Images of psychopathology

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Brain imaging continues to provide important data about brain structure, neurotransmitter function and the physiological basis of cognitive processes, as these relate to schizophrenia and mood disorders. A unifying theoretical perspective, however, that can clarify the precise nature of the biological basis of these diverse psychiatric conditions is lacking. It is becoming increasingly evident that a lesion model is inappropriate and that a more relevant characterisation will be found in terms of disorders of functional interconnections between brain regions.

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Abbreviations

fMRI	functional MRI
MRI	magnetic resonance imaging
NAA	*N*-acetyl aspartate

Introduction

The technical possibilities provided by new brain imaging techniques are formidable. With regards to psychiatric research, technical advances continue to outstrip experimental paradigms and the range of theories tested. Indeed, most recent studies demonstrate little in the way of a coherent theoretical underpinning and, as a consequence, fail to provide a convincing biological account of psychotic illness. Within these limitations, many interesting data are beginning to emerge from psychiatric studies encompassing brain structure, neurochemical and functional abnormalities. What is missing is a conceptual paradigm shift that can bring these disparate results into focus. In this review, we shall discuss recent studies of brain structure and function in schizophrenia and in mood disorders.

Schizophrenia

Structural brain abnormalities

The search for structural brain abnormalities in schizophrenia continues to be dominated by a 'regions of interest' approach, which implicitly assumes a segregated regional deficit. Using proton magnetic resonance spectroscopy, Yurgelun-Todd *et al.* [1] have reported a reduction in the ratio of *N*-acetyl aspartate (NAA) to creatinine in the temporal lobes of patients with schizophrenia. This observation might suggest neuronal loss or reduced neuronal integrity, but interpretation is limited by the lack of a clear biological interpretation of NAA/creatinine ratios. In keeping with this cautionary note, recent observations by Shioiri *et al.* [2] indicate that NAA levels in the basal ganglia are significantly correlated with neuroleptic dosage. Sullivan *et al.* [3] report that schizophrenic patients have significantly smaller cortical grey matter volumes, a factor that would need to be controlled for in spectroscopic studies, as this method requires large regions of interest. In this study, no changes were found in specific cortical regions.

Although the observation of enlarged ventricles in schizophrenia remains a robust finding, it remains unclear whether this difference is present from birth or represents a progressive abnormality expressed with evolution of the disease. DeLisi *et al.* [4], using magnetic resonance imaging (MRI), have presented evidence for increases in lateral ventricle volume over time, but evidence for this progressive change depends on the precise method of measurement.

A promising new approach for measuring structural brain abnormalities is voxel-based morphometry. However, there have been no recent attempts to exploit voxel-based analytic techniques. This approach permits a data-lead analysis of the brain as a whole by first 'normalising' the brain into a standard space and then identifying differences between groups anywhere within the brain volume rather than in restricted regions of interest [5]. The approach may well provide a clearer picture of brain abnormalities in schizophrenia.

No understanding of structural brain deficits is possible without a definition of the underlying neuropathology. Unfortunately, there have been few recent histopathological studies of note. One exception is the study of Honer *et al.* [6•], who have reported a detailed postmortem study that provides evidence of abnormal synaptic function in the cingulate cortex of schizophrenic patients. Benes *et al.* [7•] have also observed abnormalities in cingulate cortex consistent with a subtle miswiring of inputs to layer II of this region in schizophrenia. There is now converging evidence that anterior cingulate cortex probably has a role in higher cognitive functions relevant to psychosis (see below).

The combined impact of these studies is to support the finding of structural brain abnormalities in schizophrenic patients. The medial temporal lobes and cingulate cortex continue to receive particular attention, but the precise nature of the underlying brain abnormality remains elusive [8]. For example, we have no idea what diffuse brain volumetric loss means at the neuropathological level.

Neurochemical studies

The dopamine system remains the key focus for neurochemical studies of schizophrenia. Using a receptor/ligand approach in conjunction with functional neuroimaging, Okubo *et al.* [9••] found an increased expression of the dopamine D1 receptor subtype in the prefrontal cortex of unmedicated acute schizophrenic patients. While the technique used did not allow precise localisation to a particular region of prefrontal cortex, the findings are remarkably consistent with studies based on other approaches. For example, the functional consequences of alteration in central dopaminergic function has previously been addressed in a functional activation study using apomorphine challenge [10]. In this study, an abnormal modulatory response to dopamine perturbation was seen in prefrontal cortex specifically localised to anterior cingulate cortex. In keeping with these data, Breier *et al.* [11], using an imaging technique that combined pharmacological challenge and ligand binding, have provided direct evidence of abnormal dopamine sensitivity to amphetamine challenge in schizophrenia.

Activation studies

Interpretation of activation studies in schizophrenia is problematic because of differences in task performance between patients and controls. This problem has been discussed in detail by Weinberger and Berman [12•]. Yurgelun-Todd *et al.* [13] examined word fluency using functional MRI (fMRI) and confirmed previous studies showing reduced left frontal activation and increased temporal activation in schizophrenic patients. Crawford *et al.* [14] specifically compared patients who were good at an anti-saccade task to those who performed poorly. Patients who performed poorly showed less activity in the anterior cingulate, but no differences in dorsolateral prefrontal cortex. Taylor [15] has written a review of activation studies and concludes that the results may reflect dysfunction of distributed and interactive networks rather than localised functional lesions. In particular, interactions between frontal and temporal regions have been implicated in a number of studies of schizophrenia [13,16•,17••]. These regions have been consistently implicated in imaging studies of word finding in normal volunteers and may be involved in the semantic priming processes that have been found to be abnormal in schizophrenia and that have recently been linked to the dopamine system [18•].

