Mental Health Retrosight

Final report on Phase I

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Preface

This report sets out the findings and recommendations of Phase I of Mental Health Retrosight. This project is the first funded through the Science of Science for Mental Health Research Network (SOS for Mental Health), a joint initiative between the Graham Boeckh Foundation and RAND Europe. The report is primarily intended for the organisations who have committed to supporting Phase II of the project and the project advisory group.

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Executive Summary

1. This interim report outlines the findings and recommendations of Phase I of a multinational study – Mental Health Retrosight – to investigate the translation and payback from basic, clinical and interventional research into clinical application and community practice. With a particular focus on schizophrenia, the study aims to:
   - Identify the long term payback from mental health research;
   - Explore factors that are associated with the successful translation of research; and
   - Provide insights and policy provocations that will inform future funding policy.

2. Project Retrosight is the signature project of SOS for Mental Health – where SOS stands for the Science of Science; a network that convenes funders of mental health research in Canada, the US, the UK and elsewhere, along with mental health scientists, researchers and clinicians, and policy researchers interested in the science of science. The network is developing a ‘living’ portfolio of policy research that will lead to improvements in the effectiveness and efficiency of research funding. The Graham Boeckh Foundation has supported Phase I of Mental Health Retrosight. Phase II of the project, which includes field work, analysis, and reporting, will be supported by a consortium of funders including: the Graham Boeckh Foundation, Canadian Institutes of Health Research’s Institute of Neuroscience, Mental Health and Addiction, Alberta Innovates Health Solutions, the US National Institute of Mental Health, and English National Institute of Health Research. This report is primarily intended for these sponsors and the project advisory group.

3. As noted in our original proposal\(^1\), there is a perception that over the past 25 years there have been relatively few improvements in the care of schizophrenia patients, despite substantial research investments in both basic and applied research. For this

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\(^1\) Translating mental health research from bench-to-bedside: what works and what doesn’t (2008)
reason we examine research translation from two perspectives. The first involves prospectively tracking the impacts of research undertaken in the mid-1980s to the present day. The second involves retrospectively mapping the antecedents of today’s treatment advances.

4. The Retrosight approach involves developing case studies around research that has (or has not) translated from bench to bedside. The case studies are carefully selected to enhance generalisability, and are developed in-depth through a range of methods including key informant interviews, document and literature reviews, historgraphic analysis and bibliometrics. Once the field work has been completed, the forward-tracing case studies are systematically compared to differentiate between those that are high impact and those that are not. For clarity and succinctness we will refer to these as high and low impact case studies throughout this report, although the methods we use to characterise impact all rely on either proxies of impact or expert opinion. Case studies are then qualitatively coded to identify factors that are associated with high impact, before these factors are tested against analysis of the backward-tracing case studies. Finally, observations emerging from the analysis are developed into policy provocations for research funders.

5. Phase I of Mental Health Retrosight had two aims:
   - To identify candidates for case studies
   - To test the feasibility of the Retrosight approach in the field of mental health research

These two main aims encompassed a series of subtasks:
   - Working out the appropriate balance of forward and backward-tracing case studies
   - Developing a selection framework for forward and backward-tracing case studies
   - Drawing up a shortlist of candidate cases
   - Testing the feasibility of the case study approach by carrying out both forward and backward-tracing case studies.

**Balance of case studies**

6. An important issue that we had to resolve was the balance between the forward and backward-tracing case studies. It should be noted that there is no ‘right answer’ for this but we recommend undertaking 18 forward-tracing studies and four backward-tracing
ones. The 18 occurs as it needs to be a multiple of three (to ensure equal balance across the three countries). The four backward-tracing reflect the number of clearly definable topics identified across a range of treatment types.

**Selection of forward-tracing case studies and short list of candidate cases**

7. We explored a number of different approaches to identify forward-tracing case studies. We settled on a bibliometric approach which was based on identifying ‘hot research topics’ in the mid/late 1980s. By identifying these we aimed to select research which the scientific community gave some mark of importance to at the time. We identified highly cited research papers (HCPs) that were published between 1985 and 1990 in the three project countries. The HCPs help us identify a body of work – or a research cloud – that forms the unit of analysis for the case studies. The challenge, however, was to ensure that the papers were potentially relevant to schizophrenia (i.e. in scope) and to allocate papers appropriately to different types of research. This latter point is important as we know that different research types (eg. basic research versus applied research) have very different citation patterns; thus without controlling for research type we would bias our case study selection.

8. We addressed the issue of scope by combining pre-existing journal sets for neuroscience and mental health and adding other journals and papers based on keywords as indexed under MESH headings. This resulted in a database of c250k papers. These papers were then reduced in number through a series of filters – based on, for example, citation percentiles, keywords, country of corresponding author. The mid-list of papers was reviewed to ensure that they were in scope and to allocate them to various research types. From this process we identified a short list of 203 highly cited papers, distributed across the below matrix:

<table>
<thead>
<tr>
<th></th>
<th>Canada</th>
<th>UK</th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basic</strong></td>
<td>2</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>10</td>
<td>27</td>
<td>116</td>
</tr>
<tr>
<td><strong>Interventional</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biological</td>
<td>1</td>
<td>2</td>
<td>23</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Health</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>services/service delivery</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**Table 1. Forward-tracing case study selection matrix**
9. The first task of Phase II will be to collate the 203 papers and, working with the project advisory group, decide on the final selection of papers/case studies. This will involve some subjective judgement as we will wish to ensure that we have a suitable variety of scientific topics to focus on.

Selection of backward-tracing case studies and short list of candidate cases
10. The aim of the proposed backward-tracing case studies will be to explore how treatment advances have come about and the research and other factors that facilitated or hindered their development; therefore we wish to identify a list of interventions that were considered to be among the most significant. We used two approaches to identify our proposed list of four case studies. The first was a Delphi-like survey to gauge opinion from participants and others at the May 2010 SOS Workshop, hosted by the Graham Boeckh Foundation. The second was a review of clinical guidelines published in Canada, the UK and the US. The meshing of these two data sources results in the provisional selection of the following case studies:

- Cognitive behavioural therapy
- Early intervention
- One community-based psychosocial intervention
- Antipsychotic drugs

It should be noted that we anticipate the workload across these four case studies to be asymmetric. That is, we will need to spend more time and effort on the antipsychotic drugs case study (as a particularly broad topic, we anticipate this taking the equivalent effort of three ‘standard’ case studies), and less time on CBT and early intervention (which were part of our pilot).

11. We will work with the project advisory group at the start of Phase II to finalise the selection.

Pilot case studies
12. As summarised in Table 2, we undertook four pilot case studies (two forward and two backward) to test:

- Whether the case study approach and payback model could be applied in the mental health research arena. This included determining an appropriate unit of analysis.
- How best to structure and present backward-tracing case studies
- Some aspects of the case study selection process
<table>
<thead>
<tr>
<th>Type</th>
<th>Case Study</th>
<th>Reasons for selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forward-tracing</td>
<td>Kilpatrick: Identification of type 3 serotonin receptors in the brain</td>
<td>To test if we could carry out case studies on industry research</td>
</tr>
<tr>
<td></td>
<td></td>
<td>To test use of ‘research cloud’</td>
</tr>
<tr>
<td></td>
<td></td>
<td>To test recall of PIs for research published 20-25 years ago</td>
</tr>
<tr>
<td></td>
<td>Richardson: Identification of a growth factor for glial cells</td>
<td>To test tracking of very basic research</td>
</tr>
<tr>
<td></td>
<td></td>
<td>To test use of ‘research cloud’</td>
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<tr>
<td></td>
<td></td>
<td>To test recall of PIs for research published 20-25 years ago</td>
</tr>
<tr>
<td>Backward-tracing</td>
<td>Cognitive behavioural therapy</td>
<td>To test method of backward-tracing case studies</td>
</tr>
<tr>
<td></td>
<td>Early intervention</td>
<td>To test where a less well defined intervention could be examined through case study</td>
</tr>
</tbody>
</table>

Table 2. Pilot case studies

13. Both forward and backward-tracing case studies proved tractable. Key lessons were:

- The two forward-tracing case studies demonstrated that it is feasible to define ‘research clouds’, and in these two cases it was relatively easy to do so.
- The Kilpatrick case demonstrated the feasibility of carrying out case studies on research that was carried out in industry.
- In the full study we need to add more quantitative measures, such as bibliometric tracing and network analysis to the cases.
- Initially the Early Intervention case study proved challenging because of the variety of alternative definitions, but this was resolved through interviews with a number of experts in the field. Showing the importance of the exploratory stage in defining the strands that are considered part of any intervention.
- The key challenge is likely to be driving the backward-tracing case studies back far enough to get at details of the funding and decisions that were made around the research. The, more complete, CBT case study manages this in some instances, but we would work to add more depth in this area in Phase II case studies.
- In line with our expectations the backward-tracing case studies proved to be slightly more resource intensive than the forward-tracing ones, however, they were not drastically more so.
We would like to thank the Graham Boeckh Foundation for supporting this project and the Steering Committee of the Science of Science for Mental Health Network for their advice.

We would also like to thank:
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The researchers who agreed to participate in our pilot case studies
Tom Ling, our Quality Assurance reviewer, for his valuable feedback and suggestions
CHAPTER 1  Introduction

1.1  Background

There is a common perception that mental health research has been particularly poorly translated from bench to bedside (Insel, 2009). Mental Health Retrosight aims to help us understand why this is the case. This three year, multi-country project investigates the translation and payback from basic and clinical mental health research into clinical application and community practice. With a particular focus on schizophrenia, the study aims to: (i) identify the long term payback from mental health research; (ii) identify factors that are associated with the successful translation of research; and (iii) provide insights that will inform future funding policy.

Mental Health Retrosight is the first project funded through the Science of Science for Mental Health Research Network (SOS for Mental Health), a joint initiative between the Graham Boeckh Foundation and RAND Europe. The Network is establishing a ‘think tank without borders’ that will undertake research and analysis into mental health research funding. Phase II of the project will be supported by a consortium of research funders including Alberta Innovates Health Solutions, the Canadian Institutes of Health Research, the US National Institute of Mental Health and the UK National Institute for Health Research.

1.2  Project approach

Mental Health Retrosight will investigate research translation and payback in mental health, with a particular focus on schizophrenia. It will consider research conducted over the past 20-25 years in Canada, the US and the UK: case studies will examine research carried out in the late 1980s and early 1990s and explore how its findings, methods and ideas were built on and developed up to the present day. A complementary stream of work will look backwards in time from key treatment advances in recent years, identifying the research which contributed to their development. This methodology has been previously applied by RAND Europe and the Health Economics Research Group (HERG) at Brunel University in the fields of arthritis and cardiovascular research.

The Retrosight approach combines two established methodologies for exploring the translation of research. The first of these is the Payback Framework, a method developed by Martin Buxton and Stephen Hanney of HERG to examine the benefits from health
services research (Figure 1). It approaches the issue of research translation using individual pieces of research as starting points and tracing their impacts forward through time. The Framework’s scope has been expanded to provide a way of assessing the impact made by a wide range of biomedical research, the foundation of which was a series of studies initially supported by the North Thames NHS R&D Office. This work was further developed through a number of studies, in collaboration with RAND Europe, in a range of biomedical and health fields (e.g., arthritis, asthma), as well as in other areas (e.g., social science and arts and humanities).

The second methodology that the Retrosight approach draws on aims to trace the research antecedents of scientific advances. It was developed in the 1960s and 1970s through Project Hindsight, a US Department of Defense sponsored project on the incremental advances of military technologies; the TRACES study, commissioned by the US National Science Foundation to discern the role of non-mission-related research in technological innovation; and Retrospectroscope, a book written by Julius Comroe in response to Project Hindsight that examined clinical advances in medicine. Each of these studies worked backwards from scientific advances, identifying contributing research and mapping key events in their development.

![Figure 1. The Payback Framework](image)

**1.3 Project structure**

We address perception the relatively few improvements in schizophrenia care have emerged by combining the two methodologies described above, investigating both the impacts (or lack of) from research in ‘hot topic’ areas funded 20-25 years ago, and identifying
contributory research and contextual factors that have led to improved treatments in recent years. Figure 2 illustrates these two overlapping approaches.

Figure 2. Methodological approach

Both the forward- and backward-tracing streams of work will involve a series of systematic, structured case studies to examine the facilitators of and barriers to research translation. Case studies are especially useful in illuminating research translation because they allow detailed exploration of contextual and individual factors that are (or are expected to be) significant, and that are not easily captured by macro-level analysis.

Phase I piloted and further developed both the forward- and backward-tracing approaches to ensure their feasibility in the field of mental health. Phase II will implement these improved methods in conducting the full set of case studies on which our analysis will be based.

1.3.1 Forward-tracing case studies

The forward-tracing stream will track prospectively the impacts of research published in the period 1985-1990 through systematic and structured case studies.

A major strength of the case study approach is the depth with which each topic can be explored: the detailed format allows an extensive literature review, interviews, and bibliometric analysis to be conducted for each case. However, a consequence of this in-depth approach is that it is not practical to carry out a large number of case studies. To ensure that our findings are as generalisable as possible, a key task of Phase I has been developing a method to select an appropriate sample. This stream of work, and in particular the case study selection process, is described in more detail in Chapter 2.
1.3.2 **Backward-tracing case studies**

Backward-tracing case studies will retrospectively map the antecedents of treatment advances. They will explore both the preceding research that led to an advance and the facilitators and barriers that accelerated or held back its development.

In deciding the scope of this stream of work, schizophrenia is considered as ‘an anchor but not a fence’ in identifying advances from which to work backwards. This means that advances should have had a positive impact on the care of individuals with schizophrenia, but need not necessarily be limited to schizophrenia. This acknowledges the interlinked nature of mental health research and practice, as well as the somewhat blurred boundaries between some diagnoses. The development of the backward-tracing case methodology is discussed in detail in Chapter 4.

1.3.3 **Deriving insights for policy**

In the final stage of the project we will analyse the two streams of work and identify factors associated with impact, key characteristics of research that lead to translation, contextual factors that appear to act as facilitators or barriers, and the time course of payback from mental health research.

Building this evidence base will enable us to develop a set of generalisable policy insights to address the challenges funders face as they strive to increase the impact and efficiency of their funding.

1.4 **Phase I of the project**

The aims of Phase I were to build on the previous methodology to ensure that it could be used in the field of mental health, test the feasibility of this approach by conducting pilot case studies, and develop a means of selecting the case studies for Phase II. Figure 3 summarises the structure and tasks of Phase I which took place over a period of nine months.
Chapter 2 reviews the overall structure of the study, discussing the most appropriate balance of forward- and backward-tracing case studies. The following chapters then discuss the decisions made in terms of selecting forwards- (Chapter 3) and backwards-tracing (Chapter 4) case studies, as well as lessons from the pilot case studies (Chapter 5) that inform the methodology for Phase II. Finally, Chapter 6 sets out lessons gleaned from a similar project we have carried out in the field of cardiovascular health research.
As outlined in the introduction to this report, this project will take a case study approach to understanding research translation and the effects of research on treatment. In this chapter we explain the rationale for selecting the types and numbers of case studies.

2.1 Why combine forward and backward-tracing case studies?

We plan to use both forward-tracing and backward-tracing case studies. Both types of case study explore the journey between research and impact, but provide a different perspective on the process.

Forward-tracing case studies show how a particular piece of research developed and:

- allow both successes and failures to be followed
- enable identification of impacts in any field
- map wider benefits, including training or development of techniques
- allow the decisions for supporting the research to be scrutinised

Backward-tracing case studies work backwards from treatment advances to understand where they came from and:

- identify successful research stories, as they are linked to a treatment advance
- recognise contributions from any area of research
- can identify how treatment advances might feed back into research questions

The research team has experience of both types of research tracing, although the majority of our recent work has concentrated on tracing forwards (Grant, et al., 2003; Hanney, et al., 2003; Lewison, et al., 2005; Nason, et al., 2008; Nason, et al., 2006; Wooding, et al., 2004; Wooding, et al., 2006; Wooding, et al., 2009).

Mental health differs from the areas in which we have previously worked as there have been fewer major advances; the advances have tended to be smaller and more contested. For example, we have previously worked on cardiovascular disease for which statins, stents, and smoking cessation have, among others, been major breakthroughs. Similarly, anti-TNF therapy has been a significant advance in the area of arthritis.

The paucity of breakthroughs in mental health treatments mean that we are less likely to find forward-tracing case studies that have had an impact on patients. For this reason we think it would be valuable to complement the forward-tracing case studies with backward-tracing case studies.
The backward-tracing case studies will allow us to identify areas of research that have provided benefits to mental health treatment, and understand the processes by which this has come about. They will also provide a valuable comparison to our forward-tracing case studies, allowing us to check whether factors, such as interdisciplinary collaboration, which might be identified as beneficial in forward-tracing case studies, were also important in the backward-tracing narratives.

2.2 How many case studies should we carry out?

The challenge of a case study methodology is generalising the conclusions. For Mental Health Retrosight, we address this in two ways: first, by carrying out a relatively large number of case studies and selecting them in a way that attempts to be ‘better than random’ and, second, by providing a sample that balances some of the key characteristics of mental health research.

The first aspect is self-explanatory; the second means that we attempt to generate a sample that takes in the key characteristics of the research being examined. For forward-tracing case studies this includes selecting a balance of basic, clinical and interventional research, spread across pharmacological and psychosocial paradigms.

The details of how we intend to balance the case study selection are discussed in the next two chapters, but here we provide a brief overview of our rationale for the total number of case studies and how they are balanced between forward-tracing and backward-tracing.

To do this we simplify matters by assuming that all case studies require similar resources for completion. In our experience this is a useful planning assumption for forward-tracing case studies, and we then adjust the allocations in detail once we have done initial work on the case studies. Our pilot case studies suggested that backward-tracing case studies tend to require slightly more resources, and also may not be as similar in size. These differences, and their implications, are discussed in more detail in Chapter 4.

The first driver for the number of case studies is our desire to strengthen generalisability, by having as many case studies as possible. Our heuristic for grouping case studies, derived from our experience and one of the key texts on case studies, is that we should have 4 case studies with each key characteristic (Yin, 2003). Spreading the case studies across three countries therefore gives us a minimum of 12 case studies.

Our previous project on cardiovascular disease used 29 case studies, across three countries. This work showed that around 30 case studies is probably the limit for the mode of analysis we envisage for this study. The critical stage of analysis was our use of an international panel of evaluators to convert our qualitative case studies to quantitative measures of success by asking them to rate each case study on a number of dimensions derived from the payback categories. All of the panel members felt that with 29 case studies they were reaching the limits of how many could be recalled, rated, and compared.
This gives us a suggested range of case study numbers between 12 and 30. Maintaining a balance of case studies across Canada, the USA and UK limits that choice to multiples of three².

Our initial proposal balanced resource constraints against the desire for generalisability to suggest 24 case studies.

2.3 How do we balance between forward- and backward-tracing case studies?

There is no single right answer to this question, so here we present our reasoning in balancing resources between forward- and backward-tracking case studies. Overall we think the bulk of our effort should be focussed on forward-tracing case studies.

There is no limit to the number of forward-tracing case studies we could identify – there were hundreds of research grants awarded and papers published in the time window we have identified. However, we identified a limited number of treatment breakthroughs (see Chapter 4), thus limiting the number of feasible start points for backward-tracing case studies.

Two other factors affect the selection of backward-tracing case studies: backward-tracing case studies are unlikely to split evenly across countries – interventions will be used in a number of countries and the stories of their origins are likely to cross national boundaries. Therefore it does not seem sensible to try and balance cases across countries, in a ‘one from each’ or ‘two from each’ manner. However, backward running case studies can provide different insights on how research is developed and built upon to influence clinical practice and can be used to augment, test and reinforce observations from our forward-tracing case studies.

This leads us to suggest a split of resource of 75% for forward-tracing case studies and 25% for backward-tracing case studies.

Using our original proposal this would suggest 18 forward-tracing case studies and six backward-tracing case studies. After considering our options for backward-tracing case studies we suggest using the resource for six case studies but carrying out three smaller and one larger case study of three times the size (see Chapter 4 for detailed discussion).

² This is a pragmatic criterion based on the fact that the project will receive funding from all three countries.
CHAPTER 3  

**Forward-tracing case study selection**

This chapter reviews the selection and analysis of units of research for forward-tracing case studies.

For each piece of research selected, we will develop a detailed case study based around the Payback Framework. The research underpinning the case study will be based on a review of the scientific literature – both that coming out of the work explored in the case study and other relevant papers, reviews, textbooks and so on – and key informant interviews with the principal investigators, co-applicants, other researchers, and other key people involved. In addition, other sources of funding and collaboration at the time will be mapped, and publications emerging directly from the research will be identified for detailed bibliometric analysis.

The draft case study narratives will be shared with and cleared by the principal investigators and then independently peer-reviewed by two experts in the field, one from the same country as the case study, and one from another study country. Reviewers will be asked to assess the accuracy of both the science described and the attribution of impacts to the research.

### 3.1 Exploratory or hypothesis testing?

There are two ways of structuring case study selection. One identifies potentially important factors in the development of research for an exploratory study. The other tests the importance of particular factors or hypotheses about research development.

