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 fuzziness 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.
perseveratively on the same few brain
regions. Functional imaging studies, and
more recent structural studies, have
broadened the scope of investigation, and
made it more reliable, by using computers
to warp brain images into the same anatom-
ic space and then to map effects of inter-
est at each and every voxel in the images.
Such an approach, however, ushers in the
problems of setting an appropriate P value
for hypothesis testing when multiple
significance tests are conducted simulta-
aneously across many thousands of voxels
representing the entire brain.

Altogether, it is easy to see how this
set of operating practices could give rise
to an internally inconsistent literature, in-
cluding both false positive results due to
unrepresentative samples or uncontrolled
confounds and false negative results due
to tightly controlled hypothesis testing
on small groups. One key to solving this
problem is likely to lie in the use of
meta-analytical methods to estimate ef-
teffects of psychiatric disorder on the basis
of the pooled results of several imaging
studies (Wright et al., 2000). This could be
assisted by the creation of digital data
repositories, accessible via the internet,
available to investigators wanting to apply
common methods to amalgamated data-
sets (Governing Council of the Organiza-
tion for Human Brain Mapping, 2001). In
addition, sensitivity is also likely to be
increased through the use of alternative
statistical strategies. Computer-intensive
data resampling methods can be used in
place of asymptotic theory to approximate
more exactly the distribution of any test
statistic under the null hypothesis (Bull-
more et al., 2001; Nichols & Holmes,
2002). Prior data can be used to condition
the analysis of small samples in a Bayesian
framework (Friston et al., 2002). Multi-
variate statistics can be used to describe
sufficently distributed systems of mutually
correlated regions (Wright et al., 1999;
Meyer-Lindenberg et al., 2001). However,
larger samples and more-refined analytical
methods alone will not address the most
fundamental limitation of neuroimaging
case-control studies: neither ‘caseness’ nor
‘controllness’, defined cross-sectionally,
are sufficiently rich descriptions of the
manifest cognitive and behavioural vari-
ability we wish to relate to the (perhaps even
greater) complexity of the brain.

It is widely accepted that the major
diagnostic labels subsume a great diversity
of symptom profiles, cognitive deficits
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 rad-
ically, 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 physiolo-
ical or anatomical abnormality but to
reformulate the phenomena of psycho-
pathology in terms of normal neurocogni-
tive systems. One example that has
proved fruitful is the concept of auditory
hallucinations as a manifestation of dis-
ordered monitoring of inner speech (Frith,
1996). This model cuts across the diag-
nostic boundaries between varieties of
psychosis. Other comparable recent stu-
dies include investigation of negative
psychotic symptoms in relation to disor-
dered function of fronto-striato-thalamic
circuits (Menon et al., 2001) and charac-
terisation of obsessive and compulsive
symptoms in relation to the functional
neuroanatomy of disgust and other cardin-
al 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 popu-
lation. We now need to understand much
more exactly how the human brain nor-
manally matures and grows old, and whether
there are important male/female dimorph-
isms or racial differences in these normative
neurodevelopmental processes. This en-
hanced understanding of normal neuro-
phenotypic variability over the life cycle
will clearly be fundamental to a more pre-
cise delineation of developmental and de-
generative disorders in terms of abnormal
trajectories of brain structural or functional
change. Furthermore, the use of longitudi-
nal designs will enrich studies of psycho-
pathological 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).

WHY HAS IMAGING BEEN
LARGELY IRRELEVANT TO
OUR UNDERSTANDING
OF CAUSATION?

It might be charged that imaging is nothing
but a new phenomenology, substituting
one set of theoretically superficial labels,
such as ‘thought broadcast’, with another
set of descriptive labels, such as ‘hypo-
frontality’. This is a mistaken view. The
progressive trend in imaging is to link
symptoms to dysfunctional neurocognitive
systems and to link physiological abnorm-
alities in patients to normative principles
of large-scale neurophysiological organi-
sation, such as cognitive load–response
curves and finite activation capacity
(Braver et al., 1997; Fletcher et al., 1998;
Callcott et al., 2000). This goes well
beyond neophenomenology.

However, it is fair to say that imaging
has had little bearing thus far on questions
of aetiology and pathogenesis. The most
obvious reason for this is, again, experi-
mental design. Simple case–control com-
parisons will have little to say about
aetiology regardless of whether the compar-
sions are made in terms of psychological
test scores, plasma hormone levels or
MRI. By the same token there are clearly
designs in which imaging could be used
more incisively to address causation. One
particularly promising strategy is the con-
junction of imaging with genetics. This
can be done in the context of a classical
twin study design, in which nothing
is known about the genetic constitution of
the participants apart from their zygosity,
and the key outcome is some estimate of
the heritability of brain structure or func-
tion (Wright et al., 2003). This approach
can tell us which aspects of the brain are
most strongly influenced by genetic effects
and, generalised to include a longitudinal
dimension, it might also be used to map
age-related changes in the genetic control
of brain organisation. However, to under-
stand more specifically which genes are
critical for which aspects of normal neuro-
phenotypic variability it will be necessary
to investigate associations between single
gene polymorphisms in the general popu-
lation and imaging measures of brain
structure and function. There are only a
few examples of this exciting approach
in the literature (Egan et al., 2001;
Martinez et al., 2001) – but doubtless there
will be more. A complementary approach
is the investigation of rare and relatively
neglected disorders, such as fragile-X syndrome, velo-cardio-facial syndrome, or tuberous sclerosis, which share clearly defined genetic lesions and a risk of psycho-pathology (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 un-informative about causation; it can mediate explanatory links between genetic or other risks and cognitive or behavioural out-comes. However, to do this it must – like any other empirical technique – be incor-porated 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 examina-tion 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 infor-mation can be valuable enough in some circumstances, but in general the most useful information we might expect is pre-dictive 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 neuroscien-tific 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 fron-tostriatal response to methylenidate in children with ADHD (Vaidya et al, 1998). This early evidence suggests that neuro-imaging may provide a predictively valu-able index of individual characteristics that are inaccessible to purely psychological enquiry. Of course, these individual brain characteristics are likely to be subtle, per-haps only identifiable as quantitative depar-tures from appropriate comparison group norms. Therefore, major advances in the impact of imaging on management of indi-vidual 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 ma-turity, infrastructural investment and inter-national cooperation that does not yet exist; but these are details, surely – there remain grounds for optimism.

**DECLARATION OF INTEREST**

This work was supported by the Well-come Trust. E.B. is a shareholder and member of the Scientific Advisory Com-mity of the Brain Resource Company (http://www.brainresource.com).

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Access the most recent version at DOI: 10.1192/bjp.182.5.381

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