauer, 1982) and akathisia (Barnes, 1989).

Hirsch used the Horton data alongside two other patient samples to examine dysphoric and depressive symptoms in chronic schizophrenia (Hirsch et al., 1989). In addition to some of the scales used with the Horton sample, the team also employed the Hamilton Rating Scale for Depression (Hamilton, 1960), the Manchester Scale for rating chronic psychotic patients (Krawiecka et al., 1977), and in order to assess a broader range of symptoms, the Symptom Checklist-90 (Derogatis, 1977).

16.7 Stage 3: Primary outputs

Knowledge

The research cloud produced seven publications centred on the nature of depression in established schizophrenia. The main depression study (Barnes et al., 1989a), which was the subject of the most highly cited paper in the cloud, found that depressed mood was present in 13 percent of the long-stay patients, that this group had significantly higher scores on the MADRS and BDI, and that they were more likely to have suicidal thoughts and auditory hallucinations. The fact that no relationship was found between scores on the depression scales and severity of negative symptoms, dosage of antipsychotics or side effects of medication suggested that the depressive features were not a direct manifestation or misinterpretation of negative symptoms or induced by drug treatment. Interestingly, the depressed group and their matched controls were reassessed at follow-up three months later and the same proportion were depressed, but they were not all the same patients. Some of the control group had become depressed in the intervening period.

> It's about the attribution [of depression] to the illness as opposed to the medication or institutionalism, and I suppose that was the theme of all of this. I think our feeling was that affective disturbance was a distinct symptom domain within the schizophrenic illness and it was important that was acknowledged. (TB)

Hirsch combined the Horton Hospital data with two other ongoing studies in his department on dysphoria to produce a second paper (Hirsch et al., 1989). The resulting dataset, which added inpatients from St. Bernard's Hospital in Ealing (London) and an outpatient cohort from Charing Cross Hospital and other clinics nearby, came to broadly the same conclusions as the main study on depression in schizophrenia. The researchers asserted that their findings supported the notion of depression as a distinct component within schizophrenia.

The research team also explored patients' awareness of negative symptoms and psychological deficits in schizophrenia and produced a paper in 1993 showing that in addition to being associated with depression, the subjective experience of these deficits may in fact confer some vulnerability to depression (Liddle et al., 1993).

A number of other studies at this time produced similar findings (Koreen et al., 1993; Siris, 1991) and Barnes suggested that the findings of the case study research soon became 'lost' in the meta-analyses conducted:

> Other research groups were reporting similar findings. Looking back, everybody was trying to understand the relationship between negative symptoms, depression, and other symptom domains in schizophrenia, and understand which had a greater impact on longer-term outcomes. (TB)

The paper originally selected as the basis for this case study described the psychiatric morbidity of the long-stay population at the Horton Hospital (Curson et al., 1988). This was a somewhat opportunistic paper derived from the team's work in characterising their patient population for the depression study. As part of the wave of deinstitutionalisation happening throughout the UK at the time, Horton Hospital was due to be closed. Curson realised that the level of symptomatology they had found would have serious implications for the movement of long-stay patients into community care and although others in the team considered other aspects of the study more clinically relevant, he suggested that they submit the paper to the *British Medical Journal* (Barnes interview). This paper has been fairly well cited in the years since its publication (40 citations as of November 2011; Thomson Reuters) and has maintained its relevance partly because of the transition of long-stay patients into community care remaining a pertinent issue. Other authors have drawn on the paper's characterisation of chronic schizophrenia patients and the long-term persistence of the various symptoms described in the paper.[34]

A bibliometric analysis of the papers produced from the research cloud is shown below.

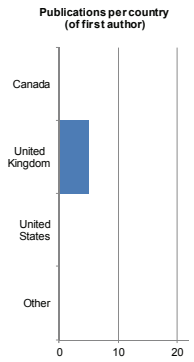
[34] Our peer reviewers suggested that the publications from the research cloud were well cited because they were intuitively helpful in understanding and organising clinical phenomena that were being observed and, importantly, provided a logical direction for therapeutic interventions. Additionally, the team members went on to have successful careers, using many of the ideas that originated from this work.

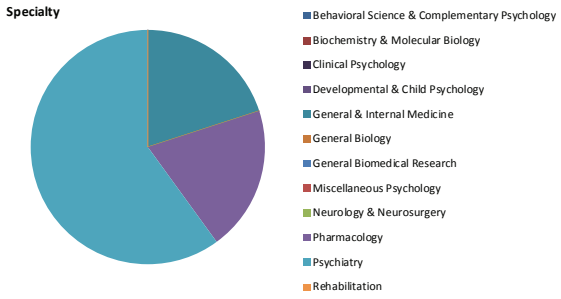
Research cloud:

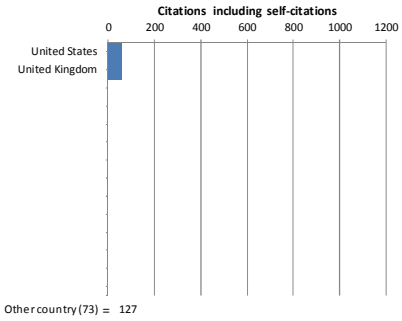
	Citations in:		**% of total citations**	**Research level of cloud papers**
WoS Indexed papers: 5	**RCT:**	17	6%	Clinical **1:** 100%
Total citations of papers: 270	**Meta-analyses:**	1	0%	**2:** 0%
of which, self-citations: 1.9%	**Indexed practice guidelines:**	0	0%	**3:** 0%
Mean citations per paper: 54	**Review articles:**	45	17%	Basic **4:** 0%
Distinct cloud citations: 230				
Second-generation cloud citations: 5,905				
Third-generation cloud citations: 63,747				

Most highly cited article: Barnes, T. R., Curson, D. A., Liddle, P. F., & Patel, M. (1989). The nature and prevalence of depression in chronic schizophrenic in-patients. Br J Psychiatry, 154, 486-491.

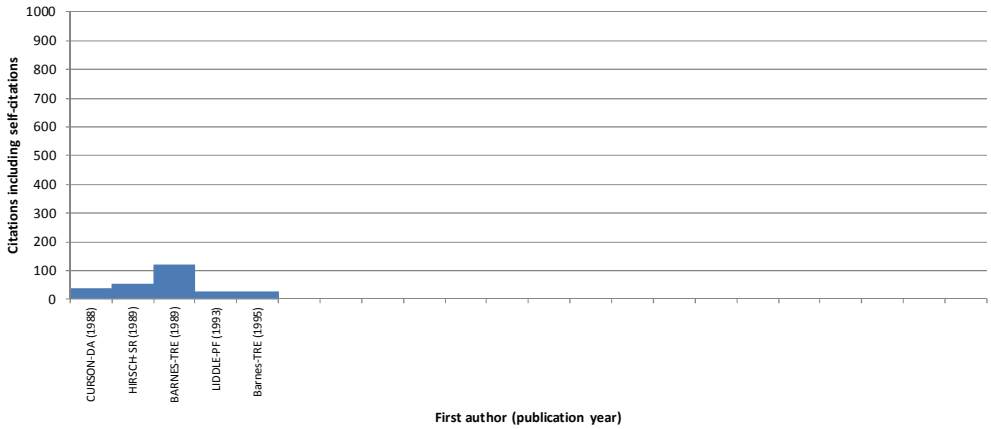
Times cited: 123

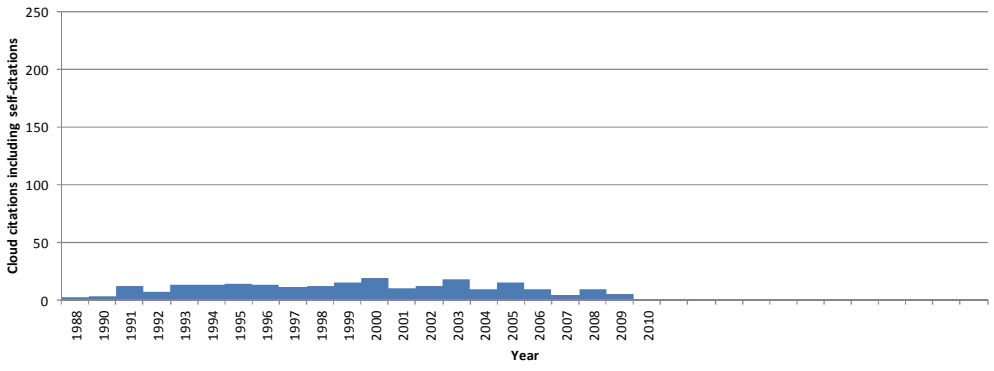






Note: Countries with more than 20 citations are displayed





Targeting future research

Effect on the researchers' careers

After benefitting from having an 'away day' to carry out research while he was at St Andrew's Hospital, Curson negotiated a similar arrangement in his subsequent positions at the Charter Clinic, Chelsea (1988–1990), the Royal Masonic Hospital (1990–1998) and, once that closed, the Roehampton Priory (1998–2003), all in London. Maintaining this research interest involved him in a number of different activities during these appointments. While spending one day a week at the Horton he was involved in the weekly 'academic afternoons', during which one of the researchers might give a presentation for other staff at the hospital. As mentioned above, Curson considered this a useful way of getting to know the hospital's staff and building up a good working relationship with them, something that was important given their necessary involvement in much of the research the team conducted. The management at the Priory were very positive about Curson's away day, as they saw it as recruiting a part-time academic, and as it was a teaching hospital and Curson was the only staff consultant with an academic post, he was expected to supervise other staff who wanted to do research as well as run the clinical audit programme and the weekly journal club for the junior medical staff. Curson was also a member of the working group tasked with updating UK-wide guidelines on the clinical management of drug misuse in the late 1990s (Department of Health et al., 1999).

Barnes commented that around the mid-1990s the demands for a clinical academic, in terms of attracting research grants, teaching, publishing in high-impact journals and so on, became more explicit. As his clinical work was taking up the majority of his time, he relinquished some of his clinical duties and took on the role of R&D Director for West London Mental Health Trust (while also remaining at Charing Cross and Westminster Medical School, which merged with Imperial College in 1997).

When Horton Hospital closed in 1997, Barnes moved to Ealing Hospital, where he worked on a first-episode psychosis study with Eileen Joyce (discussed further below). Barnes' primary interest throughout his career has been in the use of antipsychotic medication, and in particular its rational and optimal prescription. As a result of this he was involved in a number of clinical trials following the case study research, including the influential, pragmatic CUtLASS trials (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study), which showed first-generation antipsychotics were as effective as (non-clozapine) second-generation agents, and superiority for clozapine in treatment-resistant illness (Jones et al., 2006; Lewis et al., 2006).

Barnes' expertise in psychopharmacology led to him becoming Chairman of the Royal College of Psychiatrists' Special Interest Group for Psychopharmacology (2000–2004), before convening a working group in 2004 to update a consensus statement on high-dose antipsychotic treatment (Royal College of Psychiatrists), and serving as President of the British Association for Psychopharmacology between 2006 and 2008. He was also a member of NICE's Schizophrenia Guideline Development Groups in 2002 and 2009, chairing the Pharmacology Topic Group. Barnes is now also joint head of the UK Prescribing Observatory for Mental Health, which was set up in 2005 with a tapering grant from the Health Foundation's 'Engaging with Quality' initiative but is now funded

by subscriptions from member Trusts. It runs national quality improvement programmes on various aspects of prescribing practice in mental health services.

Liddle continued his work on the clustering of symptoms into positive, negative and disorganised groups and as brain imaging techniques advanced began looking for structural correlates of these subsyndromes. He moved to the University of British Columbia in Vancouver, before subsequently returning to Nottingham University.

Future work – in psychiatry

Follow-up work by the research team drew on a number of different aspects of the case study research and the work preceding it, including institutionalism, the subjective experience of depression, cognitive dysfunction and social behaviour. All of these were looked at in the context of established schizophrenia, building on the case study research to help develop a more comprehensive understanding of the complexities surrounding the more commonly documented positive and negative symptoms of the disorder.

As mental hospitals closed and inpatient populations shrank, the team's focus, and to some extent that of the research community more widely, returned to issues relevant to the successful functioning in the community of people with schizophrenia, something which Curson and Barnes had looked at initially in the seven-year follow-up study. For a number of years, attempts to understand the nature of schizophrenia had focussed on defining subgroups according to, for example, positive and negative symptoms. Indeed Liddle and Barnes (1990), continuing Liddle's work prior to his arrival at Charing Cross and Westminster Medical School, found that the three symptom-derived sub-syndromes (psychomotor poverty, disorganisation and reality distortion) were also present in patients with long-standing schizophrenia. At around the same time, a number of other groups also carried out similar factor analysis of schizophrenia symptoms (e.g. Lancon et al., 1998; Lindenmayer et al., 1994; Smith et al., 1998).

However, the team had observed from their previous work that social functioning did not necessarily correlate with the clinical symptoms of schizophrenia:

> It was possible to start looking at sub-syndromes from a behavioural point of view. And we would have argued at the time that it's probably not whether you're hearing voices that matters if you're living in the community and surviving, it's whether your behaviour is acceptable in the community and you're surviving. And we also allude to this going back to the first follow-up study, in that what we found was that certain behaviours and symptoms didn't correlate in any way with social role performance – that in fact you could be a chronic hallucinator and be looking after two kids and going to a part-time job… Psychiatrists, being doctors, talk about the symptoms. Psychologists talk about behaviours, but you've got to marry the two and they're not the same thing. (DC).

This emphasis on social behaviour led to the team working on a classification system based on behavioural characteristics to complement the existing symptom-based systems (Curson et al., 1999; Harvey et al., 1996). By this time they had been joined by Carol Harvey and Chris Pantelis from the Royal Free Hospital, who had been involved in conducting a large epidemiological survey of people with schizophrenia in South Camden, London (Pantelis et al., 1988). This provided the team with a large data set, in which social behaviour had been measured but not fully analysed, on which to carry out factor analysis of behavioural observations. The result was the description of four 'behavioural syndromes': 'thought

disturbance', 'social withdrawal', 'depressed behaviour' and 'anti-social behaviour'. This work is fairly well cited (24 citations for Harvey et al., 1996; Thomson Reuters), both in discussions of the dimensions of schizophrenia and in comparing outcomes for different groups of patients, but appears to have had little impact on practice, despite the results being replicated in a second epidemiological sample in South Westminster (Curson et al., 1999).

Around the same time, the team looked at social functioning in the context of institutionalism. This was something that had long interested Curson, ever since he discovered a book by John Wing and George Brown in the mid-1970s. This book described their seminal study 'Institutionalism and schizophrenia', a comparative investigation of the effects of social environment on schizophrenia symptoms and behaviour in three different mental hospitals (Wing & Brown, 1961, 1970). This original study had found a strong association between measures of social poverty in the hospital environments and 'clinical poverty', indicated by features such as blunted affect, poverty of speech and social withdrawal (and which is likely to overlap substantially with the more recent concept of negative symptoms). The team tested these findings with the patient population at the Horton Hospital, but found that 30 years on, very little association remained, concluding from this that the symptoms observed in long-stay inpatients in Horton Hospital were not a result of their environment (Curson et al., 1992). Curson and Barnes both suggested that the contradiction of Wing and Brown's findings may have been due to the ward environment being less restrictive than it had been 30 years earlier, a factor that Wing and Brown had found to be strongly associated with social withdrawal (Curson interview, Barnes interview).

It was a fairly widespread belief at the time that patients in institutions functioned badly because of the institution, and while the team's findings suggested that this was not the case, the question of what it was instead that caused this poor social functioning in schizophrenia still remained to be answered. Barnes commented that they had observed (but not published) that the differences in the persistence and severity of positive and negative symptoms between the long-stay patients at Horton and the outpatients and community patients they saw in Victoria did not seem enough to explain the marked difference in level of social and occupational functioning. At this point Barnes began to think that aspects of neurocognition might be important and the team (with Hazel Nelson) found that the long-stay Horton patients with schizophrenia had a mean IQ of 80, which they attributed to the effects of substantial intellectual deterioration on below average premorbid levels of functioning (Nelson et al., 1990). Although this was a single observation in one population at one point in time, the team speculated that cognitive functioning might in some way influence social behaviour and ability to function in a community setting.

This observation led Barnes to ensure that cognitive functioning was a key element of the Wellcome Trust-funded, first-episode schizophrenia study he carried out with Eileen Joyce when he moved from Horton Hospital to Ealing Hospital (e.g. Hutton et al., 1998). This study drew together a number of themes that the research team had looked at during the late 1980s and early 1990s. By this time there was a lot of interest among the research community in the concept of duration of untreated psychosis (DUP; i.e. the length of time elapsing before someone with schizophrenia was treated). Curson and Barnes' early work

on the seven-year follow-up study (Curson et al., 1985a; Curson et al., 1985b; Curson et al., 1985c) had demonstrated that people who had relapsed more frequently had poorer social function. One possible implication of this was that relapse may inhibit long-term improvement of social function or even contribute to its deterioration, a finding that was picked up by Richard Jed Wyatt in a seminal publication on the effects of untreated psychosis (Wyatt, 1991). Cited over 400 times (as of November 2011), Wyatt's paper was key in the development of the field of early intervention. When Barnes et al. returned to this topic in their first-episode study, which combined cognitive and neuroimaging measures primarily, they discovered that impairments of cognitive functioning were evident from the time that patients first presented for treatment. The fact that cognitive deficits did not develop over time or as a result of antipsychotic treatment suggested that they were a key feature of the disorder. This study also provided the team with the opportunity to follow up on their work on the subjective experience of depression. In first-episode patients they demonstrated an inverse relationship between depression and insight (Mutsatsa et al., 2006). More recently, first-episode work continued as part of the national PsyGrid study, an e-science project jointly funded by the MRC and Department of Health that collected and combined various datasets centrally and encouraged collaboration.

The patient population at the Horton Hospital was also used by Steve Milne (St Nicholas Hospital, Newcastle) in a study of social morbidity in long-stay patients. He asked Curson and Pantelis to help with the analysis and the study found substantial social dysfunction (Milne et al., 1993), adding to the growing evidence of the need for comprehensive community services in order for patients to transition successfully to life in the community.

Although it is difficult to discern any direct impact from much of the social behaviour and functioning work, it may have contributed to a better understanding of the long-stay hospital populations of the time, in turn informing the kinds of structures that needed to be in place to support people as they moved into the community (see secondary outputs, below).