At the project workshop held mid-way through Phase I, we presented a series of possible factors that could be tested (Box 1). However, because of limitations on the number of case studies, we could focus on only one or two of these factors. Further, at the workshop there was little consensus on which of these hypotheses/factors should be selected. We have therefore structured the case study selection for a more exploratory study where the emphasis is on examining a wide range of research encompassing many different characteristics, and as such, we use a case study matrix to select for a balanced diversity of case studies. For this reason we suggest including case studies from industry, if they are selected, as they present an alternative approach to research management and selection.
EXTENT OF HEALTH IMPACT  Selecting research with different levels of perceived health impact so we can compare case studies with ‘higher’ and ‘lower’ impact. For selection purposes this would have to rely on the perceptions of the PI collected through a survey.

CLINICAL EXPERIENCE  Dividing researchers on the basis of whether they have clinical experience, or dividing research based on whether there was a researcher in the team that had clinical experience. These data would have to be collected through a survey.

SOFT/CORE FUNDING  Dividing researchers, and consequently their research clouds, based on the amount of ‘soft’ or ‘discretionary’ funding they controlled. There have been previous indications that having such money allows researchers beneficial freedom to pursue their instincts. These data would have to be collected through a survey.

RESEARCH GROUP CULTURE OR PI PERSONALITY  There is evidence that the personality of the PI and the culture they develop in their research group can affect the wider impacts of their work, but as far as we are aware it has not been specifically investigated through this type of approach. The challenge would be devising a questionnaire the PIs were willing to complete but that provided a measure of these factors.

CRITICAL MASS  Dividing researchers, and consequently their research clouds, by the size of their research groups – or possibly the institutions in which they are situated – to investigate the issue of whether there are effects of scale, or critical mass, on wider impacts of research.

CURiosity-DRIVEN VERSUS MISSION-DIRECTED  Dividing research according to how much influence the funders exerted on the direction of the research: from purely curiosity-driven through to directly-commissioned research to answer a specific question. It looks like there was very little directly-commissioned research from the main funders in our sampling window, but we could potentially examine research in funders ‘expressed areas of interest’ versus other areas.

FUNDING MODE  Selecting grants that were supported by different mechanisms or types of funding – for example, comparing fellowships with grants given for particular projects. If we are not selecting grants, we would ask PIs about the funding that supported their work and how they used different types of funding. We could, however, use a survey to investigate the range of funding held by investigators to ensure representation of funding types that are of interest.

Box 1: Possible case study selection characteristics presented at the first project workshop

3.2  Time window for start of case studies

For the forward-tracing case studies, we needed to select the time window for the case studies so we could follow the outputs and outcomes of that research forward in time to the present. We selected a time window of 1985-1990, during which the research
was carried out, for several reasons. First, going back 20-25 years allowed enough time for the research to have developed into practices or interventions that might be benefitting patients. There are various estimates of how long this takes, but most estimates of the average lag from research to impact are around 17 years (Health Economics Research Group et al., 2008; Morris et al., forthcoming). Second, this reference period allows for adequate recall and data. It is short enough to enable us to talk to researchers who will recall the research and their situation at the time, and to find records about the research from organisational archives. Third, the reference period encompasses milestones in the trajectory of schizophrenia research, such as the NIMH National Plan for Schizophrenia Research, published in 1988. We were unable to identify equivalent strategy documents in the UK and Canada.

We have carried out studies using various timescales 10-14 years in the past for ARC, 12-16 years for Project Retrosight. Our experience suggests a timescale of around 15-25 years is feasible.

3.3 Deciding on a unit of analysis

For the unit of analysis for the forward-tracing case studies, we also needed to decide what ‘units’ of research to select. Here, the goal was to identify research that was seen as important at that time and understand how and why it was funded. We have chosen to examine ‘research clouds’.

Our initial plan was to use research grants as our unit of analysis and map hot topics through a range of literature based approaches. However, after working with the funders and examining their archive materials and databases it became clear that they had insufficient records from the period to allow us to compile comprehensive grant lists which we could accurately classify into the mental health area or map into hot topic areas (see Appendix A: Funder grant lists). Once this became clear we put our attempts to map hot topic issues on hold, having pursued a review of the NIMH National Plan for Schizophrenia and a review of key reviews (see Appendix B: Hot research topics).

Instead, we have chosen to examine the ‘research clouds’ that gave rise to highly cited papers in the time window 1985-1990. Research clouds are intended to be coherent units of research which correspond to a particular discovery or advance made by a research group, maybe in collaboration with others - for example in one pilot case study the research cloud is the localisation of the 5-HT3 receptor in the brain and in the second it is the identification of the key growth factor for a particular cell type. An important point is that research clouds may be supported by more than one source of funding and may give rise to more than one paper, although we will initially identify them through a highly cited paper that they have produced (Figure 4). Identifying research clouds from highly cited papers provides our filter for research that was seen as important around that time.

Research clouds are a heuristic device that seems to align with researchers’ perception of how their work is divided. In the Phase II case studies we will iterate across the forward-tracing case studies to develop research cloud definitions that support
comparability. We have resisted using papers as our unit of analysis, as papers often do not identify an exclusive unit of research – the same research may be described in a number of papers; and often do not seem to align with how researchers subdivide their work.

Figure 4. Defining a research cloud

3.4 Ensuring a balanced selection

To maximise the potential for generalising our findings, we need to ensure a balance of case studies across the key domains of research. To achieve this, the papers identified will be organised into a selection matrix to balance case studies across a series of criteria. The final selection will then be guided by the project advisory group. The proposed matrix is shown in Table 3.

We are aware that in selecting our case studies in this way, the forward-tracing stream of work will exclude research which was not seen as relevant to schizophrenia at the time but ultimately did have an impact on the field. For example, initial developments in antipsychotic medication evolved from findings in Parkinson’s disease research. Although our forward-tracing case studies will not capture such advances, research from outside the immediate schizophrenia field will be picked up in our backward-tracing case studies.

Table 3: Proposed selection matrix for forward-tracing case studies

<table>
<thead>
<tr>
<th>Domain</th>
<th>Canada</th>
<th>UK</th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Clinical</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Interventional</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosocial</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Health services/service delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.5 **Bibliometric methodology**

Bibliometrics employs quantitative analysis to measure patterns of scientific publication and citation, typically focusing on peer reviewed journal papers (Ismail et al., 2009). In the current context we used bibliometrics to facilitate the identification of hot research topics for the forward-tracing case studies. In doing so we make the working assumption that a highly cited research paper published in a peer reviewed journal is a proxy for an important stream of research, since logically scientists will cite papers they considered important at the time.

We collaborated with Vincent Larivière at Observatoire des Sciences et des Technologies (OST) at the Université du Québec à Montréal, an expert in bibliometric analysis. Using Thomson Reuters’ Web of Science, we aimed to identify and classify a short-list of highly cited papers in neuroscience and mental health research published between 1985 and 1990. The short-listed papers were then examined and further filtered to finalise proposed case studies for Mental Health Retrosight. Figure 5 below outlines this process in more detail.

![Figure 5: Schema of process to identify hot research topics using bibliometrics](image)

**3.5.1 Identification of journal set**

All neuroscience and mental health research papers with a US, UK or Canadian address published between 1985 and 1990 were identified from the Web of Science. The journal set was identified as:

- all papers published in ‘Psychiatry’, ‘Neurology’, or ‘Neurosurgery’ journals as defined by the National Science Foundation and all papers in ‘Psychiatry’, ‘Neuroscience’, ‘Clinical Neurology’ or ‘Neuroimaging’ journals as defined by Thomson Reuters;
- all papers published in journals in which 75% or more papers were retrieved using relevant MESH terms³ as summarised in Box 2;
- all paper published in other journals but retrieved using the relevant MESH terms list in Box 2.

This resulted in a dataset of 238,836 papers.

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³ All of the articles indexed in MEDLINE have been read by an indexer. Indexers read each article in order to identify and assign the terms, *from a standardized list of subject terms*, that describe the content of an article. MESH is the acronym for this master list of standardized Medical Subject Headings. Usually between 10 and 15 MeSH terms are assigned to an article to describe its content. OST maps the MESH terms from MEDLINE onto its in-house bibliometric database derived from the Web of Science.
Box 2: MeSH terms used to identify highly cited papers

Mental Disorders [F03], except Substance-Related Disorders [F03.900]
Mental Health Services [F04.408]
Mental Health [F02.418]
Neurosciences [H01.158.610]
Nervous System Diseases [C10]
Nervous System [A08]
Mental Disorders [F03]
Neurology [H02.403.600]
Neuropharmacology [H02.628.280]
Psychopharmacology [H02.628.546]

3.5.2 Grouping by research type
To facilitate the classification of papers by research type and to control for known differences in citation behaviour we classified the papers using the National Science Foundation’s ‘Research Level’ (Narin et al., 1976). This is a classification system that groups journals as being Basic (RL=4), Clinical investigation (RL=3), Clinical mix (RL=2), and Clinical observation (RL=1). At the outset we were aware that this system was potentially too crude given the unique breadth of mental health research and this was evidenced by the very small number of schizophrenia-related papers occurring in our initial sample. However, we felt it would be a useful starting point that could then be refined when reviewing the scope. We created two groups – basic research (based on RL=4) and ‘other’ (based on RL = 1, 2 and 3). As explained below, the other category is then allocated into two other groups – clinical and interventional (with interventional divided into three subgroups: biological, psychosocial and health services/service delivery). The basic group had 73,310 papers and the ‘other’ group 147,604. We excluded papers where the journal had not been classified (n=17,471).

3.5.3 Identification of highly cited papers
For the two groups of paper – basic and other – we identified the papers that were within the 85 to 95 percentile in terms of citations. We chose this range for a number of reasons. Firstly, we wanted to identify ‘hot’ papers; that is, we wanted papers that were highly cited. Secondly, we needed to ensure that we could select at least two papers from Alberta, as Alberta Innovates Health Solutions will support two case studies. Thirdly, we wanted to exclude outliers. Finally, we needed to ensure that we were comparing like-with-like in our paper selection and thus wanted a relatively tight percentile range.

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4 We explored the characteristics of these papers and they were very lowly cited: the top cited papers had 145 citations, with the median number of citations being 1 and the 90 percentile 7 citations. This is not surprising. The reason the journals were unclassified is that they had low visibility in the first place and thus publications in those journals are unlikely to be highly cited.
We calculated the citation boundary for the basic papers and other papers separately, as we knew from previous work that, on the whole, basic research is cited more than non-basic research. We also explored the variance in the citation boundaries by the other three research levels (1, 2, and 3) to ensure that it was appropriate to put them in one group in the first instance. As illustrated in Table 4, the 85 to 95 percentile range for basic research was between 29 and 61 citations; for the other group, it was 16 to 32 citations. Filtering on these ranges resulted in 7,584 papers in the basic group and 7,183 papers in the other group.

### Table 4: Citation boundaries for different research levels

<table>
<thead>
<tr>
<th>RL</th>
<th>85%</th>
<th>95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic</td>
<td>29</td>
<td>61</td>
</tr>
<tr>
<td>Other</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>39</td>
</tr>
<tr>
<td>NULL</td>
<td>5</td>
<td>11</td>
</tr>
</tbody>
</table>

3.5.4 **Grouping by country**

Using the address information of the corresponding authors we then classified the papers to the US, the UK and Canada. For Canada we also identified a subset of papers with an Alberta address to ensure that we identified two case studies from Alberta (given the support of Alberta Innovates Health Solutions). The distribution of papers by research group and country of corresponding author is provided in Table 5 below.

### Table 5: Distribution of papers across countries

<table>
<thead>
<tr>
<th></th>
<th>UK</th>
<th>US</th>
<th>Canada (Alberta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic (RL =4)</td>
<td>392</td>
<td>2641</td>
<td>216 (31)</td>
</tr>
<tr>
<td>Other (RL = 1,2 and 3)</td>
<td>1006</td>
<td>5591</td>
<td>434 (22)</td>
</tr>
</tbody>
</table>

3.5.5 **Checking whether ‘in scope’**

We were aware from the outset that the journal set was very broadly defined. We therefore wanted to further filter the papers in Table 6 to ensure they were within the scope of the project. For the ‘other’ group we did this by simply filtering on “schiz*” in the title of the paper, that is, we aimed to select papers that were explicitly focused on schizophrenia. For the basic group we decided to split it into papers that had a focus on schizophrenia and those that did not. The justification for this is that one of the interesting findings from our work in cardiovascular research is that those basic research projects that had an explicit clinical motivation tended to have a higher academic and wider impact. This is a potentially important observation that we would like to explore further.
Table 6: Distribution of papers by research level and country of corresponding author

<table>
<thead>
<tr>
<th></th>
<th>UK</th>
<th>US</th>
<th>Canada (Alberta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic (RL =4), with “schiz*”</td>
<td>2</td>
<td>4</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Basic (RL =4), without “schiz*”</td>
<td>390</td>
<td>2637</td>
<td>216 (32)</td>
</tr>
<tr>
<td>Other (RL = 1,2 and 3) with “schiz*”</td>
<td>32</td>
<td>170</td>
<td>11 (0)</td>
</tr>
</tbody>
</table>

As is apparent in Table 6, at this stage of the filtering process, there is an uneven distribution of papers. In some cases we have no candidates, in others a short-list of candidates, and others a long-list that will need further filtering. This guides some decisions for us. For example:

- The two Canadian basic research case studies have to come from 32 papers from Alberta and do not mention “schiz*” in the title (coloured yellow in the table).
- We have enough papers to shortlist the UK (n=2) and US (n=4) basic research case studies with a mention of “schiz*” in the title (coloured green in Table 6). These are listed in Table 7 below.

This leads to two additional selection tasks: to ensure the basic research papers without “schiz*” in the title for the UK, the US and Alberta are in scope, and to allocate the other research papers for the UK, the US and Canada into clinical and interventional sub-groups. Both tasks required the reviewing of titles by members of the research team (SW and AP) which inevitably means that at this stage some element of subjective judgement is involved.

Three of the 32 basic papers from Alberta with “schiz*” in the title were deemed to be in-scope by our researchers (they independently agreed on the selected papers). These are listed in Table 7 below.

The 390 UK papers and 2637 US basic papers without “schiz*” in the title (coloured blue in Table 6) were further reduced by restricting the long-list to the 90th percentile, that is the middle of our 85 to 95 percentile range. This is equivalent to 38 citations. This resulted in lists of 17 UK papers and 106 US papers. For the UK, 13 of the 17 papers were judged to be out of scope by our two reviewers (SW & AP). For the remaining four papers, there was disagreement as to whether they were in scope or not. Hence for Phase II of the study we plan to revisit this exercise and expand the percentile range to, say, 89-91%, to allow the inclusion of more papers. Our reviewers agreed that two of the 106 US basic papers without “schiz*” in the title were in-scope and disagreed on another two; hence it may also be necessary to revisit this paper set in Phase II.
3.5.6 **Filtering and allocating other papers**  
The other paper titles (coloured red in Table 6) were then reviewed by SW and AP. The papers were allocated to one of four categories: clinical, interventional–biological, interventional–psychosocial and interventional–health services/service delivery. Our reviewers agreed on the allocation of all the Canadian papers and all but one of the UK papers. For the 170 US papers they reached agreement on 145. In allocating the papers, the reviewers noted whether the title was likely to be a review paper or not. For example, of the 116 clinical US papers 49 were identified as potential review papers. In Phase II it will be necessary to remove such papers from the selection process. Across all the research types a total of 77 potential review papers were identified.

3.5.7 **Short-list of ‘hot’ research papers for consideration in case study selection**  
This resulted in the short-listing of 203 papers across the cells in the selection matrix, from which we will select case studies in consultation with the steering committee at the start of Phase II. One of the objectives of this selection is to ensure that we have a suitable mix and balance of case studies. The 203 papers (grouped by cell are) listed in Table 7.
**Table 7. Shortlisted papers**

(* denotes a possible review)

<table>
<thead>
<tr>
<th>Basic research [Need to select 6]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without “schiz” in title [Need to select 3]</td>
</tr>
<tr>
<td>Canada (Alberta) [need to select 2]</td>
</tr>
<tr>
<td>CHANGES IN STRIATAL DOPAMINE NEUROTTRANSMISSION ASSESSED WITH MICRODIALYSIS FOLLOWING RECOVERY FROM A BILATERAL 6-OHDA LESION - VARIATION AS A FUNCTION OF LESION SIZE</td>
</tr>
<tr>
<td>DOPAMINE DEPLETION IN NEONATAL RATS - EFFECTS ON BEHAVIOR AND STRIATAL DOPAMINE RELEASE ASSESSED BY INTRACEREBRAL MICRODIALYSIS DURING ADULTHOOD</td>
</tr>
<tr>
<td>SYNAPTIC MODULATION BY DOPAMINE OF CALCIUM CURRENTS IN RAT PARS-INTERMEDIA</td>
</tr>
<tr>
<td>UK [Need to select 1 or 2]**</td>
</tr>
<tr>
<td>ENHANCEMENT OF SOME 5-HT-DEPENDENT BEHAVIORAL-RESPONSES FOLLOWING REPEATED IMMOBILIZATION IN RATS</td>
</tr>
<tr>
<td>POTENTIATION BY KAINATE OF EXCITATORY AMINO-ACID RELEASE IN STRIATUM - COMPLEMENTARY INVIVO AND INVITRO EXPERIMENTS</td>
</tr>
<tr>
<td>A NOVEL NMDA ANTAGONIST, MK-801, IMPAIRS PERFORMANCE IN A HIPPOCAMPAL-DEPENDENT SPATIAL-LEARNING TASK</td>
</tr>
<tr>
<td>DIFFERENTIAL DISTRIBUTION OF GABAA RECEPTOR MESSENGER-RNAS IN BOVINE CEREBELLMUM - LOCALIZATION OF ALPHA-2 MESSENGER-RNA IN BERGMANN GLIA LAYER</td>
</tr>
<tr>
<td>** note that our reviewers did not agree on these four papers and therefore in Phase II we plan repeat the review of these papers for a wider percentile range (see text)</td>
</tr>
<tr>
<td>US [Need to select 1 or 2]***</td>
</tr>
<tr>
<td>*THE EFFECT OF SEROTONERGIC AGENTS ON HALOPERIDOL-INDUCED CATALEPSY</td>
</tr>
<tr>
<td>MODULATION OF STRIATAL ENKEPHALINERGIC NEURONS BY ANTIPSYCHOTIC-DRUGS</td>
</tr>
<tr>
<td>NORMAL-DISTRIBUTION OF REGIONAL CEREBRAL BLOOD-FLOW MEASURED BY DYNAMIC SINGLE-PHOTON EMISSION TOMOGRAPHY</td>
</tr>
<tr>
<td>HOMOVANILLIC-ACID CONCENTRATIONS IN BRAIN, CSF AND PLASMA AS INDICATORS OF CENTRAL DOPAMINE FUNCTION IN PRIMATES</td>
</tr>
<tr>
<td>*** our reviewers agreed on the first two papers, but disagreed on the second two. If necessary in Phase II we will repeat the review of papers for a wider percentile range (see text)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>With “schiz” in title [Need to select 3]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada [No selection as 2 from Alberta]</td>
</tr>
<tr>
<td>UK [Need to select 1 or 2]</td>
</tr>
<tr>
<td>*SCHIZOPHRENIA - THE CELLULAR BIOLOGY OF A FUNCTIONAL-PSYCHOSIS</td>
</tr>
<tr>
<td>QUANTITATIVE AUTORADIOGRAPHIC ANALYSIS OF GLUTAMATE BINDING-SITES IN THE HIPPOCAMPAL-FORMATION IN NORMAL AND SCHIZOPHRENIC BRAIN POSTMORTEM</td>
</tr>
<tr>
<td>US [Need to select 1 or 2]</td>
</tr>
<tr>
<td>DYSFUNCTION IN A PREFRONTAL SUBSTRATE OF SUSTAINED ATTENTION IN SCHIZOPHRENIA</td>
</tr>
<tr>
<td>*STARTLE RESPONSE MODELS OF SENSORIMOTOR GATING AND HABITUATION DEFICITS IN SCHIZOPHRENIA</td>
</tr>
<tr>
<td>DOPAMINE RECEPTOR SUBTYPE IMBALANCE IN SCHIZOPHRENIA</td>
</tr>
<tr>
<td>ORGANIZATION OF DOPAMINE D1 AND D2 RECEPTORS IN HUMAN STRIATUM - RECEPTOR AUTORADIOGRAPHIC STUDIES IN HUNTINGTONS-DISEASE AND SCHIZOPHRENIA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Research [Need to select 6]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada [Need to select 2]</td>
</tr>
</tbody>
</table>

