Schizophrenia and Brain Imaging

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INTRODUCTION: SCHIZOPHRENIA HAS A BIOLOGICAL AETIOLOGY

It is widely accepted that schizophrenia has a biological aetiology. However, the shift towards this agreement is recent, and the aetiology of schizophrenia has been the subject of lengthy and intense debate. The debate has been split between those who propose a biological aetiology and those who postulate a psychodynamic origin to schizophrenia. In the latter camp, non-biological factors such as family interaction and stressful life events (Kuipers and Bebbington, 1988) have been proposed to play a causal role in the acquisition of schizophrenia. However, the theories have received little empirical support. In addition, in the past 50 years two main lines of evidence supporting a biological role in its aetiology have become apparent. First, there was the discovery of antipsychotic drugs in the 1950s (Delay et al., 1952) and, second, the demonstration of a significant hereditary contribution to the disorder (Gottesman and Shields, 1982). These observations strongly suggest that schizophrenia has a biological basis.

However, current methodologies present challenges for research on the genetic and dopamine theories of schizophrenia. As a consequence, research has become increasingly focused on attempts to elucidate some structural or functional brain abnormality since it is widely held that schizophrenia is a disease of the brain (e.g. Ron and Harvey, 1990). The theory that some gross brain lesion characterizes schizophrenia seems unlikely. Instead, it is generally accepted that schizophrenia is characterized not by structural damage, but by functional abnormalities. This is supported by the relapsing and remitting course of the illness, fluctuations in symptoms and response to pharmacological interventions. Therefore the advent of functional neuroimaging has been important in the study of mental illness because it enables brain function and its abnormalities to be investigated. As stated by Weinberger et al. (1996): 'Functional neuroimaging in psychiatry has had its broadest application and greatest impact in the study of schizophrenia.'

A major problem is that images of brain function reflect the current mental state of the patient (i.e. symptoms) and these are very variable. Symptoms include disorders of inferential thinking (delusions), perception (hallucinations), goal-directed behaviour (avolition) and emotional expression. Current thinking generally distinguishes symptoms that comprise the presence of something that should be absent (positive symptoms) and the absence of something that should be present (negative symptoms; Crow, 1980). Factor-analytic studies of symptoms suggest that positive symptoms should be subdivided further into a psychotic group (comprising delusions and hallucinations) and a disorganized group (comprising disorganized speech, formal thought disorder, disorganized behaviour and inappropriate affect; Liddle, 1987). The diversity of symptoms in schizophrenia makes it unlikely that the pathophysiology can be accounted for by a single localized brain dysfunction. Instead, the strategy of attempting to localize specific symptoms to specific brain regions or connections between regions is encouraging, and this chapter will evaluate the results of such studies.

STRUCTURAL STUDIES

Computed Tomography (CT) Studies

The main finding from CT scan studies is that the lateral ventricles are enlarged in schizophrenic patients compared with normal controls. In the first study using this technique, Johnstone et al. (1976) found that 17 chronically hospitalized schizophrenic patients had significantly enlarged ventricles compared to normal controls. In a review of the CT literature Andreasen et al. (1990) noted that 36 out of 49 subsequent studies have replicated this finding to some extent. There have also been two meta-analyses of the CT scan data (Raz and Raz, 1990; Van Horn and McManus, 1992), which supported the finding of enlarged ventricles in schizophrenic patients. However, the extent of ventricular enlargement in schizophrenia is often small (e.g. Weinberger et al., 1979) or even non-existent in some studies (Smith and Iacano, 1986). Positive findings might be due to the control group having smaller ventricles rather than the schizophrenic patients having larger ventricles. In support of this suggestion, Van Horn and McManus (1992) found in their meta-analysis that choice of control group was a contributing factor to the variability of control ventricle:brain ratio (VBR).

Correlation between CT findings and symptoms has been investigated. Lewis (1990) reviewed 41 CT scan studies that addressed the issue of heterogeneity of schizophrenic symptoms. Only one of 18 studies found any association between increased ventricular area and chronicity of illness. Five out of 18 found evidence of a relationship with negative symptoms. Poor treatment response was found to be associated with increased ventricular area in about half the studies. Chua and McKenna (1995) reviewed the CT literature and concluded that although the finding of increased ventricular area in schizophrenic patients is widespread and replicated, the difference between schizophrenic patients and normal controls is clearly small and depends significantly on the control group chosen.

Magnetic Resonance Imaging (MRI) Studies

MRI improves on CT owing to its better spatial resolution and ability to differentiate white and grey matter. There have been several replicated findings using structural MRI scans to investigate the structure of schizophrenics' brains. A number of studies have shown evidence for reductions in overall brain size, but most of these have used poor control groups and/or small numbers of schizophrenic patients (e.g. Andreasen et al., 1986; Harvey et al., 1993). In addition this finding has not been replicated by other
Temporal lobe reductions in schizophrenia have been reported, and are especially prominent in the hippocampus (Fukuzako et al., 1997; Sigmundsson et al., 2001), parahippocampal gyrus and the amygdala (Yurgelun-Todd et al., 1996a). Suddath et al. (1990), using the identical twins of schizophrenic patients as controls, found evidence for reductions of the left temporal lobe, including the hippocampus. Kwon et al. (1999) recently replicated the finding of a reduction in volume of the left temporal lobe. Cannon et al. (1998) suggested that frontal and temporal structural changes might reflect genetic (or shared environmental) effects. In a study using a large group of patients and well-matched controls (the patients' non-psychotic siblings and a group of normal controls), they found that volume reductions of the frontal and temporal lobes were present in patients with schizophrenia and in some of their siblings without schizophrenia. However, temporal lobe reductions are equivocal, with some negative findings in the literature (e.g. Young et al., 1991). There have been many conflicting and negative results in studies attempting to locate clinical correlates with temporal abnormalities. Many studies have found no association between chronicity and temporal lobe size (e.g. Kelsoe et al., 1988; Young et al., 1991), although one study found an inverse relationship between these two factors (DeLisi et al., 1991). Size of the superior temporal gyrus has been associated with hallucinations (Barta et al., 1990) and formal thought disorder (Shenton et al., 1992).