Curson commented that few other groups published papers on the impact of deinstitutionalisation, as although this was an obvious topic to start looking at, these studies needed large patient populations, suitably trained people to conduct the assessments, and were very time consuming in terms of the amount of data collection that was needed (e.g. a 45 minute interview with each patient). The case study research team already had the relevant resources in place – primarily, people trained in conducting appropriate mental state examinations.

16.8 Interface B: Dissemination

In addition to academic publications, Barnes referred to the case study research in many lectures and talks. However, he commented that many other groups were working on similar studies and so the whole topic became well discussed in the field.

Curson commented that dissemination mattered less to him, as he was working only one day per week in research and had little academic ambition by this point. Despite this, he

was named as one of the Charing Cross Hospital researchers whose publication records were submitted as part of a Research Assessment Exercise.

16.9 Stage 4: Secondary outputs

The case study research was part of a wider body of work that contributed to a better understanding of the nature of schizophrenia in long-stay patients, including the recognition of and justification for treating depression, and the support that would need to be in place for them to move into the community. Curson suggested that there was perhaps a certain naivety to some of the policies pursued at the time:

> There was a lot of naive thinking going on. I remember at the time some of the people who were the most outspoken were some of the people who, as far as I was concerned, had never met any of these patients. They didn't know what it was like for somebody to have a chronic treatment-resistant psychosis… and to also realise that one in ten of these people either had or would have killed themselves with the lifetime suicide rate of one in ten… they're actually rather ill people and they're going to need to be cared for. (DC)

The research cloud paper that specifically focussed on the closure of mental hospitals (Curson et al., 1988) was followed by a response in the *BMJ* the next month from Michael Abrams at the Department of Health (Abrams, 1988). This letter aimed to clarify the government's community care policy, stating that the closure of hospitals was not a primary aim. He also agreed with the team's conclusion that community psychiatric facilities would need to be well organised and that inpatient treatment would need to be maintained for the most severely affected. Although Curson was dubious about the extent to which research was able to influence mental health policy at that time, he did acknowledge that the accumulation of evidence from the case study research and the work of other groups around that time (e.g. the Shenley, Friern and Scottish multisite studies mentioned previously) may have provided clinicians with 'ammunition' to support what they had observed clinically, and may have helped secure resources for the expansion of community care services.

Although clearly policy-relevant at the time, Curson commented that the team did not set out expecting to have an impact on public policy:

> We never even imagined that was a reason for publishing it in the *BMJ*! Nothing to do with public policy. (DC)

Similarly, Barnes suggested that while the work on depression and negative symptoms which was central to the research cloud did not on its own have a direct impact on policy, it was part of an accumulation of evidence that made people much more aware of these aspects of schizophrenia. This body of research, contributed to by a number of groups who influenced each other's work, increased awareness of negative symptoms as a potential prognostic factor that contributes to poor outcomes, while also demonstrating that depression may be a core element of the disorder. Among important contributions to this evidence were: the work of William Carpenter's group, which distinguished between enduring negative symptoms ('deficit' symptoms) and more transient symptoms (Carpenter et al., 1985; Carpenter et al., 1988); research on the role of depression in the course of chronic schizophrenia (e.g. Johnson, 1988); Samuel Siris and colleagues'

demonstration of the benefits of adjunctive antidepressant therapy both in an acute trial (Siris et al., 1987) and as a maintenance treatment (Siris et al., 1994); and the development of the Calgary Depression Scale, which was the first scale devised specifically for measuring the presence and magnitude of depression in people with schizophrenia (Addington et al., 1996; Addington et al., 1990). Based on this accumulation of evidence,, the team (and others in the field) argued that both negative symptoms and depression may be worthwhile treatment targets, something which is now accepted.

Around the time that the case study research was published, a draft of ICD-10 was produced that for the first time acknowledged the co-occurrence of schizophrenia and depression (World Health Organisation, 1992). However, it did so in terms of 'post-schizophrenia depression', defined as a disorder that affected people only when an episode of positive and negative symptoms receded. The description provided in ICD-10 also highlights the fact that 'it is often difficult to decide which of the patient's symptoms are due to depression and which to neuroleptic medication or to the impaired volition and affective flattening of schizophrenia itself.'

As part of a wider body of research, the team's work on depression in schizophrenia influenced the recognition of this form of depression and its treatment, as reflected in its citation in the DSM-IV Sourcebook (Widiger et al., 1994). This series of publications documented the development process of DSM-IV (American Psychiatric Association, 1994), primarily through literature reviews by the Task Force and Work Groups. Both the *British Journal of Psychiatry* article describing the main findings of the depression study at Horton Hospital (Barnes et al., 1989a) and Hirsch's follow-up paper on dysphoria (Hirsch et al., 1989) were cited as part of the evidence base.

Although the case study research has not been directly cited in practice guidelines, Barnes was a member of NICE Guideline Development Groups in the UK, as described above. He commented that even if the case study work had not been directly relevant to treatment, his research experience throughout his career has certainly influenced his contributions.

16.10 Stage 5: Applications

None identified.

16.11 Stage 6: Public engagement

None identified.

16.12 Stage 7: Final outcomes

As part of a larger body of work, the research may have contributed to a better understanding of the needs of long-stay patients returning to the community, as well as the treatment of depression in schizophrenia.

16.13 Other observations

Barnes commented that it is the positive symptoms that bring people into contact with mental health services, and that because of this, first-episode patients appear to be a very homogeneous group when first admitted. This has implications for research in terms of selecting samples that are presumed to be homogeneous.

> The clinical picture appears relatively similar across patients with schizophrenia when they're first admitted, the first episode. They all present with florid psychotic symptoms because that's what tends to bring someone to the attention of clinical services and prompt admission to hospital. Then of course things settle into a relapsing illness which may or may not include negative symptoms as part of it…. (TB)

16.14 Table of payback

Payback category	Impacts from case study
Knowledge Production	• Contributed to the growing body of evidence demonstrating that depression in schizophrenia is not due to negative symptoms or side effects of antipsychotic medication; and evidence characterising long-stay schizophrenia patients and their likely needs in the community.
Research Targeting and Capacity Building	• Led to substantial future work for the team and influenced other research groups internationally.
Informing Policy and Product Development	• Two papers cited in DSM-IV Sourcebook in relation to depression and dysphoria in schizophrenia. • As part of a wider accumulation of evidence, drew attention to the needs of long-stay patients being discharged to the community.
Health and Health Sector Benefits	• Was likely part of a wider body of evidence that influenced the treatment available to long-stay patients returning to the community.
Broader Social and Economic Benefits	• None identified.

16.15 Timeline

1975	'Better services for the mentally ill' emphasises need for comprehensive community care
1978	Curson takes consultant position at St Andrew's Hospital, Northampton and begins to spend 'away day' doing research
1985	Social Services Select Committee report highlights lack of investment in community care provision
1985	Curson, Barnes et al. publish seven-year follow-up to the MRC fluphenazine study

1988	Curson moves to Charter Clinic, Chelsea, London
1988	*BMJ* paper originally selected is published
1988–1990	Griffiths Report and follow-up white paper pave the way for the Community Care Act (1990), which allows local authorities to purchase community services from the private sector
1989	*British Journal of Psychiatry* paper on nature of depression in schizophrenia published
1990	Curson moves to Royal Masonic Hospital, London
1997	Horton Hospital closes; Barnes moves to Ealing Hospital

16.16 References

Abrams, M. (1988). Psychiatric morbidity of long stay hospital population. *British Medical Journal*, 297(6659), 1334.

Addington, D., Addington, J., & Atkinson, M. (1996). A psychometric comparison of the Calgary Depression Scale for Schizophrenia and the Hamilton Depression Rating Scale. *Schizophrenia Research*, 19(2-3), 205–212.

Addington, D., Addington, J., & Schissel, B. (1990). A depression rating scale for schizophrenics. *Schizophrenia Research*, 3(4), 247–251.

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.). Washington, DC: American Psychiatric Association.

Andreasen, N.C. (1982). Negative symptoms in schizophrenia: definition and reliability. *Archives of General Psychiatry*, 39(7), 784–788.

Åsberg, M., Montgomery, S.A., Perris, C., Schalling, D., & Sedvall, G. (1978). A comprehensive psychopathological rating scale. *Acta Psychiatrica Scandinavica*, 57(S271), 5–27.

Barnes, T.R.E. (1989). A rating scale for drug-induced akathisia. *British Journal of Psychiatry*, 154(5), 672–676.

Barnes, T.R.E., Curson, D.A., Liddle, P.F., & Patel, M. (1989). The nature and prevalence of depression in chronic schizophrenic in-patients. *British Journal of Psychiatry*, 154, 486–491.

Barnes, T.R.E., Liddle, P.F., Curson, D.A., & Patel, M. (1989). Negative symptoms, tardive-dyskinesia and depression in chronic-schizophrenia. *British Journal of Psychiatry*, 155(7), 99–103.

Barnes, T.R.E., & McPhillips, M.A. (1995). How to distinguish between the neuroleptic-induced deficit syndrome, depression and disease-related negative symptoms in schizophrenia. *International Clinical Psychopharmacology*, 10, 115–122.

Barnes, T.R.E., Milavic, G., Curson, D.A., & Platt, S.D. (1983). Use of the Social Behaviour Assessment Schedule (SBAS) in a trial of maintenance antipsychotic therapy

in schizophrenic outpatients: pimozide versus fluphenazine. *Social Psychiatry and Psychiatric Epidemiology*, 18(4), 193–199.

Barnes, T.R.E., & Trauer, T. (1982). Reliability and validity of a tardive dyskinesia videotape rating technique. *British Journal of Psychiatry*, 140(5), 508–515.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry*, 4(6), 561–571.

Bleuler, E. (1950). *Dementia Praecox or the Group of Schizophrenias (1911)* (J. Zinkin, Trans.). New York: International Universities Press.

Carpenter, W.T., Heinrichs, D.W., & Alphs, L.D. (1985). Treatment of negative symptoms. *Schizophrenia Bulletin*, 11(3), 440–452.

Carpenter, W.T., Heinrichs, D.W., & Wagman, A.M. (1988). Deficit and nondeficit forms of schizophrenia: the concept. *American Journal of Psychiatry*, 145(5), 578–583.

Crow, T.J. (1985). The two-syndrome concept: origins and current status. *Schizophrenia Bulletin*, 11(3), 471–486.

Cunningham Owens, D.G., & Johnstone, E.C. (1980). The disabilities of chronic schizophrenia – their nature and the factors contributing to their development. *British Journal of Psychiatry*, 136(4), 384–395.

Curson, D.A., Barnes, T.R., Bamber, R.W., Platt, S.D., Hirsch, S.R., & Duffy, J.C. (1985a). Long-term depot maintenance of chronic schizophrenic out-patients: the seven year follow-up of the Medical Research Council fluphenazine/placebo trial I. Course of illness, stability of diagnosis, and the role of a special maintenance clinic. *British Journal of Psychiatry*, 146(5), 464–469.

Curson, D.A., Barnes, T.R., Bamber, R.W., Platt, S.D., Hirsch, S.R., & Duffy, J.C. (1985b). Long-term depot maintenance of chronic schizophrenic out-patients: the seven year follow-up of the Medical Research Council fluphenazine/placebo trial. II. The incidence of compliance problems, side-effects, neurotic symptoms and depression. *British Journal of Psychiatry*, 146, 469–474.

Curson, D.A., Barnes, T.R., Bamber, R.W., Platt, S.D., Hirsch, S.R., & Duffy, J.C. (1985c). Long-term depot maintenance of chronic schizophrenic out-patients: the seven year follow-up of the Medical Research Council fluphenazine/placebo trial. III. Relapse postponement or relapse prevention? The implications for long-term outcome. *British Journal of Psychiatry*, 146(5), 474–480.

Curson, D.A., Duke, P.J., Harvey, C.A., Pantelis, C., & Barnes, T.R.E. (1999). Four behavioural syndromes of schizophrenia: a replication in a second inner-London epidemiological sample. *Schizophrenia Research*, 37(2), 165–176.

Curson, D.A., Patel, M., Liddle, P.F., & Barnes, T.R.E. (1988). Psychiatric morbidity of a long stay hospital population with chronic schizophrenia and implications for future community care. *British Medical Journal*, 297(6652), 819–822.

Curson, D., Pantelis, C., Ward, J., & Barnes, T. (1992). Institutionalism and schizophrenia 30 years on. Clinical poverty and the social environment in three British

mental hospitals in 1960 compared with a fourth in 1990. *British Journal of Psychiatry*, 160(2), 230–241.

de Alarcon, R., & Carney, M.W.P. (1969). Severe depressive mood changes following slow-release intramuscular fluphenazine injection. *British Medical Journal*, 3(5670), 564–567.

Department of Health. (1989). *Caring for People: Community Care in the Next Decade and Beyond*. London: HMSO.

Department of Health, Scottish Office Department of Health, Welsh Office, & Department of Health and Social Services – Northern Ireland. (1999). *Drug Misuse and Dependence – Guidelines on Clinical Management*. Norwich, UK: Her Majesty's Stationery Office.

Derogatis, L.R. (1977). *SCL-90. Adminstration, Scoring and Procedures Manual for the Revised Version*. Baltimore, MD: Clinical Psychometrics Research Unit.

Floru, L., Heinrich, K., & Wittek, F. (1975). The problem of post-psychotic schizophrenic depressions and their pharmacological induction. Long-term studies with fluspirilene and penfluridol and single-blind trial with fluphenazine-decanoate and flupenthixol-decanoate. *International Pharmacopsychiatry*, 10(4), 230–239.

Griffiths, R. (1988). *Community Care: Agenda for Action. A Report to the Secretary of State for Social Services*. London: HMSO.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery & Psychiatry*, 23(1), 56–62.

Harvey, C., Curson, D., Pantelis, C., Taylor, J., & Barnes, T. (1996). Four behavioural syndromes of schizophrenia. *British Journal of Psychiatry*, 168(5), 562–570.

Hirsch, S.R., Gaind, R., Rohde, P.D., Stevens, B.C., & Wing, J.K. (1973). Outpatient maintenance of chronic schizophrenic patients with long-acting fluphenazine: double-blind placebo. *British Medical Journal*, 1(5854), 633–637.

Hirsch, S.R., Jolley, A.G., & Barnes, T.R.E. (1990). Are depressive symptoms part of the schizophrenic syndrome? In DeLisi, L.E. (ed.), *Depression in Schizophrenia*, Washington DC: American Psychiatric Press.

Hirsch, S.R., Jolley, A.G., Barnes, T.R.E., Liddle, P.F., Curson, D.A., Patel, A., et al. (1989). Dysphoric and depressive symptoms in chronic schizophrenia. *Schizophrenia Research*, 2(3), 259–264.

House of Commons Social Services Committee. (1985). *Community Care With Special Reference to Adult Mentally Ill and Mentally Handicapped People*. London: HMSO.

Hutton, S.B., Puri, B.K., Duncan, L.J., Robbins, T.W., Barnes, T.R.E., & Joyce, E.M. (1998). Executive function in first-episode schizophrenia. *Psychological Medicine*, 28(2), 463–473.

Johnson, D.A. (1988). The significance of depression in the prediction of relapse in chronic schizophrenia. *British Journal of Psychiatry*, 152(3), 320–323.

Jones, P.B., Barnes, T.R.E., Davies, L., Dunn, G., Lloyd, H., Hayhurst, K.P., et al. (2006). Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Archives of General Psychiatry*, 63(10), 1079–1087.

Knights, A., & Hirsch, S.R. (1981). 'Revealed' Depression and Drug Treatment for Schizophrenia. *Archives of General Psychiatry*, 38(7), 806–811.

Koreen, A., Siris, S., Chakos, M., Alvir, J., Mayerhoff, D., & Lieberman, J. (1993). Depression in first-episode schizophrenia. *American Journal of Psychiatry*, 150(11), 1643–1648.

Krawiecka, M., Goldberg, D., & Vaughan, M. (1977). A standardized psychiatric assessment scale for rating chronic psychotic patients. *Acta Psychiatrica Scandinavica*, 55(4), 299–308.

Lancon, C., Aghababian, V., Llorca, P.M., & Auquier, P. (1998). Factorial structure of the Positive and Negative Syndrome Scale (PANSS): a forced five-dimensional factor analysis. *Acta Psychiatrica Scandinavica*, 98(5), 369–376.

Leff, J., Tress, K., & Edwards, B. (1988). The clinical course of depressive symptoms in schizophrenia. *Schizophrenia Research*, 1(1), 25–30.

Lewis, S.W., Barnes, T.R.E., Davies, L., Murray, R.M., Dunn, G., Hayhurst, K.P., et al. (2006). Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. *Schizophrenia Bulletin*, 32(4), 715–723.

Liddle, P.F., & Barnes, T.R.E. (1990). Syndromes of chronic schizophrenia. *British Journal of Psychiatry*, 157(4), 558–561.

Liddle, P.F., Barnes, T.R.E., Curson, D.A., & Patel, M. (1993). Depression and the experience of psychological deficits in schizophrenia. *Acta Psychiatrica Scandinavica*, 88(4), 243–247.

Lindenmayer, J.-P., Bernstein-Hyman, R., & Grochowski, S. (1994). A new five factor model of schizophrenia. *Psychiatric Quarterly*, 65(4), 299–322.

McCreadie, R.G., Wilson, A.O., & Burton, L.L. (1983). The Scottish survey of 'new chronic' inpatients. *British Journal of Psychiatry*, 143(6), 564–571.

McGlashan, T.H., & Carpenter, W.T. Jr. (1976). Postpsychotic Depression in Schizophrenia. *Archives of General Psychiatry*, 33(2), 231–239.

Milne, S., Curson, D., Wilkie, A., & Pantelis, C. (1993). Social morbidity of a long-stay mental hospital population with chronic schizophrenia. *The Psychiatrist*, 17, 647–649.

Ministry of Health. (1962). *A Hospital Plan for England and Wales*. London: HMSO.

Montgomery, S.A., & Åsberg, M. (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry*, 134(4), 382–389.

Mutsatsa, S.H., Joyce, E.M., Hutton, S.B., & Barnes, T.R.E. (2006). Relationship between insight, cognitive function, social function and symptomatology in

schizophrenia – the West London first episode study. *European Archives of Psychiatry and Clinical Neuroscience*, 256(6), 356–363.

Nelson, H.E., Pantelis, C., Carruthers, K., Speller, J., Baxendale, S., & Barnes, T.R.E. (1990). Cognitive functioning and symptomatology in chronic schizophrenia. *Psychological Medicine*, 20(2), 357–365.

Overall, J.E., & Gorham, D.R. (1962). The Brief Psychiatric Rating Scale. *Psychological Reports*, 10, 799–812.

