The eye’s mind: brain mapping and psychiatry

ED BULLMORE and PAUL FLETCHER

Over the past three decades it has become possible to visualise living human brain structure and function in astonishing detail. To pioneering investigators such as Jackson, Meynert, Wernicke, Freud, Alzheimer and Kraepelin our current capacity to image brain structure to the nearest millimetre, and cerebral haemodynamics to the nearest second, would surely have appeared heaven-sent. With these techniques, they might have envisaged a conclusion to their great project of a biological psychopathology, and a resolution of the theoretical questions they first raised about diagnosis and causation of mental disorders.

But this hasn’t happened yet. Despite the extraordinary technical developments in neuroimaging (Andreasen, 1997), scepticism is common with respect to its impact on psychiatry. What has imaging told us about schizophrenia, for example, that we did not already know? Why has imaging been largely irrelevant to our understanding of causation in psychiatry? Why has imaging made no difference to the clinician? These are important questions for neuroimaging researchers to address sincerely. After all, the expense of imaging has often been justified by the promise of clinical benefit. We need to be clear about the impact of imaging on psychiatry so far and the prospects for brain mapping and psychiatry in the future. In what follows, we focus predominantly on studies using magnetic resonance imaging (MRI) to measure brain structure or function, because the safety and versatility of MRI make it the pre-eminent form of imaging in psychiatry. However, there is important complementary information to be gained by other methods. Radioligand studies using positron emission tomography (PET) can provide otherwise inaccessible information about receptor density and endogenous transmitter release (Abi-Dargham et al, 2000). Electrophysiological techniques have better temporal resolution than functional MRI (fMRI) and impose a less constrained environment for psychological experiments. One future trend of interest will be the development of integrated or multi-modal imaging techniques, for example combining PET, fMRI and electrophysiological measurements in comprehensive investigations of all accessible aspects of human brain organisation in vivo (Dale & Halgren, 2001). However, at least in relation to psychiatry, such technical achievements are not necessarily rate-limiting: as we aim to show below, the critical factors have more to do with the ‘goodness’ of the questions we use imaging to address, which relates to the problems inherent in using 21st-century methods to investigate the biological correlates of 19th- and early 20th-century nosology.

WHAT HAS IMAGING TOLD US ABOUT SCHIZOPHRENIA, FOR EXAMPLE, THAT WE DID NOT ALREADY KNOW?

It is now perhaps forgotten that, when the first computed tomography (CT) studies of schizophrenia were reported (Johnstone et al, 1976), psychosis was customarily divided into organic and functional disorders. It was axiomatic that functional psychosis was not associated with organic or structural abnormalities of the brain; yet CT scans showed significant enlargement of the ventricles in people with schizophrenia. This discrepancy was initially negotiated, without jeopardising the nosological orthodoxy of the time, by suggestions that structural brain changes in schizophrenia were incidental or secondary, due to factors such as medication or institutionalisation. However, the intervening years have witnessed the vindication of the contrary view that schizophrenia is indeed characterised by widespread deficits in grey matter and white matter associated with diffuse enlargement of the ventricular system (Wright et al, 2000). Such observations have prompted a renaissance of Wernicke’s original idea that psychosis, as well as dysphasia, may be a disorder of associative or integrative functions. To put this in more recent terminology (Mesulam, 2000): we have resumed thinking of psychosis as a disconnection syndrome adversely affecting the structure of large-scale neurocognitive networks in the brain (Sigmundsson et al, 2001). This is an important conceptual shift, which (re)locates schizophrenia in the same frame of reference as classical and neoclassical disconnection syndromes in neurology. The shift also makes psychosis accessible and relevant to contemporary systems neuroscience (Pantelis et al, 1997; Goldman-Rakic, 2001). To the extent that imaging has materially contributed to this shift away from the concept of ‘functional psychosis’, it has already told us something we did not know (or had forgotten) about schizophrenia.

WHAT FACTORS HAVE AFFECTED THE IMPACT OF IMAGING ON PSYCHIATRY?

Reports of distributed patterns of grey matter deficit in disorders such as attention-deficit hyperactivity disorder (ADHD) (Castellanos et al, 2001; Overmeyer et al, 2001), autism (Courchesne et al, 2001) and various neurogenetic syndromes, prompt the hypothesis that disconnection syndromes might provide a model for the anatomy of neurodevelopmental disorders in general, not solely schizophrenia (Bullmore et al, 1997). However, there is little consensus on which brain regions (or networks) are critically abnormal in any given syndrome. In our view, the most salient reasons for this perceived fuzzyness of the psychiatric imaging literature are issues of sampling, data analysis and study design.