20
PREVALENCE STUDIES IN SCHIZOPHRENIA
MAGNETIC-RESONANCE-IMAGING STUDIES OF THE BRAINS OF SCHIZOPHRENIC-PATIENTS
A POSSIBLE ROLE OF HIPPOCAMPAL DYSFUNCTION IN SCHIZOPHRENIC SYMPTOMATOLOGY
A STUDY OF THE SEPTUM PELLUCIDUM AND CORPUS-CALLOSUM IN SCHIZOPHRENIA WITH MR IMAGING
A TWIN STUDY OF INDIVIDUALS WITH BOTH SCHIZOPHRENIA AND ALCOHOLISM
*AKINESIA, TARDIVE DYSMENTIA, AND FRONTAL-LOBE DISORDER IN SCHIZOPHRENIA
*NEUROPSYCHOLOGICAL DEFICIT IN SCHIZOPHRENIC SUBTYPES - PARANOID, NONPARANOID, AND SCHIZOAFFECTIVE SUBGROUPS
*LATERALITY AND FRONTALITY OF CEREBRAL BLOOD-FLOW AND METABOLISM IN SCHIZOPHRENIA - RELATIONSHIP TO SYMPTOM SPECIFICITY
*CHILDREN AT RISK FOR SCHIZOPHRENIA - CONVERGING LINES OF EVIDENCE
*COMPUTED ELECTROENCEPHALOGRAPHIC ACTIVITY MAPPING IN SCHIZOPHRENIA - THE RESTING STATE RECONSIDERED
*THE DIAGNOSIS OF SCHIZOPHRENIA
DSM-III-R SCHIZOTYPAL PERSONALITY-TRAITS IN OFFSPRING OF SCHIZOPHRENIC DISORDER, AFFECTIVE-DISORDER, AND NORMAL CONTROL PARENTS
*EPIDEMIOLOGY OF SCHIZOPHRENIA
DNA RESTRICTION FRAGMENT ANALYSIS OF THE PROOPIOMELANOCORTIN GENE IN SCHIZOPHRENIA AND BIPOLAR DISORDERS
EVIDENCE FOR REDUCED AND DYSREGULATED TURNOVER OF DOPAMINE IN SCHIZOPHRENIA
*SCHIZOPHRENIA - AGE AT ONSET, GENDER AND FAMILIAL RISK
THE HETEROGENEITY OF THE LONG-TERM COURSE OF SCHIZOPHRENIA
PRODROMAL SIGNS AND SYMPTOMS OF SCHIZOPHRENIC RELAPSE
*NEUROBIOLOGICAL STUDIES OF SENSORY GATING IN SCHIZOPHRENIA
EMOTIONAL ATTITUDES AND DIRECT COMMUNICATION IN THE FAMILIES OF SCHIZOPHRENICS - A CROSS-NATIONAL REPLICATION
*SCHIZOPHRENIA AT THE CROSSROADS - A BLUEPRINT FOR THE 80S
HYPOFRONTAL VS HYPO-SYLVIAN BLOOD-FLOW IN SCHIZOPHRENIA
MEDICATION COMPLIANCE AND SUBSTANCE-ABUSE AMONG SCHIZOPHRENIC-PATIENTS
SENSORY INPUT DEFICITS AND NEGATIVE SYMPTOMS IN SCHIZOPHRENIC-PATIENTS
A PROSPECTIVE-STUDY OF STRESSFUL LIFE EVENTS AND SCHIZOPHRENIC RELAPSE
*THOUGHT, LANGUAGE, AND COMMUNICATION IN SCHIZOPHRENIA - DIAGNOSIS AND PROGNOSIS
COGNITIVE ABNORMALITIES IN SCHIZOPHRENIC-PATIENTS AND SCHIZOTYPAL COLLEGE-STUDENTS
*SELF, IDENTITY, AND SUBJECTIVE EXPERIENCES OF SCHIZOPHRENIA - IN SEARCH OF THE SUBJECT
*PSYCHOPATHOLOGY AND CLINICAL COURSE OF SCHIZOPHRENIA - A CROSS-CULTURAL-PERSPECTIVE
ABNORMAL RESTING REGIONAL CEREBRAL BLOOD-FLOW PATTERNS AND THEIR CORRELATES IN SCHIZOPHRENIA
*DEPRESSION, HOPELESSNESS AND SUICIDE IN CHRONIC-SCHIZOPHRENIA
OCULOMOTOR ABNORMALITIES AND THEIR CLINICAL CORRELATES IN SCHIZOPHRENIA
*DRUG-ABUSE IN SCHIZOPHRENIA
STRATEGIES FOR RESOLVING THE HETEROGENEITY OF SCHIZOPHRENICS AND THEIR RELATIVES USING COGNITIVE MEASURES
IS THERE ATYPICAL HANDEDNESS IN SCHIZOPHRENIA
NEUROLOGICAL IMPAIRMENT IN VIOLENT SCHIZOPHRENIC INPATIENTS
EVENT-RELATED BRAIN POTENTIALS - A WINDOW ON INFORMATION-PROCESSING IN SCHIZOPHRENIA
PROBING PREFRONTAL FUNCTION IN SCHIZOPHRENIA WITH NEUROPSYCHOLOGICAL PARADIGMS
POSITRON EMISSION TOMOGRAPHY AND SUBCORTICAL GLUCOSE-METABOLISM IN SCHIZOPHRENIA
INCREASED VERTICAL AXON NUMBERS IN CINGULATE CORTEX OF SCHIZOPHRENICS
*THE SEARCH FOR SYMPTOMS PREDICTIVE OF SCHIZOPHRENIA
*PREDICTORS OF SHORTER-TERM, MEDIUM-TERM, AND LONGER-TERM OUTCOME IN SCHIZOPHRENIA
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*THOUGHT-DISORDER - A FUNCTION OF SCHIZOPHRENIA, MANIA, OR PSYCHOSIS*
*EARLY INSIGHT AND THE MANAGEMENT OF SCHIZOPHRENIC DECOMPENSATION*
NEUROPHYSIOLOGICAL ASSESSMENT OF SENSORY GATING IN PSYCHIATRIC-INPATIENTS - COMPARISON BETWEEN SCHIZOPHRENIA AND OTHER DIAGNOSES

Interventional research [Need to select 6]

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<tr>
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**US [Need to select 2 out of 3 subcategories]**

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<td>ANTIDEPRESSANTS IN DEPRESSED SCHIZOPHRENIC INPATIENTS - A CONTROLLED TRIAL</td>
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<td>ABSENCE OF RELATIONSHIP OF SERUM HALOPERIDOL CONCENTRATION AND CLINICAL-RESPONSE IN CHRONIC SCHIZOPHRENIA - A FIXED-DOSE STUDY</td>
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<td>COST-EFFECTIVENESS OF CLOZAPINE FOR TREATMENT-RESISTANT SCHIZOPHRENIC-PATIENTS</td>
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<td>RELATION OF NEUROLEPTIC DOSE AND TARDIVE-DYSKINESIA TO ATTENTION, INFORMATION-PROCESSING, AND PSYCHOPHYSIOLOGY IN MEDICATED SCHIZOPHRENICS</td>
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<td>HALOPERIDOL AND THIORIDAZINE DRUG LEVELS AND CLINICAL-RESPONSE IN SCHIZOPHRENIA - COMPARISON OF GAS-LIQUID-CHROMATOGRAPHY AND RADIORECEPTOR DRUG LEVEL ASSAYS</td>
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<td>HALOPERIDOL PLASMA-LEVELS AND ACUTE CLINICAL-CHANGE IN SCHIZOPHRENIA</td>
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<td>HALOPERIDOL BLOOD-LEVELS AND EFFECTS IN SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER - A PROGRESS REPORT</td>
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<td>A LONGITUDINAL ASSESSMENT OF HALOPERIDOL DOSES AND SERUM CONCENTRATIONS IN ASIAN AND CAUCASIAN SCHIZOPHRENIC-PATIENTS</td>
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<td>DEXTRO-AMPHETAMINE DIMINISHES NEGATIVE SYMPTOMS IN SCHIZOPHRENIA</td>
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<td>EFFICACY OF ADJUNCTIVE CARBAMAZEPINE IN THE TREATMENT OF CHRONIC SCHIZOPHRENIA</td>
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<tr>
<td>Family psychoeducation, social skills training, and medication in schizophrenia - the long and short of it</td>
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</table>
3.6 **Analysis**

In order to identify factors associated with high and low impact on practice, we first need a robust means to estimate the impact level of individual forward-tracing case studies. For this project we intend to build on and refine the method used in our Cardiovascular Retrosight project. In this study we estimated the impact level of each case study by using an international team of evaluators to review each case study and assess its impact in each of the payback framework’s five categories: knowledge production; research targeting and capacity building; informing policy and product development; health and health sector benefits; and broader economic benefits. To facilitate this process, we provided evaluators with a pack of summary materials, including summaries of case study narratives and payback tables, comments from peer review, and bibliometric analyses.

The impact ratings were used to categorise the case studies into high, mid and low impact groups. These groups were then used to identify commonalities and potential drivers of research impact.
CHAPTER 4 Backward-tracing case study selection

4.1 Introduction

This chapter reviews the selection and analysis of units of research for backward-tracing case studies.

As noted earlier, the backward-tracing case studies will explore how treatment advances have come about and the research and other factors that facilitated or hindered their development.

In conducting the case study research, the initial task will be to describe and delineate the advance. This will involve an extensive literature review of practice-related documents such as guidelines, product licensing information, survey data, prescribing records, policy documents and training curricula in order to:

- quantify and map the extent to which the treatment has been adopted;
- examine in detail the treatment’s intended use and any alternatives used previously, in addition or instead; and
- investigate the historical path of the advance, from which key individuals involved in its development and adoption can be identified for interview.

This will begin an iterative process of interviews and literature review which will aim to identify key decision points in the development of the advance and answer questions about both its research antecedents and contextual facilitators of translation. We will also attempt to add more quantitative measures, such as bibliometric tracing and network analysis to the cases.

4.1.1 Analysis

As information is built up around the advance being studied, characteristics of the contributing research will be recorded to identify commonalities and factors contributing to translation. Alongside this, contextual factors will be explored which may have acted as facilitators or barriers to translation of the research at each stage. An important consideration in this mapping will be the specificity of the contributing research: it might be expected that as a stream of work nears translation to treatment, contributing research would become more specific or applied. In contrast, research at earlier stages may have had relatively small impacts, but across many areas of science.
4.2 **Case study selection**

4.2.1 **Overview**
For backward-tracing case studies, we wanted to identify advances that have resulted in significant benefits to patients. As explained in Chapter 2, we planned to carry out six case studies in this stream of work.

In order to investigate a suitable range of advances we developed a set of criteria to aid our selection. In summary, we wanted to consider:

- A balance of pharmacological interventions and non-pharmacological.
- Some treatments that had been similarly adopted across the project countries and some that had not (i.e. were more prevalent in one or two countries).
- Some advances that focus on the individual and others that focus more on their environment (family, community, etc.).

Our initial approach to selection was to conduct a Delphi-like survey of various mental health stakeholders to generate a broad list of possible case study topics. On reviewing the results of this survey, two immediate candidates emerged: cognitive behavioural therapy (CBT) and early intervention.

The grouping of other responses was less clear cut that so we undertook a review of clinical guidelines for schizophrenia treatment in the three project countries. This was particularly aimed at providing a more detailed set of pharmacological advances to consider – in many cases, survey respondents had simply suggested “antipsychotic medication” or similar. This review produced a second list of interventions which we then mapped as closely as possible against the original list from the survey. By looking at the country of each survey respondent, we then ranked the guideline list for each country to determine which suggested advances had gained the most support in each.

This led to the provisional selection of the following case studies:

- **Cognitive behavioural therapy** – this clearly emerged as a priority in Canada and the UK, and was the most commonly suggested non-pharmacological intervention
- **Early intervention** – this was again a very popular suggestion, particularly in Canada and the UK.
- One **community-based psychosocial intervention**. to be selected from peer support services; supported employment; family psychoeducation; other family support interventions. These were fairly uniformly suggested across the three project countries.
- **Antipsychotic drugs** – although we identified a number of sub-topics within this from the guideline review, each would have required a more general consideration of the history of the use of antipsychotic medication. For this reason, we propose to conduct one larger case study
(in place of three smaller pieces of work) looking at pharmacological interventions. Antipsychotic medication was the most commonly suggested advance among US respondents to the survey, and also received substantial support in the UK and Canada.

Conducting the above set of case studies would mean that we would cover pharmacological treatment (antipsychotic drugs), psychosocial interventions (CBT), interventions in the environment of people with schizophrenia (community-based intervention), and advances in the way that mental health services are delivered (early intervention). We would also conduct only four case studies (instead of the six initially proposed); however, we anticipate that to comprehensively cover the important advances in the use of antipsychotics would require the equivalent work of three smaller case studies.

Further detail on the two approaches we used in selection, the Delphi-like survey and the review of clinical guidelines, is provided in the following sections.

### 4.2.2 Delphi-like survey

The aim of the survey was to identify key treatments, advances, or interventions that could legitimately be said to have improved the care and management of schizophrenia and which would also lend themselves to further research and analysis as case studies. Although the national treatment guidelines for schizophrenia in Canada, the UK and the US contain information regarding current recommended treatments and interventions for schizophrenia, the project team wanted to select advances and treatments that had already brought significant benefit to the lives of patients. Given the complexity of mental health treatment and the lack of major advances in care, the project team decided that a Delphi-like survey could potentially yield a more accurate and revealing picture of the treatments that have had a genuine and significant impact on the lives of patients with schizophrenia.

A Delphi survey is an effective means of gathering qualitative information, in this case the opinions of stakeholders on the key advances or treatments in schizophrenia care, in a structured way. In its most typical form, a Delphi survey involves using a questionnaire that asks participants to list, rank, and rate a series of items over a number of rounds interspersed with feedback collection. The aim in most instances is to drive participants to consensus on a set of issues, factors or events, but the method can be used in a more open-ended manner to reveal a range of options instead.\(^5\)

For our purposes, we decided to use the Delphi methodology to gauge opinion from mental health researchers, practitioners, service users, nurses, and other stakeholders on what they considered to be the most significant advances and treatments in the care and management of schizophrenia. To this end, we needed to pose a question to respondents which would prompt them to consider all elements of a schizophrenia patient’s care today and identify the elements of that care that have genuinely brought benefit and positive outcomes to the patient. The difficulty here was choosing language which would be meaningful across Canada, the UK, and the US and across different professions and levels of engagement with the issue of schizophrenia care. For example, although we were

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initially interested in identifying breakthroughs in schizophrenia care, we were concerned that by using that terminology we would preclude respondents from suggesting other elements of schizophrenia care that could not be considered to be a ‘breakthrough’ but which have, nonetheless, yielded considerable benefit to patients. As a result, we consulted our Steering Committee for advice on suitable wording and phrasing of the survey question and finally settled on the following:

“What are the most important interventions that have been introduced into practice for the treatment of schizophrenia in the last 5-10 years and yielded significant benefits to patients?”

A list of potential respondents to the survey was compiled from the following sources:

- Steering Committee members and their contacts
- Montreal workshop participants
- Internet searches for key organisations and individuals with an interest in mental health and schizophrenia

In total, the Delphi-like survey was sent to 113 people. Table 8 shows a breakdown of invited respondents by country and the rate of response received.

<table>
<thead>
<tr>
<th>Country</th>
<th>No. sent survey</th>
<th>No. respondents</th>
</tr>
</thead>
<tbody>
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<td>9</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>34</td>
<td>14</td>
</tr>
<tr>
<td>United States</td>
<td>39</td>
<td>7</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

We invited individuals from a wide range of schizophrenia and mental health-related organisations across the areas of research, treatment, support, and advocacy. Individuals represented researchers, clinicians, service-users, service-providers, and nurses. From the outset, we aimed to get as broad and varied a group of respondents as possible and we were particularly keen to ensure that service users were represented in the sample. The survey was administered electronically and all prospective participants were invited to forward the survey to any additional contacts they felt would be interested in taking part in the study. Assuming all of the responses were from people we directly approached, our overall response rate was 31%. Table 9 shows the breakdown of respondents by profession.
As Table 9 indicates, the majority of our respondents were either researchers or clinicians (or both). Despite inviting a number of support service organisations and patient groups to participate in the survey, we were unable to get greater representation from service users and support service providers.

The responses we received to the Delphi-like survey revealed a wide range of advances and interventions. Four interventions and treatments in particular were cited repeatedly by respondents: cognitive behavourial therapy; treatments related to second generation antipsychotics; early intervention; and support services, such as supported employment and social skills training. In addition to pharmacological treatments and psychosocial interventions, nine respondents cited the emphasis upon recovery and recovery models of care as having been of significant benefit to patients. Similarly, the change in public attitudes towards schizophrenia and the reduction of stigma surrounding the disorder was also cited by five respondents as a key development.

In order to analyse the survey responses, we tried to align similar responses in order to create a coherent final list, for example, we grouped together all responses related to the use of second generation antipsychotics. The aim of this was to identify which services that were cited could feasibly be regarded as part of a single initiative so as to make the final list smaller and more meaningful. An issue with our initial categorisations of responses was trying to ensure consistency in meaning across the countries in the study, as certain
interventions, for example, community-delivered services, may have slightly different meanings in different countries. This initial list was presented at the Montreal workshop for comment and discussion.

### 4.2.3 Review of national clinical guidelines

Following the workshop, the project team continued to scrutinise the list of survey responses and, on the advice of Steering Committee members, we undertook a comparison of the treatments and interventions discussed in the national guidelines for schizophrenia in Canada, the UK and the US. The guidelines consulted were the American Psychiatric Association Practice Guideline (US), the Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations (US), the National Institute of Clinical Excellence clinical guidelines (UK), and the Canadian Psychiatric Association Clinical Practice Guidelines (Canada).

Comparing the clinical guidelines with the responses from the Delphi-like survey resulted in the final list of potential interventions shown in Table 10 below.

### Table 10: List of interventions/treatments for 2nd round of Delphi-like survey

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<table>
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<tbody>
<tr>
<td>1</td>
<td>Family support interventions</td>
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<tr>
<td>2</td>
<td>Psychoeducational interventions</td>
</tr>
<tr>
<td>3</td>
<td>Vocational rehabilitation, including supported employment</td>
</tr>
<tr>
<td>4</td>
<td>Community treatment systems, including Assertive Community Treatment</td>
</tr>
<tr>
<td>5</td>
<td>Alcohol and substance abuse programmes</td>
</tr>
<tr>
<td>6</td>
<td>Peer support and peer-delivered services</td>
</tr>
<tr>
<td>7</td>
<td>Cognitive remediation</td>
</tr>
<tr>
<td>8</td>
<td>Psychosocial interventions for weight management</td>
</tr>
<tr>
<td>9</td>
<td>Early intervention</td>
</tr>
<tr>
<td>10</td>
<td>A culture of hope and recovery, including the recovery model of care</td>
</tr>
<tr>
<td>11</td>
<td>Cognitive behavioural therapy</td>
</tr>
<tr>
<td>12</td>
<td>Reduction of stigma i.e. greater public understanding and tolerance of schizophrenia</td>
</tr>
<tr>
<td>13</td>
<td>The use of antidepressants for depressive symptoms</td>
</tr>
<tr>
<td>14</td>
<td>Avoidance of antipsychotic polypharmacy</td>
</tr>
<tr>
<td>15</td>
<td>Management of side-effects with first generation antipsychotics by reducing dosage</td>
</tr>
<tr>
<td>16</td>
<td>Management of side-effects with first generation antipsychotics by switching to a second generation agent</td>
</tr>
<tr>
<td>17</td>
<td>Use of clozapine in treatment-resistant patients</td>
</tr>
<tr>
<td>18</td>
<td>Use of second generation antipsychotics as a frontline treatment</td>
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</table>
These two interventions were included at the suggestion of our expert advisors, who considered them to be major advances that had not been captured specifically from the clinical guideline review or Delphi-like survey. We felt it would be better to work with this wider list initially to ensure that no major advances were excluded, and then narrow this down during the selection process.
This chapter presents summaries of the pilot case studies that were carried out as part of Phase I of the project. We describe the rationale for the pilot case studies, how they were selected, and what we learned from carrying them out. We also briefly discuss the interesting observations that emerged from the case studies – although these are largely only illustrative at this stage, we feel they may be helpful in giving an idea of the kind of conclusions that Mental Health Retrosight could eventually reach. Finally, we provide brief summaries of the case studies themselves. The full case studies are included as appendices.

Our initial plan had been to carry out one forward-tracing and one backward-tracing pilot case study. This was intended to test:

- Whether the case study approach and payback model could be applied in the mental health research arena. This included determining an appropriate unit of analysis.
- How best to structure and present backward-tracing case studies
- Some aspects of the case study selection process

Once the project was underway, given the diversity of the area, and the change in unit of analysis for forward-tracing case studies, we decided that it would test the limits of our approach more effectively if we carried out four slightly shallower case studies, rather than two complete pilots. For both the forward-tracing and the backward-tracing case studies we have produced one fuller case study and one partial case study. The case studies indicate where we would add additional detail in order to use the case studies for the final study. The reasons for the selection of each case study are summarised in Table 11.

One striking observation, across both the forward- and backward-tracing case studies, was the willingness of researchers to participate in interviews. This is a very promising sign for Phase II.
Table 11: Pilot case studies

<table>
<thead>
<tr>
<th>Type</th>
<th>Case Study</th>
<th>Reasons for selection</th>
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</table>
| Forward-tracing | Kilpatrick: Identification of type 3 serotonin receptors in the brain     | To test if we could carry out case studies on industry research  
To test use of ‘research cloud’  
To test recall of PIs for research published 20-25 years ago |
| Richardson: Identification of a growth factor for glial cells | To test tracking of very basic research  
To test use of ‘research cloud’  
To test recall of PIs for research published 20-25 years ago |
| Backward-tracing | Cognitive behavioural therapy                                              | To test method of backward-tracing case studies                                                                  |
|                 | Early intervention                                                        | To test where a less well defined intervention could be examined through case study                             |

5.1 **Forward-tracing**

5.1.1 **Selection**

To select our forward-tracing case study pilots we used a bibliometric technique similar to, but simpler than, that described in Chapter 3. At the time we had only a filter for neuroscience papers available so we identified the most highly cited UK papers in the 1985-90 time window. SW then worked down that list applying a number of criteria:

- whether there was a potential link to schizophrenia
- whether the PI still appeared to be active and whether they were likely to be easy to visit (assessed through searching Web of Science for recent publications)
- whether the research had been based in academia or industry (assessed by looking at the addresses on the original publication)

We then approached the corresponding author by email to see if they were willing to participate and available on the timescale we needed. Of the two principal investigators we approached, both agreed to participate.