Pantelis, C., Taylor, J., & Campbell, P. (1988). The South Camden Schizophrenia Survey: an experience of community-based research. *Psychiatric Bulletin*, 12, 98–101.

Platt, S., Weyman, A., Hirsch, S.R., & Hewett, S. (1980). The Social Behaviour Assessment Schedule (SBAS): rationale, contents, scoring and reliability of a new interview schedule. *Social Psychiatry and Psychiatric Epidemiology*, 15(1), 43–55.

Simpson, G.M., & Angus, J.W.S. (1970). A rating scale for extrapyramidal side effects. *Acta Psychiatrica Scandinavica*, 45(S212), 11–19.

Siris, S.G. (1991). Diagnosis of secondary depression in schizophrenia: implications for DSM-IV. *Schizophrenia Bulletin*, 17(1), 75–98.

Siris, S.G., Bermanzohn, P.C., Mason, S.E., & Shuwall, M.A. (1994). Maintenance imipramine therapy for secondary depression in schizophrenia. A controlled trial. *Archives of General Psychiatry*, 51(2), 109–115.

Siris, S.G., Morgan, V., Fagerstrom, R., Rifkin, A., & Cooper, T.B. (1987). Adjunctive imipramine in the treatment of postpsychotic depression. A controlled trial. *Archives of General Psychiatry*, 44(6), 533–539.

Smith, D.A., Mar, C.M., & Turoff, B.K. (1998). The structure of schizophrenic symptoms: a meta-analytic confirmatory factor analysis. *Schizophrenia Research*, 31(1), 57–70.

Thomson Reuters. Web of Science. As of 10 September 2013: http://thomsonreuters.com/web-of-science/

Van Putten, T., & May, P.R.A. (1978). 'Akinetic depression' in schizophrenia. *Archives of General Psychiatry*, 35(9), 1101–1107.

Widiger, T.A., Frances, A.J., Pincus, H.A., First, M.B., Ross, R., & Davis, W. (eds.). (1994). *DSM-IV Sourcebook* (Vol. 1). Washington DC: American Psychiatric Press.

Wing, J.K., & Brown, G.W. (1970). *Institutionalism and Schizophrenia: A Comparative Study of Three Mental Hospitals: 1960–1968.* London, UK: Cambridge University Press.

Wing, J.K., & Brown, G.W. (1961). Social treatment of chronic schizophrenia: a comparative survey of three mental hospitals. *British Journal of Psychiatry*, 107(450), 847–861. Wing, J.K., Cooper, J.E., & Sartorius, N. (1974). *Measurement and Classification of Psychiatric Symptoms*. Cambridge, UK: Cambridge University Press.

World Health Organisation. (1992). *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organisation.

Wyatt, R.J. (1991). Neuroleptics and the natural course of schizophrenia. *Schizophrenia Bulletin*, 17(2), 325–351.

CHAPTER 17

Randomised controlled trial of an inpatient family intervention for schizophrenia and affective disorders: the importance of gender in outcome and treatment response

This case study is based on research related to the following highly cited publication, which was selected using a bibliometric analysis:

Haas, G.L., Glick, I.D., Clarkin, J.F., Spencer Jr., J.H., & Lewis, A.B. (1990). Gender and schizophrenia outcome: a clinical trial of an inpatient family intervention. *Schizophrenia Bulletin*, 16(2), 277–292.

Information was gathered from interviews with Gretchen Haas (the lead author) and Ira Glick (PI on the project), as well as desk-based research.

17.1 Summary

Haas et al. (1990) was the result of a parent study that was the first randomised controlled trial of inpatient family intervention for schizophrenia and affective disorder. Family intervention consists of a number of discrete psychological interventions where family sessions have a specific supportive, educational or treatment function and contain at least one other of the following components: problem solving/crisis management work, or intervention with the identified service user. Previous research had shown that family intervention in the outpatient environment could be beneficial for these conditions, and although intervention at the inpatient stage was widely used in the US, its effectiveness was not proven. The study was designed to accurately reflect the way such interventions were conducted in practice, and to test the effectiveness of a specific family intervention through a randomised controlled trial. Haas et al. (1990) focused on gender differences within this trial. The team found that this type of family intervention in the inpatient setting was only effective for female patients with schizophrenia or bipolar disorders. For unipolar depressive disorder and for all male patients, the treatment was found to be ineffective and even to have negative results for some groups. The work contributed to subsequent research on family interventions for individuals with bipolar disorders. However, it has not significantly influenced policy and practice related to inpatient schizophrenia treatment. Haas suggests this is partly because of a historical shift in the field of inpatient psychiatry –

away from psychosocial treatments to a more dominant reliance on pharmacological treatments for schizophrenia – from around the time that this work was conducted to the present. However, work on gender differences, including work on the psychobiology of gender differences in schizophrenia, for example Rubin, Haas, Maki et al. (2008), is ongoing in the field at large and may influence future policy changes if this treatment balance shifts.

17.2 Introduction

17.2.1 Scientific background

Family intervention consists of a series of psychological interventions where family sessions have a specific supportive, educational or treatment function. In addition, the sessions should include at least one of either problem solving and crisis management work, or intervention with the patient. At the time that this research was conducted, the role of the family and the potential value of family intervention in schizophrenia and affective disorder was well established. Previous studies on outpatient family intervention had shown that, when combined with other standard treatment approaches, including pharmacological treatment, it could lead to reduced rates of relapse as well as improved outcomes more widely (see, for example, Goldstein et al., 1978; Falloon et al., 1982; Leff et al., 1982, 1985; Kottgen, et al., 1984). However, despite being a widely recommended standard for treatment in the US, no thorough randomised controlled trials of the efficacy of family intervention in an inpatient setting had been conducted. The goal of this study was to address that deficit, and also to investigate whether there were particular patient groups for which family-based treatment, using the treatment conditions typically applied in practice, was especially beneficial. The research team expected to find that patients exhibiting worse premorbid functioning might benefit the most from inpatient family intervention approaches. Instead, they found that the more important factors in terms of different levels of effectiveness were actually gender and diagnosis.

17.2.2 Researchers' background

Gretchen L. Haas was a research associate, and later assistant professor, working on the project, with a particular interest in gender differences. At the time of the trial, Haas was new to the Cornell Medical Center, having just completed her doctoral training. Her work on this study involved conducting interviews and analysing data. Overall, her involvement in the project was fairly broad. Her dissertation had focused on parent–child interactions in latency-age (pre-teen) children, and through this she had developed an interest in gender differences which she brought to this project, and which proved important in terms of the outcomes of the work.

Ira D. Glick was the research project leader for the trial and Professor of Psychiatry at the Cornell University Medical College.

John F. Clarkin was an experienced researcher with knowledge of family therapy who contributed to this project.

James H. Spencer and **Alfred B. Lewis** were psychiatrists, and were the co-directors of the inpatient psychiatric unit at the Payne Whitney Clinic. Neither had much formal

research experience prior to this study, nor has either of them continued to conduct a significant amount of research work.

Denise Hien was a graduate student working with Haas on gender differences and schizophrenia at the later stage of Haas' work on the project while at Cornell.

17.2.3 Institution background

The research was conducted at the Payne Whitney Clinic of the New York Hospital and the Department of Psychiatry at the Cornell University Medical College, a major teaching hospital and leader in medical education and training in the US. Located on the East side of Manhattan, the PWC services a demographically diverse population in the New York City region and provides consultative and tertiary care services to individuals referred from outside the immediate service region.

17.3 Defining the research cloud

This research cloud focuses on a clinical trial of an inpatient family intervention in schizophrenia and affective disorder that took place at the Payne Whitney Clinic (PWC) in New York City in the 1980s. It was the first study to conduct a randomised clinical trial of the impact of family intervention for schizophrenia in an inpatient setting. The study produced a series of outcome papers, plus two other satellite papers, one covering the clinical significance of the study, and the other focusing on the importance of gender in terms of outcome and treatment response. The case study cloud incorporates all of this work, but with a particular focus on the role of gender, since this was the primary interest of Haas, the PI for this case study, and because this was one of the most important outcomes of the study, and with a slant towards the outcomes in relation to schizophrenia rather than affective disorder. The publications cloud is as follows:

1. Glick, I.D., Clarkin, J.F., Spencer, J.H., Haas, G.L., Lewis, A.B., Peyser, J., DeMane, N., Good-Ellis, M., Harris, E., & Lestelle, V. (1985). A controlled evaluation of inpatient family intervention. I. Preliminary results of the six-month follow-up. *Archives of General Psychiatry* 42(9), 882–886.
2. Haas, G.L., Glick, I.D., Clarkin, J.F., Spencer, J.H., Lewis, A.B., Peyser, J., DeMane, N., Good-Ellis, M., Harris, E., & Lestelle, V. (1988). Inpatient family intervention: a randomized clinical trial. II. Results at hospital discharge. *Archives of General Psychiatry*, 45(3), 217–224.
3. Spencer, J.H., Glick, I.D., Haas, G.L., Clarkin, J.F., Lewis, A.B., Peyser, J., DeMane, N., Good-Ellis, M., Harris, E., & Lestelle, V. (1988). A randomized clinical trial of inpatient family intervention. III. Effects at 6-month and 18-month follow-ups. *American Journal of Psychiatry*, 145, 1115–1121.
4. Glick, I.D., Spencer, J.H., Clarkin, J.F., Haas, G.L., Lewis, A.B., Peyser, J., DeMane, N., Good-Ellis, M., Harris, E., & Lestelle, V. (1990). A randomized clinical trial of inpatient family intervention. IV. Followup results for subjects with schizophrenia. *Schizophrenia Research*, 3(3), 187–200.
5. Clarkin, J.F., Glick, I.D., Haas, G.L., Spencer, J.H., Lewis, A.B., Peyser, J., DeMane, N., Good-Ellis, M., Harris, E., & Lestelle, V. (1990). A randomized

clinical trial of inpatient family intervention. V. Results for affective disorders. *Journal of Affective Disorders*, 18(1), 17–28.

6. Haas, G.L., Glick, I.D., Clarkin, J.F., Spencer, J.H., & Lewis, A.B. (1990). Gender and schizophrenia outcome: a clinical trial of an inpatient family intervention. *Schizophrenia Bulletin*, 16(2), 277–292.
7. Glick, I.D., Clarkin, J.F., Haas, G.L., Spencer, J.H., & Chen, C.L. (1991). A randomized clinical trial of inpatient family intervention. VI. Mediating variables and outcome. *Family Process*, 30(1), 85–99.
8. Glick, I.D., Clarkin, J.F., Haas, G.L., & Spencer, J.H. (1993). Clinical significance of inpatient family intervention: conclusions from a clinical trial. *Hospital & Community Psychiatry*, 44(9), 869–873.

17.4 Stage 0: Opportunity identification/research needs assessment

Inspiration

No previous studies had provided clear evidence – based on a randomised clinical trial approach – of the effectiveness of inpatient family intervention for patients with schizophrenia and affective disorders and their families. Several studies had looked at outpatient family intervention approaches, but the reality of practice in the US at the time was that inpatient family intervention was recommended and in many cases was easier to implement and maintain, and hence was probably more frequently used. Because of the practicalities of the situation, and in many cases the necessity of providing families with information at the critical phase of illness in any case, this approach was widely used without any strong evidence that it was beneficial. This was a clear gap in the literature and the research group identified that it would be valuable and possible for them to conduct a study in this area. Therefore, the choice to work with inpatient rather than outpatient family intervention was in order to better understand the effectiveness of a treatment approach that was already widely used, rather than because of any specific motivation related to previous research or strong hypothesis about family intervention in the inpatient setting.

Haas' motivation for conducting this study was based on her doctoral research on the socialization of sex differences in normal development and her clinical observations of individuals with schizophrenia who were included in the study and interviewed following discharge from hospital. In conducting a systematic review of the research data on gender differences in schizophrenia available as of 1985, she was impressed that there was evidence of differences in age at onset, frequency of hospitalisation and possible differences in treatment response. Most impressive in this regard were the early published clinical observations of Emil Kraepelin and data from the long-term clinical studies of Manfred Bleuler published in 1972; each noted evidence of better long-term outcomes for females. Haas was interested in investigating whether in sex differences in schizophrenia symptomatology and outcome might be characteristic of the sample included in the study.

Feasibility

One reason that the identified gap existed was because of the methodologic and pragmatic complications of mounting and carrying out research on inpatient psychosocial treatments. Integrating the trial of a psychosocial treatment of this nature into the clinical treatment taking place on an inpatient unit is challenging, particularly from an administrative and organisational perspective. It is also challenging to demonstrate the effectiveness of a secondary treatment in a setting where a well-established primary treatment or complex of treatments is already taking place. In this case, the inpatient clinical treatment being provided reflected the standard treatment process at the time, including pharmacological and other psychosocial approaches, as indicated, in each case. With a secondary treatment such as family intervention, researchers must demonstrate an incremental effect over and above the existing benefits of the other treatments taking place.

Another reason that a similar study had not been conducted before was that, in general, the people conducting inpatient family interventions were not scientists and hence did not have experience of conducting these kinds of studies. This was explained by Glick at interview:

> People that do family therapy are not scientists, they're clinicians. So they haven't had the experience or gone through the effort of designing protocols and getting funding to do such studies. That's one of the major reasons…. So that's an answer to your question of why more isn't done. It's very hard to do, it takes money and people that are interested in it aren't scientists. (IG)

By bringing together family therapists and scientists who were interested in and committed to this work, and that had the experience of designing such studies, obtaining funding and managing a research project, the team were able to conduct the research.

Potential value

As outlined above, there was a clear gap in the literature around the effectiveness of inpatient family intervention and the research promised direct implications for existing practice.

17.5 Stage 1: Inputs to research

Money, researcher time, lab/office space and consumables

The initial support for this project came from a family foundation, the Norman and Rosita Winston Foundation (1981–1983) as well as from the core funding from NIMH to Cornell, grant number 507-RR05396 (Biomedical Research Support grant to Cornell). The later stages of the work were supported by the NIMH through an additional grant directly to this project, grant MH-34466 ($180,000, 1984–1986; PI: Ira Glick). Haas notes that a lot of the research was conducted prior to the NIMH funding award being made, and that the NIMH funding actually paid primarily for the later part of the data collection and analysis. By the time the grant review committee site visit was conducted, the first cohort of patients had already been identified and the initial stages of data collection had begun. NIMH staff were impressed with the study and the work the researchers had done up to that point, and decided to fund them to ensure that the study could be fully completed. Part of the NIMH funding was also to provide a proper salary for Haas, who up until that point had been working with limited funding ($7,000) for the

work. The NIMH and foundation funding sources are acknowledged on all the study outcome publications. It is not clear whether this study would have been completed if the NIMH funding had not been awarded. Clearly it had already been set up without the direct NIMH funding in place, but there was an expectation that full funding could be secured. Whether alternative sources of funding, such as additional money from the Norman and Rosita Winston Foundation, would have been available is unclear; however, it is unlikely that the follow-up interviews and evaluation of data would have been completed in a timely fashion without such funding.

Expertise and techniques

The study's lead researcher, Glick, had been recruited to Cornell and the Payne Whitney Clinic as someone who could secure NIMH funding and who was organised and experienced and hence could get a project off the ground. He joined what was an excellent existing clinical team, including Lewis and Spencer, who were senior psychiatrists and medical directors of the inpatient unit where the study was conducted; social workers (Joanne Peyser, Nancy DeMane and Veronica Lestelle), the unit head nurse (Elizabeth Harris) and the occupational therapist (Marci Good-Ellis) are also listed in the main publications. Although all of them were considered excellent practitioners, they did not have significant research experience. However, the clinical staff were all committed to family therapy and able to provide significant input to this study. Glick had also worked on family intervention before, and Clarkin was a psychologist with previous research and family therapy experience who supervised the family intervention therapists. Haas brought a prior interest in gender differences, which proved important for the study, as well as some research experience, although she was at a fairly early stage in her career. Together, this strong clinical team and Glick, an experienced researcher who could secure funding, were crucial in making the research project a success.

17.6 Stage 2: Processes

A significant feature of the study design is that it was intended to reflect as closely as possible the reality of the way in which treatment was conducted in hospitals, since this was the treatment effect they wished to quantify. So, for example, no specific outpatient family therapy was required of either group, it was just recommended in the cases where it would be recommended in standard clinical practice, and similarly the inpatient intervention was limited to a short series of around eight sessions, similar to what would be generally employed in many hospitals. The study was designed by Glick in discussion with Lewis and Spencer, experienced clinicians, which resulted in a good reflection of true clinical practice. However, the diversity of different treatment regimes encapsulated within the trial could also have made the findings more difficult to interpret. The project began before funding was made available, but the design was rigorous and funding was sought successfully at a later stage, as described above. Otherwise, nothing was remarkable about the study design; rather it was interesting in the way in which it was able to address some of the challenges described earlier with studies of this type, and that it successfully obtained follow-up data out to 18 months.

17.7 Stage 3: Primary outputs

Knowledge

The findings from this study are published in a series of six outcome papers, with two additional papers reviewing the results from two different perspectives.

The first outcome paper (Glick et al., 1985), which covered the preliminary results of the study at the six-month follow-up stage, suggested that patients with better premorbid functioning benefitted the most from inpatient family intervention. However, after a fuller analysis including a wider data set, the conclusions of a second outcome paper were dramatically different (Haas et al., 1988). In contrast to the preliminary data, they found that the treatment effect of the inpatient family intervention was actually more effective for female patients, and particularly female patients with affective disorder rather than schizophrenia. This differential effect of the intervention based on gender was an unexpected finding, and gender differences were found to persist at the later 18-month follow-up (Spencer et al., 1988). At this point, the advantage for female patients persisted with the positive effect of the inpatient family intervention observed for female schizophrenic patients as well as those with affective disorder.

In terms of the effect on families, at the six-month follow-up there was a positive effect of the treatment on attitudes towards treatment and social support for all families. At both six and eighteen months, there was a positive effect on patient rejection and family burden for families of female patients, such that families of female patients were less likely to reject the schizophrenic patient or to consider the patient a burden. Interestingly, female patients with other diagnoses (in the psychiatric comparison group) were found to do better without the treatment. These results are described in the third outcome paper, Spencer et al. (1988).