Bilateral reduction in volume of the hippocampal formation has been associated with the severity of disorganization syndrome (Fukuzako et al., 1997).

Some studies have found frontal lobe reductions in schizophrenic patients (Harvey et al., 1993; Cannon et al., 1998; Sigmundsson et al., 2001). However, the results are inconsistent, especially in relation to the precise localization of the frontal abnormalities (Raine et al., 1992). Buchanan et al. (1998) improved on this by subdividing the prefrontal cortex (PFC) into superior, middle, inferior and orbital regions and found that patients with schizophrenia exhibited selective grey matter volume reductions in the inferior PFC bilaterally. There was no difference between the schizophrenic and control groups in any other region of the frontal lobes.

There are some MRI data that provide support for the hypothesis of disconnection between brain areas in schizophrenia. Breier et al. (1992) found that schizophrenic patients, compared with matched healthy controls, had reductions in the right and left amygdala, the left hippocampus and prefrontal white matter. Moreover, the right prefrontal white matter volume in schizophrenic patients was significantly related to right amygdala/hippocampal volume, suggesting there might be abnormal connections between these areas. Buchsbaum et al. (1997) found evidence for a decreased left hemispheric volume in frontal and temporal regions in schizophrenic patients. This result was supported by Woodruff et al. (1997a), who found that interregional correlations were significantly reduced in schizophrenics between prefrontal and superior temporal gyrus volumes. The authors propose that these results support the existence of a relative ‘fronto-temporal dissociation’ in schizophrenia.

Reversal or reduction of normal structural cerebral asymmetries may be related to the pathogenesis of schizophrenia (Crow, 1995). Lack of normal asymmetry has been especially associated with early onset of schizophrenia (Fukuzako et al., 1997; DeLisi et al., 1997). Maher et al. (1998) found that low levels of hemispheric asymmetry in the frontal and temporal areas were associated with early onset of schizophrenia, the association with frontal volume being more marked than with temporal volume. These findings are consistent with the hypothesis that failure to develop asymmetry is an important component of the pathology underlying some forms of schizophrenia.
However, disagreement about the definition of hypofrontality has caused inconsistencies in the results. Studies vary on the frontal areas in which activity was measured. Some have included all anterior regions; others have looked at frontal or prefrontal subdivisions only. The earlier studies tended to use the frontal/occipital ratio as a measure of hypofrontality, whereas recently most studies have used absolute frontal flow values with or without correction for mean total brain blood flow rates. The majority of studies, using any of these definitions, have found little evidence for statistically significant hypofrontality, and in several studies hypofrontality was due to an elevated flow in posterior regions (Mathew et al., 1988; Siegel et al., 1993). In other studies, the differences between control and schizophrenic frontal cortex metabolism are small. It is claimed that hypofrontality is not due to the drug status of the patients at scanning (Waddington, 1990). However, recently antipsychotic medication has been found to affect brain metabolism (Miller et al., 1997). Several studies have looked at clinical correlates associated with hypofrontality, but the results are inconsistent. Among those showing a positive relationship with hypofrontality are chronicity (Mathew et al., 1988), negative symptoms (e.g. Emslie et al., 1993) and neuropsychological task impairment (e.g. Paulman et al., 1990).

Researchers have attempted to correlate regional cerebral blood flow (rCBF) levels with symptom severity scores for Liddle’s three clinical subdivisions in 30 schizophrenic patients (Liddle et al., 1992). They demonstrated that the psychomotor poverty syndrome, which has been shown to involve a diminished ability to generate words, was associated with decreased perfusion of the dorsolateral prefrontal cortex (DLPFC) at a locus that is activated in normal subjects during the internal generation of words. The disorganization syndrome, which has been shown to involve impaired suppression of inappropriate responses (e.g. in the Stroop test), was associated with increased perfusion of the right anterior cingulate gyrus at a location activated in normal subjects performing the Stroop test. The reality distortion syndrome, which might arise from disordered internal monitoring of activity, was associated with increased perfusion in the medial temporal lobe at a locus activated in normal subjects during the internal monitoring of eye movements. Therefore the abnormalities of brain metabolism underlying each of the three syndromes might be widely distributed over the brain.

Using data from the same patients, Friston et al. (1992) examined correlations between rCBF and a measure of psychopathology receiving equal contributions from each of Liddle’s three subsystems. The degree of psychopathology correlated highly with rCBF in the left medial temporal region, and mesencephalic, thalamic and left striatal structures. The highest correlation was in the left parahippocampal region, and the authors proposed that this might be a central deficit in schizophrenia. A canonical analysis of the same data highlighted the left parahippocampal region and left striatum (globus pallidus), in which rCBF increased with increasing severity of psychopathology. Friston and colleagues suggested that disinhibition of left medial temporal lobe activity mediated by fronto-temporal connections might explain these findings.