The two case studies we selected were ranked as the 8th (Kilpatrick) and 31st (Richardson) most highly cited publications in neuroscience during our 1985-1990 window.

5.1.2 **Lessons and learning**

Both our case studies proved tractable, although the one more closely related to schizophrenia, Kilpatrick, proved more interesting in terms of its links to mental health.

The case studies demonstrated that it is feasible to define ‘research clouds’, and in these two cases was relatively easy to do so. These clouds seem to be of a similar order to the size of grants and it will be important to ensure comparable definitions across the case studies in Phase II. One concern with clouds was whether it would be possible to tie them back to funding, however, at least for these two case studies it was possible to identify the different roles that each funding source provided. In Phase II we will aim to go beyond the funding itself to investigate in more detail the decisions that led to the research being supported.
The Kilpatrick case demonstrated the feasibility of carrying out case studies on research that was carried out in industry, and we were able to interview a range of those involved in the area both within Kilpatrick’s company and also at a competitor organisation. We did not encounter any problems with interviews, although we could not gain access to written company records from the time.

In the full study we will attempt to add more quantitative measures, such as bibliometric tracing and network analysis to the case studies.

5.1.3 Potential policy relevant observations

We would not suggest generalising observations from two pilot case studies, however, we felt it might be useful to highlight some of the aspects of the case studies that we found most interesting. This could give a flavour of the sorts of observations Phase II might produce. It should be noted that because neither research cloud ultimately had a particular impact on schizophrenia research (because they were basic research that was only potentially relevant at the time), the observations from the pilot case studies are of relevance to neuroscience research more generally. In Phase II, the selection of basic case studies with “schiz*” in the title, as well as the inclusion of interventional and clinical research, will help to ensure that observations which are particular to schizophrenia can be identified.

Value of new techniques

In both case studies, the PIs brought new techniques to the problem they were trying to solve. While in each case the techniques themselves were not novel, they had not been previously applied to those particular problems.

Repercussions of competition

In both cases there was pretty intense competition – in Kilpatrick’s case this was between companies, and in Richardson’s case between research groups. This competition is interesting from a counterfactual point of view – that is, if the research had not been done by Kilpatrick or Richardson the answer would clearly have been found pretty soon afterwards anyway; however, the presence of competition seems to have spurred on both researchers. It is interesting to note in the Kilpatrick case study that a competitor describes intense, yet gentlemanly, competition in which it was understood that you did not let your competition try approaches that you knew to be unsuccessful.

The predictability, or not, of research

In Kilpatrick’s case the research proceeded pretty much as planned (although as it was research in industry there was no formal grant application), whereas in Richardson’s case he made his discovery in a completely different way to that envisaged in the grant application. Such observations could shed light on how grant applications should be assessed. Since research rarely proceeds as planned, it may be more important to select projects based on the talents and versatility of the individual than on the actual methodology proposed.

Alternative models of decision making

In contrast to the committee-based decision making for academic grants, the decisions about Kilpatrick’s research effectively rested with one person, the head of the neuropharmacology department at Glaxo where Kilpatrick was working.
The high level of interaction between academia and industry
The Kilpatrick case study illustrates very close ties and collaboration between industry and academia. This was a mutually beneficial situation: most leading experts on clinical work were based in universities, but pharmaceutical companies often developed the necessary compounds, and large-scale controlled trials were only feasible when backed by industry resources.

The path dependency of drug development
The Kilpatrick case study shows the path dependency of drug development. Although a number of serotonin type 3 receptor antagonists were used in research, very few were licensed and approved for use (and not for mental health indications). When interest in using such compounds for mental health indications resurfaced, the only ones commonly tested were those already licensed, which our informants considered some of the least likely to be effective.

Culture of ‘claim staking’ in industry
Informants in the Kilpatrick case study describe an interestingly split culture of competition in the pharmaceutical industry at the time. The culture meant competition between companies was fostered, but internally there was also a culture of ‘stake claiming’. This meant that one group would tend to ‘stake a claim’ and take control of each compound. The commercial value of bringing a drug to the market for a particular purpose meant that it was unusual for a compound to be pursued for more than one indication.

Importance of very small grants
In considering the range of research grants that supported his research cloud, Richardson noted that one very small grant for £4000 from the Nuffield Foundation had a value far above its monetary value. It was the first grant he won and helped build his confidence that he could win grant funding.

Value of naïveté
As an outsider moving into the field of developmental cell biology, Richardson was free from some of the field’s preconceptions and this was a key factor in allowing him to re-interpret existing findings that allowed him to shortcut to his discovery.

5.1.4 Kilpatrick
Serotonin (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 in the brain of 5-HT3 receptors (one class of serotonin receptor), previously only believed to exist peripherally.

A number of research groups, including at Glaxo, Sandoz, Beecham and Merrell-Dow, were investigating therapeutic uses of 5-HT3 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-HT3 receptors. They achieved this in 1987 and published their findings in a highly cited Nature paper the same year.
The finding that 5-HT₃ 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 these were disappointing, with no consistent evidence of positive effects, and pharmaceutical companies soon moved to focus on other areas instead.

By this time, the primary indication for which 5-HT₃ antagonists were being developed was emesis, and in particular chemotherapy-induced and postoperative nausea and vomiting. A related stream of work 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-HT₃ antagonists in psychiatry, there has been something of a recent revival of interest in the area, and there are a few indications that this work could potentially still lead to clinical application in disorders such as schizophrenia (eg. Bennett & Vila, 2010; Zhang et al., 2006; Akhondzadeh et al., 2009).

5.1.5 Richardson

This case study covers the identification of a cellular growth factor, a chemical that tells cells to grow and divide. To keep the body healthy, cells must grow and divide in the appropriate places at the appropriate times – cancer is the result of uncontrolled cell growth. In the late 1970s it was becoming clear that there were chemical signals, termed growth factors, which told cells to grow and divide. Growth factors had been identified by taking culture medium from one cell culture and showing that it could cause other cell types to grow. However, although this demonstrated that there was something, an ‘activity’, in the medium; it didn’t identify what the ‘activity’ was. At the time of this work only one proliferative growth factor had been identified as a particularly protein: platelet derived growth factor (PDGF)(Antoniades, et al., 1979). It was commonly thought that each type of cell might have its own growth factor – one for muscle cells, one for blood cells, one for nerve cells etc. And the search was on for other growth factors.

The nervous system consists of two classes of cells – the nerve cells, or neurons, themselves; and an array of support cells. The support cells are referred to as glial cells and form the ‘white matter’ in the brain. There are a range of glial cells types and they include the cells that provide the myelin insulation that coats the neurons. Although neurons were originally seen as by far the most interesting cells, over time it has become clear that the glial cells are more important, and complex, than expected.

There are some indications that glial cells may play a role in schizophrenia – although this is currently controversial. Genes involved in glial cell development have been linked to schizophrenia and changes in the amount of white matter in the brain have also been linked to schizophrenia. However these might not be causal effects – it could be that whatever is causing the schizophrenia is also causing the changes to the glial cells.

The work described in this case study concerns three types of glial cells: astrocytes, O-2A cells and oligodendrocytes.
Raff’s research group had developed a cell culture system made from rat optic nerves and shown that one of the cell types – astrocytes – produced an ‘activity’ that caused the second cell type – O-2A cells – to grow and divide. The O-2A cells were particularly interesting as they are a type of stem cell, but can also develop into oligodendrocytes, the third type of cell. The question was what was the active ingredient that the astrocytes produced to make the O-2A cells divide.

Through a key insight that allowed him to re-interpret existing experimental results, Richardson was able to show that the activity produced by the astrocytes and PDGF were one and the same, showing that one growth factor was used for multiple cell types in the body. This allowed him to label the receptor for PDGF and hence locate and track O-2A cells in the body. Through this work he showed that the O-2A cells migrated during development – a very surprising finding. Twenty years later Richardson is still working on closely related cellular systems.

5.2 Backward-tracing

5.2.1 Selection

To select the subjects of our backward-tracing pilot case studies we used the initial results of the Delphi-like exercise. In consultation with our Steering Committee we selected two of the treatment advances that had been identified: cognitive behavioural therapy (CBT) and early intervention. Other than antipsychotic medication, these two were the most commonly suggested advances.

We selected one psychosocial intervention and one relating to service delivery, as most of the identified treatment advances were psychosocial and there is less literature tracing non-pharmacological interventions. We picked CBT as a largely uncontroversial, relatively tightly defined intervention and early intervention as a more disputed and less well-defined concept in order to test the boundaries of what was feasible to conduct case studies on.

5.2.2 Lessons and learning

Again both of the case studies proved feasible – although initially the early intervention case study was challenging because of varying definitions. A key challenge for these backward-tracing case studies is likely to be driving the case studies back far enough to get at the activities that gave rise to the changes, which is likely to include funding and the decisions made around the research. The more complete CBT case study manages this in some instances, but we would work to add more depth in this area in Phase II case studies.

In line with our expectations, the backward-tracing case studies proved to be slightly more resource intensive than the forward-tracing ones, however, they were not drastically more so.

In common with the backward-tracing case studies we would look to complement our literature and key informant based narrative with bibliometric tracing.

Given the value that peer review provided in Cardiovascular Retrosight, we are keen to take advantage of it for the backward- as well as the forward-tracing case studies. Given the
broader nature of the case studies, we will explore using some form of open peer review to allow comments from and discussion among a number of reviewers.

5.2.3 Potential policy relevant observations
Again with a similar caveat to that given in the section on forward-tracing case studies, we have noted below some of the most interesting factors we see emerging from the two backward-tracing case studies.

The challenges of a pharmaceutical model of evidence
One factor that seems to have held back the development of the research in both case studies was a desire among researchers, clinicians and policy makers for blinded trials – something that may be impossible to achieve with psychosocial interventions. Such trials may provide the most incontrovertible evidence of effectiveness, but cause a problem for any intervention that cannot be tested through blinding.

The resistance of existing perceptions
The development of CBT as a therapy for schizophrenia was slowed by entrenched perceptions of the biological basis of schizophrenia, and hence the idea that it could not be affected by cognitive interventions; the perception of schizophrenia as a purely non-affective disorder and hence the idea that cognitive approaches to handling emotion would be inappropriate; and the idea that discussing symptoms with patients was counterproductive.

5.2.4 CBT
Antipsychotic medication has been the mainstay of treatment for schizophrenia since the first antipsychotic drug was developed in 1952. Although these drugs have brought considerable benefit to the lives of patients who suffer from psychosis, they are only infrequently associated with full symptom remission and functional recovery. The reasons for this include limited efficacy of antipsychotic medication in a substantial proportion of patients; the problem of severe side-effects, which some patients experience; and the unwillingness of some patients to take medication. Historically, schizophrenia has been regarded as an illness with a strong biological component. For many decades, psychological therapies were thought to add very little or in the case of psychodynamic psychotherapy, to subtract from the positive effects of medications and other somatic therapies.

The recognition of the limitations of antipsychotic drugs in the treatment of schizophrenia set the stage for the search for psychosocial approaches that might improve patient outcomes. While in the UK, increasing numbers of mental health professionals became interested in the adaption of cognitive theory and behavioural theory to the treatment of schizophrenia, in the US the focus was on strategies grounded in cognitive/behavioural

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7 According to Turkington et al, even when patients with schizophrenia fully adhere to antipsychotic medication regimes, up to 50% will have ongoing positive or negative symptoms, with 20-30% of people with chronic schizophrenia demonstrating very little symptomatic response to adequate trials of conventional antipsychotic medications. ‘Cognitive-Behavioural Therapy for Schizophrenia: A Review’. Focus. 4: 2 (2006): 223-233.

theory to help patients better manage and cope with their illness. The original form of CBT, rational emotive behaviour therapy, was developed in the 1960s by Albert Ellis, but the model of CBT which is most commonly practiced today has its origins in the work of A.T. Beck. CBT as a treatment for schizophrenia is part of a wider framework of CBT as applied to a range of mental disorders such as anxiety, post-traumatic stress disorder (PTSD), and depression. Cognitive theory is based on the notion that the cognitive processes implicated in mood and anxiety disorders occur transdiagnostically, meaning they co-occur across the psychiatric disorders. A number of studies have supported the notion that psychotic symptoms can be understood in relation to normal psychological processes and, as a result, the symptoms can be effectively treated by CBT techniques.

Cognitive behavioural therapy (CBT) of schizophrenia has developed dramatically over the last ten years (this would also be true for the US if the statement is about the research base; not applicable to the US if it is about reach/uptake). In the UK, the National Institute for Health and Clinical Excellence recommends that cognitive behavioural therapy should be made available to all people suffering with schizophrenia, particularly those with persistent hallucinations and delusions, lack of insight, and poor concordance with antipsychotic medications. Similar recommendations have been made in Canada and the US (APA: Guideline 2004 and Guideline Watch 2009; PORT schizophrenia recommendations 1998, 2004, 2010). In addition, the Netherlands, and Australia have well-developed research programmes in this area and Brazil, China, Germany, Japan, Scandinavia, and Spain are all showing an increasing interest in this approach.

5.2.5 Early intervention

There are two forms of early intervention that correspond to different stages of schizophrenia. The prodromal stage of schizophrenia starts with functional deterioration and progresses to psychotic symptoms. Early intervention in the prodromal phase involves community-level detection efforts and treatment to prevent onset and decrease morbidity. Schizophrenia’s first episode stage follows the first psychotic episode. Early intervention during this stage focuses on detecting and promptly treating those who have already experienced a psychotic episode.

13 NICE 2002
Treatment of first episodes of psychosis has been the standard of care for many years. Some studies have shown a correlation between early intervention during the first episode stage and improvement in treatment response and long-term outcomes. However, there have not been randomized control trials showing a causal link between early intervention after onset of psychosis and improved outcomes.

In the last 10 years, there have been efforts to reach individuals with treatment in the prodromal stage. Even though this is still an emerging area, some early studies have demonstrated the effectiveness of early intervention in the prodromal phase. Nonetheless, the evidence base for early intervention in the prodromal stage is not considered strong enough to warrant a definitive recommendation about early intervention in the prodromal phase.

Because of a lack of clear evidence for the effectiveness of either form of early intervention, the practice guidelines in the US, the UK, and Canada vary on the degree to which they promote early intervention. In the US, the latest American Psychiatric Association (APA) practice guidelines for the treatment of schizophrenia mention the importance of treating as early as possible during the initial episode stage but do not explicitly recommend early intervention as a treatment approach during the prodromal or first episode stage. In England, the current National Institute for Health and Clinical Excellence (NICE) guidelines on schizophrenia recommend a full range of early intervention treatments for the first episode stage while noting the lack of evidence for early intervention during the prodromal stage. Similarly, Canada’s Treatment of Schizophrenia clinical practice guidelines describe the importance of early intervention for those in the first episode stage and acknowledge the need for more studies to determine the effectiveness of early intervention during the prodromal stage.
In parallel with Phase I of Mental Health Retrosight, we have also been carrying out the analysis and write up phase of the Cardiovascular Retrosight project. This project is similar in scale to Mental Health Retrosight with 29 forward-tracing case studies across three countries, and is the largest Retrosight project we have carried out to date.

It is also worth noting that there are significant differences between Cardiovascular Retrosight and Mental Health Retrosight, reflecting the different natures of the fields and the structure of the study:

- Cardiovascular Retrosight takes grants as its unit of analysis rather than research clouds, and only included forward-tracing case studies.
- The area of mental health research is more diverse and has fewer clear-cut treatment advances than cardiovascular research.
- The grants were selected to ensure a balance of levels of impact (from low to high), whereas for Mental Health Retrosight we are selecting only clouds producing highly cited papers, and not attempting to balance our selection for high and low impact on patient care. In Cardiovascular Retrosight this selection allowed us to look for the presence of explanatory factors in high impact cases and their absence in low impact cases; this will be possible in Mental Health Retrosight, but we may not have such a wide range of impact levels in our sample.
- Cardiovascular Retrosight was designed to be more about testing hypotheses (for example, the relative value of large and small grants), but it ended up being more exploratory. Mental Health Retrosight is clearly more in the exploratory mode.
- By looking at grants selected for high impact, Cardiovascular Retrosight was in a good position to catalogue the diversity and scale of benefits from cardiovascular research. In the case of Mental Health Retrosight, although we hope to find case studies that illustrate the value of research, the project is clearly focused not on comprehensively capturing the full range and scale of possible impacts of schizophrenia research, but instead on identifying factors that are important for translation.
- There is not a perfect overlap between the areas in which we may be able to draw conclusions. For example, as the selection method for forward-tracing case studies depends on successful publication, we are unlikely to make observations about
negative results; the corollary being that given the inclusion of backward-tracing case studies there are new areas in which we may be able to make observations. Despite these differences, reflecting on the Cardiovascular Retrosight allows us to draw some lessons for Mental Health Retrosight.

6.1 **The value of peer review**

One of the key refinements of the Retrosight methodology in Cardiovascular Retrosight was the use of independent peer review as a quality check on the case studies themselves. This was very valuable in providing an external perspective on the narratives and their significance. However, it would have been even more valuable if we had scheduled the peer review to allow time to supplement the comments with additional research.

6.2 **Additional resource for analysis**

The case studies in Cardiovascular Retrosight provided a hugely detailed and nuanced collection of information on research and its translation. Although we have carried out a rigorous analysis of this, it was clear that there were further possibilities for meaningful analysis that we have not been able to pursue because of resource constraints.

6.3 **Case study authors should work across analytical and geographic boundaries**

In Cardiovascular Retrosight, we sometimes aligned the division of case study authorship along certain characteristics of case studies; for example, one researcher did all the clinical case studies and there was no overlap between the researchers carrying out case studies in different countries. This made it harder to ensure we were not seeing any authorship effects in our analysis.

6.4 **More interaction between case study researchers**

Given the diversity of research and the factors that influence it, it can be hard to know whether a particular factor – such as mentorship – was absent from a case study or merely not mentioned. We go a long way to addressing this issue through standardised case study templates and interview protocols. However these cannot include the unexpected – by increasing interaction between case study authors when an interesting factor is identified we will be able to look for it in other case studies as well.

6.5 **More date information**

It is becoming increasingly clear that the lags between when research is carried out and when it affects practice are a key factor in determining the value of research: in simple terms the faster research gets into practice, the more valuable the research (Health Economics Research Group, et al., 2008). To explore the issue of lags in more detail we would aim to collect more date information than in Cardiovascular Retrosight case studies.

Hanney, S, Frame, I, Grant, J, Green, P, and Buxton, M, *From bench to bedside: tracing the payback forwards from basic or early clinical research - a preliminary exercise and proposals for a future study*, Uxbridge, Middlesex: Health Economics Research Group, Brunel University, 2003


Morris, Z., Wooding, S., and Grant, J. (forthcoming). The answer is 17. What is the question?


Appendix A: Funder grant lists

To explore the feasibility of using grants as the unit of analysis, we compiled details of the records held by all the main funders in Canada, the UK and the US (see Table 12). We compiled this information through publicly available sources, such as the NIH RePORTER database¹⁶ and through liaison with the organisations concerned.

¹⁶ http://www.projectreporter.nih.gov/
### Table 12: Availability of archive information for selection of grant based case studies for 1985-1990

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</table>
Unfortunately, a number of the organisations did not have the grant records we would require for case study selection available in electronic form. In some instances information such as value of grant was not directly available at all.

To complicate matters further the funders did not use a single standard definition of mental health research and their records often include little more than the grant title, making reliable post hoc classification impossible.
Appendix B: Hot research topics

How the lists were compiled

- The NIMH National Plan for Schizophrenia Research published in 1988
- Literature reviews published in nationally-recognised, peer-reviewed schizophrenia and/or other related journals covering the targeted time period, including:
  - Schizophrenia Bulletin
  - Schizophrenia Research
  - Comprehensive Psychiatry
  - Psychiatry Research
  - Journal of Psychiatric Research
  - Archives of General Psychiatry
  - American Journal of Psychiatry
  - Journal of the American Academy of Child and Adolescent Research
  - Progress in Neuro-Psychopharmacology and Biological Psychiatry
The journals were identified via consultations with experts in the field and a targeted internet search.
- The 50 top-cited articles on schizophrenia research published in Schizophrenia Bulletin during or 1-2 years following the targeted time period, posted on-line monthly at http://schizophreniabulletin.oxfordjournals.org/reports/mfc1.dtl.