Full analysis of all the follow-up results for schizophrenia and affective disorder are covered in the fourth and fifth outcome papers, respectively (Glick et al., 1990; Clarkin et al., 1990). In schizophrenia, they conclude that inpatient family intervention does show benefits for patients with poor premorbid functioning but that this is limited to female patients and that the effect is not evident until the 18-month follow-up. However, the effect is seen for their families at an earlier stage, and a combination of this, post-discharge time to manifest functional improvement, and increased openness to family treatment after discharge, may account for some of the difference and the timing (later emergence) of gender differences in outcome. Improved compliance with medication treatment was not sufficient to explain the results. Male patients, in contrast, seem unaffected by the treatment, or maybe did a little worse, despite observed positive impacts on their families. A number of possible explanations are offered for this across the publications series, including differing expectations for genders, differences in level of social functioning existing prior to treatment, and the possibility that a more sustained outpatient family intervention might be more beneficial for males.

In terms of affective disorders, they found that female bipolar patients and families benefited from the intervention, while unipolar patients and families did not. In fact, for male patients and all unipolar patients a significant negative effect was observed. In the case of male patients, similar reasons are formulated to those for schizophrenia, such as differing family expectations, but for unipolar patients, the authors are less able to suggest

reasons, except for the schizophrenia focus of the inpatient family intervention. It may also be that the pattern of illness in schizophrenia is closer to that observed in bipolar disorder in contrast to unipolar depression, wherein, in a majority of cases, the severity of dysfunction, frequency of relapse and chronicity of the condition is less marked. These and the other findings spanning the study are summarised in a later paper that analyses some of the mediating variables and the factors related to outcome (Glick et al., 1991); in a further publication, the data are analysed with a focus on evaluation of the clinical significance of the findings in addition to their statistical significance (Glick et al., 1993).

The relationship between gender and outcome for schizophrenic patients is explored in more detail in the target publication, also based on this data, which details the outcomes mentioned above and explores potential reasons for these differences (Haas et al., 1990). Notable is the assertion that families of female patients were more reliable in attending and being on time for the inpatient family intervention sessions and that they were also more supportive in terms of patient compliance with treatment and showed a significant reduction in critical attitudes towards patients, where no such reduction was seen in the families of male patients. Four possible explanations for the differences in treatment response observed are outlined:

1. Differing social and occupational roles between genders – expectations are perhaps higher for males and families may be less realistic in their expectations regarding the long-term progress of the patients.

2. Differing traditional sex-role socialisation norms, in which females are more dependent on the family, meaning they may be more open to family support and family intervention approaches.

3. Some studies show that schizophrenic females have superior social skills to males, and this improved social premorbid and intermorbid functioning may make them better able to interact with family members.

4. Sex differences in symptomatology, such as higher levels of alcoholism, substance abuse and antisocial behaviour amongst males, were observed at admission and follow-up, which may have contributed to both poor outcome and poor response to family treatment.

Haas suggests that the publications relating to this research were highly cited partly because they were first-hand evidence about the effectiveness of the approach, but also because the findings, particularly those regarding gender differences, were rather unexpected at that time.

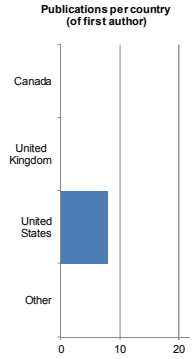
A bibliometric analysis of the papers produced from the research cloud is shown below.

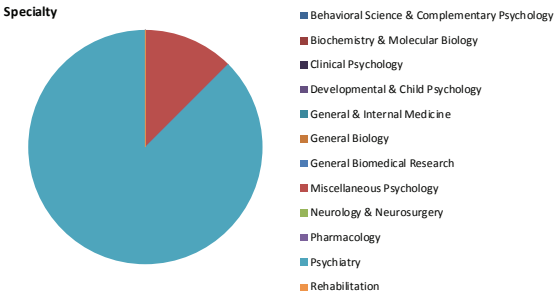
Research cloud:

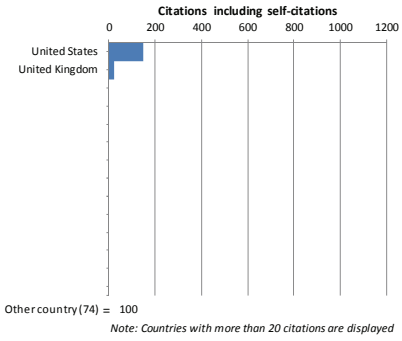
	Citations in:		% of total citations	Research level of cloud papers	
WoS Indexed papers: 8	**RCT:**	34	10%	Clinical **1:**	88%
Total citations of papers: 357	**Meta-analyses:**	8	2%	**2:**	0%
of which, self-citations: 2.0%	**Indexed practice guidelines:**	7	2%	**3:**	0%
Mean citations per paper: 45	**Review articles:**	110	31%	Basic **4:**	0%
Distinct cloud citations: 252					
Second-generation cloud citations: 9,103					
Third-generation cloud citations: 132,752					

Most highly cited article: John F. Clarkin, Ira D. Glick, Gretchen L. Haas, James H. Spencer, Alfred B. Lewis, Joanne Peyse, Nancy DeMane, Marcie Good-Ellis, Elizabeth Harris and Veronica Lestelle (1990). A randomized clinical trial of inpatient family intervention V. results for affective disorders. Journal of Affective Disorders Volume 18, Issue 1, Pages 17-28

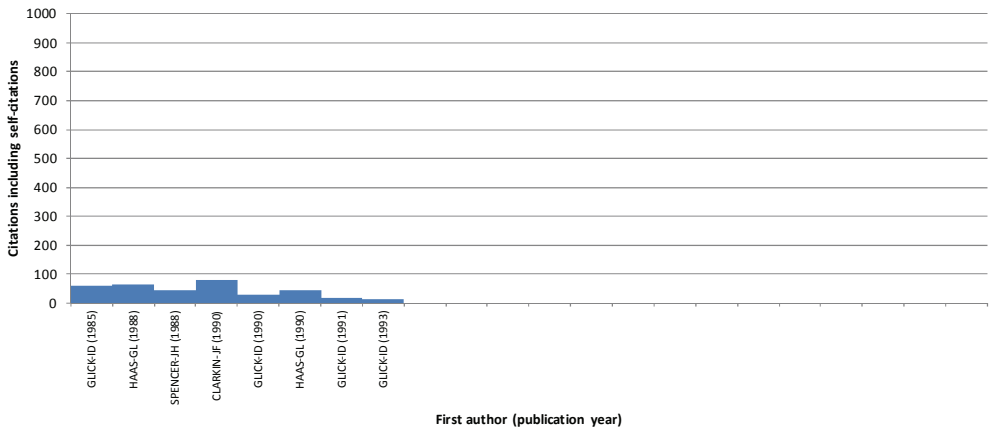
Times cited: 81

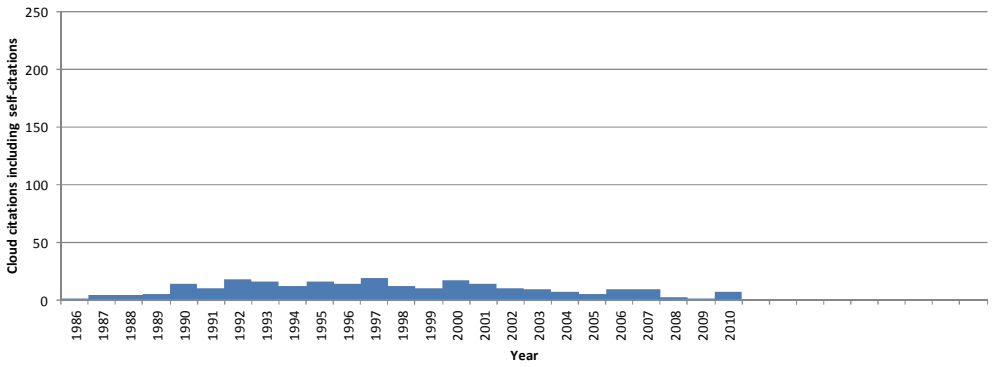






Note: Countries with more than 20 citations are displayed





Targeting future research

Effect on the researchers' careers

In terms of the experience gained, Haas found that this study, her first position following graduate school, provided excellent hands-on research experience and was very educational in terms of providing clinical exposure to individuals with schizophrenia. She was able to conduct a wide range of interviews with patients and their families and learn about their personal experiences with the disorder; this, she felt, provided a very helpful introduction to a career in this area. She was promoted from Research Associate to Assistant Professor of Psychology in Psychiatry in 1984, and again to Associate Research Professor of Psychology in 1989, partly due to the work conducted in this study.

Haas received a FIRST (First Independent Research Support and Transition) Award, entitled 'Sex Differences in Schizophrenia', from the NIMH to look at sex differences and schizophrenia (MH-43613, $349,987, 1987–1993). With this grant, she set up and conducted a longitudinal study looking at gender differences in schizophrenia. Through this grant she was able to employ graduate students such as Denise Hien, who has continued to focus on gender differences and the psychiatric status and healthcare needs of women during her career as an NIMH-funded researcher, though not in the field of schizophrenia. Haas was also able to provide primary research mentoring and data analytic support to Lisa Dixon, MD, then a psychiatric resident who, with Haas, conducted her initial studies on substance use in schizophrenia. Dixon has gone on to conduct federally funded research on family interventions in schizophrenia.

Haas did not continue to look at gender differences after the NIMH grant, largely because of situational factors involving a move from New York to Pittsburgh, where she accepted a position as Associate Professor of Psychiatry. Haas' other research interest was suicide, and under the direction of J. John Mann, she and a group of colleagues established a suicide research centre at Cornell University Medical Center, where she served as director of the clinical evaluation core. Investigators from this NIMH-funded research centre were invited to join the faculty at the University of Pittsburgh. When Haas moved, the longitudinal component of the research was limited, and it was challenging for Haas to continue this work remotely. When she came to renew the grant on sex differences while based at Pittsburgh, the work was not funded for a variety of reasons, perhaps partly because there was already another group of researchers working in this area at University of Pittsburgh, and partly because Haas had moved and couldn't directly continue working with the team and the cohort already established. From then on, although Haas retained an interest in gender and schizophrenia, directing some of her students to look at these issues, her work has focused on suicide and mental illness.

As noted above, this was the first research experience for the two psychiatrists, Lewis and Spencer, who were involved in this work. Neither of them went on to do significant further research, but their involvement with this study may have had an impact on their thinking and their clinical work.

Clarkin continued to work in the area of psychosocial intervention, an field in which he had been working previously, and it is not clear the extent to which this study was significant in the course of his research career. Similarly, Glick continued to conduct research, but he was also a well-established researcher in the field before this study was

conducted, and there is not clear evidence that this study made a specific impact on the path of his later career.

Future work

As described above, the work did have some impact on Haas' research, as she went on to do a follow-up study looking at the role of gender in schizophrenia. The results of this subsequent work were primarily presented in the form of conference presentations and published abstracts (Haas et al., 1991, 1999; Haas, Escobad et al., 1995; Haas, Sweeney et al., 1995; Hien et al., 1992; Maki et al., 2004; Dickey et al., 1998; Aguilar et al., 1995) rather than journal publications, reflecting the importance Haas placed on this form of dissemination (as described in the next section). The follow-up work looked at sex differences with a particular focus on premorbid functioning (Hien et al., 1998); however, Haas did direct later students and colleagues to consider gender differences in areas ranging from treatment response (Rubin et al., 2008) to interaction with the family (Wuerker et al., 1999). She has maintained an interest in the area and was invited to co-author two book chapters on this topic (Haas & Castle, 1998; Haas & Garratt, 1998). Haas has suggested that she intends to conduct further work in this area with a focus on the now large cohort of individuals recruited into a longitudinal study of first episode schizophrenia or other psychotic disorders as part of the NIMH-funded Conte Center for the Study of Mental Disorders (Schizophrenia) (PI: David Lewis, MD), where Haas serves as a Co-Investigator and Co-Associate Director of the Clinical Services Core.

Regarding inpatient family interventions, it is important to note that there were many other people working in this area. Gerard Hogarty and Carol Anderson were both doing research on family interventions and psycho-education at the same time (e.g. Hogarty et al., 1991) at the University of Pittsburgh. However, there were some distinctions between the work. Hogarty's study compared individual treatment conditions so that the salient interventions can be identified. However, in the Haas study the intervention combined treatment modalities so that that we have no idea about the efficacy of either intervention. Haas suggests that the Cornell and University of Pittsburgh investigators communicated and shared information and that the atmosphere was collaborative. She also noted that in practice, family therapy in the US has focused more on work with the families of children rather than adult patients. Internationally, others working on family intervention (though often in the outpatient setting) around that time included Levene et al. (1989), Tarrier et al. (1988, 1989), Vaughn et al. (1992), Zastowny et al. (1992) and McFarlane et al. (1994, 1995).

The inpatient family intervention study was featured in a few schizophrenia guidelines and reviews, as described below. It has also been featured in reviews of bipolar disorder (e.g. Swartz & Frank, 2001).

It is difficult to determine which groups were directly influenced by the findings on gender differences in schizophrenia, since this was by no means the only work on this subject showing that there were differences between the sexes both in terms of the course of the disease and treatment response. However, it was one of the first pieces of work to show these gender differences in response to psychosocial rather than pharmacological treatment. In this sense, it may have been influential in shifting the focus away from looking at differences in brain chemistry, and towards a broader neuro-developmental approach to

understanding these differences. Haas mentioned a number of researchers with whom she had discussed issues relating to gender differences at conferences and meetings, and indeed some of these researchers, including Elaine Walker and Jill Goldstein, who did a significant amount of work in this area, do cite the target study in some of their publications (e.g. Walker & Lewine, 1993; Goldstein, 1997). However, one cannot attribute any of their work directly to this study, and it is likely that the influence of this work is only as part of a larger body of work.

17.8 Interface B: Dissemination

Academic dissemination

Although the papers in the research cloud were highly cited, Haas felt that dissemination at conferences, both in presentations and during the informal discussions that took place at the meetings, was important.

> I think that, in addition to published literature, the meetings and the networks that are developed in face-to-face dialogue with people who are enthusiastic about the same questions [that you are] is really key, they're important…. I think that, certainly for younger people [sic] I was a young investigator, it was critical to me to have colleagues that were interested in the area, that were enthusiastic, that helped me say 'this is important'…. (GH)

In 1989 Haas was invited to present her NIMH-funded work on sex differences in schizophrenia at a meeting of NIMH-funded investigators of gender and minority issues in schizophrenia. On the significance of this experience, at interview Haas added:

> …And for the head of NIMH to be coming to this meeting, and to get invited right at the time when I had just gotten a grant, was really a stamp of approval and support for what I was trying to do. (GH)

Haas also presented her work at the International Congress on Schizophrenia Research in 1987, and contributed to these meetings biannually from then on. This led to interest in the work and discussion with a number of researchers who conducted important work on gender differences including Elaine Walker and Carol Tamminga. Haas also presented at a NIMH conference on gender in 1989. A discussion with Jill Goldstein at that conference led to Haas being invited to write a paper on gender differences in clinical outcome for a special issue of *Schizophrenia Bulletin* on gender differences in schizophrenia (Volume 16, Issue 2, 1990).

Wider dissemination

Glick stressed that communication with NAMI (the National Alliance on Mental Illness, a nationwide advocacy group for the mentally ill and their families in the US) was important in disseminating and discussing the work.

> I did a lot of work with [NAMI], indeed I wrote some papers with them and I publicised the study. We worked with them closely we used them, we consulted with them…. They're nothing but helpful. (IG)

Although Haas has significant links with advocacy groups through her work on suicide, there was not as much interest among patient and family groups in her research on gender differences and inpatient family intervention. She has presented the work at NAMI

meetings, but did not find that there was as much interest and engagement compared to her work on suicide prevention. Glick did engage more extensively with NAMI in disseminating the work as described previously, and the project team communicated with them throughout the project and subsequently.

17.9 Stage 4: Secondary outputs

The work from this study has featured in a number of Cochrane reviews to differing extents. In the review of psycho-education for schizophrenia (Xia et al., 2011), the analysis concluded that psycho-education is beneficial for both families and patients. The inpatient family intervention trial was one of the studies that contributed to this conclusion. The intervention study is also mentioned in the review of family intervention for schizophrenia (Pharoah et al., 2006), but is excluded from the analysis as it looks at intervention at the inpatient stage, which is not the focus of the review. The work is also covered in the review of family therapy for depression (Heuken et al., 2009), and is noted as one of the best quality studies in this area. However, conclusions differ so significantly between studies that the review is unable to draw any substantive conclusions in terms of recommendations for practice.

The work is described in the American Psychological Association (APA) guidelines on treatment for bipolar disorder (Hirschfield et al., 2003) and its findings for this patient group are clearly explained as part of the recommendations for possible treatment approaches. The work is also featured in the APA guidelines on treatment of schizophrenia (Lehmen et al., 2004). In the section discussing gender, it is used as part of the evidence that women have a better course of illness and better outcomes. It also refers to this study in describing the possible role of family and societal expectations in gender differences, as demonstrated in the quote below.

> While such differences may be biologically mediated, psychosocial factors, including family and societal expectations, may also affect outcome. Haas and colleagues (1988) noted that social and occupational role demands may result in unrealistic family expectations of men with schizophrenia, and this issue should be dealt with in treatment. (Lehmen et al., 2004)

We have not found any instances of this work being cited in other guidelines (including NICE, SIGN and Canadian practice guidelines).

17.10 Stage 5: Applications

Although the work is cited quite widely and included in guidelines, it is challenging to determine whether the findings had an influence on practice, partly because the study's mixed message made it difficult to recommend a consistent and comprehensive policy. The work suggests that in terms of clinical efficacy, inpatient family intervention shows statistically significant efficacy only in females, and only for specific diagnoses. Family intervention was already being employed when the study was conducted, and often in inpatient situations; in the US, its use in inpatient settings has declined over the past two decades, according to Haas. Haas suggests that this change in clinical practice is not necessarily due to any specific research, but rather to the difficulties of conducting such

interventions in inpatient settings, where hospital stays are much shorter, and a decline in capacity to do this – partly due to the limited number of clinicians receiving formal training in family interventions, and partly as a result of a prominent shift in focus from psychosocial to biological research in psychotic disorders.

