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Review Article

Schizophrenia – a Brain Disease?
A Critical Review of Structural and Functional Cerebral Abnormality in the Disorder

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Background. With genetic and neurochemical findings pointing to a biological aetiology, considerable effort has been devoted to finding direct evidence of brain abnormality in schizophrenia.
Method. CT, MRI, post-mortem and functional imaging studies are reviewed to assess which structural and/or functional brain abnormalities have been consistently demonstrated.
Results. The only well-established structural abnormality in schizophrenia is lateral ventricular enlargement; this is modest and there is a large overlap with the normal population. There is no consensus on the presence of any localised structural abnormality from MRI and post-mortem studies, but the most promising findings concern temporal lobe limbic structures. Hypofrontality is not a well-replicated finding in schizophrenia under resting conditions, but the evidence is stronger for a selective association with negative symptoms. A number of studies have found hypofrontality under conditions of neuropsychological task activation. However, findings in these studies are divided and a recent methodologically sophisticated study has failed to confirm it, although this study suggested a decoupling of prefrontal and temporal function.
Conclusion. Schizophrenia is characterised by minor structural abnormality which, in the case of lateral ventricular enlargement, may be better understood as a risk factor than a causative lesion. The functional imaging findings are not transparent but suggest that, as a disorder, schizophrenia shows complex alterations in regional patterns of activity rather than any simple deficit in prefrontal function.

Although the concept of schizophrenia has been in existence for nearly a century and has proved clinically useful, there has been no identification of any underlying causal pathology. One important reason for this lack of aetiological evidence has been the fact that investigation of the disorder has been coloured by a protracted dispute between the biological and psychodynamic schools of thought. For a considerable period the psychodynamic approach held sway, and research was directed mainly to examining the roles of abnormal family interaction (Hirsch & Leff, 1975) and stressful life events (Day, 1981; Bebbington & Kuipers, 1988), with negative and modest results respectively. In recent years, the hypothesis that schizophrenia is a biological brain disease has spectacularly gained the upper hand. The origins of this paradigm shift can be traced directly to two incontrovertible findings: first, the hereditary contribution to the disorder and, secondly, the antipsychotic effect of neuroleptic drugs.

As reviewed by Gottesman (1991), it has been known from the early years of the century that schizophrenia shows a tendency to cluster in families. That this familiality reflects heredity was eventually confirmed in a number of twin and adoption studies. The genetic contribution to schizophrenia may be large (McGuffin *et al*, 1994) or small (Torrey, 1992), but in either case the lack of complete concordance in monozygotic twins suggests that non-genetic factors also play a part. Additionally, it is unknown whether the genetic predisposition to develop schizophrenia is expressed in some relatively direct biological way, or whether what is inherited is merely a vulnerability that depends on other factors – quite possibly of a psychosocial nature – for its clinical expression.

The discovery in the 1950s that certain drugs have a therapeutic effect on schizophrenic symptoms led directly to the dopamine hypothesis of schizophrenia, and this became the dominant force motivating biological research for the next 20 years. With cerebrospinal fluid (CSF) studies producing weak or negative findings (Heritch, 1990), and after it became clear that post-mortem studies would always be confounded by the effects of neuroleptic treatment in life (Seeman, 1987), hopes of a definitive answer to the question of a functional dopamine excess in schizophrenia came to rest on studies using functional imaging to quantify D_2 receptor densities in drug-naive patients. Unfortunately two studies using

positron emission tomography (PET) and sophisticated methods of analysis (Wong *et al*, 1986; Farde *et al*, 1987; see also Farde *et al*, 1990; Tune *et al*, 1992) have produced completely contradictory results, and five further studies (Crawley *et al*, 1986; Martinot *et al*, 1990, 1991; Hietala *et al*, 1994; Pilowsky *et al*, 1994) have found evidence of at most minor alterations in D_2 receptor numbers.

With a genetic theory facing limitations and with the dopamine hypothesis showing little prospect of resolution, biological approaches to the aetiology of schizophrenia have come to rely increasingly heavily on attempts to identify a structural or functional brain abnormality in the disorder – the lesion of schizophrenia. Opinion on the status of this work is divided, even polarised. Some (e.g. Ron & Harvey, 1990; Pilowsky, 1992) appear to believe that, notwithstanding some conflicting findings, evidence linking schizophrenia to organic disease of the brain has been established beyond reasonable doubt. Others are more cautious: the same contradictions and uncertainties among the biological findings led Leff (1991) to observe that the history of schizophrenia has been replete with breakthroughs that subsequently turned out to be illusory.

Have convincing differences been demonstrated between the brains of schizophrenic patients and normal individuals? Or, in a way reminiscent of an earlier generation of psychodynamically oriented studies, is the evidence in support of such a view failing to consolidate over time? This review examines studies of brain structure and function in the disorder in order to determine which abnormalities have been established beyond reasonable doubt. The major criterion used to judge this will be the reproducibility of the various claims across studies. Such an approach can of course fall prey to the marked clinical heterogeneity within schizophrenia, and so it is also pertinent to consider whether, when there is a lack of consistency among the findings in an area, abnormality might be selectively associated with a particular subgroup of patients, such as those with chronic illnesses, those showing negative symptoms and so on. The scope of the review will be restricted to studies that provide the most direct indices of brain structure and function, i.e. computed tomography (CT) scan, magnetic resonance imaging (MRI), post-mortem and functional imaging.