Hot topic list from NIMH National Plan

Important areas of research identified in NIMH National Plan for Schizophrenia Research published in 1988

1. Clinical Phenomenology (with a particular emphasis on identifying well-defined homogeneous populations of the disorder for study)
   a. Clinical description and diagnosis
   b. Specific symptoms versus characteristic symptoms
   c. Biological subtyping of schizophrenia
   d. Conceptual boundaries and genetic approaches
   e. Neurotransmitters, neuroendocrine systems, and selection of informative populations:
   f. Neuropathology and structural approaches:
g. Medication versus disorder issues:

h. Specific gaps in present knowledge requiring special attention:
   i. Relationships between identified abnormalities in schizophrenia and clinical heterogeneity (e.g., SPEM, abnormalities in vestibular functioning, and neurological soft signs)
   ii. Personality disorders within the schizophrenia spectrum
   iii. Evaluation of subsyndromal degrees of schizophrenia-like pathology
   iv. Need for improvement in standardization and definition of clinical samples
   v. Inclusion of both cross-sectional and longitudinal components in studies of schizophrenia
   vi. Continued research on definitional and boundary issues
   vii. Continued basic research in both phenomenology and nosology
   viii. More research in normal individuals and animals to better understand phenomenology
   ix. Integration of neurobiology into research in nosology and phenomenology
   x. Development of postmortem tissue banks

2. Genetics, Immunology, and Virology
   a. Molecular genetic linkage studies
   b. Candidate gene studies, such as neurotransmitter system (esp. dopamine) receptors, synthesizing enzymes, degrading enzymes, and vesicular transport proteins; neuropeptides and their receptors, precursors, and precursor peptidases; neurotubular, neurofibrillary, and other structural proteins; neurodegenerative factors; secondary messenger system proteins; immune and viral mediating proteins
   c. Longitudinal family studies
   d. Pathophysiologival marker studies
   e. Infectious tissue transmission studies
   f. Screening body fluids and immune functions
   g. Subtyping and spectrum studies incorporating multilevel diagnoses, such as DMS-III schizophrenia, nonaffective psychotic disorders, nonpsychotic schizotypal and borderline personality disorders, and other nonpsychotic mental disorders
   h. Psychiatric registers
   i. International epidemiology focused on collaborative epidemiological studies, immigrants’ risk, mutable risk factors, and overall geographic prevalence
   j. Animal research focused on pilot studies of candidate genes, assaying suspected environmental factors, evaluating intron gene mutants, multiple allele analysis for modes of interaction, multiple mutants in the same gene, mutant rescue
   k. Development of cell and fluid banks

3. Neuroimaging and Nueropathology
a. Neuroimaging (study of living patients with schizophrenia)
   i. Improving and expanding techniques that elucidate structure
      1. Computed tomographic (CT) scanning studies with larger numbers of patients
      2. Magnetic resonance imaging (MRI) or nuclear magnetic resonance (NMR) studies using image enhancement agents (e.g., paramagnetic cations), particularly in selected populations where detailed neuroanatomical information is available
   ii. Improving and expanding techniques for the study of function
      1. Positron emission tomography (PET) studies particularly related to dopamine receptor systems, the limbic system, and the hippocampus and amygdala
      2. Single photon emission computed tomography (SPECT) for studying function by imaging when cyclotrons or radiochemists are not available
      3. Regional cerebral blood flow (rCBF) for studying cortical functions in schizophrenic patients
      4. Computerized electroencephalography (CEEG) for studying cortical abnormalities in schizophrenia and in combination with other neuroimaging devices such as CBF or SPECT
      5. Further development of magnetoencephalography (MEG) as a neuroimaging research tool
      6. Further development of in vivo nuclear magnetic resonance spectroscopy (NMRS) in humans, particularly with regard to providing molecular and metabolic insights into brain function that are not possible with other existing technologies

b. Neuropathology (study of the brain of deceased patients)
   i. Combining traditional neuropathology studies with more modern methods of quantification, such as neuronal morphometrics
   ii. Neuronal morphometrics studies
   iii. Post-mortem neurochemistry for testing neurochemical hypotheses for schizophrenia
   iv. In vitro DNA and RNA hybridization studies
   v. Autoradiographic localization of drug and neurotransmitter receptors and other binding sites within the brain by light microscopy
   vi. Immunocytochemistry for providing information on structures that are difficult to define or dissect in human brains

4. Neurochemistry (study of brain chemistry) and Neuropharmacology (study of the effects of drugs on the central nervous system)
   a. Molecular biology
      i. Linkage studies for identifying the locus of a genetic abnormality
      ii. Study of candidate genes
      iii. Use of differential hybridization
iv. Genomic regulation of the dopamine system, and cloning the genes for the dopamine receptor and for key enzymes influencing and controlling dopamine system function

b. Developmental neurobiology
   i. Prenatal influences on brain development, especially factors that abnormally influence the activity of neurotransmitters, receptors, and other aspects of synaptic transmission
   ii. Developmental molecular biology, including how extragenetic factors influence gene expression
   iii. Preclinical and clinical models focused on critical periods of normal and abnormal brain development
   iv. Examinations of the expression of proteins that occur with synapse formation in specific brain regions using immunocytochemistry and in-situ hybridization techniques
   v. Studies of developmental plasticity
   vi. Studies of the influence of specific prenatal and postnatal stressors on the expression of particular genes important in stress response

c. Neuroendocrinology and stress
   i. Modification of gene expression at the cellular level
   ii. Examination of the nature of brain-hormone interactions
   iii. Specific attention to hormones (e.g., sex hormones and glucocorticoids) that alter or modify CNS dopamine system function
   iv. Endocrine and immune system relationships
   v. Further characterization of the model linking stress and CNS dopamine systems

d. Neuropharmacology
   i. Neuroleptic mechanisms
      1. Development of new pharmacological agents that do not mimic old drugs and provide added therapeutic effects
      2. Further elucidation of the mechanism of action of currently available antipsychotic drugs
      3. Attaining a better understanding of the pharmacological processes involved in mediating the clinical effects of neuroleptic drugs
      4. Application of developing technologies, such as PET and molecular biological techniques to identify and/or confirm specific pathophysiological defects in CNS dopamine function in subsets of schizophrenic patients
   ii. Addressing pharmacological differences between typical neuroleptics (those that produce extrapyramidal side effects) and atypical neuroleptics (those that do not)
iii. Research on transduction mechanisms that translate the neurotransmitter-receptor interaction into a biochemical and electrical response within the receptive cell
iv. Research on peptide systems and their relationship to dopamine system function
v. Studies on the neurochemical consequences of simultaneous neuroleptic/GABAergic interaction in specific CNS dopamine systems
vi. Modeling putative neurochemical and behavioral components reflecting the pathophysiology of schizophrenia
vii. Extension of neurochemical and pharmacological findings to nonhuman primate models

e. Imaging
i. Assessment of the function of dopamine systems in the human brain using PET technology
ii. Using PET for studying mechanisms of neuroleptic drug action
iii. Creative ligand development for PET and SPECT which label non-DA receptors that are also affected by neuroleptics or are known to modify CNS dopaminergic function
iv. Using PET and SPECT to understand shifts in neurobiological function associated with experimental cognitive tasks or with drug treatment
v. Coupling of functional imaging techniques with both primate and rodent studies
vi. Use of highly sensitive magnetic resonance spectrometers (when they become available) for exploring intracellular metabolism

5. Basic Behavioral Sciences
a. Studies of human information processing focused on attention, perception (e.g., parallel distribution processing), language, memory, performance (e.g., motor systems)
b. Studies of emotional expression (e.g., affective dysfunction/flattening), the psychophysiology of emotion, and interrelationships among expressive, physiological, and subjective systems
c. Studies of emotional sensitivity and faulty social and emotional communication
d. Studies of social relations and interpersonal behaviors
e. Studies of personality differences, including psychosocial, emotional, and other behavioral patterns
f. Studies of genetics, behavior, and schizophrenia related to topics such as populations and size of families, diagnostic conventions, use of markers or indicators
g. Use of primate models to reproduce certain characteristic features of the human phenomenon for careful study under conditions of control not possible in human studies
6. Treatment, Services, and Environmental Factors
   a. Treatment research
      i. Pharmacologic
         1. Expand search beyond dopamine antagonist drugs to other neural systems that may play an important role in determining schizophrenic behavior
         2. Develop drugs based on the differentiation of the dopamine system into receptor subtypes
         3. Research on drugs that improve treatment response, prevent relapse, influence the course of the illness, and reduce side effects, esp. tardive dyskinesia (TD)
            a. Efforts to develop animal and tissue models for drug development
            b. Studies of the physiology, biochemistry, and pharmacoresponsivity of the neural systems underlying normal thought and emotion, and testing them for relevance to the study and treatment of patients with schizophrenia
         4. Independent support for the assessment of new compounds
         5. Identification and characterization of schizophrenic subgroups relevant to particular treatment approaches
      ii. Psychosocial and social factors
         1. Studies that address the socioenvironmental influences on behavior and CNS function
         2. Studies that test hypotheses related to interaction of environmental stressors (e.g., environmental events, personality characteristics, subjective experience, individual adaptive mechanisms and capabilities) with schizophrenia
         3. Studies that assess psychosocial treatments and apply existing treatments to unstudied subgroups
      iii. Integration of psychosocial and medication treatment
         1. Integration of psychosocial treatment intervention research approaches into novel drug strategies as they are developed
         2. Determine whether greater gains with novel drugs may be achieved when psychosocial treatments are introduced concurrently
   b. Services research (i.e., organization and financing of service delivery systems and the policies that affect them)
      i. Assessments of cost-benefit of specific services and system-level interventions
      ii. Experimental trials of case management
      iii. Examination of strategies to ensure continuity of care
      iv. Research on how policy decisions affect schizophrenic patients, their families, and the community
v. Studies on the impact of State service systems on treatment delivery and outcomes

**Hot topic list from major studies related to schizophrenia published between 1985-1990**

1. **Pharmacology**: Major focus on dopamine
   a. Mediator of reward and motivational processing
   b. Dysfunctions
   c. Role in development of delusions and hallucinations, stereotyped thought and behavior, and negative symptoms
   d. Role in improvement of sensory function when schizophrenia patients treated with neuroleptic drugs
   e. Interaction between familial or genetic deficits in sensory functioning in schizophrenic patients and possible abnormalities in dopamine metabolism
   f. Relationship between emergence of psychotic symptoms to dopamine-driven associative and reinforcement learning
   c. In large drug trials, clozapine found superior to chlorpromazine and haloperidol in treatment resistant schizophrenic patients
   d. Differing clinical responses for persons with moderate plasma levels of haloperidol versus those with low or high levels (Baldessarini et al, 1990); led to recommendations for monitoring plasma levels of antipsychotic medications under certain circumstances
   e. Weighing the risks of extrapyramidal side effects (EPS) against those of side effects of anti-Parkinson agents (Rifkin and Siris, 1987; Davis et al, 1989)

2. **Neurobiology**: studies of sensory gating reveal evidence about pathophysiology of schizophrenia; Mechanism by which noradrenergic hyperactivity in mania and other psychiatric illnesses might mimic some pathophysiological deficits in schizophrenia (Robert Freedman’s group; Waldo et al, 1988)

3. **Biogenetics**: biological variables that may be markers of genetic liability to schizophrenia disorders (e.g., attention and information processing, smooth pursuit eye movement)

4. **Pathology/ pathogenesis**: suggesting brain is not normal (e.g., nonspecific histopathology in limbic system, diencephalon, prefrontal cortex) and that the pathology occurs early in development and causative process is inactive long before diagnosis is made

5. **Brain studies/brain imaging**:
   a. Correlation of brain imaging findings with neuropsychological deterioration (Bilder et al, 1988)
   b. PET study of brain regional interactions (Volkow et al, 1988)
   c. Neuroimaging studies that show nicotine effects during task conditions that require patient to maintain attention

6. **Depression in schizophrenia** (Leff et al, 1988; Siris et al, 1988)
7. Relationship between epilepsy, psychosis, and schizophrenia (Stevens, 1988)
8. Abnormal neurotensin levels (Nemeroff’s group; Lindstrom et al, 1988)
9. Semantic priming in schizophrenia (Manschreck and colleagues)
10. Weight gain in schizophrenia pre-atypical neuroleptic use (Viewig et al, 1988)
11. Analysis of viral hypothesis (Torrey et al, 1988)
12. Pain insensitivity in schizophrenia
13. Impaired olfactory detection
14. Positive effects of nicotine on vigilance, attention, and rapid information processing
15. Variable rates of short and long term outcomes
16. Definitions/measurements of recovery and factors affecting relapse
Appendix C: Full Delphi-like survey

Delphi-like survey email invitation

Dear [Name]

We are carrying out an international research project that will assess the translation of mental health and schizophrenia research into clinical application and community practice. The aim of the project is to better understand the origins of knowledge in mental health care and to improve the translation of research into treatments and medical practice.

As part of this project, we would like to invite stakeholders to help identify key advances in schizophrenia care. These findings will enable us to select case-studies for this project. The aim is not to come up with a definitive list of advances but to help us shortlist those considered most relevant to practice and the research study. All responses will be treated as confidential and will not be published individually. A link to an online questionnaire can be found here:

https://spreadsheets.google.com/viewform?formkey=dFExek1xUlVRMXVDOT11UFRncm9sMGc6MQ

It will take approximately five minutes to complete.

The project is part of a collaborative initiative, SOS for Mental Health, which is led by the Graham Boeckh Foundation and RAND Europe and supported by several international public and not-for-profit partners, including the US National Institutes of Mental Health, the Canadian Institutes of Health Research and the National Institutes for Health Research in England.

We would be grateful if you could respond by April 27th.

We would also appreciate it if you would forward this email, with the survey link, to anyone else you think might be interested in contributing to this study.

Thank you for your help.

Steve Wooding
Survey text

Improving the Lives of Patients: Significant Developments in Schizophrenia Care

We are carrying out an international research project that will assess the translation of mental health and schizophrenia research into clinical application and community practice. The aim of the project is to better understand the origins of knowledge in mental health care and to improve the translation of research into treatments and medical practice.

As part of this project, we would like to invite stakeholders to help identify key advances in schizophrenia care. These findings will enable us to select case studies for the project. The aim is not to come up with a definitive list of advances but to help us to short-list those considered most relevant to practice and the research study. The survey takes approximately five minutes to complete. All responses will be treated as confidential and will not be published individually.

The project is part of a collaborative initiative, SOS for Mental Health, which is led by the Graham Boeckh Foundation and RAND Europe and supported by several international public and not-for-profit partners, including the US National Institutes of Mental Health, the Canadian Institutes of Health Research, and the National Institute for Health Research in England.

We would be grateful if you could respond to the survey by April 27th 2010.

What are the most important interventions that have been introduced into practice for the treatment of schizophrenia in the last 5-10 years and yielded significant benefits to patients?

In answering this question we would like you to consider the most significant new interventions or advances in treatments and any other developments that have improved outcomes for patients. These might include psychosocial and behavioural therapies, pharmacological or other biological treatments, health service interventions, and other developments that have influenced practice since 2000 and that you consider a major improvement. Please include up to 10, using the text boxes below.

One

Two

Three

Four

Five
Please use the box below if you have any other comments

To help us analyse the results you have given, it would be helpful to have some information about you and your role. Your responses will be only be seen by the research team.

In which country do you work?
- Canada
- UK
- USA
- Other, please specify below

How would you describe your role/interest in schizophrenia (service user, nurse, research funder, etc.)

Please answer yes or no to the following questions:
• Would you be willing to take further part in this study?
• Would you be interested in receiving outputs from this study?

What is your email address? (We will only use this information to send you updates if you have answered yes to either of the questions above).

Thank you for the taking the time to complete the questionnaire.
Appendix D: Kilpatrick case study

Identification and distribution of 5-HT₃ receptors in rat brain using radioligand binding

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


Summary

Serotonin (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 in the brain of 5-HT₃ receptors (one class of serotonin receptor), previously only believed to exist peripherally.

A number of research groups, including at Glaxo, Sandoz, Beecham and Merrell-Dow, were investigating therapeutic uses of 5-HT₃ 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-HT₃ receptors. They achieved this in 1987 and published their findings in a highly cited Nature paper the same year.

The finding that 5-HT₃ 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 these were disappointing, with no consistent evidence of positive effects, and pharmaceutical companies soon moved to focus on other areas instead.

By this time, the primary indication for which 5-HT₃ antagonists were being developed was emesis, and in particular chemotherapy-induced and postoperative nausea and vomiting. A related stream of work 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-HT₃ antagonists in psychiatry, there has been something of a recent revival of interest in the area, and there are a few indications that this work could potentially still lead to clinical application in disorders such as schizophrenia.

Introduction

Scientific background

The cloud of research investigated in this case study provided the first direct evidence for the existence of 5-HT₃ receptors in rat brain tissue and their distribution, based on high affinity binding of the potent 5-HT₃ receptor antagonist ³H-GR65630 to rat brain tissue. This work was published in *Nature* in December 1987 (Kilpatrick, Jones, & Tyers, 1987).

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 around 15 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 their seminal paper identifying two distinct subtypes in the guinea pig ileum (Gaddum & Picarelli, 1957). They termed the two types D receptors and M receptors.

This classification remained unchallenged for over 20 years, and it wasn’t until the work of John 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 (Hoyer interview).

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-HT3 receptor (Bradley, et al., 1986). At this time it was still believed only to exist peripherally (in contrast to the 5-HT1 and 5-HT2 classes of receptor, which had been identified in the brain). The 5-HT3 receptor differs from other 5-HT receptors in that it is the only one which is a ligand-gated ion channel – the other classes are all G protein coupled receptors. This does have its advantages, in that compounds acting at 5-HT3 receptors do not tend to cross-react with other receptors.

Initial work on developing 5-HT3 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). Glaxo had developed ondansetron with the same aim, but a pilot study at a migraine clinic in West Germany in 1985 produced surprising results: 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). Mike Tyers, head of the neuropharmacology department at Glaxo at the time, believed that the 5-HT3 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 in patients 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-HT3 antagonists, MDL 72222 and ICS 205930 were also being evaluated for anti-emetic 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-HT3 receptors antagonists were investigated in pharmaceutical companies.

Throughout this period, research had continued to look at other potential targets for 5-HT3 antagonists, particularly psychiatric disorders. 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. In these studies, ondansetron and other 5-HT3 antagonists were found to block the activity of dopamine, amphetamine and 2-methyl-5-HT in limbic brain areas of the rat and marmoset (Costall & Naylor, 2004), supporting the hypothesis that serotonin may be involved in the modulation of dopamine activity through 5-HT3 receptors – raised dopamine activity has long been implicated in contributing to schizophrenia symptoms.

At this time there was still no definitive evidence for the existence of 5-HT3 receptors in the brain; instead it was believed that the antiemetic properties of 5-HT3 antagonists were a result of activity at receptors in the gut. However the promising findings from animal models of apparent effects in anxiety and psychosis suggested that these compounds were indeed active centrally.

PI Background
Gavin Kilpatrick 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 which 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.

**Dramatis Personae**

**Gavin Kilpatrick** – corresponding author on selected paper; Senior Scientist, Glaxo Research and Development.

**Brian Jones** – Kilpatrick’s boss at Glaxo.

**Mike Tyers** – Head of neuropharmacology department at Glaxo; developed and patented ondansetron.

**Daniel Hoyer** – competitor at Sandoz, who was also using radioligand binding to localise 5-HT3 receptors.

**Brenda Costall and Robert Naylor** – Researchers at Bradford University who collaborated with Glaxo and carried out much of the behavioural work on 5-HT3 in animal models.

**Ed Sellers** – Researcher in Canada who worked with Glaxo in looking at use of ondansetron in addiction.

**John Fozard** – Researcher first at Merrell-Dow and then Sandoz who led much of the revival of interest in the 5-HT field in the late 1970s.

**Defining the research cloud**

This case study covers the research carried out at Glaxo to show the existence of 5-HT3 receptors in the brain. The research cloud begins when Gavin Kilpatrick joined Glaxo in 1985 and includes the work done at Glaxo to map the distribution of 5-HT3 receptors in a number of species and using several techniques.

**Stage 0: Opportunity Identification/Research Needs Assessment**

*Existing knowledge*

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-HT3 antagonists, which it was widely believed would have a role in managing pain, particularly in association with migraine. Work done by Brenda Costall and Robert Naylor at Bradford University also suggested a possible application in psychiatric disorders, including anxiety, schizophrenia and Alzheimer’s disease, evidence which suggested the presence of 5-HT3 receptors in the brain.
Research team experience/expertise
Gavin Kilpatrick had substantial experience in conducting radioligand binding studies, having used the technique to study dopamine receptors during his PhD at the Institute of Psychiatry. At the time, radioligand binding was not used within Glaxo, however it was recognised that this would be vital expertise for the 5-HT₃ work and was a factor in the decision to bring Kilpatrick on to the team.

Availability of resources
The technique of radioligand binding requires a high-affinity compound which has specific activity for the receptor of interest. 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-HT₃ work.

Internal company environment
Glaxo was in the process of moving its research base from Greenford to Ware around the time that Kilpatrick joined. The CNS group was the last to transfer, so went from having a lot of lab space at Greenford to being fairly cramped at Ware. However, the move did allow greater interaction with other research groups within Glaxo, including the cardiovascular group which was already working on 5-HT₃.

Kilpatrick characterises the research environment in Glaxo at the time as fairly academic. Although the company had a clear commercial drive to develop drugs, a reasonable amount of freedom was afforded to some researchers 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.” (Kilpatrick interview)

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 atmosphere, management were a bit hands off.” (Kilpatrick interview).