> Now, what's happened with marital and family therapy is a story unto itself. I've talked to Carol Anderson, a leader in the field of family psychoeducation, about this; it has dried up, I think, because it's hard to do, it's hard to teach…. I teach here in our medical center in Pittsburgh – one of the hotbeds of training and research in family intervention... we've reflected on why this leading medical center has never adopted a teaching focus on family interventions in practice with adults who have schizophrenia, even though psychoeducation, and family interventions were key to the outcomes of one of our leading researchers, Gerry Hogarty; I don't know why that is, except that it's hard to do; it requires large commitments of personnel and the collaboration of clinical leaders and researchers who are committed to seeing the implementation of and training in evidence-based clinical interventions. The NIMH is now leading the charge to promote implementation science research that aims to investigate how evidence-based treatments can be implemented. This is critical to move the product of research findings into the field of everyday practice… And the psychoeducation work that was somewhat related to this, continues to go on but in a very ad hoc fashion. (GH)

One important exception to this is the work of Armando Rotondi who, with Anderson and Haas, has conducted NIMH- and VA-funded research on the impact of internet-based family psycho-education and group intervention in schizophrenia. This work has led to cutting-edge publications on the effects of internet-based interventions for schizophrenia. This is also somewhat in contrast to the situation in the UK, where family intervention should be offered as standard according to NICE practice guidelines for all patients with schizophrenia and their families, including in the inpatient situation.

It terms of gender, significant research before and since this study has taken place. However, the evidence on specific treatment programmes indicated by, and tailored to, gender have not been formulated, meaning that differential assignment to treatment by gender does not take place, despite this being well discussed in the literature, well known in clinical practice and even covered in guidelines as described above. Haas also discussed this at interview, suggesting that the shift in focus to medication and away from psychosocial treatment has meant that these differences are less recognised in practice, but that this has started to change in recent times, and that she thinks gender differences may start to take on greater importance in the coming years with the re-emergence of psychosocial treatment.

> I teach psychosocial treatments for schizophrenia to our residents here and we talk about [gender differences in clinical characteristics but] we don't talk a lot about gender differences because there hasn't been enough in the literature about gender specific treatments. There is a recognition, though, that [in general] women have better social skills; that is recognized, I'd say, by clinicians as well as in the literature, and that [in general] women with schizophrenia have better social skills and they have better communication skills and they are, in some cases, easier to work with, but not always. The other thing is that with a tremendous emphasis on pharmacologic treatment, this is my other opinion about this, people have pinned their hope on antipsychotics…. Up until, I'd say the last three to five years, that has been a major focus. Now you see more of a growing interest in psychosocial treatments such as cognitive remediation and cognitive

> behavioral therapy for psychosis… with people jumping on this 'bandwagon', both in England and in the United States. There will become, I think, more of an interest in titrating psychosocial treatments [for individuals] and that's where you're going to see the interest in gender differences emerge again; that's my guess. I would place a huge bet on that. (GH)

Glick suggests that one reason that the research conducted in this study may have been slower to have an impact on practice has been budget reductions (in both the US and other countries, including the UK), meaning that there is less time and money available to conduct inpatient family intervention, particularly as there is pressure to cut the length of inpatient stays. As there is less time to spend with the family, particularly in the inpatient setting, these findings become less relevant to clinical practice.

17.11 Stage 6: Public engagement

None identified.

17.12 Stage 7: Final outcomes

It is difficult to attribute any final outcomes to this work, as it has had a limited or at least not easily identified impact on practice in relation to schizophrenia and bipolar disorder. This is probably related to other wider changes and trends in the field away from psychosocial treatment rather than anything specific to this work.

17.13 Table of payback

Payback category	Impacts from case study
Knowledge Production	• Demonstrated an unexpected gender difference in treatment response to family intervention. • Provided evidence on the effectiveness of inpatient family intervention for schizophrenia and affective disorder.
Research Targeting and Capacity Building	• Contributed to Haas' promotion. • Led to follow-on funding for Haas' research in schizophrenia that supported her early career mentoring of research trainees – two of whom (Hien and Dixon) have gone on to lead federally funded mental health research: Hien on women's mental health and Dixon on family interventions in schizophrenia. • Haas retained an interest in gender differences, though this has not been the focus of the bulk of her subsequent research.
Informing Policy and Product Development	• Cited in three Cochrane reviews. • Cited in APA guidelines for the treatment of bipolar disorder and

	schizophrenia. In bipolar guidelines forms only evidence for efficacy of one particular treatment option.
Health and Health Sector Benefits	• None identified, though Haas suggests this may change in future if focus shifts from medication to psychosocial treatment.
Broader Social and Economic Benefits	• None identified.

17.14 Timeline

1981	Haas comes to Cornell as a Research Associate; funding received for the study from the Norman and Rosita Winston Foundation
1984	Haas promoted to Assistant Professor of Psychology in Psychiatry; NIMH grant MH-34666 for the study awarded
1985	Preliminary results published
1987	Haas receives NIMH award (MH-43613) on 'Sex differences in schizophrenia'; Haas presents work at International Congress in Schizophrenia Research and Annual Meeting of the American Psychological Association (APA)
1988	Results at discharge and six months published
1989	Haas presents work at NIMH conference on gender and minorities; Haas promoted to Associate Research Professor of Psychiatry
1990	Follow-up results for both schizophrenia and affective disorders published; suicide centre set up; Haas moves to Pittsburgh; special issue of *Schizophrenia Bulletin* on gender difference published with article by Haas et al.
1991	Mediating variables and outcomes paper published
1993	Clinical significance analysis published
2003	APA guidelines on treatment of bipolar disorder published, referencing this work
2004	APA guidelines on treatment of schizophrenia published, including a section on gender difference that references Haas' work

17.15 References

Aguilar, E.J., Bagwell, W.W., Haas, G.L., Sweeney, J., Schooler, N.R., Pettegrew, J.W., & Keshavan, M.S. (1995). Cerebral asymmetry, gender and early schizophrenia. *Schizophrenia Research*, 15(1–2), 75.

Clarkin, J.F., Glick, I.D., Haas, G.L., Spencer, J.H., Lewis, A.B., Peyser, J., DeMane, N., Good-Ellis, M., Harris, E., & Lestelle, V. (1990). A randomized clinical trial of inpatient family intervention. V. Results for affective disorders. *Journal of Affective Disorders*, 18(1), 17–28.

Dickey, W.C., Haas, G.L., Keshavan, M.S., & Sweeney, J.A. (1998). Gender and familial history as predictors of patterns of premorbid functioning in first-episode schizophrenia. *American Journal of Epidemiology*, 147(11), S54–S54. Suppl. S Abstract, 216.

Falloon, I., Boyd, J., Mcgill, C., Williamson, M., Razani, J., Moss, H., & Gilderman, A. (1982). Family management in the prevention of exacerbations of schizophrenia. *New England Journal of Medicine,* 306(24), 1437–1440.

Glick, I.D., Clarkin, J.F., Haas, G.L., & Spencer, J.H. (1993). Clinical significance of inpatient family intervention: conclusions from a clinical trial. *Hospital & Community Psychiatry*, 44(9), 869–873.

Glick, I.D., Clarkin, J.F., Haas, G.L., Spencer, J.H., & Chen, C.L. (1991). A randomized clinical trial of inpatient family intervention. VI. Mediating variables and outcome. *Family Process*, 30(1), 85–99.

Glick, I.D., Spencer, J.H., Clarkin, J.F., Haas, G.L., Lewis, A.B., Peyser, J., DeMane, N., Good-Ellis, M., Harris, E., & Lestelle, V. (1990). A randomized clinical trial of inpatient family intervention. IV. Followup results for subjects with schizophrenia. *Schizophrenia Research*, 3(3), 187–200.

Glick, I.D., Clarkin, J.F., Spencer, J.H., Haas, G.L., Lewis, A.B., Peyser, J., DeMane, N., Good-Ellis, M., Harris, E., & Lestelle, V. (1985). A controlled evaluation of inpatient family intervention. I. Preliminary results of the six-month follow-up. *Archives of General Psychiatry* 42(9), 882–886.

Goldstein, M. (1997). Sex differences in schizophrenia: epidemiology, genetics and the brain. *International Review of Psychiatry*, 9(4), 399–408

Goldstein, M., Rodnick, E., Evans, J., May, P., & Steinberg, M. (1978). Drug and family therapy in the aftercare of acute schizophrenics. *Archives Of General Psychiatry,* 35, 1169–1177.

Haas, G.L., & Castle, D.J. (1997). Sex differences in schizophrenia. In Keshavan, M.S., & Murray, R.M. (eds.), *Neurodevelopment & Adult Psychopathology*, New York: Cambridge University Press, 155–177.

Haas, G.L., & Garratt, L.S. (1998). Gender differences in social functioning. In Mueser, K.T., & Tarrier, N. (eds.), *Handbook of Social Functioning in Schizophrenia*, Needham Heights: Allyn & Bacon, 149–180.

Haas, G.L., Escobar, M., Sweeney, J.A., & Keshavan, M.S. (1995). Sex-differences in age at onset in schizophrenia – Evidence for a subgroup of females with delayed illness onset. *Schizophrenia Research*, 15(1–2), 12.

Haas, G.L., Glick, I.D., Clarkin, J.F., Spencer, J.H., Lewis, A.B., Peyser, J., DeMane, N., Good-Ellis, M., Harris, E., & Lestelle, V. (1988). Inpatient family intervention: a

randomized clinical trial. II. Results at hospital discharge. *Archives of General Psychiatry*, 45(3), 217–224.

Haas, G.L., Glick, I.D., Clarkin, J.F., Spencer, J.H., & Lewis, A.B. (1990). Gender and schizophrenia outcome: a clinical trial of an inpatient family intervention. *Schizophrenia Bulletin*, 16(2), 277–292.

Haas, G.L., Keshavan, M.S., & Sweeney, J.A. (1999). Sex differences in schizophrenia a century after Kraepelin: a critical review of the findings. *Schizophrenia Research*, 36(1–3)SI, 133.

Haas, G.L., Sweeney, J.A., Garrat, L., & Keshavan, M.S. (1995). Sex-differences in the 3-factors model of schizophrenia. *Biological Psychiatry*, 37(9), 640.

Haas, G.L., Sweeney, J.A., Hien, D.A., Goldman, D., & Deck, M. (1991). Gender differences in schizophrenia. *Schizophrenia Research*, 4(3), 277.

Henken, T., Huibers, M.J., Churchill, R., Restifo, K.K., & Roelofs, J.J. (2009). *Family Therapy for Depression (Review)*. Cochrane Database of Systematic Reviews.

Hien, D.A., Haas, G.L., & Cook, H. (1998). Gender difference in premorbid social adjustment and intimacy motivation in schizophrenia. *Journal of Clinical Psychology*, 54(1), 35–48.

Hien, D.A., Haas, G.L., & Cook, H. (1992). Impact of gender and premorbid adjustment on intimacy motivation and asociality in schizophrenia. *International Journal of Psychology*, 27(3/4), 463.

Hirschfield, R.M.A., Bowden, C.L., Gitlin, C.L., Keck, M.J., Perlis, R.H., Suppes, T., Thase, M.E., & Wagner, K.D. (2003). Practice guideline for the treatment of patients with bipolar disorder. APA guidelines. *Focus*, 1, 64–110.

Hogarty, G.E., Anderson, C.M., Reiss, D.J., Kornblith, S.J., Greenwald, D.P., Ulrich, R.F., Carter, M., & EPPICS Research Group (1991). Family psychoeducation, social skills training, and maintenance chemotherapy in the aftercare treatment of schizophrenia II. Two-year effects of a controlled study of relapse and adjustment. *Archives of General Psychiatry*, 48, 340–347.

Kottgen, C., Sonnichsen, I., Mollenhauer, K., & Jurth, R. (1984). Group therapy with the families of schizophrenic patients: results of the Hamburg Camberwell-family interview study III. *International Journal of Family Psychiatry,* 5(1), 83–94.

Leff, J., Kuipers, L., Berkowitz, R., Eberlein-Vries, R., & Sturgeon, D. (1982). A controlled trial of social intervention in the families of schizophrenic patients. *British Journal of Psychiatry,* 141, 121–134.

Leff, J., Kuipers, L., Berkowitz, R., & Sturgeon, D. (1985). A controlled trial of social intervention in the families of schizophrenic patients: two year follow-up. *British Journal of Psychiatry,* 146, 594–600.

Lehman, A.F., Lieberman, J.A., Dixon, L.B., McGlashan, T.H., Miller, A.L., Perkins, D.O., & Kreyenbuhl, J. (2004). *Practice Guidelines for the Treatment of Patients with Schizophrenia*. Second Edition. APA.

Levene, J.E., Newman, F., & Jefferies, J.J. (1989). Focal family therapy outcome study: I. Patient and family functioning. *Canadian Journal of Psychiatry*, 34, 641–647.

Maki, P.M., Rubin, L.H., Haas, G.L., Keshavan, M.S., & Sweeney, J.A. (2004). Sex differences in cognitive response to medication in first episode schizophrenia. *Biological Psychiatry*, 55, 131S. S8 Abstract, 468.

Pharoah, F., Mari, J., Rathbone, J., & Wong, W. (2010). *Family Intervention for Schizophrenia*. Cochrane Database of Systematic Reviews.

Pharoah, F., Mari, J., Rathbone, J., & Wong, W. (2006). *Family Intervention for Schizophrenia*. Cochrane Database of Systematic Reviews.

Rubin, L.H., Haas, G.L., Keshavan, M.S., Sweeney, J.A., & Maki, P.M. (2008). Sex difference in cognitive response to antipsychotic treatment in first episode schizophrenia. *Neuropsychopharmacology*, 33(2), 290–297.

Spencer, J.H., Glick, I.D., Haas, G.L., Clarkin, J.F., Lewis, A.B., Peyser, J., DeMane, N., Good-Ellis, M., Harris, E., & Lestelle, V. (1988). A randomized clinical trial of inpatient family intervention. III. Effects at 6-month and 18-month follow-ups. *American Journal of Psychiatry*, 145, 1115–1121.

Swartz, H.A., & Frank, E. (2001). Psychotherapy for bipolar depression: a phase-specific treatment strategy? *Bipolar Disorder*, 3, 11–22.

Tarrier, N., Barrowclough, C., Vaughn, C., Bamrah, J.S., Porceddu, K., Watts, S., & Freeman, H. (1989). Community management of schizophrenia: a two-year followup of a behavioural intervention with families. *British Journal of Psychiatry*, 154, 625–628.

Tarrier, N., Barrowclough, C., Vaughn, C., Bamrah, J.S., Porceddu, K., Watts, S., & Freeman, H. (1988). The community management of schizophrenia. A controlled trial of a behavioural intervention with families to reduce relapse. *British Journal of Psychiatry,* 153, 532–542.

Vaughan, K., Doyle, M., McConaghy, N., Blaszczynski, A., Fox, A., & Tarrier, N. (1992). The Sydney intervention trial: a controlled trial of relatives' counselling to reduce schizophrenic relapse. *Social Psychiatry and Psychiatric Epidemiology*, 27(1), 16–21.

Walker, E.F., & Lewine, R.J. (1993). Sampling biases in studies of gender and schizophrenia. *Schizophrenia Bulletin*, 19(1), 1–7.

Wuerker, A.K., Haas, G.L., & Bellack, A.S. (1999). Racial and gender differences in expressed emotion and interpersonal control in families of persons with schizophrenia. *Family Process* 38(4), 477–496.

Xia, J., Merinder, L.B., & Belgamwar, M.R. (2011). *Psychoeducation for Schizophrenia*. Cochrane Database of Systematic Reviews.

Zastowny, T.R., Lehman, A.F., Cole, R.E., & Kane, C. (1992). Family management of schizophrenia: a comparison of behavioral and supportive family treatment. *Psychiatric Quarterly*, 63, 159–186.

CHAPTER 18 Treatment Strategies in Schizophrenia (TSS)

This case study is based on the research that produced the paper:

Schooler, N.R., Keith, S.J., Severe, J.B., & Matthews, S. (1989). Acute treatment response and short term outcome in schizophrenia: first results of the NIMH treatment strategies in schizophrenia study. Treatment Strategies in Schizophrenia Collaborative Study Group. *Psychopharmacology Bulletin*, 25(3), 331–335.

Information was gathered from interviews with Nina Schooler, Alan Bellack and John Kane, as well as from desk-based research.

18.1 Summary

The US National Institute of Mental Health's (NIMH) Psychopharmacology Research Branch funded the Treatment Strategies in Schizophrenia (TSS) study, which brought together two streams of research, or research clouds. The first addressed whether dosage reduction strategies could reduce the risk of tardive dyskinesia (involuntary bodily movements) and other neurologic effects caused by anti-psychotic drugs, and still prevent relapse. The second looked at whether different types/intensities of family treatment would differ in their ability to prevent relapse. Though each of these components encompassed large bodies of research in their own right, together they resulted in a 'thin' research cloud since the two streams were not typically explored in single studies.

Each of five centres received a $175,000 grant per year for five years ($875,000 total per centre, $4,375,000 total for the study). The study received a substantial amount of external support from Janssen-Cilag (both US and German offices), which provided all of the medication supplies.

The TSS results indicated that both the low-dose and intermittent dosage reduction strategies increased relapse when compared to standard dose treatment, though when compared against each other, the intermittent treatment led to higher rates of rescue medication and a shorter time to rehospitalisation. The intermittent treatment also increased hospitalisation. There was no difference in effects between the two family treatments in measures sensitive to effects of medication, although there were benefits in medication compliance and overall the findings support the engagement of families within a psycho-educational framework. While the study was considered worthwhile at the time, aspects of it were considered obsolete almost as soon as it was finished because of the

introduction of a new generation of antipsychotics that have a substantially lower risk of causing tardive dyskinesia.

18.2 Introduction

18.2.1 Scientific background

At the time of the study, the efficacy of first-generation antipsychotics in the maintenance treatment of schizophrenia had been established and new findings were being reported as to the potential of psychosocial family interventions in preventing relapse and forming a part of a maintenance treatment strategy. However, little work had been done in a controlled research environment in relation to family interventions and, moreover, even less had been done to look at the interaction of medications and psychosocial treatments. The NIMH extramurally funded TSS study brought together these two independent areas of research – psychopharmacology and psychosocial interventions for treating schizophrenia – in the first long-term multicentre maintenance study of its kind.

Psychopharmacology researchers were interested at the time in finding both a way to use antipsychotics to prevent relapse and to limit the risk of side effects caused by the antipsychotics such as tardive dyskinesia, secondary negative symptoms, and others. There was a desire to understand whether a balance could be achieved between reducing side effects and still achieving the benefits antipsychotic drugs offered in producing symptom remission, preventing relapse and improving functioning beyond an improvement in psychopathology.