Neuroreceptor Imaging of Antipsychotics using PET

Dopamine Receptors

Many studies have shown evidence that the density of dopamine (DA; in particular D2) receptors is increased in schizophrenic brains (Wong et al., 1986; Breier et al., 1997). Early PET and single photon emission computed tomography (SPECT) receptor imaging studies focused on striatal D2 receptors. However, Okubo et al. (1997) used PET to examine the distribution of D1 and D2 receptors in the brains of drug-naive or drug-free schizophrenic patients. Although no differences were observed in the striatum relative to control subjects, binding of the radioligand to D1 receptors was reduced in the prefrontal cortex of schizophrenics. Other studies using PET have produced contradictory results or only very weak evidence of an abnormality in DA receptor number in schizophrenia (e.g. Crawley et al., 1986; Farde et al., 1987; Pilowsky et al., 1994).

In a meta-analysis of 15 brain-imaging studies comparing indices of dopamine function in drug-naïve or drug-free patients with schizophrenia, Laruelle (1998) found that, compared to healthy controls, patients with schizophrenia present a significant but mild elevation of D2 receptor density parameters. However, other meta-analyses have shown that a significant proportion (up to a third) of schizophrenic patients cannot be discriminated from normal healthy controls in terms of D2 dopamine density (Zakzanis and Hansen, 1998; Soares and Innis, 1999). The discrepant results might in part be due to the diversity of PET methodology used in these studies.

Receptor Imaging and Antipsychotic Drug Action

PET and SPECT receptor imaging can be used to explore receptor targets for antipsychotic drug action in living patients. It is widely accepted that the ‘typical’ antipsychotics (such as haloperidol and perphenazine) bind mainly to the D2 receptor (Kapur, 1998). There is also broad agreement that unwanted extrapyramidal (parkinsonian) side effects of antipsychotic drugs result from high striatal D2/D3 receptor blockade by these drugs. PET receptor-binding studies have found that 60–80% D2 occupancy provides optimal antipsychotic response with little extrapyramidal side effects (Kapur, 1998).

Recent attention has been focused on the involvement of serotonin (5-HT) in the pathophysiology of schizophrenia and its role in mediating antipsychotic drug effects, especially for ‘atypical’ antipsychotics, such as clozapine, olanzapine, risperidone and Quetiapine. At clinically relevant doses, atypical antipsychotics tend to have a higher affinity for 5-HT receptor subtypes than for D2 receptors and are associated with fewer extrapyramidal side effects (Lieberman et al., 1998; Silvestri et al., 2001). Atypical antipsychotics differ widely in their D2 occupancy. The D2 occupancy of risperidone had been found to be within the typical range (over 60%), while that of clozapine is significantly lower (under 60%). Some atypical antipsychotics such as Quetiapine have very low (Gefvert et al., 2001) and only transient D2 occupancy, which nevertheless seems to be sufficient for mediating an antipsychotic effect (Raedler et al., 1999; Kapur et al., 2000a).

The D2 occupancy seems to be the important mediator of response and side effects in antipsychotic treatment (Kapur et al., 2000b). Freedom from motor side effects results from low D2 occupancy, not from high 5-HT2 occupancy (Kapur and Seeman, 2001). If the D2 occupancy is too high (it exceeds 80%), antipsychotics lose some of their ‘atypical’ properties and produce a higher incidence of extrapyramidal side effects (Kapur et al., 1999; Kapur and Seeman, 2001) and negative subjective experiences such as depression (de Haan et al., 2000).

Cognitive Activation Studies

Functional neuroimaging is most frequently used to evaluate the regional cerebral responses to a particular cognitive or sensorimotor process. Typically, subjects are scanned while performing an activation task, which engages the cognitive/sensorimotor process of interest, and a baseline task, which engages all components of the activation task except the cognitive/sensorimotor process of interest. Regions that show significantly more activity in the experimental state than in the baseline state are considered to be involved in the cognitive/sensorimotor process of interest. These task-specific
activity patterns can then be compared between patients and control subjects to determine how the condition affects brain function. Several types of task that have been used to evaluate brain function in schizophrenic patients are discussed in this chapter.

**Task-Based Studies of Executive Function**

In behavioural studies the most striking impairments are seen when schizophrenic patients perform the various complex executive tasks associated with the frontal lobes. Brain imaging makes it possible to identify the abnormal pattern of brain activity associated with this abnormal performance.

**Wisconsin Card Sorting Task (WCST)**

Schizophrenia is largely characterized by impairments in planning and execution and therefore tasks that involve this kind of planning and modification of behaviour have been exploited in the scanner. Several researchers have investigated brain activity in schizophrenic patients while they perform a version of the WCST. This task is known to activate the DLPFC in normal controls, and is particularly sensitive to damage to DLPFC (Berman et al., 1995; Nagahama et al., 1996). In the typical computerized version of the WCST subjects view a computer screen that displays a number of stimuli. These stimuli differ along three dimensions: colour, shape and number. On each of a series of trials the subjects have to match a target stimulus with one of the four standard stimuli. However, the match is not exact, but has to be made in terms of either colour, shape or form. Subjects are not informed of how to make the match, but are informed after each choice whether they are right or wrong. They have to determine from trial and error which dimension is correct. After subjects have made a series of correct responses, the rule is changed and subjects must determine the new rule for matching.

Weinberger et al. (1986) measured rCBF using Xe133 inhalation SPECT in 20 medication-free patients with chronic schizophrenia and 25 normal controls during the WCST and a number-matching control task. During the WCST but not during the control task normal subjects showed increased DLPFC rCBF, whereas patients did not (patient performance was worse than that of the controls). Furthermore, in patients, DLPFC rCBF correlated positively with WCST performance. The authors suggest that this result shows that the better DLPFC was able to function, the better patients could perform the task. However, this conclusion is based on an ill-founded assumption. It is impossible to determine whether task-related underactivation causes or reflects poor task performance. This is a crucial issue in cognitive activation studies, and will be discussed in more detail throughout the chapter.