This isn’t a working environment which was unique to Glaxo. Daniel Hoyer suggested there was similar openness at Sandoz at the time, both in terms of the freedom afforded to some researchers and a willingness to collaborate externally, and that this was also the case at other pharmaceutical companies such as Merck, Lilly and Janssen. He commented that although this situation has now changed, the extent to which the direction of work is internally or externally driven has always depended to some extent on the individuals involved and their personal networks. “In spite of all the efforts that are being put in by industry into research, they always tend to believe a little bit more what is outside [the company] than inside, just because key opinion leaders tend to be, in many cases, in universities.” (Hoyer interview)

Interface A: Peer Review / Project Specification, Selection and Commissioning
Stage 1: Inputs to Research

Financial
The research was funded solely by Glaxo, with head of department Mike Tyers approving work to take place in neuropharmacology.

Knowledge and expertise / techniques
The CNS group at Glaxo consisted of around 30 people, of whom around six worked in neuropharmacology. 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 in 5-HT for some time. In fact, a group at Sandoz led by Daniel Hoyer published the first account of using radioligand binding to investigate 5-HT₃ receptors just a few weeks before Kilpatrick et al.’s *Nature* paper (Hoyer & Neijt, 1987).

The neuropharmacology group at Glaxo were 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-HT₃ 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.

Equipment, infrastructure and space
The research was carried out at Glaxo’s research headquarters in Ware. 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.

Collaborators
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” (Hoyer interview).

Collaborations between industry and academia were particularly common. 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. 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, it’s almost impossible.” (Hoyer interview).

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-HT3 story was when research was at its peak” (Costall, personal communication).

The Glaxo group worked closely with Brenda Costall and Robert Naylor at Bradford University on testing 5-HT3 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.

[More detail to be added following delayed interview with Brenda Costall]

**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-HT3). This was in contrast to some other pharmaceutical companies at the time; for example, Beecham used a project system. In this model, a group would be given a therapeutic target which would be addressed through a number of different approaches. Although this 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-HT3 antagonists had already been developed at the company, and Kilpatrick’s initial binding work used GR38032 (ondansetron), which proved unsuccessful. However, within a year or so of his arrival at Glaxo, GR65630 was developed and the radiochemical group was tasked with developing a radioligand of high specific activity. From this, Kilpatrick was able to develop a binding assay and demonstrate the presence and distribution of 5-HT3 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).

**Stage 3: Primary Outputs**

**Knowledge**

The first publication emerging from the research cloud was a paper published in *Nature* in 1987 by Kilpatrick, Brian Jones and Mike Tyers. This paper described the team’s work to identify 5-HT3 receptors through radioligand binding and was the first to provide direct evidence for their existence in the brain. Binding of the 5-HT3 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-HT₃ 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-HT₃ antagonists found in studies of anxiety and psychosis in animal models (eg. Costall, Domeney, Kelly, Naylor, & Tyers, 1987; Jones, Oakley, & Tyers, 1987). Kilpatrick did suggest 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 may have only identified a 5-HT₃ binding site (Bradley, 1987). The lack of any overt physical response in radioligand binding studies (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, an attitude that 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 the past (binding where there was not actually a functional receptor), these had been in the very early days, before the receptors had been properly characterised.

The editorial also specifically mentioned that GR65630 had not been shown to produce any behavioural effects, and although this may suggest no functional activity in the central nervous system, Jones argued that such findings can also indicate a compound that is in fact psychoactive, but with a very good side effect profile. For example, in the case of an anti-depressant, the drug should have no observable effect on someone who is not depressed (Jones interview).

The discovery of 5-HT₃ 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-HT₃ 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-HT₃ receptors (Kilpatrick, Butler, Hagan, Jones, & Tyers, 1990).

Kilpatrick and his colleagues also developed a potent 5-HT₃ 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-HT₃ receptor.

**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 this 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-HT3 work and by the early 1990s the stream of work had completely stopped. Kilpatrick moved on to an entirely different area—H-3 receptors.

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 in the stream of research 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 the 5-HT3 and H-3 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.

Currently Kilpatrick is still working in neuroscience, although not in psychiatry, as Chief Scientific Officer of the biopharmaceutical company PAION. Much of his current work is around the development of a sedative agent with very fast onset and offset.

The 5-HT3 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-HT3 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-HT3 receptors are present in the brain, research on the receptors proceeded in a number of distinct directions, both through the work of the team at Glaxo and in other industry and academic labs.

The work by Brenda Costall and Robert Naylor at Bradford University during the 1980s had provided promising evidence of behavioural effects of 5-HT3 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-HT3 receptors may well prove useful in the treatment of psychiatric conditions such as schizophrenia, anxiety and depression. However, the subsequent clinical trials in humans, for which Kilpatrick and Jones both often acted as pre-clinical consultants, failed to replicate the expected effects and by the early to mid 1990s it had become fairly clear that a commercial product was not going to emerge at that time (Kilpatrick interview).

The Glaxo team also collaborated with a group at the University of Toronto led by Edward Sellers. Sellers’ group was investigating the use of 5-HT3 antagonists in treating
drug and alcohol dependence, but despite producing some evidence of their beneficial effects, this has yet to be adopted as a standard treatment.

One of the challenges in conducting clinical trials of 5-HT₃ 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 could potentially have been an issue in some of the early unsuccessful trials (Jones interview).

**In other areas**

As discussed previously, by the time the Glaxo team demonstrated the presence of 5-HT₃ receptors in the brain, the antiemetic properties of 5-HT₃ 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 with 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-HT₃ field were focused. 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-HT₃ receptors, and where tropisetron, one of the first 5-HT₃ 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 selling over a billion dollars a year.

This success, though, may actually have hindered progress in investigating the use of 5-HT₃ antagonists more widely. As new compounds are costly to develop, the fact that ondansetron (and other similar compounds, 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-HT₃ 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-HT₃ 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.**” (Jones interview).

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 (Hoyer interview). This may be due in part to a culture in some companies of silo-based working limiting the extent to which the same compound was investigated in different functional areas, but is also due to the fact that major drug breakthroughs are rare enough and commercially valuable enough to generate intense competition and attract huge investment in area showing promise. The resultant focus on emesis, alongside the negative results of the early clinical trials in anxiety...
and psychosis, may have discouraged pharmaceutical companies from pursuing these alternative indications further.

“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.” (Hoyer interview)

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 disseminated well within what was a fairly small field. Many of the groups working on 5-HT3 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 (Hoyer interview).

Stage 4: Secondary Outputs
Despite Glaxo’s substantial investment in clinical trials of 5-HT3 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.” (Kilpatrick interview)

The company focused 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 (Kilpatrick interview). Glaxo was awarded the European Prix Galien in oncology for ondansetron in 1990.
Before Glaxo ended their 5-HT3 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-HT3 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% 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 anti-emetic properties and IBS use) of 5-HT3 antagonists. Despite earlier clinical trials failing to support the use of ondansetron in schizophrenia, a number of studies in recent years 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). As Brian Jones commented “I think it is still an open question to be honest whether these things have psychoactive properties.” (Jones interview).

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 untreated patient populations. Hoyer suggested that this may be one reason behind the reluctance of pharmaceutical companies to pursue the use of 5-HT3 receptor antagonists in psychiatric disorders (Hoyer interview).

In a somewhat roundabout way, tropisetron 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-HT3 antagonist, but instead to its action at the α7 nicotinic acetylcholine receptor.
Stage 5: Applications

Although the case study research did not lead directly to clinical application, as discussed above, it did contribute to the body of knowledge that led to both alosetron and ondansetron being widely used in the treatment of irritable bowel syndrome and chemotherapy-induced and postoperative emesis respectively.

Stage 6: Public Engagement

None identified.

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-HT₃ receptor work did. Ondansetron revolutionised care for cancer patients undergoing chemotherapy and is still widely used today, and has made billions of dollars for Glaxo over the past 20 years. 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.

Table of payback

<table>
<thead>
<tr>
<th>Payback category</th>
<th>Impacts from case study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge Production</td>
<td>A number of papers were published showing the existence of 5-HT₃ receptors centrally in a number of species and using various methods.</td>
</tr>
<tr>
<td>Research Targeting and Capacity Building</td>
<td>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-HT₃ receptors in the brain, a finding which stimulated further research on their functional properties by a number of groups.</td>
</tr>
<tr>
<td>Informing Policy and Product Development</td>
<td>Indirectly contributed to the development to clinical use of ondansetron and alosetron.</td>
</tr>
<tr>
<td>Health and Health Sector Benefits</td>
<td>Indirectly contributed to the health benefits brought by ondansetron and alosetron.</td>
</tr>
<tr>
<td>Broader Social and Economic Benefits</td>
<td>Although only indirectly related, ondansetron and alosetron are both still in clinical use today.</td>
</tr>
</tbody>
</table>
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 Merrel Dow patents the first potent selective M receptor antagonist, MDL 72222 (bemesetron)

1982/3  Sandoz develop ICS 205930 (tropisetron) (Richardson).

1983  Hoyer joins Sandoz and works primarily on 5-HT1 and 5-HT2 receptors

1983  Tyers at Glaxo develops ondansetron (GR38032).

1985  Kilpatrick joins Glaxo, tries identifying 5-HT3 receptors in the brain through radioligand binding using ondansetron .

1985  Glaxo pilot 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 proceed to evaluate ondansetron in patients for anti-emetic activity.

Mid-late 1980s  5-HT3 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 Bradford.

1986  M receptor reclassified as 5-HT3 receptor (Bradley et al.)

1986  Development of compound GR65630 at Glaxo.

1987  Fozard leaves Merrell Dow for Sandoz.


Oct 1987  Hoyer and Neijt publish first report of using radioligand binding to identify 5-HT3 receptors (using tropisetron).


1989  Jones leaves Glaxo for Beecham.

January 1991  ondansetron granted FDA approval as Zofran.

Early 1990s  Clinical work on role of 5-HT3 receptors in psychiatric disorders leads to little.
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.

References


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).


Appendix E: Richardson case study

A role for platelet-derived growth factor in normal gliogenesis in the central nervous system

This partial case study is based on the research cloud surrounding the paper:


The case study was prepared as a pilot for a larger set of case studies on research in mental health and neuroscience in the late 1980s, which aims to examine the development of the research, its translation, and the range of impacts arising from it.

The case study is based largely on interviews with the principal investigator and another researcher associated with the grant. If this case study were to be used as part of the main dataset we would also:

- Define the research cloud in terms of research papers, in addition to conceptually.
- Follow up additional references to corroborate information from interviews about the status of the science and prevalent views in the field.
- Interview additional key researchers involved in the case, probably including: Mark Noble, Nigel Pringle, Monique Dubois-Dalcq.
- Contact other researchers whose work was affected by the identification of PDGF and the O-2A experimental system eg Bengt Westermark
- More detailed examination of the sources of support for the work – including examination of institutional or funder archives where available.
6.6 **Summary**

This case study covers the identification of a cellular growth factor, a chemical that tells cells to grow and divide. To keep the body healthy, cells must grow and divide in the appropriate places at the appropriate times – cancer is the result of uncontrolled cell growth. In the late 1970s it was becoming clear that there were chemical signals, termed growth factors, which told cells to grow and divide. Growth factors had been identified by taking culture medium from one cell culture and showing that it could cause other cell types to grow. However, although this demonstrated that there was something, an ‘activity’, in the medium; it didn’t identify what the ‘activity’ was. At the time of this work only one proliferative growth factor had been identified as a particular protein: platelet derived growth factor (PDGF) (Antoniades, HN et al., 1979). It was commonly thought that each type of cell might have its own growth factor – one for muscle cells, one for blood cells, one for nerve cells etc. And the search was on for other growth factors.

The nervous system consists of two classes of cells – the nerve cells, or neurons; and an array of support cells. The support cells are referred to as glial cells and form the ‘white matter’ in the brain. There are a range of glial cell types and they include the cells that form the myelin insulation that coats the neurons. Although neurons were originally seen as by far the most interesting cells, over time it has become clear that the glial cells are more important, and complex, than expected. The work described in this case study concerns three types of glial cells: astrocytes, O-2A cells and oligodendrocytes.

Raff’s research group had developed a cell culture system made from rat optic nerves and shown that one of the cell types – astrocytes – produced an ‘activity’ that caused the second cell type – O-2A cells – to grow and divide. The O-2A cells were particularly interesting as they are both a type of stem cell, and can also develop into oligodendrocytes, the third type of cell. The question was what active ingredient the astrocytes produced to make the O-2A cells divide. This is illustrated in Figure 6.

![Figure 6: Lineages of O-2A cells showing that the 'activity' (which Richardson showed to be PDGF) is secreted by astrocytes and causes O-2A cells to divide into more O-2A cells. The alternative way for O-2A cells to develop is into oligodendrocytes.](image)

Because of a key insight that allowed him to re-interpret existing experimental results Richardson was able to show that the activity produced by the astrocytes and PDGF were one and the same. This revealed that growth factors were re-used in different contexts in
the body. Having now identified PDGF as the activity he was able to label the receptor for PDGF and hence locate and track O-2A cells in the body (Hart, IK et al., 1989, Pringle, NP et al., 1992). Through this work he showed that the O-2A cells migrated widely during development – a very surprising finding. Twenty years later Richardson is still working on closely related cellular systems.

6.7 Introduction

Scientific background
Raff’s group had been trying to identify individual cell types in the nervous system using antibodies, which recognised surface proteins on the nervous system cells. As well as allowing them to mark specific cell types, the antibodies also allowed them to isolate and purify individual cell types (Raff, MC et al., 1979). They had previously applied this technique to cells of the immune system, and had decided that the nervous system cells would be an interesting area to extend into.

Raff’s group prepared their cell cultures from rat optic nerve and could culture these isolated cells in the test tube. At the time it was very unusual to be able to purify a single cell type of otherwise normal cells that could be grown in culture, other culture cells tended to be derived from cancer cells which had lost the ability to regulate their own growth. Raff’s group had also been able to identify and isolate a number of different cell types from the culture including O-2A cells, oligodendrocytes and astrocytes (Raff, MC et al., 1979). From the point of view of this case study the relationships are that: O-2A cells can produce either more O-2A cells or oligodendrocytes – i.e. they are a type of stem cell; oligodendrocytes work to support nerve cells; and astrocytes could make O-2A cells grow and divide if they were grown together in the same culture. This had been shown by Mark Noble, a post doc in Raff’s lab (Noble, M et al., 1984). He had also shown that the astrocytes themselves weren’t necessary for this, just something that they secreted into the culture medium. The remaining challenge was to identify this something. In fact Noble had also shown that PDGF could make O-2A cells divide in culture – but because it was thought that each cellular system would have its own growth factors – it was assumed that PDGF was substituting for the ‘real activity’ rather than that they were one and the same.

PI Background
Richardson had tried his hand at a diverse range of science. He originally studied physics at university before doing a PhD in biophysics. He then moved into biology for his first post doc which was in molecular genetics, and consolidated this with his second post doc (at the National Institute for Medical Research at Mill Hill) in molecular cell biology working to identify nuclear localisation signals – the signals on proteins that route them to the nucleus (Kalderon, D et al., 1984, Richardson, WD et al., 1988). This case study covers the appointment that was Richardson’s move to independence in his own lab.

6.8 Dramatis Personae

William Richardson – corresponding author of selected paper, lead scientist in research cloud
Martin Raff – Professor in Department of Zoology, responsible for recruiting Richardson and deriving cell system on which Richardson worked. Was moving from immunology into cell biology.

Mark Noble – independent researcher who had been a post-doc in Raff’s lab, competitor to Richardson.

Nigel Pringle – Richardson’s technician. Richardson inherited him when he arrived at UCL.

Monique Dubois-Dalcq – a researcher on sabbatical in Raff’s lab at the time of this work.

6.9 Defining the research cloud

This case study covers the research cloud that identified PDGF as the growth factor for a certain type of nervous system cells: O-2A cells. It starts with Richardson’s appointment at UCL and ends with the successful identification of PDGF which was reported in the paper we initially identified.

[Identification and review of accompanying papers is omitted in this partial case study]

6.10 Stage 0: Opportunity Identification/Research Needs Assessment

Scientific Curiosity and Technical Skills

Richardson was keen to establish himself as an independent researcher and hence needed an interesting system to work on. The key driving factor was Richardson’s and Raff’s curiosity about how cell development is regulated. And this looked like a problem that was ripe for solving with the techniques that Richardson knew. He brought in techniques from molecular biology that Raff’s group didn’t have. Although in the end these weren’t the techniques that provided the solution.

“[We] hardly, even [saw it as] neurobiology. We saw it as cell biology.” - Richardson

The work was done in nervous system cells because that experimental system was available.

“…like [Richardson], we were interested in these cells, as a cell biological system - the fact that it was in the nervous system was a bonus but it wouldn’t have mattered because we were interested in what makes [the cells] proliferate and what allows them to survive, what makes them differentiate when they do, yeah - it could have been working in the liver, the skin or anything else.” - Raff

6.11 Stage 1: Inputs to Research

There were a series of inputs to this research cloud, and in this case study the timing was particularly critical.

Scientific timing

The first growth factor - PDGF – had been identified less than a decade before. The search was therefore on for other growth factors for other cellular systems. Raff had developed an ideal system for this search as they could isolate, and grow, two types of cell, one of which
stimulated the other to divide. All Richardson had to do was identify what the factor that carried out this 'activity' was.

**Experimental system**
As noted above Raff had developed a cell culture system - based on the rat optic nerve – whose cells could be grown in culture and the different types of cells identified and isolated. This followed on from Raff’s work identifying and isolating cells of the immune system.

**Financial**
New blood lectureship brought Richardson into the department and into contact with Martin Raff and hence introduced him to the experimental system. The Departmental money allowed Richardson to start doing experiments before he had won a grant. Winning a small grant from Nuffield, although it was tiny, gave him the confidence that he could win grants and provided a useful piece of equipment. These two sources of funds sustained him until he won his first MRC project grant – for the identification of the growth factor - which happened relatively quickly.

**New Blood Lectureships**
The New Blood Lectureships were created by the government and charities to address the problem of an aging population of academics in the UK across diverse disciplines. Upper age limit for recipients was 35 years. Martin Raff, as a Professor in the Department of Zoology, applied for and won a New Blood Lectureship post for his department. Richardson applied for, and won, this position. Richardson was selected because Raff felt he was a good molecular biologist, not because of an interest in O-2A proliferation. This grant supported Richardson’s salary, but did not provide for laboratory or research costs.

**Departmental Money**
When Richardson joined UCL he took on a technician who was already in the department and knew its systems and politics. It turned out there was departmental research money that was not widely known about and the technician was key in allowing Richardson to make use these resources – possibly as much as £80,000.

**Nuffield start up grant**
Richardson’s first task on arriving in the department was to secure a research grant. The first grant he won was a £4,000 ‘New Lecturers’ grant from the Nuffield Foundation, he used this to buy a fluorescence microscope. This grant provided useful equipment – they still use the microscope today – but also helped build Richardson’s confidence that he could win research grants.

**MRC project Grant**
The first significant grant that Richardson won was a 3-year MRC project grant, titled “Identification of an astrocyte-derived growth factor”. This grant was awarded and covered most of the work in this research cloud.

**Naïveté**
Richardson feels that his inexperience in the field was an important factor in the success of this work. It allowed him to see through, or blinded him to, the preconceptions that had developed in the field:
“I mean, lack of knowledge of the literature, I think that’s really a key advantage, to not know the literature.” - Richardson

**Skills and Expertise**

This research cloud used mainly skills – such as immunofluorescence microscopy - that Richardson had developed in his previous post doc and research training, but transferred to the new experimental system of the O-2A cell cultures.

**People**

In addition to Richardson, three people played key roles in this research cloud: Martin Raff, Nigel Pringle and Monique Dubois-Dalcq.

Martin Raff, as a leading light in the zoology department, was involved in winning the New Blood Lectureship for UCL and in recruiting Richardson to UCL. As a researcher, Raff also developed the cell culture system that Richardson was to use.

Nigel Pringle was the technician that Richardson started working with when he arrived in the department, as discussed earlier Pringle was important in helping Richardson identify sources of funding within the department. Pringle remained working with Richardson for the next 20 years.

Monique Dubois-Dalcq played a key role in providing influence to the project. She was on sabbatical in Raff’s lab and looking for interesting projects. Because she was more senior she was willing to approach Bengt Westermark – the researcher who identified PDGF and get access to his reagents – something Richardson says he would have been unwilling to do.

**Space**

The university also provided space.

6.12 **Stage 2: Processes**

When Richardson started working to identify the ‘activity’ from astrocyte conditioned medium that caused O-2A cells to divide there were already clues as to its identity. It was known that PDGF caused O-2A cells to divide in culture, but it was thought that it was mimicking the ‘real’ growth factor. This belief stemmed from the fact that PDGF couldn’t be found in two places where the ‘activity’ was believed to be present: in the developing brain, where O-2A cells were dividing, and in gliomas, cancers of glial cells where O-2A cells were also dividing rapidly. This belief was probably shaped by the assumption that each cell system would have its own growth factor(s).

When Richardson started at UCL he was able to start work quickly as Raff’s lab already had the O-2A culture system up and running. The initial intention was to purify mRNA from astrocytes – the messages that determined which proteins the astrocytes are making – and micro-inject these into a particularly large cell type: xenopus oocytes. This should have made the oocytes produce the same proteins the astrocytes were making. By splitting up the mRNA from the astrocytes and testing which fractions allowed the oocytes to make proteins that stimulated O-2A cells to divide they could identify which message was responsible for the ‘activity’ and hence identify the gene involved. Although theoretically feasible this approach would have been very time consuming and labour intensive.
The urgency of the task was increased by competition with another lab. Mark Noble was previously a post doc in Raff’s lab, but had by this time left to set up his own lab at the Imperial Cancer Research Fund. Richardson had initially expected to be collaborating with Noble but from an initial visit to his lab it was clear that there would be little collaboration. Noble’s approach was to collect large quantities of the culture medium in which astrocytes or glial cancer cells had been grown, he could then fractionate this medium to isolate the factor that caused O-2A cells to divide. He planned to sequence the protein from that fraction to identify the ‘activity’. Although a different approach to Richardson’s it was similarly laborious.

