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HOW WILL RESEARCH IN NEUROSCIENCE INFLUENCE THE PRACTICE OF PSYCHIATRY IN THE NEXT TEN YEARS?

By Jonathan O'Keeffe

'Give me a place to stand and I'll move the world.' – Archimedes of Syracuse

Psychiatry differs from other clinical specialties in several important respects. At a basic level, physical examination of the body is conspicuously absent in psychiatry. The diagnostic process employs almost no physical laboratory-based tests such as blood, urine, or CSF (cerebrospinal fluid) analysis. Nor are the various imaging modalities instrumental in diagnosing a psychiatric condition. Such investigations are almost ubiquitous elsewhere in medicine, yet insofar as they are utilized in psychiatry they are overwhelmingly aimed at excluding non-psychiatric conditions. Moreover, modern-day psychiatry is, more than any medical specialty, a minefield of controversy. Psychoanalysis, for example, still widely practised, is viewed by many psychiatrists in the field as little more than quackery (Webster 1996), and even within the disciplined ranks of those committed to neurobiological models of disease disagreement exists as to whether schizophrenia and bipolar disorder represent distinct pathologies (Maier, Zobel and Wagner 2006). As if the unusual nature and degree of internal debate regarding psychiatric theories and therapies were not enough, controversy extends so far as to question the very existence of psychiatric conditions. As Thomas Szasz, Professor of Psychiatry at Syracuse University, famously opined, '"mental illness" is not the name of a biological condition' (Szasz 1973).

From a neuroscientific standpoint, psychiatric illness is a real biological phenomenon, reflecting underlying dysfunction of the CNS (central nervous system). However the immense complexity and apparent species-specificity of the human brain pose formidable challenges to the understanding and investigation of mental illness. On this view controversy within psychiatry is usually attributed to the poor state of knowledge, possible in the modern era only because of the complexity of mental illness, and compounded by the absence of straightforward animal models of disease which might otherwise ease enquiry.

However, with the rise of neuroscience over the past twenty years a spirit of optimism has emerged in psychiatry, to which the proliferation of journals trumpeting titles such as *Molecular Psychiatry* and *Biological Psychiatry* is testament. The nineties, dubbed the 'Decade of the Brain' (Blakemore 2000), witnessed major breakthroughs in fundamental neuroscience, such as elucidation of the crystal structure of ion channels (Doyle et al. 1998) and receptor diversity in the olfactory system (Malnic et al. 1999). In the hubbub of plaudits and Nobel prizes that has ensued, one might be forgiven for supposing that a new dawn in psychiatry is all but upon us. After all, with such advances in fundamental neuroscience, how can psychiatry fail to make progress?

I will argue that the prospects for progress in psychiatry as a consequence of neuroscientific understanding are real, but limited in scope, at least over the next decade. Change over this timescale is most likely to be evident in diagnostics, as a consequence of advances in characterisations of underlying pathophysiologies. On the other hand, the potential for significant therapeutic advances, if it exists at all for conditions like schizophrenia, presupposes the development of techniques for

targeted manipulation of the brain, which are (with the tenuous exception of deep brain stimulation) still in their infancy. For, like Archimedes, psychiatry too needs a place to stand if theoretical insights are to be translated into tangible results. Neuroscience is providing some solid answers as to where those places might be, but there is no guarantee that they will prove any more practical than for Archimedes.

Psychiatric diagnostics: a place to stand

'The second principle is that of division into species according to the natural formation, where the joint is, not breaking any part as a bad carver might.' – Plato

While the diagnostic challenge is common to all specialties, few conditions can compare for sheer elusiveness to that of or in psychiatry. Schizophrenia illustrates the general pattern.[1] As one of the top ten causes of disability in the developed world (Murray et al. 1990) it attracts large quantities of research funding, albeit small relative to its prevalence and enormous economic impact (Knapp, Mangalore and Simon 2004). Yet researchers have sought in vain a consistent histological or biochemical marker for this condition, with positive results largely limited to differences in population averages between patients and healthy controls (e.g. Holmes et al. 2006), rather than disease subtypes, e.g. depression versus schizophrenia. Furthermore, it is not obvious that the differences found between schizophrenic and non-schizophrenic brains, such as in total volume, are immediately related to the underlying pathology. A genetic diathesis does appear to be important, with concordance between identical twins consistently around 50%, and several specific genes implicated, but the relationship is at best probabilistic and suggests a genetic susceptibility rather than a genetic condition (Harrison and Wienberger 2005). Instead, the diagnosis of schizophrenia is based on uncovering clinical features such as the presence of Schneiderian first rank symptoms (e.g. reports of auditory third person hallucinations, thought insertion and broadcasting) in the patient's history, and through mental state examination. This situation is expedient, given the poverty of hard biological criteria available, and similar observations apply to other psychiatric conditions, leading to an important question: Why should the entire class of disease apportioned to psychiatry so persistently evade definition in some or one of the biochemical, genetic or other paradigms fundamental to the rest of medicine, and what might be done to meet the challenge? The answer to that question stems from an appreciation of the nature of mental processes, which in turn throws light on the question of how neuroscience might place psychiatry on a firmer diagnostic footing.