Another confounding factor in activation studies is the possibility that different patterns of activity may be associated with different symptomatic syndromes of schizophrenia. Imaging studies of normal volunteers have repeatedly shown how sensitive the technique is to differences of mental state. It is therefore inevitable that there will be considerable differences in brain activity within a cross-section of patients showing a wide range of symptoms. Liddle [19] has reviewed evidence for the importance of studying syndromes within the diagnosis of schizophrenia. For example, in the report of reduced prefrontal dopamine receptor binding [9••], it was noted that reduced binding was associated with the presence of negative features such as emotional withdrawal. The syndrome approach can also be extended to studying brain activity in relation to specific symptoms. Frith [16•] proposes that brain imaging studies must be interpreted in terms of the underlying cognitive processes, and combines physiological and psychological level descriptions that provides a framework for understanding hallucinations and delusions. David *et al.* [20•] have demonstrated, using fMRI that during auditory hallucinations, there is inhibition of the response of auditory cortex to external auditory stimuli. In a particularly elegant study, Spence *et al.* [21••] have shown that delusions of control are associated with excessive activity in parietal cortex during the performance of a random movement selection task. This observation may relate to the excess activity seen in temporal cortex when schizophrenic patients perform word-generation tasks [17••]. Both sets of results may reflect abnormal connectivity between distant brain regions and a lack of modulatory control by components of prefrontal cortex.

Mood disorders

Neural function in depressed patients

A central role for the cingulate cortex in mediating emotional experience was first postulated on anatomical grounds by Papez [22]. In depressed patients, a rostral cingulate region, highlighted in early studies [23], fails to activate normally when subjects perform a complex planning task [24]. Functional activity in a similar region has now been shown to be predictive of drug responsiveness, with hypometabolism predicting nonresponsiveness and hypermetabolism predicting responsiveness [25•]. Using both functional and structural neuroimaging, Drevets *et al.* [26••] have highlighted a localised functional and morphometric abnormality in a ventral component of the anterior cingulate cortex of patients with bipolar affective disorder (i.e. patients with episodes of mania and depression) and unipolar patients with a family history of depression but not mania (so-called familial pure depressive disorder or FPDD).

Activation studies

An important issue raised by these studies is the role of these different components of the cingulate cortex in normal cognition. Recent neuropsychological and functional neuroimaging studies provide some clues. Neuropsychological studies by Damasio and colleagues [27] have shown that a ventromedial prefrontal region, which overlaps with the subgenual cingulate, is important in evaluating future outcomes of on-going behaviour. Elliott *et al.* [28•], in a recent functional neuroimaging experiment, have shown that a similar region is activated when normal subjects monitor feedback in a guessing task. More recently, the same group has shown that depressed patients, performing an identical task, fail to activate this region when processing feedback [29]. These

data, therefore, suggest that ventral cingulate may play a role in evaluation of feedback, in terms of rewards and punishment, of current and future behaviour. This formulation is consistent with a more general role for the anterior cingulate cortex in the control of action through attention and response selection. The combined impact of these studies suggest that this region is an important target for histopathological and neurochemical assessment.

Measuring cortical interactions and its relevance to psychiatry

Psychiatric research, for the greater part, in its attempt to find a functional or structural deficit, implicitly subscribes to a concept of strict localisation or functional segregation. A contrasting perspective on brain function is based on the premise that higher cognitive function is a property of interactions between functionally specialised, and anatomically separate, brain regions [30]. Questions related to integration of function are of considerable theoretical importance in psychoses in which abnormal integration has long been proposed as a fundamental deficit [31,32]. A number of generic approaches, involving measures of functional and effective connectivity, now provide a framework within which questions of functional integration can be addressed using functional neuroimaging data [33–35]. An abnormal pattern of fronto-temporal connectivity, reflecting aberrant functional connectivity, has recently been reported in acute nonmedicated schizophrenic patients [17••]. So far, no studies have used fMRI to assess connectivity in schizophrenia. Morrison-Stewart *et al.* [36•] have confirmed previous electroencephalography (EEG) studies showing reduced coherence (presumably reflecting reduced connectivity) in the pattern of brain activity while patients performed frontal tasks.

Conclusions

The focus in this review has been on the major psychiatric syndromes of mood disorder and schizophrenia. In both disorders, functional neuroimaging is beginning to provide critical data. A limitation of much work in the field is its atheoretical nature. This renders it difficult to assess whether findings are spurious or provide a meaningful analysis of reported deficits. An increasing realisation is a necessity to approach the study of psychopathology from the perspective of cognitive neuroscience, which can provide an analysis of deficits that can bridge symptoms, cognitive processes and neurophysiological mechanisms. In relation to neurophysiological mechanisms, an important emerging perspective in neuroimaging involves measuring brain function in terms of both interactions and integration between widespread brain regions. This perspective may provide the necessary paradigmatic framework for understanding the mysterious nature of psychopathology.

Acknowledgements

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