Daniel et al. (1991) used SPECT to study the effect of amphetamine (a DA agonist) and a placebo on rCBF in 10 chronic schizophrenic patients while they performed a version of the WCST and a matched control task. On placebo no significant activation was seen during the WCST compared with the control task. In contrast, significant activation of the left DLPFC occurred on the amphetamine trials. Daniel and colleagues point out that patients' performance improved with amphetamine relative to placebo and that with amphetamine, but not with placebo, a significant correlation was found between activation of DLPFC and performance on the WCST task. Again this is a finding that is difficult to interpret: did amphetamine facilitate task performance, which then caused an increased rCBF in the PFC? Or did amphetamine cause PFC activity to increase, which facilitated performance?

Volz et al. (1997) used functional magnetic resonance imaging (fMRI) to investigate activity during the WCST in 13 chronic schizophrenics on stable neuroleptic medication. They also showed evidence for lack of activation in the right PFC and a trend towards increased left temporal activity during the WCST compared to normal controls. However, again the task performance was different between the two groups and therefore the results remain ambiguous. In addition, this study was limited because a one-slice imaging technique was used, so no information about the activation pattern in adjacent brain regions was obtained.

Better WCST performance correlated with rCBF increase in prefrontal regions for controls and in the parahippocampal gyrus for patients in two recent studies (Ragland et al., 1998; Riehemann et al., 2001). The results suggest that schizophrenia may involve a breakdown in the integration of a fronto-temporal network that is responsive to executive and declarative memory demands in healthy individuals.

**Tower of London Task**

The Tower of London task involves high-level strategic planning among a number of other processes (Shallice, 1982). In this task subjects have to rearrange a set of three balls presented on a computer screen, so that their positions match a goal arrangement also presented on the screen. The complexity of the task, in terms of the number of moves necessary to complete the task, can be varied.

Andreasen et al. (1992) used SPECT during the Tower of London task in three different groups: 13 neuroleptic-naive schizophrenic patients; 23 non-naive schizophrenic patients who had been chronically ill but were medication free for at least 3 weeks; and 15 healthy normal volunteers. The Tower of London task activated the left mesial frontal cortex (probably including parts of the cingulate gyrus) in normal controls, but not in either patient group. Both patient groups also lacked activation of the right parietal cortex, representing the circuitry specifically activated by the Tower of London in normal controls. Importantly, decreased activation occurred only in the patients with high scores for negative symptoms. The authors therefore suggested that hypofrontality is related to negative symptoms and is not a long-term effect of neuroleptic treatment or of chronicity of illness. Again, schizophrenic patients performed poorly on the tasks involved, so whether less activation of the PFC was due to poorer performance or vice versa cannot be resolved.

**The Component Processes Underlying Executive Function**

One problem with studies that employ complex executive tasks is that these tasks involve many processes. For example, the WCST involves choosing a strategy, remembering the previous responses in order to learn by trial and error, attending to one dimension rather than another, and so on. In the absence of a series of carefully constructed comparison tasks it is not possible to relate the various brain regions activated with each of the component processes. In the following section studies that employed simpler tasks with far fewer component processes are reviewed.

**Motor Tasks**

Even tasks that require no more than the production of a simple sequence of movements can be associated with abnormal patterns of brain activity in schizophrenia. Mattay et al. (1997) studied seven patients with schizophrenia and seven normal subjects while they performed a finger movement task of increasing complexity. Patients showed greater ipsilateral activation in the primary somatosensory and lateral premotor regions and had a significantly lower laterality quotient than normal subjects. These functional abnormalities increased with the complexity of the task. The authors proposed that these results demonstrate a functional disturbance in the cortical motor circuitry of schizophrenic patients. Schröder...
et al. (1999) asked 12 patients and 12 healthy controls to produce sequences of movements at three different speeds during fMRI. Both groups showed increasing activity with increasing speed in sensorimotor cortex and supplementary motor area (SMA). However, the patients showed less overall activation than the controls. The differences were most marked in a subgroup of patients who were drug free at the time of testing. Both these studies raise the possibility of a fundamental but subtle problem of motor control associated with schizophrenia.

**Willed Action**

Willed action involves a ‘higher’ stage in the control of action. There is a fundamental distinction between actions elicited by external stimuli and actions elicited by internal goals (acts of will). Routine actions are specified by an external stimulus. In contrast, in willed (or self-generated) acts, the response is opened-ended and involves making a deliberate choice. Willed actions are a fundamental component of executive tasks. In normal subjects, willed acts in two response modalities (speaking a word, or lifting a finger), relative to routine actions, were associated with increased blood flow in the DLPFC (Brodman area 46; Frith et al., 1991). Schizophrenic patients typically show abnormalities of willed behaviour. In chronic patients, intentions of will are no longer properly formed and so actions are rarely elicited via this route. This gives rise to behavioural negative signs (e.g. poverty of speech and action) (Frith, 1992).

In a recent PET study, subjects had to make voluntary joystick movements in the experimental condition, stereotyped (routine) movements in the baseline condition, and do nothing in a control rest condition (Spence et al., 1998). The authors analysed data from 13 schizophrenic patients, comparing two occasions when symptoms were severe and when they had subsided, and included data from a normal control group to clarify the role of the left DLPFC in volition. The DLPFC was activated by normal controls for the free choice task only. However, it was not activated by schizophrenics with symptoms, but became activated when their symptoms decreased. The authors noted that the DLPFC was also activated during the stereotyped joystick movement task in schizophrenic patients in remission, in contrast to a control group. Spence and colleagues concluded that, since hypofrontality was evident in schizophrenics who can perform the experimental task, the DLPFC is not necessary for that task. In addition, hypofrontality seems to depend on current symptoms. They suggested the reason for previous equivocal hypofrontality results is that schizophrenics with a varying amount and combination of symptoms are being compared with normal controls. However, these results provoke another question. What is the functional significance of DLPFC activation in normal controls and patients without symptoms if schizophrenic patients with symptoms can perform the task without recruiting the DLPFC?