The majority of imaging studies have scanned modest numbers of patients and comparison participants in a cross-sectional case–control design. The study participants are almost never ascertained by random sampling from the relevant populations and may not always be well matched in terms of potentially confounding factors such as age, gender, medication, race, IQ and task performance. Most structural imaging data have been analysed by ‘region of interest’ morphometry – a labour-intensive approach, inevitably unreliable, and tending to focus scientific attention
and drug histories. Each of these aspects of heterogeneity may be associated with variation in brain function and structure. This potentially enormous within-group neurophenotypic variability may mask between-group differences. More radically, it suggests that we might do better to investigate patients defined in terms of symptoms, or dimensions of correlated symptoms, rather than time-honoured diagnostic entities (Liddle, 2001). The most forward-looking examples of this approach have aimed not simply to map a symptomatic disturbance to a physiological or anatomical abnormality but to reformulate the phenomena of psychopathology in terms of normal neurocognitive systems. One example that has proved fruitful is the concept of auditory hallucinations as a manifestation of disorderly monitoring of inner speech (Frith, 1996). This model cuts across the diagnostic boundaries between varieties of psychosis. Other comparable recent studies include investigation of negative psychotic symptoms in relation to disordered function of fronto-striato-thalamic circuits (Menon et al, 2001) and characterisation of obsessive and compulsive symptoms in relation to the functional neuroanatomy of disgust and other cardinal emotions (Phillips et al, 2000). If this trend persists, the success of psychiatric imaging research will be accompanied by a subversion of traditional psychiatric diagnoses.

Imaging has already refreshed our awareness that human brain structure and function are sensitive to many factors, especially age and gender, which are non-pathologically variable in the general population. We now need to understand much more exactly how the human brain normally matures and grows old, and whether there are important male/female dimorphisms or racial differences in these normative neurodevelopmental processes. This enhanced understanding of normal neurophenotypic variability over the life cycle will clearly be fundamental to a more precise delineation of developmental and degenerative disorders in terms of abnormal trajectories of brain structural or functional change. Furthermore, the use of longitudinal designs will enrich studies of psychopathological states or incipient disorders, e.g. first episode of psychosis, which may be associated with sub-acute changes in the brain over time (David et al, 1996; Thompson et al, 2001).
neglected disorders, such as fragile-X syndrome, velo-cardio-facial syndrome, or tuberous sclerosis, which share clearly defined genetic lesions and a risk of psychosis (Kwon et al., 2001; Ridler et al., 2001; van Amelsvoort et al., 2001). Finally, and most challengingly, we can anticipate multi-centre imaging studies designed on epidemiological principles and appropriately scaled to elucidate the role of genetic or environmental risk factors in broader, multi-factorial syndromes of major public health interest, such as serious mental illness or borderline learning disability.

Crucially, imaging is not inherently uninformative about causation; it can mediate explanatory links between genetic or other risks and cognitive or behavioural outcomes. However, to do this it must – like any other empirical technique – be incorporated in experiments with an ambition to explain causally.

**WHY HAS IMAGING MADE NO DIFFERENCE TO CLINICAL PRACTICE?**

There are economic constraints on psychiatric access to neuroimaging. Access to scanners may be rationed to favour examination of patients with medical or surgical conditions considered to be more acute, more life-threatening or remediable. What could imaging possibly tell us about a single psychiatric patient that would be worth the cost of the scan?

We know that extra diagnostic information can be valuable enough in some circumstances, but in general the most useful information we might expect is predictive rather than diagnostic. Is the patient likely to respond to antidepressant or antipsychotic medication with a prolonged latency of clinical effect? Is the patient more likely to benefit from a new, expensive drug than from an older, generic alternative? How likely is the patient to become violent, or to start drinking or taking drugs again? What is the long-term prognosis? These are commonly occurring questions in practice, with definite implications both financially and for clinical management, which we often have to answer vaguely.

We suggest that there is no neuroscientific reason why it should not be possible, in future, for imaging to help us to answer these questions probabilistically instead. For example, fMRI has already been combined with pharmacological challenges to show differences in working memory function related to short-term atypical antipsychotic treatment (Honey et al., 1999) and to define abnormalities in frontal striatal response to methylphenidate in children with ADHD (Vaidya et al., 1998). This early evidence suggests that neuroimaging may provide a predictively valuable index of individual characteristics that are inaccessible to purely psychological enquiry. Of course, these individual brain characteristics are likely to be subtle, perhaps only identifiable as quantitative departures from appropriate comparison group norms. Therefore, major advances in the impact of imaging on management of individual patients will probably need to await the creation of large reference databases of brain images acquired from the general population, and widely agreed standards of data analysis, which can be accessed via the internet as a basis for quantitative analysis of the extent to which a patient’s image is abnormal or predictive of some clinically important outcome. Admittedly this assumes a level of methodological maturity, infrastructural investment and international cooperation that does not yet exist; but these are details, surely – there remain grounds for optimism.

**DECLARATION OF INTEREST**

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