In the early 1980s there was also increasing evidence that psychosocial treatments could play an important role in improving patient outcomes. In particular, at the time of the TSS study, six controlled studies of family interventions had been conducted and though there were differences in the interventions employed, the results of improved patient outcomes were similar. Only three studies, though, reported two-year follow-up results and of these it was only the study of Falloon et al. (1982) using behavioural family therapy that reported a reduction in relapse rates. In addition, Falloon's model of family intervention was one where the family chose the problems they wanted to work on. Some of the other family intervention models were based heavily on the therapist developing the direction of the treatment, and this introduced too many variables that were difficult to control in a multisite study. Therefore, Falloon's model was selected as the basis for the study.

Bringing these two areas together, the TSS study had two components: three dosage strategies (low, intermittent, standard) and two family treatment strategies (applied family treatment and supportive family treatment). The interactions between these two components, as well as the comparisons within them, were studied in five research sites in the USA in order to determine the impact of dose reduction of antipsychotic medication and family treatment on relapse and rehospitalisation rates during maintenance treatment. Though each individual component of the research had a significant amount of work behind it, the overlap of these two components was comparatively under-researched.

18.2.2 Researcher backgrounds

Nina Schooler was the co-principal investigator of the TSS study. Schooler started working at NIMH in 1963 as a research social psychologist. She moved up through the

ranks and in 1980 was appointed Chief of the Schizophrenic Disorders Section and Assistant Chief of the Pharmacologic and Somatic Treatments Research Branch. At the time the study was initiated, Schooler was Acting Chief of the latter research branch and soon was to become (in 1985) the Assistant Chief of the Schizophrenia Research Branch. Schooler left the NIMH in 1988 partway through the TSS study due to internal issues, but was able to retain her leadership position on the study through a professional services contract with NIMH.

Prior to leading the TSS study, Schooler had been working on multicentre studies for many years and had previously been leading one looking at prevention of relapse using long acting injectable fluphenazine decanoate or oral fluphenazine hydrochloride. The TSS study was the largest major study that Schooler had led to date.

Samuel Keith was the other principal investigator for the TSS study. Keith was at an earlier point in his career than Schooler and was 'ready' to lead a big national study. By the time the study finished, Keith was Director of the Schizophrenia Research Program. When he left the NIMH in the early 1990s to become a Chair of the Department of Psychiatry at the University of New Mexico, he was Acting Deputy Director of NIMH.

The TSS study had five sites around the country. The principal investigators at each site and their psychosocial or psychopharmacological expertise are listed below:

- John M. Kane, MD – Principal Investigator at the Albert Einstein School of Medicine and Hillside-Hospital-Long Island Jewish Medical Center; psychopharmacology expertise.
- Jeffrey A. Leiberman, MD – Co-Principal Investigator at the Albert Einstein School of Medicine and Hillside-Hospital-Long Island Jewish Medical Center; psychopharmacology expertise.
- Margaret Woerner, PhD – Co-Principal Investigator at the Albert Einstein School of Medicine and Hillside-Hospital-Long Island Jewish Medical Center; psychopharmacology expertise.
- Alan S. Bellack, PhD – Principal Investigator at the Medical College of Pennsylvania and Eastern Pennsylvania Psychiatric Institute; psychosocial expertise.
- George M. Simpson, MD – Co-Principal Investigator at the Medical College of Pennsylvania and Eastern Pennsylvania Psychiatric Institute; psychopharmacology expertise.
- Ira D. Glick, MD – Principal Investigator at Cornell University Medical College and Payne Whitney Clinic; psychopharmacology and psychosocial expertise.
- Allen J. Frances, MD – Co-Principal Investigator at Cornell University Medical College and Payne Whitney Clinic; general psychiatry expertise.
- William A. Hargreaves, PhD – Principal Investigator at University of California at San Francisco and San Francisco General Hospital; psychosocial expertise.

- Marc Jacobs, MD – Co-Principal Investigator at University of California at San Francisco and San Francisco General Hospital; psychosocial expertise.
- Philip I. Ninan, MD – Co-Principal Investigator at Emory University and Grady Memorial Hospital; psychopharmacology expertise.
- Rosalind M. Mance, MD – Co-Principal Investigator at Emory University and Grady Memorial Hospital; psychosocial expertise.

The study had two consultants who were responsible for the psychosocial aspect of the study: **Ian Falloon** (MD) and **Christine McGill** (PhD) worked across all the sites in ensuring there was consistent application of the family intervention component of the study.

Finally, **Joanne Severe** (MS) worked at NIMH as the main coordinator responsible for running the multicentre trial. **Susan Matthews** was another NIMH collaborator.

18.3 Defining the research cloud

The TSS research cloud sat above two much larger and more substantial research areas: dosage of antipsychotics and family psycho-educational and therapeutic interventions. Each 'supporting' area could be thought of as asking the following questions, respectively:

- *Can you reduce medication dosage and still succeed in preventing relapse? Prior studies had looked at low dosage and intermittent dosage separately, not simultaneously.*
- *Can family treatment improve outcomes and prevent relapse? Prior studies had compared family intervention to no family intervention, but no studies had looked at different types of interventions and compared them against each other.*

Schooler described the TSS study as belonging to a cloud that brought these two research areas together. A list of the papers in the TSS research cloud is below.

Initial paper used to identify the research cloud:

1. Schooler, N.R., Keith, S.J., Severe, J.B., & Matthews, S. (1989). Acute treatment response and short term outcome in schizophrenia: first results of the NIMH treatment strategies in schizophrenia study. Treatment Strategies in Schizophrenia Collaborative Study Group. *Psychopharmacology Bulletin*, 25(3), 331–335.

Other papers in the research cloud:

2. Glick, I.D., Jacobs, M., Lieberman, J., Simpson, G., & Schooler, N.R. (1989). Prediction of short term outcome in schizophrenia: depressive symptoms, negative symptoms, and extrapyramidal signs. Treatment Strategies in Schizophrenia Collaborative Study Group. *Psychopharmacology Bulletin,* 25(3), 344–347.
3. Schooler, N.R. (1995). Integration of family and drug treatment strategies in the treatment of schizophrenia: a selective review. *International Clinical Psychopharmacology*, 10, 73–80.
4. Schooler, N.R., & Keith, S.J. (1993). The clinical research base for the treatment of schizophrenia. *Psychopharmacology Bulletin,* 29(4), 431–446.

5. Mueser, K.T., Sengupta, A., Schooler, N.R., Bellack, A.S., Xie, H., Glick, I.D., & Keith, S.J. (2001). Family treatment and medication dosage reduction in schizophrenia: effects on patient social functioning, family attitudes, and burden. *Journal of Consulting and Clinical Psychology,* 69(1), 3–12.

6. Schooler, N.R. (1993). Reducing dosage in maintenance treatment of schizophrenia. Review and prognosis. *The British Journal of Psychiatry,* 22, 58–65.

7. Schooler, N.R., Keith, S.J., Severe, J.B., Matthews, S.M., Bellack, A.S., Glick, I.D., Hargreaves, W.A., Kane, J.M., Ninan, P.T., Frances, A., Jacobs, M., Lieberman, J.A., Mance, R., Simpson, G.M., & Woerner, M.G. (1997). Relapse and rehospitalization during maintenance treatment of schizophrenia. The effects of dose reduction and family treatment. *Archives Of General Psychiatry,* 54(5), 453–463.

8. Keith, S.J., Bellack, A.S., Frances, A., Mance, R., & Matthews, S.M. (1989). The influence of diagnosis and family treatment on acute treatment response and short term outcome in schizophrenia. Treatment Strategies in Schizophrenia Collaborative Study Group. *Psychopharmacology Bulletin,* 25(3), 336–339.

18.4 Stage 0: Opportunity identification/research needs assessment

Inspiration

There were two main sparks of inspiration for this study: emerging evidence about the effects of dosage reduction strategies in preventing relapse and increasing evidence about the effects of family intervention in improving patient outcomes. Each is discussed briefly below.

At the time the TSS study was being developed, there was a keen interest in dosage reduction strategies for antipsychotic drugs. The efficacy of antipsychotics had already been established, as had their ability to reduce the risk of relapse after hospital discharge or the treatment of an acute exacerbation. In the first year following hospitalisation, research had shown that relapse rates were around 30 percent for patients taking antipsychotics, but much higher for patients receiving placebo (Schooler et al., 1980). However, these first-generation antipsychotics had many side effects, in particular tardive dyskinesia. In addition, in some cases, where akinesia or secondary 'negative' symptoms that could mimic depression set in, patients could even be more symptomatic after a year of antipsychotic drug treatment (Schooler et al., 1980).

This led to a desire to examine different dosage reduction strategies to prevent relapse, including continuous low-dose and targeted (or intermittent) treatment. Kane et al. (1984, 1986) had shown that reduced drug treatment could limit the risk of tardive dyskinesia. Use of low-dose strategies had also been tested in several different studies. The findings indicated that if dosage was reduced to 10–20 percent of a 'standard' dose, then there were reduced side effects and relapse rates were not significantly increased in the first year following the initial reduction in dosage (Marder et al., 1984; Hogarty et al., 1988). However, dosage reduction below this amount or for longer periods of time than one year was found to result in a higher rate of relapse or the worsening of symptoms (Kane et al., 1985; Marder et al., 1987).

> It was becoming increasingly clear that patients with schizophrenia needed to stay on medication in order to prevent the recurrence of psychosis. But it also had become clear that there was risk of developing tardive dyskinesia. …So we thought that we have a risk benefit trade-off here and is it possible that if we use much much lower doses of the antipsychotic medications during this long-term maintenance phase of treatment could we reduce the risk of tardive dyskinesia? So that was part of the impetus for those studies. (Kane, 2011)

Targeted or intermittent treatment strategies were used because it was thought that patients might only need medication during times when they were about to relapse or when they were particularly disturbed by psychosis. However, continued monitoring is needed with these strategies so that appropriate interventions can be made when patients are about to relapse or their psychosis is worsening. Moreover, the studies of targeted or intermittent treatment strategies had mixed results when compared to the studies of dosage reduction strategies, with some showing no significant differences in relapse and rehospitalisation, while others showed symptom exacerbations. A two-year study by Carpenter et al. (1987) was the longest study, and it showed that there were no significant differences in relapse and rehospitalisation when patients were treated intermittently with antipsychotics.

Drawing on both the encouraging findings from the low-dose studies and the potentially interesting findings about intermittent dosing, the TSS study was the first to compare directly the two dosage reduction strategies against each other and with standard dosing strategies.

The second spark of inspiration for this study was the increasing evidence that psychosocial treatments, in particular those that involved working with families, could have a positive effect on patient outcomes. There were six studies that had reported at that time (Falloon et al., 1982; Goldstein et al., 1978; Kottgen et al., 1984; Leff et al., 1982; Leff et al., 1985; Tarrier et al., 1988), all of which shared certain elements in common (Schooler et al., 1989):

- Enlistment of the family in a positive clinical alliance
- Education about schizophrenia
- Teaching of both communication and problem-solving skills
- Encouragement to families to expand social networks of themselves and the patient.

Though there was an interest in seeing how these family interventions would affect relapse, the researchers were clear that the psychosocial intervention was about getting the family to work better together to affect the course of the disease in a positive way.

> We explicitly viewed schizophrenia as a substantially biological disease where there [were] environmental factors that potentially contributed to onset but definitely contributed [more] to course. And that what we were trying to do is teach the family to communicate more effectively without casting blame or aspersions. And part of the goal of the intervention was to help families move forward in their own lives separate from the patient. Many of the families were isolated, their lives were tied up in caring for their child which added to stress. (Bellack, 2011b)

Therefore, looking at these two emerging bodies of evidence together, it was clear to Schooler at the time that drawing them together could be worthwhile and interesting.

> Tardive dyskinesia, late occurring involuntary movements, were a huge problem with the older antipsychotics, less so with the current ones. And as a result… both of these dose reduction strategies, in the same study, compared to keeping people on medication throughout the course of treatment was what made this unique in that these two strategies had been looked at separately, but never in a single study. Meanwhile, on the other side of the fence, there was a lot of interest in family interventions. And indeed, the British literature, led initially by studies by John Wing and Julian Leff, and then studies by Leff that looked at treatment, family treatment, to deal with what was called high expressed emotion… had suggested that there were factors in family environment that could influence outcome. And in particular, could prevent relapse. So this seemed like an opportunity to join both of those together. (Schooler, 2011b)

Feasibility

A range of factors made the TSS study feasible at the time, including the experience and expertise of the researchers (Schooler and Keith at NIMH, as well as the researchers at the five sites), and the resources and organisational support provided by the NIHM extramural research programme and the sites.

Schooler and Keith were both at NIMH in the extramural research division: Schooler in the Psychopharmacology Research Branch and Keith in the Clinical Research Branch. Later reorganisation created a Schizophrenia Research Branch with Keith appointed as Chief and Schooler as Assistant Chief. The Psychopharmacology Research Branch had historically functioned much like the NIMH intramural faculty to design and conduct studies that met the criteria for intramural research, but were funded extramurally, so they had experience in study design and running of multicentre trials. The TSS study built on the existing knowledge of how to design a study that 'allows a test of both additive and interactive effects of two treatment modalities' (Schooler, 1995, 74), in particular ones that looked at the interaction of medication and psychosocial treatments. Two earlier studies that Schooler had been involved in also followed this model (Hogarty et al., 1974; Hogarty et al., 1979).

Resources from NIMH and the five sites were a critical element of feasibility. As will be discussed in more detail below, the TSS study was only able to provide a fixed amount per year and it was made very clear to applicants for the study that this would not be enough to fully fund the research. In addition to proving that they had the expertise and ability to carry out the study, the centres also had to provide assurances that they would be able to make up the funding shortfall.

> One of the requirements was that the amount of the grant was fixed. …And the statement was made that this was not expected to adequately support the study, and that the sites would be expected to contribute to the support of the study. And they had to explain how they would do that. And they needed to have expertise, which would ensure that they could do the study. (Schooler, 2011b)

The study was not only feasible because of the support provided by NIMH, but also because of the way NIMH was structured internally and the way resources and support

were made available to fund this kind of research. At the time, NIMH was organised into two areas: an extramural research area where the primary mission was the distribution of research funds to investigators in the field and an intramural research area, which was an in-house research operation focusing on research with high public health significance and that the field was not otherwise doing. Historically, the Pyschopharmacology Research Branch within the extramural area also initiated, designed and conducted major multicentre trials if they were ones that the field would not otherwise conduct. At the time of the TSS study, the Pyschopharmacology Research Branch had just finished its previous study and was ready to move to the next multicentre trial.

Potential value

According to the researchers involved, the value of the TSS study was in its potential for clinical changes to improve the lives of patients. First, the dosage reduction component represented a change in clinical practice that could reduce side effects like tardive dyskinesia and have a positive effect on relapse. Secondly, the family intervention component also held promise for improving patient outcomes.

Further evidence of this value is seen in the way the study was funded. Since funding came through the extramural research programme it had to fulfil two important criteria: first, the research had to have high public health significance; secondly, the researchers could only do research that justifiably would not be done by the rest of the field.

> In conducting research as government employees in the extramural program, there was always the concern that we not just be entertaining ourselves as researchers, but that we be doing research that had 1) high public health significance, and 2) was research which the field independently was not submitting grants to do. …So the studies that we generally undertook were studies that were hard to do. And this study qualified on the grounds that it was looking at a combination of medication, and a psychosocial treatment, which required a broad range of expertise and that it would have to be multicentre, which required substantial coordination. (Schooler, 2011b)

18.5 Stage 1: Inputs to research

Money, researcher time, lab/office space and consumables

Each of the five centres received a $175,000 grant per year for 5 years ($875,000 total per centre, $4,375,000 total for the study). The study also funded indirect costs for the sites, which was standard practice for NIMH funding. As discussed previously, it was made clear that the grant alone was not expected to adequately support the study. The sites were expected to contribute to the support of the study through internal funds, but the sources of this support were never discussed.

> It was one of those things that was awkward to ask. …I never had a sense, and I interacted very, very closely with all of the sites… we never had the sense that we were being given a hard time because people didn't have the funds to do what they needed to do. (Schooler, 2011b)

The PIs who were interviewed confirmed that they didn't recall the extra funding being a difficult thing to track down in their institutions.

> I'm sure that we were getting support from our department. I'm sure that was true of the others because at that time that was a lot of money and a pretty prestigious project. (Bellack, 2011b)

The NIMH staffing for the study was an in-kind financial input while Schooler was at the NIMH. After leaving in 1988, her time to continue to lead the study was covered by a professional services contract.

The study received a substantial amount of support from Janssen-Cilag, which provided all of the medication supplies. This funding was facilitated by personal contacts that Schooler had with colleagues at Janssen-Cilag that had developed over several years at conferences and in other professional settings. It turned out that this was a much bigger source of support than just the medication because the different dosages required different preparations. For example, the injection fluids for the different doses had to be developed for each dosage. The low-dose concentration, in particular, was problematic because the standard diluting factor could not be used. The Janssen-Cilag scientists came up with an alternative, but this was a different colour from standard diluting factor. As a result, in addition to developing the new diluting factor, Janssen-Cilag also had to individually wrap the vials to disguise the type of dose. As Schooler points out, this meant their overall contribution was substantial.

> And in fact, I couldn't tell you what the amount of money was that this cost the company. I suspect that it was more, that ultimately it was more than the amount that the government paid. (Schooler, 2011b)

Prior to approval as a extramural study, the TSS study concept went through several stages of internal review to make sure that it met the appropriate criteria discussed above. In particular, the focus was on ensuring that the research would not be competing with the wider field.

> Because in order to do a study like this, one of the reasons for not doing something 'the field might do', is that as the government agency that gives money to the field, you're not supposed to be competing with them. (Schooler, 2011b)

At the time the TSS study was getting off the ground, it was felt that less money was available than had been at previous points in the NIMH's history. Therefore, there were more rounds of internal review and approval than might have otherwise been the case, in order to ensure that this really was worthwhile research that met all the appropriate criteria for funding.

In addition to internal approval, the selection process for the TSS to identify the sites where the study would be conducted was very competitive and there was a lot of interest in taking part in the study. As Schooler recalled, 'anybody who is anybody' ended up applying, even people who had little experience in clinical trials or in schizophrenia. She believed part of the reason for this was that it was guaranteed income for five years, but that there were other factors, as well, specifically the opportunity to be part of a potentially important study.