The key insight that allowed Richardson to short-cut his planned approach was realizing that PDGF existed in different forms. The only source of PDGF at that time was from blood plasma – from pigs or humans, for example. Noble and his collaborators had been using PDGF from pig blood, which turned out to be different to PDGF from many other animals, including humans. Pig-derived PDGF is a homodimer of B-type subunits, whereas most other PDGF (including human) is a heterodimer of A and B-type subunits. At the time of Richardson’s arrival at UCL only the B chain had been recognized but soon after his arrival the A chain was isolated and sequenced by James Scott and colleagues at the MRC Clinical Research Centre in Harrow (Betsholtz, C, et al., 1986). Richardson recognized the potential significance of this, and obtained reagents from the key researchers at Harrow and quickly showed that astrocytes and glial cancer cells made large amounts of this PDGF A chain, whereas they made little or no B chain (which was what previously had misled Noble and colleagues into supposing that the growth factor must be something other than PDGF).

Richardson was then able to carry out a series of further experiments to demonstrate that the activity produced by astrocytes that stimulated O-2A cells to divide and PDGF were one and the same.

Work in parallel

Throughout this initial phase of work on PDGF Richardson continued his work on the signals that send proteins to the nucleus inside cells. He did this to protect himself should the PDGF research not work out.

“Yes, I was hedging my bets, basically, as you do.” - Richardson

6.13 Stage 3: Primary Outputs

Knowledge

The paper that forms the centre of the research cloud reported the identification of PDGF as the growth factor that stimulated O-2A cells in the body. It was cited 212 times in the 5 years after its publication placing it in the top 5% of research articles; and has now been cited >500 times.

The paper used a series of approaches – antibody labelling, separation columns, comparison of activity of conditioned serum and PDGF, receptor competition and the presence of PDGF messenger RNA in the rat brain – to demonstrate that the active ingredient making O-2A cells divide in the body was PDGF. Previously, it had been
known that PDGF could make O-2A cells divide in the test tube, but it had been thought that a different protein played that role in the body.

The paper was particularly significant because at the time PDGF was the first and only proliferative growth factor that had been identified (Heldin, CH et al., 1979). Prior to Richardson’s work it was widely believed that every cell type would have its own growth factor; this paper showed that this was not the case and that different cellular systems shared growth factors. In addition to showing this reuse the paper also identified the first growth factor for the nervous system.

Interestingly, this was an initial disappointment to Richardson:

“It would have been nice to discover a brand new growth factor.” - Richardson

However this turned into a blessing in disguise because as the factor was already known many of the tools – for example supplies of purified protein - already existed, which speeded up further research.

Targeting future research

After PDGF was identified as the growth factor for O-2A cells, Richardson began to work on the receptors for PDGF. Again they couldn’t identify the receptors directly but they could show there were two receptors because PDGF bound in two different ways. Eventually both the Alpha and Beta types of the receptor were cloned. It turned out later that each receptor was made up of two subunits which would be either Alpha or Beta, but the O-2A cells were expressing receptors composed only of Alpha chains.

The receptors provided Richardson with a marker for the O-2A cells, as they were known to express the receptor. Unfortunately, the antibodies that Richardson had for the receptors did not work on tissue prepared for microscopy so they could not be used to identify the cells. Identifying the genes for the receptors meant that in situ hybridisation – a technique that labels cells producing the instructions to make particular proteins – could be used to identify the cells instead. Richardson had never done in situ hybridisation, which was a relatively new technique. But he and his technician – who was very happy to try new techniques - decided to learn it.

“…so we decided to learn how to do in situ hybridisation in cut sections … these were all new things… …in situ hybridisation was really new and only a few labs did it and you had … dip the slides into photographic emulsion in the dark, so you’d be working away in the dark, dipping these things and … feeling around … putting them to dry in the dark and then wrapping them all up in … foil and putting them in the back of the freezer for three months [then developing them to see if you had a signal]” - Richardson

They got hold of some recipes and then used trial and error to perfect their protocol. Subsequently they put their protocol and recipes on the web and it has been used by various other researchers.

The in situ hybridisation revealed that the O-2A cells were starting off in one place in the spinal cord and then migrating out. This was the first demonstration of migration in a non-neuronal cell type.
Interest in the O-2A cells that Richardson was working on is still high, at a recent Cold Spring Harbour Symposium of 200 people, “Glia in Health & Disease” [July 22-26 2010] Raff estimated that 30%-40% of the presentations concerned O-2A cells.

Richardson still works on cell biology and O-2A cells. He has two current interests. Firstly, how O-2A cells are themselves generated– Richardson was the first to provide evidence that they are produced from the same set of stem cells that generates motor neurons, a finding which itself was a surprise and took time to be accepted in the field (Sun, T, et al., 1998; confirmed by Lu, QR, et al., 2002; Zhou, Q, et al., 2002 and Takebayashi, H, et al., 2002). Secondly, he is interested in the potential role of oligodendrocytes in some forms of learning and memory in the adult mouse brain.

Effect on researchers’ careers
Richardson considers this discovery a key stepping stone in his career

“It’s not often you can identify a paper … which was the start of something. And that was definitely the start, because it really started with the identification of PDGF as a growth factor and by a combination of application and serendipity… [this] was the first paper, the first funding, everything stemmed from that.” – Richardson

A view that is endorsed by Raff, who was at the time a collaborator and major figure in the department:

“Oh no question. Yeah it made him an internationally recognised neurobiologist, in a way, and he spent the rest of his career, a large part of his career, studying these cells and he went on…. …it was, for him, an absolutely transforming paper and study - absolutely fundamental.” - Raff

Richardson went on to identify the PDGF receptor and used the receptor to locate and track the O-2A cells in the developing nervous system (Pringle, NP et al., 1992, 1993). This revealed that O-2A cells migrate out from a few locations in the central nervous system, a finding which gave rise to a small field of research on O-2A migration. From a technical point of view the identification of PDGF allowed O-2A cells to be cultured in a fully defined medium – ie every component of the medium was known – this was an important methodological break through.

Richardson is still at UCL, now a Professor, and continues to work on cell fate and basic glial cell biology and its relation to memory and learning.

Informing future research

Key contributor to experimental system for cell growth and differentiation
Richardson’s identification of PDGF as the growth factor of O-2A cells meant these cells could now be grown, and differentiated into oligodendrocytes in defined media. That is a medium made up of known components, any of which can be manipulated. Previously, all culture mediums for cells included ingredients such as cell extracts or medium from other cells cultures, which contained many unknown components. This was a major experimental advance in terms of cell biology, and attracted other cell biologists who had been working on other systems (such as cancer) to look at the brain cell system:

“There are very few systems - I’m not even aware that there is another system - where the cells will go on and proliferate in culture in a purified population without serum or
without tissue extract, you know everything that you’ve added to the medium, and they’ll go on and divide and then they’ll stop and they’ll differentiate - it’s almost unique! To have that in a brain cell type - so I think that attracted a lot of people into the field.” – Martin Raff

**Sparked interest in cell migration**

As mentioned above, after perfecting in situ hybridisation Richardson was able to show that the O-2A cells migrated through the spinal cord from where they originated. Although cell migration wasn’t a new idea – it had been shown previously for neurons – it had been thought that this was the only type of cell that migrated, that others were formed in situ. There was initial scepticism about the discovery:

“Well it was a shock, I think, for people to - in fact I’m not sure everybody believed it right after that - that this very narrow column of cells in the spinal cord… …over time, migrated throughout the central nervous system. No one had any idea that it worked like that, for any of the glial cells. This was a breakthrough - no question.” – Raff

This discovery of the O-2A migration has lead to a small field of researchers working on how the migration is regulated:

“So, yes, and then that has sort of spawned a whole kind of cottage industry of looking at oligodendrocyte development in people.” - Richardson

6.14 **Interface B: Dissemination**

As a basic scientist, working before the age of public engagement with science, Richardson’s work was primarily disseminated through academic papers and through presentations at conferences.

6.15 **Stage 4: Secondary Outputs**

None identified

6.16 **Stage 5: Applications**

None identified

6.17 **Stage 6: Public Engagement**

None identified

6.18 **Stage 7: Final Outcomes**

None identified
6.19 **Wider Significance**

Glial cells have generally been seen as less interesting than the neurons themselves. Glial cells act as support cells, and the exact role of oligodendrocytes has remained unclear. However, over time it has become clear that they may be much more than passive support cells, that there are important signalling conversations between neurons and their support cells. This is leading increasingly to the idea that the support cells themselves may play important roles in memory, aging and disease.

**In stem cells and aging**

It was long assumed that the brain cannot regenerate and that there is very little cell division in the adult brain. However, Raff showed, prior to 1987 that the O-2A cells are present in the adult brain; although they had no idea what they were doing as oligodendrocytes were thought to be very long lived cells and myelin turns over only very slowly.

This became even more interesting when Martin Raff that showed that although O-2A cells normally give rise to oligodendrocytes they can be convinced to produce neurons, which raises the possibility that O-2A cells are the stem cells of the adult brain. Richardson was initially somewhat sceptical of this possibility but has recently shown that O-2A cells continue to make oligodendrocytes in the brains of adult mice. There has also been work using MRI scans in humans showing that the amount of white matter in the brain increases with age, but they declines in line with old age cognitive decline. Taken together these are suggestions of an important role for O-2A cells in brain repair and maintenance.

**Importance in Multiple Sclerosis**

Multiple Sclerosis (MS) is a disease in which the body’s own immune system attacks the myelin that insulates the nerves. MS is characterised by periods of relapse (when demyelination is occurring) and remission (when there can be some remyelination). O-2A cells and oligodendrocytes are likely to be important in those periods of remission, and there is a lot of interest in why this repair process becomes steadily less effective with each cycle.

**In Schizophrenia**

There are some indications that glial cells may play a role in schizophrenia – although this is currently controversial. Genes involved in glial cell development have been linked to schizophrenia and changes in the amount of white matter in the brain have also been linked to schizophrenia. However these might not be causal effects – it could be that whatever is causing the schizophrenia is also causing the changes to the glial cells.

**In Brain Cancer**

The commonest brain tumours are those that resemble, and are presumably formed from, glial cells. These cancers – “glioma” and “glioblastoma” – are among the most intractable of all cancers because of their location and invasiveness into surrounding healthy brain tissue. It has been recognized for a long time that PDGF, the growth factor that drives normal proliferation of healthy oligodendrocyte precursor cells (O-2A cells), is greatly over-produced in some gliomas, as are PDGF receptors, and certain other key proteins, which are involved in normal glial cell development and biology. Understanding how
these proteins are mis-regulated in glial tumours, and finding ways to tame them again, could eventually have a major impact eventually in controlling brain tumours.

6.20 Counterfactual

Had the New Blood Lectureships not been on offer it is unlikely that Richardson would have ended up at UCL working with Raff. Indeed Richardson had already accepted another job offer at the time he was awarded the lectureship, which he then had to turn down.

However, given that Mark Noble was working on the same problem, it was likely that PDGF would have been identified as the growth factor for O-2A cells within a few years of this work. It is less clear whether the follow on work that identified the migration of O-2A cells would have happened similarly rapidly as this required applying a new technique and applying it to the problem.

6.21 Table of payback

<table>
<thead>
<tr>
<th>Payback category</th>
<th>Impacts from case study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge Production</td>
<td>Identification of PDGF as a key growth factor in the nervous system, demonstrating the growth factors were reused in different cellular systems.</td>
</tr>
<tr>
<td>Research Targeting and Capacity Building</td>
<td>Development of a fully characterised cell culture system that has been widely used to explore neuronal development.</td>
</tr>
<tr>
<td></td>
<td>Identification of PDGF as neuronal growth factor allowed identification of receptor and hence location of O-2A cells by in situ hybridisation, which revealed that cell migration was not exclusive to neuronal cells and gave rise to a small field studying glial cell migration.</td>
</tr>
<tr>
<td></td>
<td>The biology of O-2A cells has formed the basis of Richardson’s career and this research cloud was key in establishing Richardson as an independent research and in this new field.</td>
</tr>
<tr>
<td></td>
<td>Attracting groups working on PDGF into the neuroscience because they could apply their existing expertise in a newly defined cellular system.</td>
</tr>
<tr>
<td>Informing Policy and Product Development</td>
<td>None identified</td>
</tr>
<tr>
<td>Health and Health Sector Benefits</td>
<td>None identified</td>
</tr>
<tr>
<td>Broader Social and Economic Benefits</td>
<td>None identified</td>
</tr>
</tbody>
</table>

6.22 Partial Timeline

Late 1970s – PDGF is identified as the first proliferative growth factor
Martin Raff develops the rat optic nerve culture system that this work depended on.

Early 1980s – Martin Raff, Mark Noble and others in Raff’s lab discover that astrocytes secrete an ‘activity’ that causes O-2A cells to proliferate.

Late 1980s – Mark Noble leaves Martin Raff’s lab and sets up his own lab at the Imperial Cancer Research Fund.

1986 – Richardson appointed to New Blood Lectureship at UCL and starts work to identify the ‘activity’ alongside continuing work on nuclear localisation.

1988 – Case study paper published “A role for platelet-derived growth factor in normal gliogenesis in the central nervous system”

1993 – Richardson and Pringle identify the migration of O-2A cells.

6.23 References


Appendix F: Cognitive behavioural therapy case study

Summary

Antipsychotic medication has been the mainstay of treatment for schizophrenia since the first antipsychotic drug was developed in 1952. Although these drugs have brought considerable benefit to the lives of patients who suffer from psychosis, they are only infrequently associated with full symptom remission and functional recovery. The reasons for this include limited efficacy of antipsychotic medication in a substantial proportion of patients; the problem of severe side-effects, which some patients experience; and the unwillingness of some patients to take medication. Historically, schizophrenia has been regarded as an illness with a strong biological component. For many decades, psychological therapies were thought to add very little or in the case of psychodynamic psychotherapy, to subtract from the positive effects of medications and other somatic therapies.

The recognition of the limitations of antipsychotic drugs in the treatment of schizophrenia set the stage for the search for psychosocial approaches that might improve patient outcomes. While in the UK, increasing numbers of mental health professionals became interested in the adaption of cognitive theory and behavioural theory to the treatment of schizophrenia, in the US the focus was on strategies grounded in cognitive/behavioural theory to help patients better manage and cope with their illness. The original form of CBT, rational emotive behaviour therapy, was developed in the 1960s by Albert Ellis, but the model of CBT which is most commonly practiced today has its origins in the work of A.T. Beck. CBT as a treatment for schizophrenia is part of a wider framework of CBT as

17 According to Turkington et al, even when patients with schizophrenia fully adhere to antipsychotic medication regimes, up to 50% will have ongoing positive or negative symptoms, with 20-30% of people with chronic schizophrenia demonstrating very little symptomatic response to adequate trials of conventional antipsychotic medications. 'Cognitive-Behavioural Therapy for Schizophrenia: A Review'. Focus, 4: 2 (2006): 223-233.


applied to a range of mental disorders such as anxiety, post-traumatic stress disorder (PTSD), and depression. Cognitive theory is based on the notion that the cognitive processes implicated in mood and anxiety disorders occur transdiagnostically, meaning they co-occur across the psychiatric disorders. A number of studies have supported the notion that psychotic symptoms can be understood in relation to normal psychological processes and, as a result, the symptoms can be effectively treated by CBT techniques.

Cognitive behavioural therapy (CBT) of schizophrenia has developed dramatically over the last ten years (this would also be true for the US if the statement is about the research base; not applicable to the US if it is about reach/uptake). In the UK, the National Institute for Health and Clinical Excellence recommends that cognitive behavioural therapy should be made available to all people suffering with schizophrenia, particularly those with persistent hallucinations and delusions, lack of insight, and poor concordance with antipsychotic medications. Similar recommendations have been made in Canada and the US (APA: Guideline 2004 and Guideline Watch 2009; PORT schizophrenia recommendations 1998, 2004, 2010). In addition, the Netherlands, and Australia have well-developed research programmes in this area and Brazil, China, Germany, Japan, Scandinavia, and Spain are all showing an increasing interest in this approach.

Definitions

Cognitive behavioural therapy refers to a range of interventions and techniques that are drawn from both cognitive therapy and behaviour therapy. The Cochrane Review discussed the difficulties of providing a single, unambiguous definition of cognitive behaviour therapy, given the variety of interventions that have been ascribed this label, but uses the following definition:

‘Cognitive behaviour therapy (CBT) is an evidence-based talking therapy that attempts cognitive and behavioural change based on an individualised formulation of a client’s personal history, problems, and world view. In CBT links are made between the person’s feelings and patterns of thinking which underpin their distress. The patient is encouraged to take an active part by:

1. Examining the evidence for and against the distressing belief
2. Challenging the habitual patterns of thinking about the belief

23 NICE 2002
3. Using reasoning abilities and personal experience to develop rational and personally acceptable alternative explanations and interpretations.26

When used to alleviate psychotic symptoms in people with schizophrenia, CBT is seen as an adjunctive treatment whose function is to augment the effects of antipsychotics (APA; PORT 2010). Key elements of CBT for schizophrenia include “the collaborative identification of target problems or symptoms and the development of specific cognitive and behavioral strategies to cope with these problems or symptoms” (PORT 2010).

**Development of CBT as a treatment of schizophrenia**

The development in the early 1950s of antipsychotic medication led to a dramatic transformation in the treatment of schizophrenia. Previously, institutionalisation was the standard method of care, and though the government had begun to shut down these facilities, the development of chlorpromazine and other antipsychotic medications greatly accelerated the move away from institutionalised care. At this time, biological thinking about schizophrenia and psychoses was the dominant model and biological treatments remained the established management approach for the next 30 years. A key outcome of this mainly pharmacological treatment culture was that practitioners limited their verbal interactions with patients to diagnosing their condition and prescribing a suitable medication.27 Some of the earliest attempts at a psychological approach to the treatment of schizophrenia were Freida Fromm-Reichman’s 1950 work on psychotherapy for psychotic patients28 and H.S. Sullivan’s 1947 Conceptions of Modern Psychiatry which included a modification of psychoanalysis designed to enhance better integration into a hospital environment. These pioneering efforts increased awareness of the psychological processes and personal impact of schizophrenia.29 Although there was little interest in schizophrenia from the cognitive and behaviour therapy community, an early case study by A.T. Beck appeared in 1952 which successfully applied CBT techniques in the treatment of a schizophrenic patient.

Throughout the 1970s, as the move from institutionalised treatment gathered pace, psychological and social research into factors that might contribute to relapse in people living in community settings, such as stressful life events and communication difficulties in families (high expressed emotion), stimulated the development of family interventions to prevent relapse.30 These family interventions, which often included education for family members about schizophrenia, developed into what is now known as ‘psychoeducation’ or ‘family psychoeducation’.31

From the late 1970s onwards, the theoretical understanding of schizophrenia had been changing with stress-vulnerability models that incorporated psychological and social
elements being developed and empirically tested. This theoretical interest in the psychotic process itself, and the more optimistic attitude that psychosocial treatments could have a significant benefit in the days of de-institutionalisation and community care, set the scene for the development of CBT approaches to reduce the symptoms of schizophrenia.

As CBT was originally developed for the treatment of patients with non-psychotic disorders, such as depression or anxiety, it was this model that informed the development of specialised CBT treatments for psychoses. The research that was being carried out into intrusions and safety behaviour in anxiety disorder was transferred into theoretical models of psychosis and broader cognitive models of schizophrenia were subsequently developed.

Earlier forms of CBT for schizophrenia focused on improving coping, building social and independent living skills, and increasing compliance using behavioural strategies such as linking tablet taking to another activity. Negative symptoms were targeted by providing graded activity programmes. These approaches have continued to be applied where deficit symptoms of schizophrenia and improving functional outcomes are the main focus of intervention.

The move towards applying CBT techniques to the treatment of schizophrenia was slow as a number of concerns remained about the nature of the illness and its amenability to cognitive or behavioural therapeutic approaches, some of them misperceptions. In 1986, A.S. Bellack, in his AABT Presidential address, termed schizophrenia ‘the forgotten child of behaviour therapy’; a description that reflected the dominance of anxiety and depression in the literature about CBT. Bellack argued that schizophrenia had been ignored by behaviour therapists because of four mistaken assumptions: (a) the belief that the diagnosis is an over-generalised label and the disorder does not exist, (b) the belief that the disorder has a biological basis and, thus, is not in the purview of behaviour therapy, (c) the belief that schizophrenia is adequately treated by medication, making behaviour therapy superfluous, and (d) the belief that it is too severe for behaviour therapy.

