Functional neuroimaging in mental disorders

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Recent advances in functional neuroimaging allow us to map neural activity in the living human brain with precise spatial and temporal resolution and provide an unprecedented opportunity to examine the neurocognitive components of mental disorders. In this article we aim to summarize the main functional neuroimaging findings in the major psychiatric disorders and the different methodological approaches that have been used to study them. We will discuss studies of the resting state and of activation during the performance of cognitive tasks, and studies focused on specific psychiatric symptoms. We will also review work on functional connectivity, discuss future directions in the field and consider how functional neuroimaging may contribute to clinical practice.

Key words: Functional neuroimaging, functional magnetic resonance imaging (fMRI), positron emission tomography (PET), mental disorders

Functional neuroimaging techniques – such as single photon emission computed tomography (SPECT), positron emission tomography (PET), functional magnetic resonance imaging (fMRI) – allow mapping of the physiology of the brain by measurement of blood flow, metabolism, and receptor-ligand binding. Research applying these techniques to mental illness has grown rapidly over the last two decades and has improved our understanding of the mechanisms underlying psychiatric disorders. In this article, we review functional neuroimaging studies of blood flow and glucose metabolism in mental illness. Neurochemical imaging and spectroscopy studies are not included.

RESTING STATE STUDIES

Early functional neuroimaging studies investigated brain activity in patients who were in the 'resting state'. The most robust finding in studies of resting cerebral blood flow (CBF) or metabolism in schizophrenia was decreased activity in frontal cortex (termed 'hypofrontality') relative to controls. However, some studies did not find differences between patients and controls in resting frontal activity, and others reported 'hyperfrontality' (1,2). Analogous findings have been described in depressive disorder, with several studies reporting decreased frontal activity, particularly in the dorsolateral prefrontal and anterior cingulate cortex, although again these results have not been consistent. Discrepant findings across resting state studies may be attributable to clinical heterogeneity: patients may differ in symptom profile, symptom severity, the duration of illness, and medication status. Another potential factor is that 'rest' may comprise a diversity of emotional and cognitive states in different subjects and across different studies.

One way of addressing the issue of the heterogeneous character of the resting state is to examine the correlation between regional CBF (rCBF) and symptom dimensions. Liddle et al (3) reported that each of three symptom dimensions in schizophrenia (negative symptoms; formal thought disorder; delusions and hallucinations) was associated with a specific pattern of rCBF. Bench et al (4) employed the same approach with three symptom factors in depressive disorder (anxiety; psychomotor retardation; cognitive performance) and found that each was associated with a particular pattern of resting blood flow. While this approach has proved useful, activity measured during scanning is related to clinical ratings made outside the scanner. There is no means of controlling or measuring cognitive or emotional processes during the scan itself.

COGNITIVE ACTIVATION STUDIES

If subjects carry out a cognitive task during scanning, the cognitive and emotional processes that are active during the scan in different subjects are more likely to be similar than if subjects are scanned at 'rest'. Moreover, by selecting tasks which engage specific cognitive or emotional processes, the investigator can focus on functions that are thought to be particularly relevant to a given disorder. Thus, tasks involving 'executive' functions have been extensively examined in schizophrenia. As in resting state studies, many of these investigations have detected abnormal prefrontal responses in patients relative to controls. While 'hypofrontal' activation has often been reported, recent work has indicated that the nature of the activation can depend on which cognitive task is used, the level of task difficulty, and whether patients perform it as well as controls (5). Thus, using fMRI, Curtis et al (6,7) found that while patients with schizophrenia showed less prefrontal activation than controls during verbal fluency, activation in the same groups did not differ when they performed a semantic decision task. Using a graded memory task, Fletcher et al (5) demonstrated that patients with schizophrenia showed normal prefrontal activation until the demands on working memory were high and their performance deteriorated. There is also evidence that prefrontal activation can vary with the mental state of the

patient at the time of scanning: Fu et al (8) found that the degree to which prefrontal activation was reduced in patients with schizophrenia was related to the severity of positive symptoms of psychosis. Some authors have thus concluded that the term 'hypofrontality' is of limited utility (9).