**Verbal Fluency**

Verbal fluency tasks involve subjects having to generate words to a given cue. For example, subjects might have to produce a word beginning with a certain letter, a different letter being presented every 5 seconds. This can be seen as a task that involves willed action since subjects have to choose for themselves precisely which word to say. Verbal fluency tasks engage a distributed brain system similar to that engaged by motor response selection tasks associated with willed action (Frith et al., 1991).

Schizophrenic patients showed reduced left PFC activation and increased left temporal activation relative to control subjects during a verbal fluency task in an fMRI study (Yurgelun-Todd et al., 1996b). However, the lack of frontal activation by cognitive tasks in schizophrenic patients has not consistently been located in the PFC. Dolan et al. (1995) and Fletcher et al. (1996) used a factorial design in PET to test the effect of apomorphine, a non-selective dopamine agonist, which when given in very low doses as in this experiment acts primarily on auto-receptors, thus decreasing the release of endogenous dopamine. Brain systems engaged by a paced verbal fluency task in unmedicated schizophrenic patients and normal controls were studied. Activation of the DLPFC was normal, but they found a failure of task-related activation in anterior cingulate cortex and deactivation of the left superior temporal gyrus in the schizophrenic subjects (see Figure XVII-8.2). Fletcher and colleagues therefore suggested that schizophrenia is associated with both segregated (anterior cingulate) and integrative (fronto-temporal) functional abnormalities. Cingulate activation was restored by low-dose apomorphine in schizophrenics. Additionally, the abnormal fronto-temporal pattern of activation in schizophrenic subjects was normalized by this neuropharmacological intervention. Overall, in schizophrenic subjects the effect of apomorphine was to modify the pattern of brain activity, making it more similar to that seen in control subjects. The interpretation of the apomorphine-induced reversal of the deactivation in the left temporal lobe in schizophrenic subjects is unclear. It might reflect a direct influence of apomorphine on the temporal lobe; alternatively the reversal could be due to a ‘downstream’ effect of the change in anterior cingulate function. The authors interpret the absence of the normal reciprocal interaction between the frontal and the superior temporal cortex in schizophrenia (the failure of task-related deactivation of the superior temporal gyrus in the schizophrenic group) as suggesting the presence of impaired functional integration. This is an important concept, especially given the relatively large amount of evidence showing a lack of temporal deactivation in the presence of a lack of frontal activation in schizophrenia.

The finding of normal prefrontal activation found in this study is in agreement with a study in which task performance was optimized by pacing the task (Frith et al., 1995). Using PET, these researchers investigated rCBF of 18 chronic schizophrenic patients and six normal controls matched for age, sex and premorbid IQ, while they performed (a) paced verbal fluency, (b) paced word categorization and (c) paced word repetition. The schizophrenic patients were split into three groups according to their verbal fluency task performance level. All patient groups showed the same pattern of left PFC activation as control subjects, independent of their level of performance. However, in the left superior temporal cortex, all patient groups failed to show a normal deactivation when verbal fluency was compared with word repetition. Again this result was interpreted to reflect abnormal functional connectivity between frontal and temporal cortex.

Friston and Frith (1995) performed an additional analysis of their data from the same three groups of schizophrenic patients according to the level of task performance: poverty (no words), odd (wrong words) and unimpaired. They used special analytic techniques to assess cortico-cortical interactions. Normal controls showed negative fronto-temporal interactions whereas all the schizophrenic patients showed positive interactions, mostly between the left PFC and infero-temporal cortex. Friston and Frith suggested that this might represent a failure of the PFC to inhibit the temporal lobes. They postulated that the temporal lobes may be required to recognize the consequences of actions initiated by the frontal lobes in order to integrate action and perception.

**Verbal Self-Monitoring**

Patients with schizophrenia with auditory hallucinations and delusions show impairments on tasks that require monitoring self-generated actions. This is true for motor actions (Frith and Done, 1989; Blakemore et al., 2000; Frith et al., 2000) and verbal self-monitoring tasks (Johns et al., 2001). In particular, when patients...
Memory impairments are especially enduring symptoms in schizophrenia (Green, 1996), with memory storage particularly affected (Feinstein et al., 1998). The DLPFC and the hippocampal formation have been subject of investigation in schizophrenia, as these are involved in various aspects of memory (Goldman-Rakic and Selemon, 1997; Arnold, 1997). The DLPFC is activated by semantic processing during encoding and retrieval, while hippocampal activation is associated with the detection of novelty and the creation of associations during encoding in normal individuals (Schacter et al., 1997; Dolan and Fletcher, 1997).

