Psychiatric Research- where from and where to?

Peter Woodruff
Professor of Academic Clinical Psychiatry, Sheffield University.
Declarations of interest

• I have previously received funding from the following: Astra-Zeneca, Pfizer, Janssen-Cilag, Roche, Lundbeck, Cambian Healthcare, Medical Research Council (UK), The Economic and Social Research Council (UK) The Wellcome Trust, The John Templeton Foundation, and other Medical Charities.

• I have worked in the NHS and USA Health systems

• I currently work for a University that does not impose a bar on my ability to speak freely

• I do unpaid work for the Royal College of Psychiatrists who do not place a bar on my ability to speak freely
Psychiatric Research- where from and where to?
Emil Kraepelin (1856-1926)  
Eugen Bleuler (1857-1939)
REGIONAL CEREBRAL BLOODFLOW (rCBF) AND SYNDROMES OF SCHIZOPHRENIA

Psychomotor poverty syndrome

Disorganization syndrome

Reality distortion syndrome

Negative correlations

Positive correlations

CEREBRAL VENTRICULAR SIZE AND COGNITIVE IMPAIRMENT IN CHRONIC SCHIZOPHRENIA

Eve C. Johnstone  T. J. Crow
C. D. Frith    Janet Husband
L. Kreef

Divisions of Psychiatry and Radiology, Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ

Summary  By comparison with age-matched controls in employment, 17 institutionalised schizophrenic patients were shown by computerised axial tomography of the brain to have increased cerebral ventricular size. Within the group of schizophrenic patients increased ventricular size was highly significantly
Northwick Park Hospital and Clinical Research Centre who were matched with the index group for age, and as closely as possible for premorbid occupational attainment. The mental states of the patients and controls were assessed in terms of the rating scale devised by Krawiecza et al. A total score of positive features of schizophrenia (delusions, hallucinations, and thought disorder) and negative features of schizophrenia (retardation, flattening of affect, and muteness) was derived from this rating. The cognitive functioning of the patients and controls was assessed on the clinical tests devised by Withers and Hinton. Physical examination was carried out and routine testing of all patients included full blood-count, erythrocyte-sedimentation rate, serum B₁₂ and folate, specific serology, liver-function tests, and thyroid-function tests.

EMI scans of the brain were obtained in 17 of 18 schizophrenics and from 8 controls. Tomographic sections through the brain were taken beginning at and continuing parallel to the orbitomeatal line, at 1 cm intervals to the vertex. Two images at comparable levels were selected for each patient. One showed the body of the lateral ventricles and the other showed the anterior and posterior horns of the lateral ventricles together with the third ventricle. The images were photographed and the area of the ventricles in each photograph was measured with a planimeter, an instrument which measures the area contained within a circumference. These measurements were made blindly on two separate occasions by two independent investigators, giving four measurements on each subject. No attempt was made in this study to assess the size

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Correlation coefficient</th>
<th>No. of patients</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age vs. ventricular size</td>
<td>( r = -0.21 )</td>
<td>13</td>
<td>N.S.</td>
</tr>
<tr>
<td>Cognitive function vs. ventricular size</td>
<td>( r = -0.70 )</td>
<td>13</td>
<td>( P &lt; 0.01 )</td>
</tr>
<tr>
<td>Positive features vs. ventricular size</td>
<td>( r = -0.24 )</td>
<td>13</td>
<td>N.S.</td>
</tr>
<tr>
<td>Negative features vs. ventricular size</td>
<td>( r = -0.38 )</td>
<td>13</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

Ventricular size in patients and controls.

Each point represents average of four measurements on photograph.

The correlation between the measurements obtained by the two separate observers (cut 1, \( r = 0.96, P < 0.001 \); cut 2, \( r = 0.94, P < 0.001 \)) and apparently this is a reliable method of measuring ventricular size. The correlation between the measurements at the two levels in the same patient was high (cut 1 vs. cut 2, \( r = 0.68, P < 0.001 \)), and this suggests that minor variation in exact site of the tomographic sections is unlikely significantly to affect assessment of ventricular size.

The figure shows the mean of the four measurements of ventricular size. Leucotomy is associated with increased size of ventricles in the schizophrenics.
Severity of hallucinations by STG volume for patients with schizophrenia

Rajarethiannam et al., 2000 after Barta et al., 1990
The world’s first Functional MRI

Belliveau et al., 1991
Woodruff et al., *Lancet* 1995
External speech during auditory hallucinations

Woodruff et al., 1997 Am J Psych
External speech after recovery

Woodruff et al., 1997
“Auditory hallucinations compete with external speech for common neurophysiological resources”

Motor activations at two points in Time
4 - 6 weeks apart

Normal subjects activate Left DLPFC at T1 and T2 (4-6 weeks later)

Normals at T1

Schizophrenics fail to activate Left DLPFC at T1

Normals at T2

T1

T2

T2 minus T1

Schizophrenics

Left DLPFC activates at T2
Prefrontal activation and social recovery in schizophrenia

Lee et al., Am J Psych. 2005
The Emerging Role of Neuroimaging in Psychiatry: Characterizing Treatment-Relevant Endophenotypes

The research agenda for DSM-V emphasizes a need to translate basic and clinical neuroscience research findings into a new classification system for all psychiatric disorders based upon pathophysiologic and etiological processes (1-4). It is becoming increasingly clear, however, that we need to move toward identifying endophenotypes that not only reflect underlying pathophysiologic processes specific to a disorder but that also mediate response to specific treatments to help guide our treatment choice for individuals as early as possible in their illness course.