Measuring brain activity while subjects perform cognitive tasks has also been used to investigate the biological bases of specific symptoms (as opposed to a disorder). For example, Kircher et al (10) employed a sentence completion task in conjunction with fMRI to examine semantic processing in patients with schizophrenia who exhibited formal thought disorder. They found that the activation in right temporal cortex, that was normally evident in controls and in non thought-disordered patients, was significantly attenuated in patients with thought disorder. Using joystick movement tasks during PET scanning, Spence et al (11) examined motor processing in schizophrenic patients with passivity phenomena. The latter engaged the right inferior parietal cortex more than patients with no passivity phenomena, and failed to show this when they were scanned again after remission. The same approach has been used to examine patients who have a trait vulnerability for a specific symptom but are not expressing this at the time of scanning. Using PET, McGuire et al (12) studied schizophrenic patients with and without history of auditory hallucinations while they were performing a task that engaged the monitoring of inner speech. Although the patients were asymptomatic at the time of study, those with a strong history of auditory hallucinations showed reduced activation in areas implicated in inner speech monitoring compared with patients with no history of hallucinations and controls. These findings have since been replicated and extended using fMRI (13).

STUDIES MEASURING SYMPTOMS ON-LINE

A relatively direct way of exploring the relationship between psychopathology and brain activity is to scan patients while they are actually experiencing a given symptom. In schizophrenia, this approach has been used in several studies of auditory hallucinations. Studies using SPECT (14), PET (15,16) and fMRI (17,18) have tried to capture the pattern of brain activity while patients were perceiving auditory hallucinations. While initial studies highlighted the involvement of different areas, such as the left inferior frontal cortex (14), the anterior cingulate gyrus (15), the lateral temporal cortex (17), and subcortical nuclei (16), recent work suggests that auditory hallucinations are mediated by a distributed network of areas that includes all of these regions (18). Because fMRI permits the acquisition of large numbers of images in a single patient, it is possible to study two different symptoms occurring at different times in the same individual. Thus Shergill et al (19) studied a patient with schizophrenia who was experiencing both auditory and tactile hallucinations and showed that the former were associated with activity in the lateral temporal cortex whereas the latter were correlated with activation in the somatosensory and posterior parietal cortex (Figure 1).

While the above studies examined patients with 'spontaneous' hallucinations, symptoms can also be studied following their experimental provocation. This approach has been often applied in studies of anxiety disorders. Thus, obsessive-compulsive symptoms have been provoked in the scanner by presenting patients with obsessive-compulsive disorder (OCD) with potential contaminants (that elicit handwashing), and have been associated with activation in orbitofrontal and cingulate cortex, and in the striatum (20-22). Words, pictures, and sounds redolent of traumatic events have been employed to provoke symptoms in patients with post-traumatic stress disorder (PTSD) (23-25), which have been associated with decreased medial prefrontal and inferior frontal activation. Rauch et al (26) analyzed pooled PET data from symptom provocation paradigms in OCD, simple phobia and PTSD, and suggested that activation in inferior frontal and orbitofrontal cortices, insula, basal ganglia and brain stem were common across different anxiety disorders.