> I think what it was, was… guaranteed – it was clearly going to be guaranteed money, if it came. And so it was a pretty good deal. And I also think that our group, we had a good reputation in the field as being nice to work with, is my sense. But the study… Some of

> the people who I knew well who applied who got it said that it was the kind of thing that if it was going to happen, they wanted to be part of it. (Schooler, 2011b)

Knowledge

The background knowledge of Schooler and Keith and of the investigators at the selected sites was an important factor in the research. Dosage reduction strategies for first-generation antipsychotics (second-generation drugs were only just coming onto the scene) were being considered as a way of reducing side effects like tardive dyskinesia and still preventing relapse. Family interventions were also just starting to gain ground as a potentially viable intervention. The two areas of research on their own were raising interesting questions, but when considered together there were some exciting opportunities for synergy and advancement of knowledge.

> Well 1984 was a lifetime ago in terms of what people thought were viable interventions for schizophrenia and what people thought were critical issues in both onset and maintenance or exacerbations and episodes. …There was this sort of archaic blame the family approach… the next iteration of it was expressed emotion. …And it was still early on in use of the second generation antipsychotics. People were not as attuned to side effects. …So there were a lot of things that were cutting edge that were far removed from clinical practice. This was sort of an opportunity to both do innovative psychopharmacology that really was attuned to side effects and to titrating medication in a way to maximise effectiveness rather than just overdosing people. …And there was really an unusual opportunity to do innovative behaviourally oriented psychosocial treatment partnered up with [the innovative] psychopharmacology. Hopefully really be able to have a different kind of impact. (Bellack, 2011b)

Expertise and techniques

Pharmacological and psychosocial expertise was an important selection criterion for the TSS study. Each site had pharmacological expertise, including some of the early contributors to the field's main studies (e.g. John Kane). Of the five centres that were ultimately selected, four had the required experience and expertise to gain funding. The fifth site was at Emory University, and though Emory's expertise was not as strong as the others Schooler and Keith convinced NIMH to release extra funding for it because it would allow them to include a minority population in the study.

> We were able to persuade another section of the NIMH to fund the fifth site on the grounds that it would be a minority site. Emory was the grant holding centre, but it was done at a hospital called Grady Memorial Hospital, which is in Center City, Atlanta, and which serves a largely black, largely disadvantaged population. And that was a mechanism that allowed us to get an additional site funded, and to expand the general scope of the study. (Schooler, 2011b)

One of the PIs at the Philadelphia site commented that he felt his site had the requisite experience on both the pharmacological and psychosocial end. He also commented that his proposal focussed on many of the pragmatic aspects of the research and this might have set them apart in showing they had thought through the practicalities.

> It turned out to be an enormously complicated study and it was much more complicated to do it than it sounded just by reading the core research design…. And my proposal was probably a bit [overly detailed] in drawing out some of the pragmatic considerations in terms of staffing group size, number of sessions and what not…. Which what I learned

> later from Nina I was the only one who really thought about it that concretely so that was probably a factor. (Bellack, 2011b)

Another PI had already done several of the low-dosage studies discussed above and he felt that his ideas probably shaped and contributed to the final study and this may have been a reason why his centre was selected as a site.

> So there were different groups that were pursuing those two different lines of investigation. And this was an opportunity to bring them together so I'm sure [for example] Marvin Herz contributed his perspective and I contributed my perspective…. (Kane, 2011)

Another important input to the research was the psychosocial expertise of Ian Falloon and his associate, Christine McGill. They provided guidance, support and training to all the sites on the behavioural family management intervention used in the study. None of the PIs had any experience with the behavioural family therapy model but no one considered this to be a problem.

> I had no prior experience with the model. What I had expertise and experience with was behavioural treatments and learning interventions for people with schizophrenia. And I had a lot of experience in doing manualised protocols. So rather than the family piece being something that I was familiar with it was all the other attributes of doing a large-scale multisite control trial that I was really expert at…. Kim Mueser (the junior psychologist) had a background in families. (Bellack, 2011b)

Looking back on it, Schooler reflected on the selection of the psychosocial technique in the following way:

> So the issue was there were three candidates for a psychosocial intervention that we looked at. And one was a family treatment that had been developed by Carol Anderson and Jerry Hogarty at Pittsburgh. The second was Falloon's family treatment, what he called behavioral family management. And the third was a very different kind of model of assertive case management, which later became a case management act intervention, which was being developed at the University of Wisconsin in Madison, Wisconsin. …The reason we chose the Falloon treatment was because the Falloon treatment depended on the family to identify what the problems were that they wanted to work on. …We felt that since the families would be involved, having the families determine what the problems were that they were going to work on would be a better model than the other Anderson model. …This was something that the leadership of the trial, that would've been Sam Keith, who was then at NIMH, and I, decided, as it were, on our own. (Schooler, 2011b)

Outside the group of core PIs on the study, the family management clinicians were largely women and had social work, psychology or nursing backgrounds with a mean of 7+ years of experience. Only about a quarter had experience with behavioural methods prior to joining the study. At least one of the sites hired a psychosocial junior researcher specifically to help run the psychosocial treatments and do the 'day to day clinical supervision' (Bellack, 2011b).

Samples/patients

Since the study sites were so dispersed and each dealt with a different clinical population, it was difficult to get a sense of the effect this might have had on the study. Moreover, retention rates were not reported by site for the study. One PI felt that since the medical

school he was working for at the time was relatively new, there were not a lot of competing proposals from within other parts of the school and this enabled them to make a strong argument that they could capture the patient population very well, perhaps better than other sites competing for funding could (Bellack, 2011). In addition, as was mentioned above, there was one significant difference between sites in the patient populations included, in that one had a larger minority population participating in the study, but there is little indication that this affected the overall study in anyway. Apart from this comment, there was no indication from any of the researchers that there were particular issues among the sites that may have altered or had an effect on the study in any way.

Collaborators

Other than Ian Falloon and Christine McGill, there were no formal collaborators on the study.

18.6 Stage 2: Processes

Over the period 1985–1991, the TSS study recruited 528 acutely ill patients. Inclusion criteria for participation in the study were DSM-III-R diagnosis of schizophrenia or schizoaffective disorder, aged between 18 and 55 years, living with or having more than superficial contact with family, living close enough to the clinic to permit home visits, and providing informed consent. Some 93 percent of the patients were recruited during hospitalisation and the rest were outpatients recruited when they visited clinics due to psychotic exacerbations.

The TSS study had two components:

- Dosage strategy: low, intermittent dosage or standard dosage (3 groups).
- Family treatment strategy: applied family treatment (home visits and monthly support meetings) or supportive family treatment (monthly support meetings) (2 groups).

It is important to note that in both study components the strategies had never been compared against each other.

Patients were randomly assigned to either the applied family treatment or supportive family treatment groups following a period of stabilisation in the hospital or as an outpatient. It should be noted that 'family' here was an inclusive concept and was taken to mean anyone who was important to the patient, including, for example, clergyman, siblings, partners of siblings, etc. One of the PIs recalled using the term 'all comers' (Bellack, 2011a) as opposed to family to reflect this more inclusive approach. Individuals in the applied family treatment group had individual meetings in the home to assess the functional status of the patient and the family knowledge of schizophrenia. These home meetings were an important difference between the two groups, but in the end did not actually improve family compliance, contrary to initial belief. Home sessions were held weekly for 13 weeks and then monthly until the end of the first year of the maintenance phase. The sessions followed a detailed training manual and included presentation of educational material and training in communication skills followed by teaching and practice of problem-solving skills. Families in both groups were invited to monthly group

meetings throughout the stabilisation and maintenance phases. Meetings were led by a family management clinician and lasted 1.5 hours. They covered issues about what was happening with the patient's treatment and discussed issues raised by the participants. Families in the supportive family management condition were only invited to these monthly group meetings and, moreover, were relied on to initiate contact with the physicians and attend the meetings.

Dosing strategies were more straightforward to administer in a standard way, but psychosocial interventions were much more dependent on the people delivering them. The study design tried to ensure fidelity to the behavioural family therapy model by retaining Falloon and McGill as trainers and advisors throughout the project. Family management clinicians went through extensive training with Falloon and McGill and then were videotaped in a session to ensure fidelity. Nevertheless, there were still problems since the protocol for the family management work was not always feasible to implement in a consistent way given the number of clinicians and sites.

Only 313 patients eventually reached stabilisation and could enter the medical maintenance phase of the study. Of these, 58 percent in the applied family management group and 61 percent in the supported family management group were assigned to one of the three dosing strategies: low, intermittent or standard dosage.

The TSS group hypothesised that 'targeted treatment would require more added medication and result in higher relapse rates and more rehospitalisation than low-dose treatment, which in turn would require more added medication and result in higher relapse rates and more rehospitalisation than the standard dose' (Schooler et al., 1997, 456). They also hypothesised that applied family management would be more effective than supported family management and that the between-group differences would be reduced in the medication arm. In other words, they thought that applied family management would in and of itself be important to patient recovery and so the significant effects of medication dosage reduction would be lessened for this group.

One of the problems with the research design, though, was that there was no control group for the psychosocial treatments, and therefore no way to measure whether behavioural change was a direct result of the two family therapy treatments.

> Well I think one of the problems with TSS is that there was no control group for the psychosocial intervention. We were able to compare the more intensive management with the less intensive management, [but] we didn't have a 'no treatment' comparison group to say 'Well okay what's the impact of either one of the two alternative approaches.' (Kane, 2011)

In order to try and address this to some extent at one of the sites (Philadelphia), the researchers received a grant from NIMH to do an assessment of whether behaviour change was actually occurring in the families. This was an additional component that was added to the study after it began.

18.7 Stage 3: Primary Outputs

Knowledge

Schooler et al. (1989) reported baseline data from the study. Schooler initiated the publication as a means to convene all those involved at a meeting and have everyone's name on a paper. The main outcome paper from the TSS study as a whole was Schooler et al. (1997), published seven years after the study finished enrolling patients.

The study findings confirmed existing knowledge that there were differences in the benefits of medication from the different dosing strategies, but since patients may not relapse for weeks or months after stabilising, dosage reduction is problematic as there is no immediate response against which to judge success or failure. However, they did find that both the low-dose and intermittent-dosage reduction strategies increased relapse when compared to standard treatment. The intermittent dosage also increased hospitalisation, while the low dose did not have this effect. The authors estimated that about 50 percent of patients could be sustained for two years on a low dosage, but that it was difficult to predict which patients these would be. The findings about dosage were not necessarily what was expected, but were also not surprising. The study did not elicit a particularly strong reaction in either direction from industry.

> I would imagine that people in industry were sort of reassured to some extent that continuous treatment was the best way to go and that that made it easier for them to say 'Well people need to stay on these drugs…'. (Kane, 2011)

The study also found no difference between the two family treatments and no added benefit of applied family management on the need for rescue medication, delay of relapse, or rehospitalisation. However, the two-year rehospitalisation rates for patients receiving either standard or low dosage and participating in either one of the family management groups were lower than those for usual care conditions reported in other studies. Thus, they conclude on the basis of their findings and the strength of other studies published at the time (referenced above) that there is support for the engagement of families within a pyschoeducational framework and for the development of family support groups within a patient's overall clinical treatment. Despite this conclusion, some of the PIs felt some disappointment that there was not a clearer difference between the two family management treatments.

> I guess I was surprised that the intensive family therapy didn't work better than the supportive strategy. (Kane, 2011)

Schooler, in particular, was disappointed because of the implications this kind of finding could have had for transforming clinical practice. She had been hopeful that there would be clearer differences between the treatments so that they could begin to develop protocols for implementing family management as standard practice.

The applied family management, which was conducted in the home, was also expected to improve patient compliance. However, this did not end up being the case and patient/family compliance was no different between the two groups, further underscoring the benefits of some family treatment, but not necessarily one kind over the other.

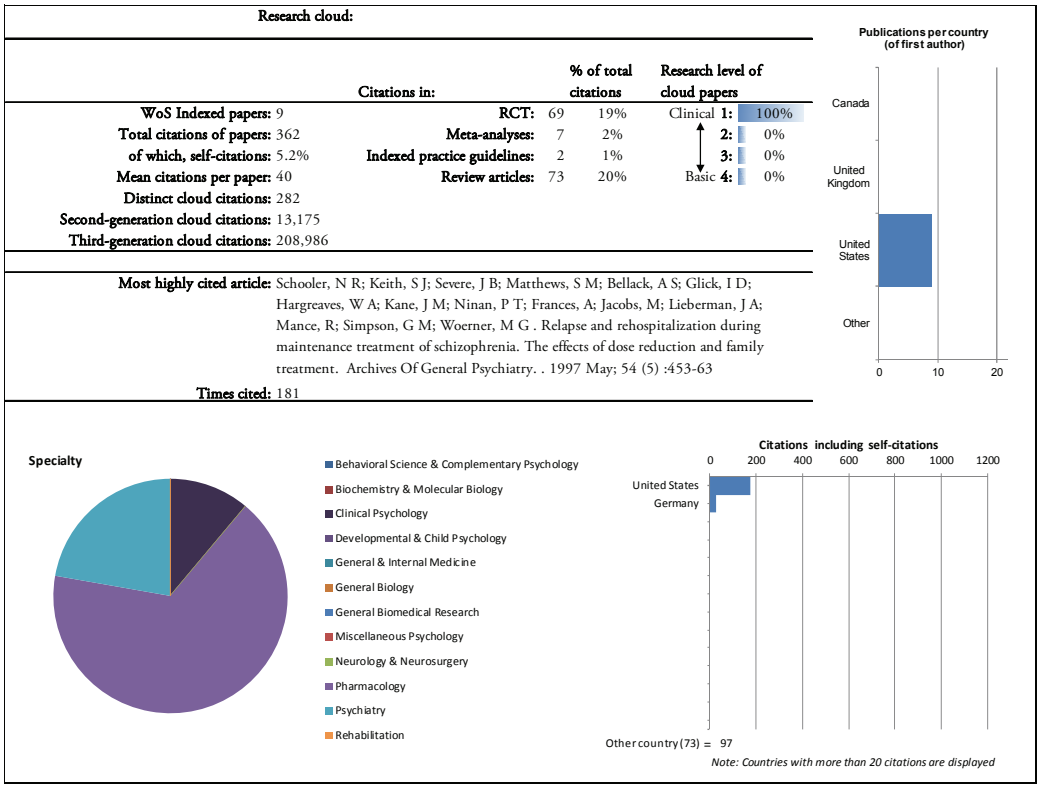
There were five different clinical sites for the TSS study and the researchers were attentive to socio-demographic and patient differences within the sites. For example, the Emory site

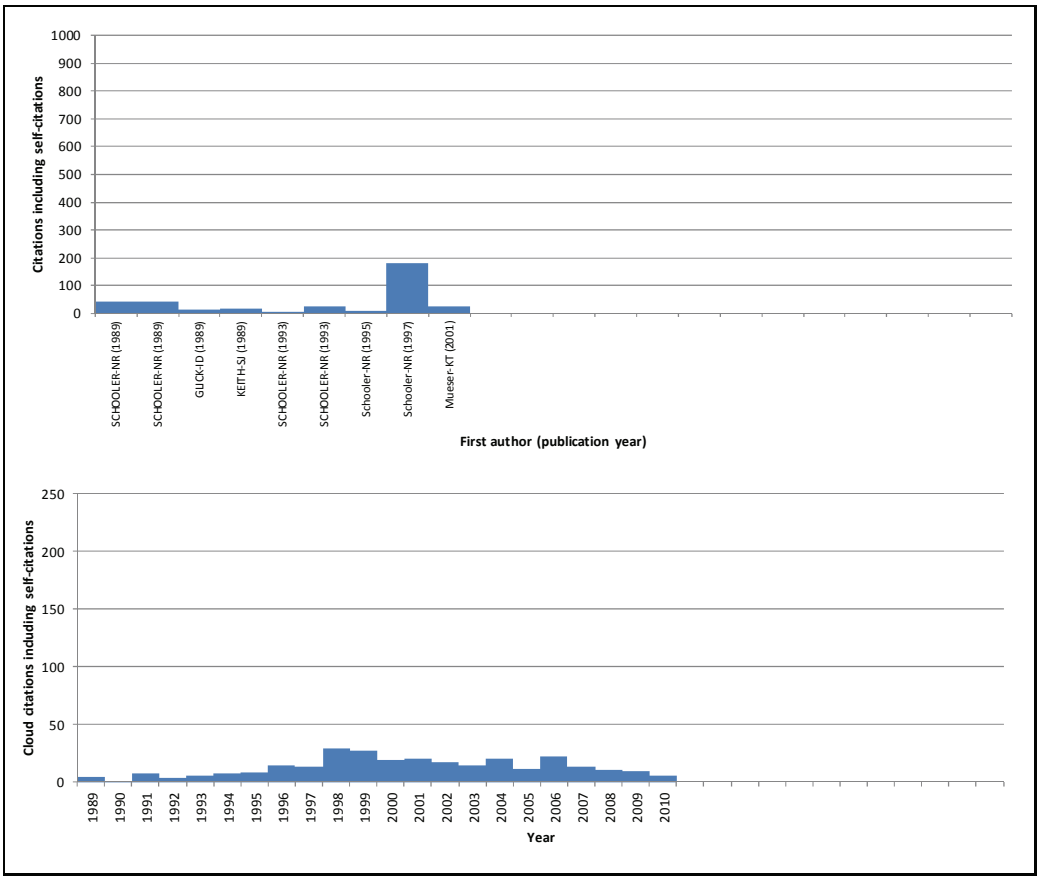
was an inner city hospital called Grady Memorial and the vast majority of patients were poor African Americans. In contrast, the Hillside and Payne Whitney sites were (and are) private hospitals, which meant at that time a more affluent and white patient population. However, there was no within and across site analysis of differences in patient outcomes. Schooler speculated that even if they had wanted to do this, they would not have had adequate statistical power (Schooler, 2011a).

While the study was designed to fill an important gap in knowledge when it was designed, it was obsolete almost as soon as it was finished because of the introduction of a new generation of antipsychotics that significantly reduced the risk of tardive dyskinesia – the main side effect that dosage reduction was designed to combat.

The authors felt that the study was highly cited because of its importance as the single extramural study of the 1980s funded by the NIMH and its uniqueness in looking at the interactions between psychosocial and psychopharmacological interventions. Moreover, not only did the study look at the interactions between the two interventions, it also compared aspects of each intervention in one study that hadn't been looked at before: applied family management versus supportive family management and the comparison of the different dosing strategies against each other. All of this together led to this being a study that, though perhaps viewed as less impactful than expected by the authors, was still highly cited in the wider literature.

A bibliometric analysis of the papers produced from the research cloud is shown below.