In this issue of the journal, three articles highlight the need in psychiatry for improved means of identifying as early as possible subgroups of individuals with a given psychiatric disorder who will respond preferentially to a specific treatment. Two of these articles demonstrate that neuroimaging techniques may provide a methodology to help us achieve this ultimate goal.

In one article, Frank et al. present data identifying a subgroup of individuals from a larger group of 233 female adults with unipolar depression who were able to achieve remission with interpersonal therapy alone and for whom maintenance interpersonal therapy, even at a frequency of only one visit per month, was a good method of prophylaxis. In contrast, they show that 40% of patients who responded to the same basic treatment received by the subgroup as a whole relapsed within a year of follow-up.

“Can neuroimaging really help us achieve the goal of identifying treatment-relevant endophenotypes in unipolar depression or, indeed, other psychiatric disorders?”
The political power of neuroimaging to the benefit of psychiatry

“Congressional and NIMH staffers agree that the images, beyond the words, carried great weight in the political discourse that ultimately led to the first mental health parity act in the United States, in 2008”.

Gene–environment interactions in psychiatry: joining forces with neuroscience

Avshalom Caspi and Terrie E. Moffitt

Abstract | Gene–environment interaction research in psychiatry is new, and is a natural ally of neuroscience. Mental disorders have known environmental causes, but there is heterogeneity in the response to each causal factor, which gene–environment findings attribute to genetic differences at the DNA sequence level. Such findings come from epidemiology, an ideal branch of science for showing that gene–environment interactions exist in nature and affect a significant fraction of disease cases. The complementary discipline of epidemiology, experimental neuroscience, fuels gene–environment hypotheses and investigates underlying neural mechanisms. This article discusses opportunities and challenges in the collaboration between psychiatry, epidemiology and neuroscience in studying gene–environment interactions.
Importance of loss and social environment

• Past loss of mother before the age of 11 increased the risk of depression amongst women; past loss through death increased the risk of psychotic depression amongst everyone (Brown et al., 1977).

• significant life events predicted psychosis 3-weeks later (Brown and Birley 1968).

• ‘Expressed emotion’ was toxic (Leff, Vaughn and others)
Tranquillity: effective connectivity of primary auditory cortex – Hunter et al. Neuroimage 2010

Parameter estimates are a measure of covariation with primary auditory cortex under the tranquil and non-tranquil conditions, compared with fixation. Brain map shows regions exhibiting enhanced connectivity with primary auditory cortex under the tranquil condition compared with the non-tranquil condition (n = 12; random effects; p < 0.001, uncorrected, for display purposes).
The Psychiatrist who won the Nobel Prize for Medicine

Julius Wagner-Jauregg (1857-1940)
Chlorpromazine trial 1954: the first effective medicine for schizophrenia

Jean Delay (1907-1987)
Arvid Carlsson 1923-
A Half-Century of Neurotransmitter Research: Impact on Neurology and Psychiatry (Nobel Lecture)**

Arvid Carlsson[a]

KEYWORDS:
- dopamine
- neurotransmitters
- Nobel lecture
- Parkinson's disease
- signal transduction

Beginnings

My encounter with dopamine followed an incredible sequence of fortunate events. I had been working on calcium metabolism using radioactive isotopes, which had then just become commercially available. This work had resulted in my doctoral thesis in 1951 and a series of subsequent papers, including two doctoral theses by students of mine. Our results had become somewhat visible internationally, for example, in an invitation to a Gordon Conference in New England in 1955. The reason why I left this field of research was that, in connection with a competition for an associate professorship in pharmacology, the expert committee let me know that in their opinion calcium metabolism did not occupy a central position in pharmacology. I therefore turned to Professor Sune Bergström (Figure 1), who was at that time head of the Department of Physiological Chemistry at the University of Lund, Sweden. This department was located in the same building as our Pharmacology Department. Professor Bergström had already been very helpful in several instances when I had had a professional problem of some kind. Incidentally, Dr. Bengt Samuelsson was at that time working with Professor Bergström in the same department. This letter was forwarded via the late Dr. Sidney Udenfriend to his superior, the late Dr. Bernard B. Brodie (Figure 2), head of the famous Laboratory of Chemical Pharmacology at the National Heart Institute. That is how I came to work under Dr. Brodie for about five months, starting in August 1955. The timing of my arrival there was extremely fortunate. Brodie and his colleagues had just made a breakthrough discovery a few months before, namely that the administration of reserpine, a recently introduced antipsychotic and antihypertensive drug, caused the virtually complete disappearance of serotonin from the brain and other tissues[1,2] (Figure 3).

Figure 1. Sune Bergström (1944).

Figure 3. Brain level of serotonin four hours after administration of various intravenous doses of reserpine. (Taken from ref.[2])
Sigmund Freud (1856-1939)

Carl Jung (1875-1961)
Psychological therapy in Psychiatry

Aaron Beck, Psychiatrist: 1921-
Selective serotonin reuptake inhibitors (SSRIs) and routine specialist care with and without cognitive behaviour therapy in adolescents with major depression: randomised controlled trial.


BMJ 2007; 335:142
Conclusions

Psychiatry needs to:

• Nurture its roots embedded in clinical medicine
• Improve validity of diagnoses without discarding them
• Understand the biology of behaviour, genes and environment
• Maintain expertise in assessing evidence and delivering treatment
• Collaborate with Industry to develop newer medicines
• Assess and further develop physical and psychological treatments
Psychiatry's 200th birthday