The CNS has evolved as an information processor. That is, it utilises salient information available in its environment to produce an adaptive output, be it motor, endocrine-autonomic, or otherwise. The point that emerges, variously considered uncontroversial by some (such as neuroscientists Steven Pinker and Simon Baron-Cohen), and outrageously reductionist by others (Le Fanu 2009), is that psychiatric illnesses are disorders of information processing. Disordered information processing is seen as the proximate cause underlying any psychiatric illness, even where the ultimate cause is not (as with psychosis in Cushing's Syndrome, for example). As such, the pathological process underlying a psychiatric condition is likely to involve features of the CNS directly related to this function, such

[1] The emphasis on schizophrenia to illustrate various points in this essay is principally an expedient of limitations in space, but it is also chosen as somewhat representative of the psychiatric conditions, so far as that is possible.

as synaptic transmission, the intrinsic firing properties of neurons and the dynamics of neuronal networks. Furthermore the brain is an inherently unstable system, as is evidenced both by its sensitivity to change, and by the high lifetime prevalence of epilepsy: 2-5% (Neligan and Sander 2009). It would not therefore be surprising if very small variations – in the way synaptic weights are modified in response to experience, for example – could mean the difference between mental illness and health.

One might reasonably challenge this conception of mental disease, however, with the charge that it is an *ad hoc* justification of a sham specialty, defining a special class of 'elusive' disease, ephemeral enough to be all but invisible in the laboratory, but real enough, in the minds of psychiatrists at least, to justify ECT (electroconvulsive therapy) and medication with grisly and sometimes fatal side-effects. This argument has often been made, but fails to do justice to the nature of genuine psychiatric illness, and is itself *ad hoc,* since conditions of a similar nature are found elsewhere in medicine. One example is cardiac arrhythmias, to which we briefly turn.

In cardiac arrhythmias the heart supports patterns of electrical activity which impair its adaptive function, pumping blood efficiently (and without thrombosis). One does not and would not expect to find reliable causal correlates of an arrhythmia in blood tests or static imaging, for example, because the disorder is primarily an electrical one with an essential temporal dimension. Moreover, perfectly healthy hearts will transiently slip into arrhythmia without deleterious effects (Podrid and Kowey 2001, 414)—a fact which squares rather neatly with the observation that many of us experience mild psychiatric symptoms, be they brief hallucinations or excessive anxiety, at some point(s) in life (Bentall and Slade 1985). Where hard causal disease correlates of arrhythmia are demonstrable they are closely related to the electrical properties of the myocytes, such as the Long QT channelopathy Romano Ward Syndrome. A single defective potassium channel appears solely at fault in almost every case of this condition, but can result in a complex dynamic arrhythmia (torsade de pointes) that can progress to ventricular tachycardia and death. The myocardium in this condition is otherwise completely normal and appears so microscopically that the diagnosis must be made by ECG (electrocardiography).

If the analogy between cardiac arrhythmias and mental disorders is valid, it yields the prediction that it should be possible, in principle at least, to observe pathological electrical behaviour in mental illness using the ECG equivalent, the EEG (electroencephalography). This turns out to be the case, and supports the notion that psychiatric diagnostics will not progress by developing more sophisticated blood tests or the like, but by an increased ability to characterise the electrical activity of the brain. In schizophrenia, for example, using qEEG (quantitative EEG) researchers have found desynchronisation in the theta frequency occurring in new onset, treatment naive, schizophrenics (Koenig et al, 2001), with some studies now claiming high sensitivity and specificity in diagnosis on the basis of qEEG alone, although results are not unanimous (Boutros et al. 2009). Furthermore, EEG analysis may soon furnish clinicians with accurate predictions of response to antipsychotics (Galderisi 2002), potentially enabling them to withhold treatment selectively from those patients whose prognosis worsens *with* antipsychotic therapy. While such claims should be treated with caution (Galderisi et al. 2009) there seems little reason to doubt that, hand in hand with advances in the neurophysiology of the condition, the next ten years will bring only improved data collection and analysis in this field. A qEEG may soon be considered essential to confirmation of diagnosis and