Targeting future research

Effect on the researchers' careers

The study did not have a real impact on the career development of the principal investigators at each site as many were already fairly well established in their fields. For the most part, they continued working as clinical researchers in either psychopharmacology or psychosocial areas of research. The Emory site was a slight exception as they had two comparatively less established PIs, one of whom now has a good career working for Merck in the pharmaceutical industry and the other has continued working in academia.

The study was more influential for some of the more junior members of the research teams, including two psychiatrists who developed careers in relapse prevention, and for the therapists who provided the family treatment, many of whom (according to Schooler) left the study with a much more positive view of research. One of the junior psychologists whose career was helped by the TSS study was Kim Mueser at the Philadelphia site. He went on to have a prominent career and Bellack felt that this was in part because of his role in the TSS study.

> …The psychologist is Kim Mueser who now is a senior investigator, one of the leading authorities on psychosocial treatment of people with schizophrenia, very widely published, internationally travelled. And this really kicked his career off. (Bellack, 2011b)

Other junior researchers who went on to have prominent careers include Delbert Robinson, MD, who is still at The Zucker Hillside Hospital and is a leader in first episode schizophrenia research; Peter Weiden, MD, who was at the Payne Whitney Cornell site

and is a senior clinical trial investigator in psychopharmacology in schizophrenia; and Martha Shumway, PhD, at University of California San Francisco, who is a services and health economic researcher and who started her interest in the area through TSS.

Future work

By the end of the study, second-generation antipsychotics had emerged that made the relevance of the dosage reduction component unclear. They were thought to have fewer side effects and so there was less need for dosage reduction. However, the study authors still believed that more work could be done related to dosing, efficacy and other issues.

> The treatment of schizophrenia stands at a junction as significant as that represented by the introduction of antipsychotic agents in the 1950s. New antipsychotic agents, not restricted in use like clozapine, are available or on the horizon. We have little information regarding their efficacy in maintenance treatment. New psychosocial treatments for schizophrenia are being developed, including primary prevention strategies. Ideally, new medications and psychosocial treatments will prompt a generation of studies to investigate their additive and interactive effects. (Schooler et al., 1997, 461)

When asked about the significance of this statement and the thinking behind it, Schooler noted:

> Well, it was very striking for me. I had had the opportunity to be involved as a site investigator in the Risperidone studies. By the time this came out, I was involved in Clozapine trials. And it really seemed to me that we were at a dramatic shift in what we could do in schizophrenia. I believe that, you know, if you ask me today was it as dramatic as I thought it was when I wrote that, when I wrote [those] words in 1996, I would say no. …The other, newer antipsychotics…, they're better than the older drugs, [but still] have their own enormous problems. (Schooler, 2011b)

Though the dosing strategies may have been outdated by the time the study finished, there was still research that came out of the psychosocial component of the study. For example, Bellack's work looking at how to measure behaviour change among the families led to his development of a behavioural assessment tool that is still used in some research today. In the TSS study, Bellack found that while family management did have an effect on patient outcomes, this had nothing to do with behaviour change within the families themselves.

It is interesting to note that this kind of large, multicentre study has not been done again through the NIMH extramural programme, in part because of problems with the study design and scope of the project.

> One is it was not a good design because there wasn't really a viable control. Another is that it's inordinately expensive and complex. And the other is that you can't do 'no treatment' arms for people with schizophrenia. (Bellack, 2011b)

> I would say it is a shame because I think there has been insufficient controlled research on these various domains of treatment to be able to assess their relative impact in a measurable way, i.e. the effect size that one can produce in symptomatic response or relapse prevention with medication vs. family or individual psychosocial treatments. So we're sort of, we're making assumptions and often patients receive less in the way of psychosocial treatments than might be ideal. (Kane, 2011)

Kane supported this view by pointing out that the current NIMH RAISE study faced similar problems in study design and that it was probably telling that it was the first of its

kind to be done for many years. The fact it was being done, though, should be seen as a positive development for the field.

> So I would suggest that [RAISE] is an example of where we are conducting an exploratory rather than explanatory trial, because basically although we are randomising clinics and therefore patients to give an enhanced intervention versus usual community care we have not divided up the various treatment domains in any randomised way. So at the end of the day the patients in the experimental group are getting both state-of-the-art psychosocial treatment and state-of-the-art psychopharm treatment, but we will not be able to measure the relative effects of each independently. (Kane, 2011)

Bellack also pointed out that additive effects in general were difficult to demonstrate in people with really serious illnesses and that this compounded the challenges of the study, and of the field more broadly.

> I don't think that for any disorder that we treat there is really good evidence of the additive effects of psychopharm and psychosocial interventions. In most of the literature for people with lower levels of distress or milder illnesses, psychopharm and psychosocial both work reasonably well. For people with more serious illnesses it's hard to build a case that the combination is much more effective because for people with serious illnesses [interventions] were not very effective period. So now that's probably a little bit of an overgeneralization but it's not a blatant overgeneralization. (Bellack, 2011b)

There were additional collaborations by the authors after the study and many of them continued to work together on other projects.

The study can also be thought of as advancing interest in maintenance treatment, an area in which there was not a lot of research at the time (as Kane points out in a quotation earlier in this case study), and arguably still an under-researched area today (Remington, 2010).

18.8 Interface B: Dissemination

Academic engagement

There was little academic dissemination of the work outside published papers and presentations at academic conferences. There was an intention to publish more than what ultimately came out, with a 'publication group' set up within the study team and across the sites.

Despite the perceived lack of publications, there are still over 60 papers listed as linked to the TSS study grants. In addition, the work was disseminated as standard practice in academic conferences and lectures. In this way, it became ingrained in the way people spoke about their research.

Wider engagement

There was no active wider engagement with the public about the research findings.

18.9 Stage 4: Secondary outputs

Secondary outputs are those that arise outside the academic context of the research. The TSS study is cited in different national clinical guidelines that help to inform practice. The

2004 APA Clinical Practice Guidelines cites the 'Relapse and rehospitalization' paper (Schooler et al., 1997) twice when discussing pharmacologic treatments and adherence to the medication regimen and dosage strategies:

> However, Schooler et al. compared three medication strategies using fluphenazine decanoate: a continuous moderate dose (12.5–50 mg every 2 weeks); a continuous low dose (2.5–10 mg every 2 weeks); and targeted, early intervention (fluphenazine only when the patient was experiencing symptoms). They found that both continuous low-dose and targeted treatment increased the use of rescue medication and the rate of relapse, while only targeted treatment increased the rate of rehospitalization.

> However, Schooler et al. found that low-dose fluphenazine decanoate (2.5–10 mg every 2 weeks) increased the relapse rate and the use of rescue medication, compared to a continuous moderate dose (12.5–50 mg every 2 weeks).

The 1997 paper is also cited in the NICE Guidelines when discussing treatment with depot/long-acting injectable antipsychotic medication:

> There is also some evidence to suggest a better global outcome with depot as compared to oral antipsychotics (Adams et al., 2001) with a reduced risk of rehospitalisation. (Schooler, 2003; Tiihonen et al., 2006)

NICE also includes the TSS study in its review of family intervention versus control studies. The NICE guidelines recommend family intervention, finding that there is robust and consistent evidence for its efficacy.

There were positive impacts on the family practitioners who worked with the families. They gained from working with other people outside their institutions and grew to have a better appreciation for the value of research.

> My sense [is] for many people, working on a trial like this has just been a transformative experience. One of the things that happens in multicentre [research], and I've seen that in this study and in others that I've been involved with, is that most people have no sense of the world outside their own institution. And what people always say is it's just so wonderful to get to know these people from other institutions to come together, to form groups in this way. …And I still run into people who'd participated in this study, who say, 'Oh, I remember when we did the TSS study. It was so great.' (Schooler, 2011b)

18.10 Stage 5: Applications

There was limited opportunity for adoption by practice of the study. By the time the study was completed, first-generation antipsychotics had been eclipsed by second-generation ones and the negative findings about the difference in family treatment also meant that some of the findings were not as immediately relevant as they might have been.

> Essentially, I think that one of the things about the study is the dose reduction part had been, by '97, had been really overtaken by events. So that was not relevant, although it's citable in other kinds of contexts. And the family treatment, we didn't show a difference. So the statement, well, you know, a little bit [of family therapy] is good enough is a very hard thing to [disseminate]…. (Schooler, 2011b)

In addition, Schooler noted that any kind of adoption of a psychosocial model in the US is very difficult. However, one PI pointed out that the current RAISE study being funded by

NIMH is looking again at the combined effects of pharmacological and psychosocial treatments.

Policy implications of this work were also limited as the turnover at NIMH meant that there was no one left who would have seen it as highly policy relevant.

> There had been enough change at the NIMH by the time this study finished. …There was nobody who was there by then, who, from a policy perspective, would've seen this as highly relevant. (Schooler, 2011b)

Therefore, overall there was limited adoption in practice of the findings of the TSS study. It was felt that since by the time the study was published the move had been made to using second-generation antipsychotics and so the findings of the study were not as relevant to patients and patient outcomes in relation to dosing strategies and reduction of side effects. However, there were benefits from the family management strategies, which did give support for psychosocial approaches to patient treatment. These contributed to some guidelines and potentially improved patient outcomes in the UK, where family intervention is explicitly recommended in the NICE guidelines.

18.11 Stage 6: Public engagement

None identified.

18.12 Stage 7: Final outcomes

There were no final outcomes identified in relation to improvements for health and the health sector, nor for social or economic benefits.

18.13 Table of payback

Payback category	Impacts from case study
Knowledge Production	• Study found that targeted or intermittent dosage not good enough and family treatment did not show a difference. • 9 total papers from TSS directly with 'Relapse and rehospitalization during maintenance treatment of schizophrenia' the most influential. • Over 50 papers linked to TSS study grants.
Research Targeting and Capacity Building	• TSS Collaborative Study Group formed as a result of the study. • Contributed to career development of junior researchers. • Developed the capacity of clinicians to implement interventions and conduct research. • Led to future research on assessing behaviour change.
Informing Policy and Product Development	• Dose reduction strategies and family treatment included in clinical guidelines and reviews.

Health and Health Sector Benefits	• None identified.
Broader Social and Economic Benefits	• None identified.

18.14 Timeline

1963	Schooler joins the NIMH as a Research Social Psychologist
1980	Schooler becomes Chief, Schizophrenic Disorders Section and Assistant Chief Pharmacologic and Somatic Treatments, Research Branch, NIMH
1985	Keith becomes Director of the Schizophrenia Research Branch
1985	Schooler becomes Assistant Chief, Schizophrenia Research Branch, NIMH
1988	TSS study begins enrolling patients
1989	Preliminary data from TSS published
1995	TSS study ends
1997	Final data from TSS published

18.15 References

Adams, C.E. & Fenton, M.K.P. (2001). Systematic meta-review of depot antipsychotic drugs for people with schizophrenia. *British Journal of Psychiatry*, 179, 290-299.

Bellack, A.S. (2011a). *RE: Email communication.* Communication with Morgan Jones, M.

Bellack, A.S. (2011b). *RE: Telephone interview with Alan S. Bellack.* Communication with Morgan Jones, M.

Carpenter, W.T., Heinrichs, D.W., & Hanlon, T.E. (1987). A comparative trial of pharmacologic strategies in schizophrenia. *American Journal of Psychiatry,* 144(11), 1466–1470.

Falloon, I., Boyd, J., Mcgill, C., Williamson, M., Razani, J., Moss, H., & Gilderman, A. (1982). Family management in the prevention of exacerbations of schizophrenia. *New England Journal of Medicine,* 306(24), 1437–1440.

Glick, I.D., Jacobs, M., Lieberman, J., Simpson, G., & Schooler, N.R. (1989). Prediction of short term outcome in schizophrenia: depressive symptoms, negative symptoms, and extrapyramidal signs. Treatment Strategies in Schizophrenia Collaborative Study Group. *Psychopharmacology Bulletin,* 25(3), 344–347.

Goldstein, M., Rodnick, E., Evans, J., May, P., & Steinberg, M. (1978). Drug and family therapy in the aftercare of acute schizophrenics. *Archives Of General Psychiatry,* 35, 1169–1177.

Hogarty, G.E., Goldberg, S., Schooler, N.R., Ulrich, R.F., & The Collaborative Study Group (1974). Drug and sociotherapy in the aftercare of schizophrenic patients: II. Two-year relapse rates. *Archives Of General Psychiatry,* 31(5), 603–608.

Hogarty, G.E., McEvoy, J.P., Munetz, M., Dibarry, A.L., Bartone, P., Cather, R., Cooley, S.J., Ulrich, R.F., Carter, M., & Madonia, M.J. (1988). Dose of fluphenazine, familial expressed emotion, and outcome in schizophrenia. *Archives Of General Psychiatry,* 45(9), 797–805.

Hogarty, G.E., Schooler, N.R., Ulrich, R.F., Mussare, F., Ferro, P., & Herron, E. (1979). Fluphenazine and social therapy in the aftercare of schizophrenic patients: relapse analyses of a two-year controlled study of fluphenazine decanoate and fluphenazine hydrochloride. *Archives Of General Psychiatry,* 36(12), 1283–1294.

Kane, J.M. (2011). *RE: Telephone interview with John M. Kane.* Communication with Morgan Jones, M., Pollitt, A., & Horvitz-Lennon, M.

Kane, J.M., Rifkin, A., Woerner, M.G., Reardon, G., Kreisman, D., & Blumenthal, R. (1985). High dose vs. low dose strategies in the treatment of schizophrenia. *Psychopharmacology Bulletin,* 21(3), 533–537.

Kane, J.M., Woerner, M.G., Lieberman, J., & Kinon, B. (1986). Tardive dyskinesia and drugs. *Drug Development and Research,* 9(1), 41–51.

Kane, J.M., Woerner, M.G., Weinhold, P., Wegner, J., Kinon, B., & Borenstein, M. (1984). Incidence of tardive dyskinesia: 5 year data from a prospective study. *Psychopharmacology Bulletin,* 20(1), 387–389.

Keith, S.J., Bellack, A.S., Frances, A., Mance, R., & Matthews, S.M. (1989). The influence of diagnosis and family treatment on acute treatment response and short term outcome in schizophrenia. Treatment Strategies in Schizophrenia Collaborative Study Group. *Psychopharmacology Bulletin,* 25(3), 336–339.

Kottgen, C., Sonnichsen, I., Mollenhauer, K., & Jurth, R. (1984). Group therapy with the families of schizophrenic patients: results of the Hamburg Camberwell-family interview study III. *International Journal of Family Psychiatry,* 5(1), 83–94.

Leff, J., Kuipers, L., Berkowitz, R., Eberlein-Vries, R., & Sturgeon, D. (1982). A controlled trial of social intervention in the families of schizophrenic patients. *British Journal of Psychiatry,* 141, 121–134.

Leff, J., Kuipers, L., Berkowitz, R., & Sturgeon, D. (1985). A controlled trial of social intervention in the families of schizophrenic patients: two year follow-up. *British Journal of Psychiatry,* 146, 594–600.

Marder, S., Van Putten, T., Mintz, J., Lebell, M., Mckenzie, J., & May, P. (1987). Low- and conventional-dose maintenance therapy with fluphenazine decanoate. *Archives Of General Psychiatry,* 44(6), 518–521.

Marder, S., Van Putten, T., Mintz, J., Mckenzie, J., Lebell, M., Faltico, G., & May, P. (1984). Costs and benefits of two doses of fluphenazine. *Archives Of General Psychiatry,* 41(11), 1025–1029.

Mueser, K.T., Sengupta, A., Schooler, N.R., Bellack, A.S., Xie, H., Glick, I.D., & Keith, S.J. (2001). Family treatment and medication dosage reduction in schizophrenia: effects on patient social functioning, family attitudes, and burden. *Journal of Consulting and Clinical Psychology,* 69(1), 3–12.

Remington, G. (2010). Antipsychotic dosing: still a work in progress. *American Journal of Psychiatry,* 167(6), 623–625.

Schooler, N.R. (2011a). *RE: Email communication with Nina R. Schooler.* Communication with Morgan Jones, M.

Schooler, N.R. (2011b). *RE: Personal interview with Nina R. Schooler.* Communication with Morgan Jones, M., & Schultz, D.

Schooler, N.R. (2003). Relapse and rehospitalisation: comparing oral and depot antipsychotics. *Journal of Clinical Psychiatry,* 64 (suppl. 16), 14-17.

Schooler, N.R. (1995). Integration of family and drug treatment strategies in the treatment of schizophrenia: a selective review. *International Clinical Psychopharmacology*, 10, 73–80.

Schooler, N.R. (1993). Reducing dosage in maintenance treatment of schizophrenia. Review and prognosis. *British Journal of Psychiatry,* 22, 58–65.

Schooler, N.R., & Keith, S.J. (1993). The clinical research base for the treatment of schizophrenia. *Psychopharmacology Bulletin,* 29(4), 431–446.

Schooler, N.R., Keith, S.J., Severe, J.B., & Matthews, S. (1989). Acute treatment response and short term outcome in schizophrenia: first results of the NIMH treatment strategies in schizophrenia study. Treatment Strategies in Schizophrenia Collaborative Study Group. *Psychopharmacology Bulletin*, 25(3), 331–335.

Schooler, N.R., Keith, S.J., Severe, J.B., Matthews, S.M., Bellack, A.S., Glick, I.D., Hargreaves, W.A., Kane, J.M., Ninan, P.T., Frances, A., Jacobs, M., Lieberman, J.A., Mance, R., Simpson, G.M., & Woerner, M.G. (1997). Relapse and rehospitalization during maintenance treatment of schizophrenia. The effects of dose reduction and family treatment. *Archives Of General Psychiatry,* 54(5), 453–463.

Schooler, N.R., Levine, J., Severe, J.B., Brauser, B., Dimascio, A., Klerman, G.L., & Tuason, V.B. (1980). Prevention of relapse in schizophrenia: an evaluation of fluphenazine decanoate. *Archives Of General Psychiatry,* 37(1), 16–24.

Tarrier, N., Barrowclough, C., Vaughn, C., Bamrah, J.S., Porceddu, K., Watts, S., & Freeman, H. (1988). The community management of schizophrenia. A controlled trial of a behavioural intervention with families to reduce relapse. *British Journal of Psychiatry,* 153, 532–542.

Tiihonen, J., Lönnqvist, J., Wahlbeck, K., Klaukka, T., Tanskanen, A., & Haukka, J. Antidepressants and the Risk of Suicide, Attempted Suicide, and Overall Mortality in a Nationwide Cohort. (2006) *Archives of General Psychiatry*, 63(12), 1358-1367.