Several functional neuroimaging studies have failed to find evidence for abnormal activation of temporal or frontal cortex in schizophrenia during memory tasks (Busatto et al., 1994, using a verbal memory task with SPECT; Ragland et al., 1998, using a Paired Associate Recognition Test with PET). Other studies have shown rCBF changes that overlapped in the schizophrenic and control groups, with a trend towards patients showing smaller activations than controls in frontal and superior temporal cortical regions (e.g. Ganguli et al., 1997, using a verbal free-recall supraspan memory task). These differences may be due to the different type of memory tasks used by each group. Other groups have found evidence for hypofrontality during memory tasks. Carter et al. (1998) used PET to evaluate rCBF associated with the 'N-back' working memory (WM) task, during which subjects are presented with a sequential series of items and have to press a button when a presented item has already been presented a certain number (N) of items earlier. This task activates the PFC as a function of WM load in normal subjects. Under low WM load conditions, the accuracy of both groups in the N-back task was equal, but when the memory load increased the patients' performance deteriorated more than did that of control subjects. The rCBF response to increased WM load was significantly reduced in the patients' right DLPFC. Callicott et al. (1998) investigated blood oxygen level-dependent (BOLD) signal changes in 10 patients with schizophrenia and 10 controls performing a novel N-back WM task, using fMRI. After removing confounds and matching subjects for signal variance (voxel stability), decreased DLPFC activity and a tendency for overactivation of parietal cortex were seen. However, these findings are difficult to interpret in the context of abnormal task performance in patients. There may be nothing inherently abnormal about the physiology of the frontal cortex in schizophrenia, but patients may be failing to select frontally mediated cognitive strategies because of abnormal connectivity between otherwise normal regions.

Wiser et al. (1998) measured rCBF during a long-term recognition memory task for words in schizophrenic patients and in healthy subjects using PET. The task was designed so that performance scores were similar in the patient and control subjects. This memory retrieval task did not activate PFC, precuneus and cerebellum in patients as much as it did in the control group. This finding...
suggests that there is a dysfunctional cortico-cerebellar circuit in schizophrenia.

Hypofrontality has not always been found in studies using modified tasks to optimize the performance of schizophrenic subjects. Hypofrontality was not found in a study by Heckers and colleagues (1998), in which they used PET to evaluate 13 schizophrenic patients and a group of normal control subjects during memory retrieval tasks. In this study activation of the PFC correlated with effort of retrieval, and hippocampal and parahippocampal activation occurred during successful retrieval in normal control subjects, a finding consistent with previous studies of memory in normals (Schacter et al., 1996; Dolan and Fletcher, 1997). The schizophrenic patients recruited the PFC during the effort of retrieval but did not recruit the hippocampus during conscious recollection. In addition to the task-specific hippocampal underactivation, the authors observed a generally higher overall level of non-specific hippocampal activity, supporting previous metabolic studies (e.g. Liddle et al., 1992). The authors suggested that high baseline hippocampal activity together with an absence of task-specific activation demonstrates abnormal cortico-hippocampal functional integration in schizophrenia. The schizophrenic patients showed a more widespread activation of prefrontal areas and parietal cortex during recollection than controls, and the authors propose that this overactivation represents an 'effort to compensate for the failed recruitment of the hippocampus'. This interpretation again moves away from the simple notion of dysfunction in isolated brain regions explaining the cognitive deficits in schizophrenia, and towards the idea that neural abnormality in schizophrenia reflects a disruption of integration between brain areas.

Fletcher et al. (1998) used PET to compare rCBF in memory-impaired and non-impaired schizophrenic patients with normal controls during a parametrically graded memory task. They found that DLPFC activity correlates with memory task difficulty and performance in the control group. In contrast, for both schizophrenic groups DLPFC activity levels plateaued as task difficulty increased, despite a significant difference in performance between the two schizophrenic groups. The authors therefore suggested that hypofrontality in schizophrenics correlates with task difficulty rather than task performance, since the memory-impaired schizophrenic group performed worse than the non-impaired, even though both groups showed no increase in PFC activity as task difficulty increased.

Unlike the control group, there was no inferior temporal/parietal deactivation in either schizophrenic group. The authors suggest that the lack of deactivation of these areas might represent a temporoparietal disconnect in schizophrenia. Indeed they suggested that because temporal/parietal activations were not correlated with performance, they therefore might represent a core pathology of schizophrenia. This study improves on previous cognitive activation studies in which the confound of non-matched task performance occurs.

Further evidence for abnormal integration between brain areas in schizophrenia comes from a study that specifically investigated the functional integration (Fletcher et al., 1999). Functional integration considers complex cognitive processes as emergent properties of interconnected brain area, building on the idea that simple cognitive processes can be localized in discrete anatomical modules (referred to as 'functional segregation'). Brain areas A and B may be functionally connected if it can be shown that an increase (or decrease) of activity in area A is associated with an increase (or decrease) in area B, which can be shown empirically by analysis of covariance. In this case, activity in A might cause activity in B, or activations in A and B might be caused by changes in another area (C), which projects to A and B. Alternatively, areas A and B may be effectively connected if their relationship can be shown to be causal. This requires a more complex approach in which the anatomical components of a cognitive system are defined. Connections between these regions are designated on the basis of empirical neuroanatomy and the connections are allocated weights or path strengths by an iterative least-squares approach in such a way that the resultant functional model of interregional influences best accounts for the observed variance-covariance structure generated by the functional neuroimaging observations (Friston et al., 1993).

A simplified version of effective connectivity (Friston et al., 1997) was employed by Fletcher et al. (1999) to evaluate effective connectivity between regions in the data from their PET study of a graded memory task in schizophrenia. They demonstrated that in control subjects, but not in the schizophrenic patients, the product of PFC and anterior cingulate gyrus (ACG) activity predicted a bilateral temporal and medial PFC deactivation. The authors interpreted these results as showing that in schizophrenia there is an abnormality in the way in which left PFC influences the left superior temporal cortex, and this abnormality is due to a failure of the ACG to modulate the prefronto-temporal relationship (see Figure XVII-8.3).
network of other cortical and subcortical areas. There are two distinct approaches to the study of the physiological basis of auditory hallucinations. The first, called the state approach, asks what changes in brain activity can be observed at the time hallucinations are occurring. The second, called the trait approach, asks whether there is a permanent abnormality of brain function present in patients who are prone to experience auditory hallucinations when they are ill. This abnormality will be observable even in the absence of current symptoms.