Symptom provocation has also been used in depression. Liotti et al (27) studied transient sadness, provoked by autobiographical memory script, in remitted depressive patients and actively depressed patients, using PET. They found that mood challenge in the remitted patients produced rCBF decrease in medial orbitofrontal cortex, which was also evident in active depressive patients but not in the healthy controls, consistent with a trait marker of depression. In schizophrenia, formal thought disorder

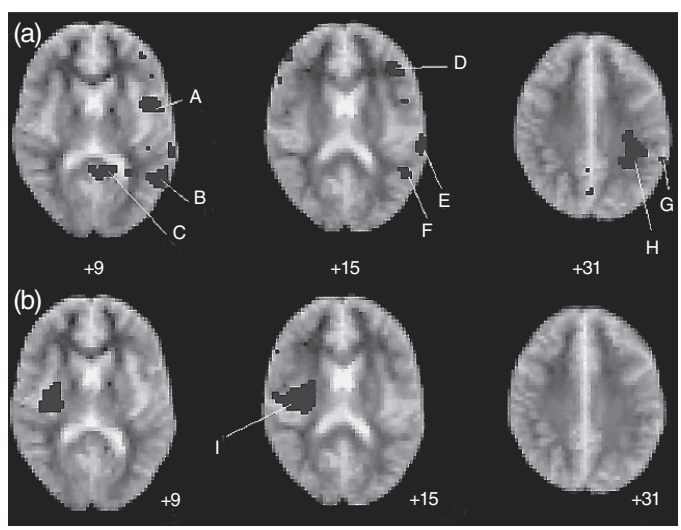

Figure 1 - Brain areas active during different types of hallucination in a patient with schizophrenia. Black voxels in row (a) indicate foci of activation associated with somatic hallucinations (A to H). Those in row (b) correspond to auditory hallucinations (I). The left side of the brain is shown on the right side of each image. The axial level (z coordinate in Talairach and Tournoux space) is shown below each slice. Adapted from Shergill et al (19).

has been induced by asking patients to interpret ambiguous pictures. Both McGuire et al (28), using PET, and Kircher et al (29), using fMRI, found that the severity of formal thought disorder was inversely correlated with activity in the left superior temporal cortex (Figure 2).

TREATMENT STUDIES

Functional imaging provides an opportunity to assess the effects of clinical treatments on brain function. Patients can be scanned before and after treatment, and changes in brain activity pattern may be related to improvements in symptoms and/or cognitive function within the same subjects.

Using a variety of interventions – including antidepressant drugs, electroconvulsive therapy, transcranial magnetic stimulation, sleep deprivation, and psychotherapy – functional imaging studies have examined activity before and after the treatment of major depressive disorder (MDD). The most robust finding is a normalization of resting frontal hypometabolism after treatment, while findings in other regions are inconsistent. However, recent studies suggest that various factors – including medication type (30), duration of treatment (31), symptom profile (32), treatment modality (medication vs. psychological treatment) (33,34), and the placebo effect (35) – can affect the pattern of brain activity change in MDD.

Changes in resting activity have also been reported after treatment with selective serotonin reuptake inhibitors (SSRIs) and cognitive behavioral therapy (CBT) in OCD. Successful treatment of OCD with SSRIs was associated with a decrease in caudate metabolism (36,37), as was successful CBT (36,38). Recently, Saxena et al (39) reported that the regional metabolic response to treatment with SSRIs was different in OCD to that in MDD. In OCD, symptomatic improvement was associated with decreased metabolism in right caudate, right putamen, right ventrolateral prefrontal cortex, bilateral orbitofrontal cortex, and thalamus, but these changes were not evident in MDD. It should be noted, however, that treatment study findings in OCD have not been entirely consistent (40).