By the late 1980s, cognitive behavioural therapy had expanded enormously and its application to other areas was increasingly considered. Building on successful treatment studies in affective disorder, CBT was becoming the established treatment of choice for

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32 e.g. Zubin & Spring, 1977; Nuechterlein, 1987.
33 See, for example, Morrison, 2001; Morrison, Haddock & Tarrier, 1995
34 See, for example, Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001.
36 E.J. Weiden, T. Mott, N. Curcio. Recognition and management of neuroleptic noncompliance. In: C.L.
37 D. Meichenbaum and R. Cameron. Training schizophrenics to talk to themselves: a means of developing
38 G.E. Hogarty, C.M. Anderson, D.J. Reis et al. Family psychoeducation, social skills and training, and
maintenance chemotherapy in the affercare treatment of schizophrenia: II. Two-year effects of a controlled
many non-psychotic conditions. According to Tarrier and Wykes, ‘[i]t was inevitable that CBT would be tried as a possible treatment for schizophrenia.’ 41 There was a growing recognition that cognitive theory and interventions for anxiety, social phobia, PTSD and obsessive-compulsive disorder (OCD) could also find application within the practice of CBT for psychosis. 42 An example of this is the work of Chadwick et al 43 which, leading on from Beck’s work on OCD, demonstrated that voices could be conceptualised as intrusive thoughts.

A number of single case studies emerged from the UK throughout the 1980s and, on the basis of this early evidence, randomised controlled trials began to take place in earnest from the early 1990s onwards. It was from this point that the evidence for the efficacy of CBT for schizophrenia began to accumulate and, with the publication of the RCT results, the subject received greater attention from the wider research and clinical community, both in the UK and overseas.

The evidence base for the efficacy of CBT has primarily come from randomised trials in the UK. Throughout the 1990s a small number of UK-based researchers championed the development of cognitive behavioural interventions for psychotic patients, either as direct therapies for specific symptoms; 44 as a way of enhancing patients’ coping skills; 45 or as part of a normalising strategy designed to make patients more accepting of what would otherwise be disturbing experiences. 46

A number of studies, including Kingdon and Turkington, 47 and Fowler et al, 48 described how CBT for disorders such as anxiety and depression could be adapted for and applied to the treatment of schizophrenia. There are a number of ways in which CBT was amended for schizophrenia. Stigma, for example, was addressed by identifying the negative assumptions that people held about schizophrenia and then providing evidence that some of these experiences are common in the general population (normalising). By providing alternative explanations for the symptoms of schizophrenia, patients were able to adopt a more positive outlook on their condition and potential for recovery. 49 CBT for schizophrenia also involved shorter sessions than CBT for other disorders. The sessions are more flexible and homework is simplified. 50 In addition, the role of sleep disturbance,

44 For example, Bentall et al., 1994; Chadwick and Birchwood, 1994; Chadwick and Lowe, 1990; Fowler and Morley, 1989; Garety et al., 1994; Haddock et al., 1993.
45 For example, Tarrier et al., 1990; Tarrier et al., 1993.
affect, and safety behaviours (for example, behaviours such as avoidance that maintained faulty beliefs) was identified to produce ‘mini-formulations’ of positive symptom maintenance.51

A one day conference held in June 1991 on ‘Psychological Approaches to the Management of Psychosis’ at University of Liverpool was a key event in crystallising the emerging interest in this subject. The conference confirmed the interest of mental health professionals in exploring possible value of these methods as an adjunct – or alternative – to traditional psychopharmacological approaches in the management of psychosis. A specific cognitive behavioural approach that aims to enhance compliance with medication was also developed towards the mid 1990s. In the UK, this approach is now commonly known as ‘adherence therapy’52. In the US, CBT strategies aimed at improving medication adherence and helping patients manage their illness form the backbone of “illness management and recovery,” a multi-component intervention “designed to help individuals with serious mental illness collaborate with professionals, reduce their susceptibility to the illness, and cope effectively with their symptoms.”53 The first International Conference on Psychological Treatments for Schizophrenia was held in Cambridge, UK in 1995 and annual meetings between UK and North America-based researchers were held, at the instigation of A.T. Beck, from 1998 onwards.

Key developments are set out in the timeline below.

52 Kemp et al., 1996. NICE full guideline p. 28
Adoption of CBT for schizophrenia in national guidelines

CBT is recommended as a standard of care for individuals with schizophrenia in the Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations in the US, which in turn led the American Psychiatric Association (APA) to do the same in its 2004 practice guidelines; the Canadian Psychiatric Association treatment guidelines; and the National Institute for Health and Clinical Excellent (NICE) treatment guidelines in the UK.

In the UK, the National Institute for Clinical Excellence (NICE) first recommended that CBT be offered to individuals with residual symptoms of schizophrenia in 2002. The NHS then adopted CBT as a treatment for schizophrenia in 2003. In 2009, the updated NICE guidelines stated that CBT should be routinely used in the treatment of schizophrenia. According to the Cochrane Review, CBT has yet to become as widely available for people with schizophrenia as it is for people with other disorders, such as depression.

In the US, the 1st set of PORT recommendations published in 1998 mentioned “behavioral and cognitive skills training approaches” among other psychological treatments with suggestive yet limited empirical evidence of benefit when “added to pharmacotherapy for persons with schizophrenia” (PORT, 1998). By its 2004 update however, PORT researchers were able to cite many more methodologically sound studies; on a scale 1-3 where 1 is best, they rated the level of evidence as 1.67 (SD 0.59) (PORT, 2004). In its latest update (2010), CBT continues to be profiled as a recommended psychosocial treatment with a strong evidence base (PORT, 2010).

The 2005 Canadian clinical practice guidelines also endorse the use of CBT as a treatment for schizophrenia, advising that ‘[c]ognitive therapy should be offered to treatment-resistant patients.’ The guidelines further state that ‘Cognitive-behavioural interventions should be considered in the treatment of stress, anxiety and depression in patients with schizophrenia [...]’.

Issues and Questions regarding the use of CBT for schizophrenia

Despite clear indications that CBT for psychotic symptoms is beneficial, questions remain, including why CBT works for some patients and not for others. A key objection made by those who question the efficacy of CBT for schizophrenia is that one of the most widely quoted trials in support of its efficacy employed neither a control intervention nor

56 Ibid. 36S.
58 Kuipers et all, 1997
blind evaluations.\textsuperscript{59} Most recently, a 2010 article in \textit{Psychological Medicine}\textsuperscript{60} stated that no trial employing both blinding and psychological placebo has found CBT to be effective in either reducing symptoms or preventing relapse in schizophrenia. Similarly, despite claims by Sensky et al\textsuperscript{61} that the use of CBT leads to sustained clinical improvement in schizophrenia, the 2004 Cochrane review\textsuperscript{62} found no convincing evidence of its effects in the longer term. PORT researchers recently summarized the problem areas in the evidence base for CBT. These are inconsistent findings regarding its effects on residual psychotic phenomena, and a paucity of evidence regarding its effects on depression, suicidal tendencies, relapse, recent onset schizophrenia, and acute psychotic exacerbation in chronically ill patients.

Another important issue is the degree to which CBT may be feasibly implemented in routine practice and delivered with fidelity (integrity). In the US, workforce limitations and issues related to the financing and organization of the specialty mental health system have limited the adoption of psychosocial interventions and tipped the balance in favour of medication-based treatment.\textsuperscript{63}

Implementation considerations rather than intrinsic patient-differences justify the call for US-specific research on the effectiveness of CBT for schizophrenia.

\section*{Future uses of CBT for Schizophrenia in the UK}

In the last 5-10 years, therapeutic approaches to the treatment of schizophrenia have developed beyond the original cognitive theory to include, for example, meta-cognitive therapy (MCT), compassionate mind training (CMT) and the method of levels (MOL). According to S. Tai, these ‘third-wave’ approaches make some theoretical departures from the traditional cognitive (behavioural) therapy but they are broadly similar in their applications to the field.\textsuperscript{64} These new approaches are still in an embryonic stage but it is thought that they have the potential to influence the future application of CBT to schizophrenia.

\textsuperscript{61} Sensky et al 2000
\textsuperscript{62} Jones et al, 2004
Appendix G: Early intervention case study

Summary

There are two forms of early intervention that correspond to different stages of schizophrenia. The prodromal stage of schizophrenia starts with functional deterioration and progresses to psychotic symptoms. Early intervention in the prodromal phase involves community-level detection efforts and treatment to prevent onset and decrease morbidity. Schizophrenia’s first episode stage follows the first psychotic episode. Early intervention during this stage focuses on detecting and promptly treating those who have already experienced a psychotic episode.

Treatment of first episodes of psychosis has been the standard of care for many years. Some studies have shown a correlation between early intervention during the first episode stage and improvement in treatment response and long-term outcomes. However, there have not been randomized control trials showing a causal link between early intervention after onset of psychosis and improved outcomes.

In the last 10 years, there have been efforts to reach individuals with treatment in the prodromal stage. Even though this is still an emerging area, some early studies have demonstrated the effectiveness of early intervention in the prodromal phase. Nonetheless, the evidence base for early intervention in the prodromal stage is not considered strong enough to warrant a definitive recommendation about early intervention in the prodromal phase.

Because of a lack of clear evidence for the effectiveness of either form of early intervention, the practice guidelines in the US, the UK, and Canada vary on the degree to which they promote early intervention. In the US, the latest American Psychiatric Association (APA) practice guidelines for the treatment of schizophrenia mention the importance of treating as early as possible during the initial episode stage but do not explicitly recommend early intervention as a treatment approach during the prodromal or first episode stage. In England, the current National Institute for Health and Clinical Excellence (NICE) guidelines on schizophrenia recommend a full range of early intervention treatments for the first episode stage while noting the lack of evidence for early intervention during the prodromal stage. Similarly, Canada’s Treatment of Schizophrenia clinical practice guidelines describe the importance of early intervention for those in the first episode stage and acknowledge the need for more studies to determine the effectiveness of early intervention during the prodromal stage.
Definitions

The pathway to schizophrenia starts with a premorbid stage, moves to a prodromal stage, and then to the first episode stage. The premorbid stage is typically asymptomatic although there may be some motor, social, or cognitive deficits. The early prodromal stage is characterized by functional deterioration which is typically followed by onset of full blown psychotic symptoms. During this prodromal stage, these symptoms progressively increase before the first episode. The first episode stage has been identified as a “critical period” in the course of schizophrenia.

There are two distinct forms of early intervention both of which encompass a range of treatments. For those in the prodromal stage, early intervention takes the form of community-based early detection efforts and treatment to prevent the onset of schizophrenia and decrease morbidity. As such, early intervention in the prodromal phase is a primary prevention approach. For those in the first episode stage, the main component of early intervention involves detection and prompt treatment with antipsychotic medications and psychosocial treatments for those exhibiting psychotic symptoms. Although treatment is based on the same components of treatment for established schizophrenia, clinical researchers have adapted these interventions for their specific application to people in the prodromal or first episode stages of schizophrenia. Early intervention after the onset of psychosis is a secondary prevention approach meant to reduce the severity and duration of the disease after the first episode. Overall, the two aspects of early intervention that distinguish it from standard care are early detection and phase specific treatment.

Development of Early Intervention

While treatment of first episodes of psychosis has the standard of care for many years, the evidence is mixed about the effectiveness of early intervention during this post-onset phase. Three categories of studies of early treatment with antipsychotic medications provide evidence related to the effectiveness of early intervention for those in the first episode stage; however, these studies were largely conducted before early intervention was conceptualized as a treatment approach. First, epidemiological studies examined changes in incidence related to introduction of different treatment approaches. These studies show declining incidence of schizophrenia over the last 60-70 years. Second, mirror-image studies compared similar patients before and after introduction of antipsychotics. The results of these studies indicate improvements in the course of disease after the introduction of antipsychotic medications in the 1950’s. Third, delayed intervention studies compared a treatment group who received early intervention with antipsychotics to a wait list control


group that received delayed treatment. These studies generally found that delaying intervention led to poorer outcomes although the evidence is not clear cut.\textsuperscript{67}

Through these and other studies, the duration of untreated psychosis has been established as a predictor of outcomes for first-episode schizophrenics. As a result, a number of studies have sought to determine the effectiveness of early intervention treatments on outcomes.\textsuperscript{68} Two of the key trials were conducted in Norway and Australia. The 1993-1994 Norwegian TIPS (Early Treatment and Intervention of Psychosis) project compared those patients recruited when there was an early detection program to those recruited prior to its availability. In this study, there was a significantly shorter duration of untreated psychosis for the treatment group. In 1996, the Australian Early Psychosis Prevention and Intervention Centre (EPPIC) program was developed to prevent first episodes using early detection and specialized treatment.\textsuperscript{69} When compared to a comparison group served at the clinic before EPPIC started, the treatment group did not show any significant improvement in the duration of untreated psychosis. The treatment group did have significantly lower levels of negative symptoms and significantly higher quality of life scores.\textsuperscript{70} Collectively, these and other studies provide some evidence of a correlation between early intervention for the first episode and improvements in treatment response and long-term outcomes.\textsuperscript{71} However, there are no randomized control trials that show a causal link between early intervention after onset of psychosis and improved outcomes.\textsuperscript{72}

In the last 10 years, there have been efforts to reach individuals with treatment in the prodromal stage before the first episode. Even though this is still an emerging area, some early studies have demonstrated the effectiveness of early intervention in the prodromal phase. The Buckingham Study (1984-1988) in England was the first study to focus on very early detection of psychosis. This study used a screening checklist to detect prodromal symptoms. Those who screened positive were assessed and then treated with low-dose medication, family education about schizophrenia, and social skills training. The results of the study showed a dramatic reduction in the incidence of schizophrenia in the community. These results have had a major impact on the field. In Germany, the Bonn Early Recognition Study examined the transition rate to psychosis and the predictors of


this transition for those referred to a psychiatric clinic from 1987-1991 for diagnosis. In Australia, the 1996 PACE (Personal Assessment and Crisis Evaluation) study involved a clinic-based randomized control trial with the treatment group receiving anti-psychotics during the prodromal phase. The treatment group was less likely to move to psychosis than the control group. In the United States, the 1997-2003 industry-funded PRIME (Prevention through Risk Identification, Management, and Education) study involved a randomized control trial to compare the efficacy of olanzapine in delaying or preventing conversion to psychosis and reducing symptoms during the prodromal stage. This study failed to show active treatment advantage in delaying or preventing conversion to psychosis; although olanzapine did reduce positive prodromal symptoms. Despite some promising results, the evidence base for early intervention in the prodromal stage is not considered strong enough to warrant a definitive recommendation about early intervention in the prodromal phase. For example, the results from the randomized control trial of the PACE study need to be replicated with a double-blind placebo-controlled design.

**Timeline**

1950s  Antipsychotic medications for schizophrenia introduced.

1980s  Studies in Australia and England found a link between delays to treatment and poor outcomes; Early intervention during the 1st episode stage began as a treatment approach in Australia.


1987-1991  Bonn Early Recognition study of early intervention in the prodromal stage in Germany

1990s  Evidence of the effectiveness of early intervention and cognitive behavioural therapy for psychosis emerged.

1992  Agency for Health Care Quality and Research and the National Institute of Mental Health created the Schizophrenia Patient Outcomes Research Team (PORT) in the United States.


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1994 EPPIC program for early intervention in the first episode stage developed in Melbourne, Australia.

1996 First international conference held in Melbourne.

1996-1999 PACE project of early intervention in the prodromal stage in Australia.


1997-2003 PRIME study in the United States of early intervention with olanzapine during the prodromal stage.

1998 Founding of International Early Psychosis Association (IEPA) in Victoria, Australia.

1999 Early intervention mentioned in England’s National Service Framework (NSF) for Mental Health.

2000 Robert Wood Johnson Foundation funded the Portland Identification and Early Referral (PIER) program for early intervention during the first episode stage in the United States.\(^{77}\)

2000 England’s National Health Service Plan required the development of early intervention services for first episode psychosis.

2001 Initiative to Reduce Impact of Schizophrenia (IRIS) convened a group to discuss early intervention services for psychosis; England’s Mental Health Policy Implementation Guide prioritized the development early intervention teams.\(^{78}\)

2002 National Institute of Mental Health in England (NIMHE) launched; IRIS and WHO developed standards of care for early psychosis.

2002-present First Episode Research Network (FERN) formed in England

2004 IEPA and WHO issued an international consensus declaration.\(^ {79}\)

2004-present Director of Mental Health for WHO released the “Newcastle” declaration at the UK national early intervention conference; NIMHE created the National Early Intervention Development Programme to support early intervention policy development.

2007 IEPA launched journal Early Intervention in Psychiatry


Adoption of Early Intervention for Schizophrenia in National Guidelines

In the US, the American Psychiatric Association (APA) 2004 practice guidelines for the treatment of schizophrenia note that it is important to treat as early as possible in the initial episode with close observation and documentation of signs and symptoms so progression can be tracked. However, early intervention as a treatment approach is only mentioned briefly in a section on psychosocial treatments with very limited evidence bases.80 The guidelines indicate that more studies are needed before treatment recommendations are warranted. The 2009 Guideline Watch for Schizophrenia provides an update on studies since the release of the 2004 practice guidelines. In this update, intervening early and early intervention as a treatment approach are not mentioned at all.81 In 2010, the researchers on the Schizophrenia Patient Outcomes Research Team (PORT) updated their schizophrenia treatment recommendations to recommend the use of antipsychotic medications other than clozapine/olanzapine during the first episode stage.82,83 However the updated PORT recommendations did not recommend psychosocial interventions during this stage because of the limitations of the evidence base.84

In England, the 2002 National Institute for Health and Clinical Excellence (NICE) guidelines on schizophrenia noted the emergence of comprehensive treatments using an early intervention approach but did not find sufficient evidence to recommend an early intervention model.85 The 2009 update to the NICE guidelines on schizophrenia acknowledged that studies have now shown the benefits of early intervention. The guidelines describe early intervention as identification and therapy for those in the prodromal phase and pharmacological and psychosocial intervention for those in the first episode phase, both delivered by a specialized treatment team. Importantly, the NICE guidelines state that "Providing treatment for people in a possible prodromal phase of schizophrenia is an interesting but potentially controversial area, which at present is outside the scope of this guideline.” The current NICE guidelines recommend providing

early intervention services that include the full range of pharmacological, psychological, social, occupational, and educational interventions during the first episode stage.\textsuperscript{86}

In Canada, the 2005 Treatment of Schizophrenia clinical practice guidelines describe early psychosis treatment services in the service delivery section. The guidelines note that early intervention services for those in the first episode stage are important because of the trajectory of psychosis after the first episode, the link between phase specific treatment and outcomes, and the increased likelihood of negative outcomes when treatment is delayed. The guidelines acknowledge that the evidence of the relationship between early psychosis services and reducing the duration of untreated psychosis and improving treatment outcomes is still scant.\textsuperscript{87} The guidelines include a discussion of the prodromal stage as a special issue noting that there is only preliminary evidence of the effectiveness of antipsychotics and cognitive behavioural therapy during this stage.

In 2005, the International Early Psychosis Association published interventional clinical practice guidelines for early psychosis.\textsuperscript{88} For the premorbid and prodromal stages, the guidelines define criteria for having an “at-risk mental state” and standards of care for those found to be at-risk. The guidelines note that antipsychotic medications are warranted during these stages only when the patient is diagnosed with a psychotic disorder. For the first episode stage, the guidelines detail standards of care for access, location of treatment, and initial management using anti-psychotic medications and cognitive-behavioural therapy.

**Issues and Questions Regarding Early Intervention for Schizophrenia**

There are a number of issues related to using early intervention as an approach for treatment of schizophrenia. While studies have shown a correlation between early intervention services during the first episode stage and outcomes, a causal link has not been established. As a result of this and differing views on standards of evidence, the clinical and practice guidelines provide varying recommendations related to early intervention during the first episode stage. Because of only weak evidence related to the effectiveness of early intervention during the prodromal stage, the guidelines generally do not address early intervention for this stage. Research on early intervention has also been constrained by ethical concerns with randomized control trials given the known importance of the time period after the onset of psychosis. Because longer periods of untreated psychoses have been linked to poor long-term outcomes and the critical period hypothesis, researchers are reluctant to conduct random assignment and deny some patients treatment during the first episode stage. Finally, in the first episode stage, early intervention aims to decrease the period between the first episode and treatment. However, the duration of untreated psychosis is affected by different factors, including different patterns of onset, difficulties


recognizing the symptoms, availability of treatment, and acceptance of treatment. Together, these present challenges to determining the effectiveness of early intervention as a treatment approach for prevention and early treatment of schizophrenia.89

**Current and Future Uses of Early Intervention for Schizophrenia**

Despite its relatively weak evidence base, early intervention is widely used in the United States, Europe, and Australia. In England, national and large scale evaluations of early intervention services are being conducted by the First Episode Research Network (FERN) and National EDEN. FERN is a collaborative effort of centers across the country providing early intervention services throughout the country. The goal of FERN is to identify the factors involved in improving outcomes for those receiving early intervention services during the first episode stage. Member clinics collect standardized measures and pool data to address specific research questions. National EDEN is a national evaluation of early intervention services for psychosis using sites in England involved with the Mental Health Research Network. Similar to FERN, the project aims to examine the effectiveness of early intervention services during the first episode stage on outcomes. With 940 participants, enrolment into the study ended in 2009.

In the US, the Robert Woods Johnson Foundation launched its Early Detection and Intervention for the Prevention of Psychosis Program (EDIPP) to replicate and expand on the PIER program results. The National Institutes of Mental Health awarded a large grant in 2009 to a consortium of researchers for the Recovery After an Initial Schizophrenia Episode (RAISE) study with the aim of developing treatment models for people experiencing their first episode of schizophrenia.

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