State Studies

Silbersweig et al. (1995) used PET to study brain activity associated with the occurrence of hallucinations in six schizophrenic patients. Five patients with classic auditory verbal hallucinations demonstrated activation in subcortical (thalamic and striatal) nuclei, limbic structures (especially hippocampus) and paralimbic regions (parahippocampal and cingulate gyri and orbito-frontal cortex). Temporo-parietal auditory–linguistic association cortex activation was present in each subject. One drug-naive patient had visual as well as auditory verbal hallucinations, and showed activations in visual and auditory/linguistic association cortices. The authors propose that activity in deep brain structures seen in all subjects may generate or modulate hallucinations, and that the particular sensory cortical regions activated in individual patients may affect their specific perceptual content. Importantly this study pointed to the possibility that hallucinations coincide with activation of the sensory and association cortex specific to the modality of the experience, a notion that has received support from several further studies.

David et al. (1996) used fMRI to scan a schizophrenic patient while he was experiencing auditory hallucinations and again when hallucination free. The subject was scanned during presentation of exogenous auditory and visual stimuli, and while he was on and off antipsychotic drugs. The BOLD signal in the temporal cortex to exogenous auditory stimulation (speech) was significantly reduced when the patient was experiencing hallucinating voices, regardless of medication. Visual cortical activation to flashing lights remained the same over all four scans, whether the subject was experiencing auditory hallucinations or not.

A similar result was obtained by Woodruff et al. (1997b), who used fMRI to study seven schizophrenic patients while they were experiencing severe auditory verbal hallucinations and again after their hallucinations had subsided. On the former occasion, these patients had reduced responses in temporal cortex, especially the right middle temporal gyrus, to external speech, compared to when their hallucinations were mild. The authors thus proposed that auditory hallucinations are associated with reduced responsivity in temporal cortical regions that overlap with those that normally process external speech, possibly due to competition for common neurophysiological resources.
Recently, Dierks et al. (1999) used event-related fMRI to investigate three paranoid schizophrenics who were able to indicate the onset and offset of their hallucinations as in the study by Silbersweig et al. Using this design they found that primary auditory cortex, including Heschl’s gyrus, was associated with the presence of auditory hallucinations. Secondary auditory cortex, temporal lobe and frontal operculum (Broca’s area) were also activated during auditory hallucinations, supporting the notion that auditory hallucinations are related to inner speech. Finally hallucinations were also associated with increased activity in the hippocampus and amygdala. The authors suggested that these subcortical activations could be due to retrieval from memory of the hallucinated material and emotional reaction to the voices, respectively. A similarly elegant design was employed in a recent fMRI study (Shergill et al., 2000). They found that frontal and temporal speech areas and several other cortical and subcortical regions were activated during auditory hallucinations.

**Trait Studies**

The finding that auditory hallucinations are associated with activation of auditory and language association areas is consistent with the proposal that auditory verbal hallucinations arise from a disorder in the experience of inner speech (Frith, 1992). This was investigated by McGuire et al. (1996). They used PET to evaluate the neural correlates of tasks that engaged inner speech and auditory verbal imagery in schizophrenic patients with a strong predisposition to auditory verbal hallucinations (hallucinators), schizophrenic patients with no history of hallucinations (non-hallucinators) and normal controls. There were no differences between hallucinators and controls in rCBF during thinking in sentences. However, when imagining sentences spoken in another person’s voice, which entails both the generation and monitoring of inner speech, hallucinators showed reduced activation of the left middle temporal gyrus and the rostral supplementary motor area, regions activated by both normal subjects and non-hallucinators. Conversely, when non-hallucinators imagined speech, they differed from both hallucinators and controls in showing reduced activation in the right parietal operculum (see Figure XVII-S.4). McGuire and his colleagues suggest that the presence of verbal hallucinations is associated with a failure to activate areas concerned with the monitoring of inner speech.

**Visual Hallucinations**

The neural correlates of visual hallucinations also seem to be located in the neural substrate of visual perception. At least part of the activity in the brain associated with the experience of visual hallucinations is located in the visual cortex. For example, using SPECT Hoksbergen et al. (1996) found that visual hallucinations were associated with hypoperfusion in the right occipito-temporal region, which showed partial normalization after the visual hallucinations had subsided. Howard et al. (1997) used fMRI to investigate the visual cortical response to photic stimulation during and in the absence of continuous visual hallucinations. When visual hallucinations were absent photic stimulation produced a normal bilateral activation in striate cortex. During hallucinations, very limited activation in striate cortex could be induced by exogenous visual stimulation. Similarly, ffytche et al. (1998) found activity in ventral extrastriate visual cortex in patients with the Charles Bonnet syndrome when they experienced visual hallucinations. Moreover, the content of the hallucinations reflected the functional specialization of the region, for example, hallucinations of colour activated V4 (the human colour centre; Zeki et al., 1991).

In conclusion, functional neuroimaging studies suggest that hallucinations involve an interaction between the neural systems dedicated to the particular sensory modality in which the false perception occurs and a widely distributed cortico-subcortical system, including limbic, paralimbic and frontal areas. Intersubject variability in the specific location of the sensory activation associated with the hallucination could arise from differences between the patients in the sensory content and experience of their hallucinations.