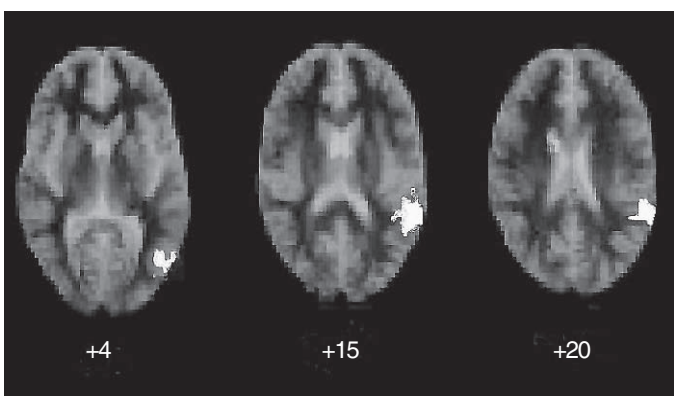

Figure 2 - Neural correlates of formal thought disorder in schizophrenia. When patients were talking there was an inverse correlation between the severity of thought disorder and activity in the left superior temporal gyrus (white voxels). The left side of the brain is shown on the right side of each image. The axial level (z coordinate in Talairach and Tournoux space) is shown below each slice. Adapted from Kircher et al (10).

In schizophrenia, the effects of treatment with typical and atypical antipsychotics on neural activity have been compared. A PET study found that haloperidol treatment was associated with decreased resting CBF in frontal regions but increased CBF in the basal ganglia compared to risperidone, whereas risperidone treatment was associated with decreased rCBF in cerebellar regions compared to haloperidol (41). Using fMRI, Honey et al (42) found that after substitution of risperidone for typical antipsychotics, schizophrenic patients showed increased activation during a working memory task in the right prefrontal cortex, supplementary motor area, and posterior parietal cortex. The effects of psychological interventions in schizophrenia, such as CBT, remain largely uninvestigated.

FUNCTIONAL CONNECTIVITY

Theoretical models suggest that psychiatric disorders involve a disruption of the normal integration of different cognitive processes and activity in different brain regions. Functional connectivity refers to the temporal relationship between activity (as measured using functional imaging) in topographically distinct areas. Using PET data, Friston and Frith (43) found that healthy subjects, when performing a verbal fluency task, showed an inverse correlation between activity in prefrontal and superior temporal cortex. This correlation was absent in patients with schizophrenia. A similar difference in fronto-temporal correlations during verbal fluency task was described by Fletcher et al (44). Using the same task, Spence et al (45) found disturbed correlation between activity in left prefrontal and cingulate cortex in patients with schizophrenia, while Shergill et al (46) reported differences in the correlation between frontal and temporal activity in an fMRI study of covert verbal generation. These studies indicate that the correlation between activity in different regions in schizophrenia is perturbed, but cannot show whether there is a causal relationship between them. Path analysis can provide further information about the direction of the putative interactions between regions. Jennings et al (47) used this approach to examine PET data from a semantic processing task and found that schizophrenic patients showed a negative connection from left inferior frontal to left temporal cortex, which was positive in the controls, and a positive connection from the right frontal pole to the anterior cingulated cortex, which was negative in the controls (Figure 3). While these studies have yielded promising results, some studies have failed to detect differences in functional connectivity between patients and controls (48), and because this approach is relatively new, further research is required to develop the methodology.

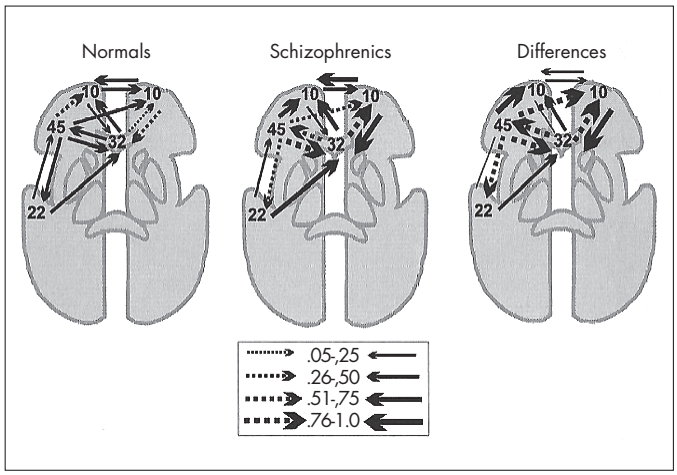

Figure 3 - Functional networks as defined by path analysis of functional imaging data from patients with schizophrenia and controls. The width of the arrow indicates the strength of the connection between each pair of areas. Positive path coefficients are represented as solid black arrows, and negative as dashed arrows. This particular analysis suggests that there are differences in functional connectivity between patients and controls. Adapted from Jennings et al (47).