treatment choice. Similar arguments apply to other psychiatric conditions, especially depression, where promising qEEG results have also been obtained (Grin-Yatsenko et al. 2010).

MEG (magnetoencephalography) might prove useful for similar reasons to EEG,[2] having, as it does, an extremely high millisecond temporal resolution but with superior spatial resolution. On the other hand, MEG is blind to currents with no component tangential to the surface of the scalp, arguably reducing its utility as a probe. However, and practical issues such as expense aside, much less research has been conducted with MEG compared to EEG. For example, a pubmed search (April 2011) with 'MEG schizophrenia' yields 93 results compared to 2825 results for 'EEG schizophrenia', more than an order of magnitude's difference. Given this disparity, the jury is probably still out regarding whether MEG will ultimately contribute anything clinically over and above qEEG.

Much has been made of fMRI (functional magnetic resonance imaging) as a window onto the brain, and there are many intriguing findings in literature on it, such as the activation of the auditory cortex during auditory hallucinations in schizophrenia (Dierks et al.1999). It could, in principle, aid the diagnostic process; however, the observations made about the nature of psychiatric disease suggest that such technology is, broadly speaking, likely to become less rather than more relevant in the future, in both neuroscience and psychiatry. This is a consequence of the level at which fMRI observes the brain, or effectively blood flow. As we have observed, psychiatric disease relates to information-processing in the brain, essentially an electrochemical phenomenon with an inalienable temporal dimension[3] By analogy with arrhythmias, it may be possible to learn much from patterns of blood flow in the heart (functional impact, for example), but the ideal diagnostic tool should access information at the actual level of the pathology, as an ECG does in the case of an arrhythmia. Similar considerations, writ large, imply that conventional structural CT (computer tomography) and MRI imaging are still less likely to contribute significantly to psychiatric diagnosis.

In recent times the field of genetics has perhaps received more column inches in the popular and professional media alike than any other, culminating in the sequencing of the human genome, which 'holds the keys to transforming medicine and understanding disease' (*CNN*, 'Human genome sequence completed'). James le Fanu has argued that this 'New Genetics' was a mirage, firstly because genetic causes of disease are of marginal importance, contributing only to a minority of cancers, for example,[4] and are typically dwarfed by other contributors, such as ageing (Le Fanu 1999). Secondly, he argued that because the complexity of genomic interactions is so extreme, predicting a phenotype from a genome is essentially impossible. The thesis is controversial, but it has, in fairness, undoubtedly been borne out in psychiatry, with approximately zero impact on present practice and little to suggest the future will prove any different. Genotyping might, in principle, aid in drug selection on the basis of receptor characterisation, but in the absence of drugs targeted to different genotypes the point is hardly more than academic. Furthermore, the quintessentially multi-factorial

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[2] However it should be noted that both EEG and MEG suffer from relative insensitivity to the dynamics of deep subcortical brain structures, such as the limbic system, dysfunction of which has been implicated in most major psychiatric conditions.

[3] Temporal resolution for fMRI is about 6-7 seconds, 3-4 orders of magnitude away from the millisecond scale at which the brain functions.

[4] Even hereditary breast cancer, associated with BRCA 1 and 2, accounts for only 5-10% of the total disease burden.

and often transient nature of mental illness argues against the usefulness of a genetic test as a clinical tool.

Therapeutics: moving the world?

Historically, psychiatry has advanced in the main by sheer serendipity. Chlorpromazine, the first antipsychotic, was an 'antiemetic' when Henri Laborit, a French naval surgeon, noticed in 1951 that it caused sedation without narcosis, while the psychoactive effects of lithium were first observed in guinea pigs while investigating a completely different compound, urate (lithium urate was used as a convenient soluble form of urate). The fact that chlorpromazine acts via dopamine blockade was not ascertained for more than a decade after commencing its use in psychotic patients, and the relevant target for mood stabilisation in lithium therapy is a mystery to this day (Le Fanu 1999).