**Thought Disorder**

McGuire et al. (1998) scanned six schizophrenic subjects with PET while they described a series of ambiguous pictures, which provoked different degrees of thought-disordered speech in each patient. The severity of thought disorder was correlated with rCBF across the 12 scans, controlling for differences in the total number of words articulated. Verbal disorganization (positive thought disorder) was inversely correlated with activity in the inferior frontal, cingulate and left superior temporal cortex, areas implicated in the regulation and monitoring of speech production. The authors propose that this reduced activity might contribute to the articulation of the linguistic anomalies that characterize positive thought disorder. Verbal disorganization was positively correlated with activity in the parahippocampal/anterior fusiform region bilaterally, which may reflect this region’s role in the processing of linguistic anomalies.

**Passivity Symptoms**

Spence et al. (1997) performed a PET study in which subjects had to make voluntary joystick movements in the experimental
condition, and stereotyped (routine) movements in the baseline condition, and do nothing in the rest condition. They investigated a group of schizophrenic patients with passivity (delusions of control) and without (the same group in remission), and a group of normal controls. Schizophrenic patients with passivity showed hyperactivation of inferior parietal lobe (BA 40), the cerebellum and the cingulate cortex relative to schizophrenic patients without passivity (see Figure XVII-8.5). Similar results were found when schizophrenic patients with passivity were compared with normal controls. A comparison of all schizophrenics with normal controls revealed hypofrontality in the patients. When patients were in remission, and no longer experienced passivity symptoms, a reversal of the hyperactivation of parietal lobe and cingulate was seen. Hyperactivity in parietal cortex might reflect the patient’s experiencing the movement as ‘unexpected,’ as if it were being caused by some external force.

OBSTACLES TO FUNCTIONAL NEUROIMAGING AND SCHIZOPHRENIA STUDIES

Subject Matching

It is important that patients are matched to the control group on as many factors as possible, but the best way to match IQ and education level is uncertain. It is not clear whether the control group’s education level should be matched to the patient’s parental or premorbid education level. However, both of these are superior to matching controls to patients’ current IQ level, which may be considerably impaired by illness.

Another question is whether the control group should be normal or psychiatric. Normal controls are important in order to establish a baseline model of the neural circuitry involved in an experimental task. However, there are several problems with using non-psychiatric controls. These include the fact that normal controls are not taking medication, hospitalized or affect-flattened, factors that might cause the patients to be more or less motivated, to attend or think more or less, or that might have a direct effect on rCBF. Since psychiatric patients will be more matched on these factors they may be a preferable control group. However, there are also problems with using psychiatric patients as controls. There is the question of which psychiatric population should be used. Should they be taking the same medication, or is hospitalization the more important factor? They might not be able to perform the experimental task for some reason that is different from that causing impairment in schizophrenic patients. Therefore, comparing schizophrenic with depressed patients, for example, may reveal activity specific to depression or to schizophrenia.

Experimental Tasks

As has been discussed at length throughout this chapter, there is a conceptual problem with applying the approach of cognitive activation studies to patient groups. It is difficult to interpret patterns of brain activity that differ between control and patient groups when the performance of the two groups on tasks differs in terms of degrees of efficiency and success. Any difference in brain activity between the two groups could represent a critical abnormality in schizophrenia and might cause poor task performance, or alternatively it might reflect poor performance. It is difficult to distinguish these two alternatives. Recent studies have employed tasks on which performance of the patient and control group is matched. However, there is also a problem with interpreting the results of activation studies in which the task performance of the patient and control group is matched. What do differences in brain activity mean in the context of normal task performance? If an area is activated more in the controls than in the patient group during such a task, the functional significance of that activation is difficult to understand—it is clearly not necessary for performing the task. The most obvious interpretation is that patients and controls are using different strategies to achieve similar task performance. Therefore, interpretational difficulties remain: what is the nature of the relationship between differences in brain activity and behaviour? How do these two variables relate to the schizophrenic state? These problems have not been resolved, and remain when interpreting data from studies in which task performance of patient and control groups is matched.

Symptom-Specific Groups

Schizophrenia is a heterogeneous illness, comprising a variety of different symptoms. Using groups of patients defined by diagnosis (schizophrenia) may explain the inconsistent and equivocal results of functional imaging studies, since each symptom may be associated with a different brain pattern or functional abnormality. Attempts have been made to correlate cognitive brain activity with specific symptoms or clinical signs. However, as reviewed here, the results are inconsistent.

A clear advantage of using symptom-specific schizophrenic groups is that the control group can comprise people with a diagnosis of schizophrenia, who are thus matched in terms of medication and hospitalization, but who do not have a particular symptom. Better still, the same group of schizophrenic patients can be used as their own control group if and when the symptom evaluated remits (see the study by Spence et al., 1998). However, a clear shortcoming of using symptom-specific groups is that little can be discovered about schizophrenia as a syndrome.

OVERALL CONCLUSION

Although there has been no specific, replicated finding peculiar either to the syndrome of schizophrenia or to a particular symptom, there have been repeated findings of frontal and temporal abnormalities in schizophrenia, in both resting metabolism and cognitive activation studies. PET and SPECT studies have shown that the density
of DA (in particular D2) receptors is increased in schizophrenic brains, and that typical antipsychotic drugs bind mainly to D2 receptors whereas atypical antipsychotics bind mainly to 5-HT receptors. It is becoming increasingly evident from PET and fMRI studies that schizophrenic patients show abnormal interactions between brain regions during cognitive tasks. There is currently little direct evidence in favour of the hypothesis of functional disconnection, and several regions have been found to function abnormally, but with no unequivocal evidence for the consistent involvement of any particular region. However, the majority of positive findings suggest that a disruption of cortico-cortical (and cortico-subcortical) integration is a core feature of the schizophrenic syndrome. Future studies would do well to investigate this possibility, using methods of evaluating functional or effective connectivity to evaluate the influence of one brain region over another.

REFERENCES