Most of these studies have been carried out in schizophrenia, but there has been analogous work on other disorders. For example, Shaw et al (49) recently applied another analytic method (canonical variates analysis) to PET data from a working memory task in PTSD patients.

FUTURE DIRECTIONS

Integration of functional imaging and other data

To date, most neuroimaging studies in psychiatric disorders have involved a single type of scan: thus functional and structural imaging studies have usually been carried out separately. More recently, particularly with the increasing availability of MRI (which permits the acquisition of functional, volumetric and spectroscopic data with the same camera), investigators have been collecting different types of imaging data from the same subjects. Partly because the methodological problems in integrating data from distinct imaging modalities are not trivial, few such studies have been completed, but these are likely to emerge in the near future. Integrating the findings from functional imaging in psychiatric disorders with those from structural imaging would significantly advance our understanding of their pathophysiology. For example, some functional imaging studies suggest that there is a disruption of functional connectivity in schizophrenia. However it is unclear whether this reflects an underlying abnormality of the anatomical connections between cortical areas. This issue can be addressed using diffusion tensor imaging (DTI), an MRI technique which permits assessment of the integrity of white matter tracts. Initial applications of DTI in schizophrenia indicate that there may be abnormalities in cortico-cortical connections (50), and it would be particularly interesting to examine how such changes are related to disturbances in functional connectivity in the same patients.

It may also be useful to integrate functional imaging data with information from non-imaging techniques. Transcranial magnetic stimulation (TMS) is a newly developed technology that can be used to noninvasively stimulate or inhibit selected regions of cerebral cortex. Combining TMS with functional neuroimaging makes it possible to examine the effects of modulating activity in a given region on the activity in other areas, particularly those it is connected to (51). One limitation of fMRI/PET techniques is their relatively low temporal resolution. Electroencephalography (EEG)/magneto-encephalography (MEG) signals have a higher temporal resolution but poorer spatial resolution. Integration of information from fMRI/PET and EEG/MEG has the potential to combine their respective advantages and provide data with high spatial and temporal resolution. Although collecting both types of data in the scanner is technically difficult, such studies are beginning to be done. For example, Mathiak et al recently carried out simultaneous recording of fMRI and MEG data while subjects were performing a mismatch paradigm (52). Applying such combined paradigms in patients (as opposed to volunteers) will present an additional challenge.

Clinical applications

While there has been a great deal of research using functional imaging in mental disorders, to date there has been relatively little use of functional imaging for purely clinical purposes. At present, diagnosis and assessment of prognosis and effectiveness of treatments are largely dependent on the clinical history and current psychopathology. Neuroimaging has yet to play a significant role in these areas, but there are signs that this is a possibility. For example, there is some evidence that the treatment of OCD and depression can normalize increased regional brain metabolism. Moreover, the severity of pretreatment abnormalities in these disorders can help to predict which patients will respond to treatment (30,53,54). In schizophrenia there is evidence that the severity of volumetric abnormalities (gray matter volume) in first episode patients are associated with a relatively poor prognosis (55). Other work with structural MRI suggests that subjects with prodromal signs of psychosis who later develop psychosis differ from subjects who do not, in having reduced gray matter volume in the prefrontal, cingulate, and medial temporal cortex (56). Since perturbations of regional brain function may be evident before macroscopic loss of gray matter, functional imaging may be a more powerful means of detecting differences of these types than structural imaging. However, to date there have been few studies of this type and further work is needed to explore this.

A key issue with all of the above is that the functional

imaging differences are quantitative rather than qualitative, and evident at the group level rather than the individual level. A key challenge for future work is to develop means of using data form a single patient to inform clinical assessment and management.

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