Unfortunately, the spring of serendipitous drug discovery appears to be running dry, despite colossal screening programmes utilising combinatorial chemical synthesis among, other advanced techniques. This trend is, in fact, seen across the board, with the U.S. FDA (Food and Drug Administration) reporting an overall reduction in the number of new compounds entering the approval process each year (Balaram 2004).

A rationally-designed psychiatric drug would, on the other hand, constitute an unprecedented advance, but expectations of such an advance in the next decade is fairly unrealistic. Moreover, it seems reasonable, given their apparent complexity, to suppose that the understanding of psychiatric conditions is likely to lag behind other fields. The dearth of rational therapies elsewhere thus indicates they may be many decades in coming to psychiatry.

On a more positive note, it has recently become clear that a certain class of psychosis is due to antibodies against NMDA-receptors in the CNS, leading to its effective treatment with immunosuppressants such as steroids (Pruss et al. 2010). This is a surprising and welcome development, as such patients would previously have largely been labelled and treated as schizophrenics, often chronically and ineffectively. More speculatively, an interesting possibility is that neuroscience may soon identify an infectious agent responsible for a proportion of schizophrenia, the existence of which is supported by evidence such as the increased incidence among winter births (Pulver et al. 1992). The next decade may see vaccination or other treatment against schizophrenia at the prenatal stage, depending on the agent identified. Obstetricians would be probable administrators, and the effects on psychiatric practice (presumably a reduction in the prevalence of schizophrenia) would take (much) more than a decade to ramify fully, but the prospect is a remarkable one. While such examples should serve to illustrate the depth of uncertainly surrounding much psychiatric theory and practice even today, they also demonstrate that progress is being made and new avenues of enquiry opening with each advance in understanding.

Lastly, we turn to recent promising developments in DBS (deep brain stimulation) for OCD (obsessive compulsive disorder) and treatment-resistant depression. At present only pilot studies have taken place, but the results are encouraging, with response rates of 66% typically (Greenberg et al. 2008). In July 2009 Medtronic announced it had received CE (Conformité Européene) Mark approval for the use of DBS in severe treatment resistant OCD, with a large multicentre trial to follow (Medtronic Press Release 2009). Preliminary results in depression are arguably still more

promising, with a large multicentre trial by St Jude Medical targeting the subgenual cingulate now under way (St Jude Medical, online). That the introduction of a stimulating electrode into the brain can alleviate symptoms of OCD and depression is surely another example of serendipity, since it is not understood how this intervention works, if indeed it does.[5] However, it is one driven by the neuroscientific conception of mental illness I have outlined, and the more-than-passing resemblance to cardiac pacing is, I would argue, no coincidence. That said, pending the outcome of future trials, psychosurgery may soon become widespread as a viable option for these and perhaps other conditions. And unlike the destructive psychosurgery previously (and occasionally still) practised in the UK, DBS is non-destructive, adjustable and reversible.

Even if current hopes for DBS should prove unfounded, the technology has potential implications for side-effect alleviation, since essentially the same procedure can be used to deliver drugs to a localised (therapeutic) target, while sparing sites associated with undesirable sites of action. This might prove especially important for schizophrenia and other psychoses, since the prospect of DBS for these apparently distributed multisystem disorders is much less promising.

Conclusion

Neuroscience holds the potential to aid in the characterisation of mental disease, principally through enhancing data collection and analysis pertaining to the level of the disease process. This should soon aid in diagnosis and treatments selection, and may conceivably feed back to alter the very categories of disease employed. qEEG looks especially promising in this respect, and may supply the first objective supplement to psychiatric diagnosis. However, mental illness represents a heterogeneous group of largely chronic and subtle conditions, in which one should expect only slow progress, especially in therapeutics. Perhaps the most obvious change a jobbing psychiatrist will notice over the next ten years will be an influx of young enthusiasts suscribing to the view of mental disease with a neurobiological approach, and accepting the daunting but exciting challenges it implies.

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[5] While the neuronal mechanisms of DBS efficacy are murky to say the least, it should be noted that the targeting of specific nuclei has been guided in part by a systems level understanding of the brain. For example, the subgenual cingulate is a target in current trials for depression, and was proposed on the basis of solid fMRI data supporting its role in the disease (Johansen-Berg et al. 2008).

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