Structural brain abnormality in schizophrenia

CT scan studies

The first CT scan study in schizophrenia was carried out by Johnstone *et al* (1976). They reported that a sample of 13 chronically hospitalised schizophrenic patients had significantly larger lateral ventricles than eight normal volunteers; in some cases the enlargement was considerable. Reviewing the many subsequent replications of this finding, Andreasen *et al* (1990*a*) noted that 36 out of 49 further studies which compared schizophrenic patients and controls under blind conditions found some increase in lateral ventricular size. Two formal meta-analyses of the CT scan literature (Raz & Raz, 1990; Van Horn & McManus, 1992) have also supported the conclusion that significant differences exist between patients and controls.

However, it has also become clear that the degree of ventricular enlargement in schizophrenia is for the most part small. In the first study with a large sample size (Weinberger *et al*, 1979), it was found that 60% of a group of 58 chronic schizophrenic patients had lateral ventricular dimensions within the control group range. In an even higher percentage the scans were reported by radiologists as being within normal limits. Only in 10 of the 58 cases could the presence of clinically significant ventricular enlargement be agreed on, and in most cases this was described as mild or borderline. Modest to begin with, the degree of lateral ventricular enlargement in schizophrenia also seems to have lessened over time: in their meta-analysis Van Horn & McManus (1992) found that year of publication was a significant determinant of the effect size. As this was a predictor of control but not schizophrenic ventricular size, they concluded that this trend was at least partly attributable to methodological problems associated with the selection of controls.

The potential importance of the control group in studies of lateral ventricular enlargement in schizophrenia had already been highlighted by Smith & Iacono (1986). These authors compared 14 studies in which significant lateral ventricular enlargement had been found with seven studies where no differences between patients and controls had been found. When they plotted the mean ventricle: brain ratio (VBR) for the schizophrenic patients and the controls in each of the two sets of studies as a scatter diagram, they obtained the result illustrated in Fig. 1. For the schizophrenic patients, the range of mean VBR values in the positive studies was similar to that in the negative studies. On the other hand, the corresponding values for the controls differed, with the control subjects in the positive studies having noticeably smaller VBRs than those in the negative studies. In short, the finding of lateral ventricular enlargement in schizophrenia appeared to be due to the controls having smaller ventricles rather than the schizophrenics having larger ones.

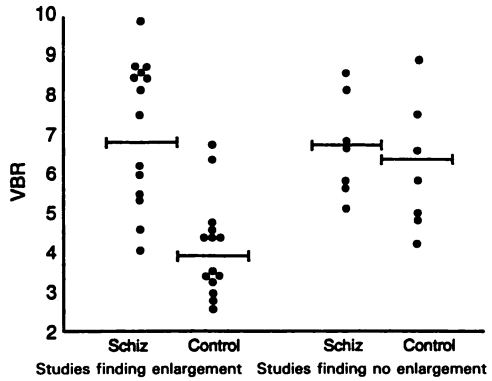

Fig. 1 Smith & Iacono's (1986) comparison of mean VBR values for schizophrenic patients and controls in studies finding and failing to find significant lateral ventricular enlargement (© The Lancet Ltd).

The reasons why controls in negative studies might have smaller ventricles than those in positive studies are unclear. Smith & Iacono's (1986) suggestion was that the use in several of the studies of normal scans drawn from radiology files (e.g. patients who had been investigated for headache with negative results or the asymptomatic relatives of patients with Huntington's disease) could have led to individuals with lateral ventricular dimensions at the extreme upper end of the normal range being excluded, on the basis of their scans having been reported as borderline, larger than expected for their age, etc. The net result would be a truncation of the control range and a downward biasing of the mean. This explanation was disputed by Raz *et al* (1988) who found that the size of the VBR difference did not differ between studies employing healthy volunteer or medical controls. However, in the meta-analysis of Van Horn & McManus (1992), choice of control group emerged as a factor contributing to the variability of control VBR. Whatever the reason, when Lewis (1990) reviewed 20 CT scan studies that compared schizophrenic patients with control groups made up of prospectively ascertained normal volunteers, only eight were found to show significant lateral ventricular enlargement, with a further three reporting marginal increases.

Recently, there have been two CT scan studies of schizophrenia that have been both large scale and have paid particular attention to the problem of controls. Andreasen *et al* (1990*a*) compared 108 patients meeting DSM–III (American Psychiatric Association, 1980) criteria for schizophrenia with 75 prospectively ascertained normal volunteers. The two groups were matched not only for age and sex, but also height, weight and level of education. Potential control subjects were interviewed and excluded if they had a history of significant medical disorder, head injury, substance abuse or even psychiatric illness. VBR was found to be greater in the schizophrenic group than in the controls. The magnitude of the difference was small and its significance, at $P<0.04$, was relatively weak given the size of the samples. When only the patients and controls under the age of 50 were considered, the level of significance became somewhat higher ($P=0.01$) despite the reduction in numbers (ventricular size increases disproportionately after late middle age, which could tend to obscure differences). As found previously, there was a substantial degree of overlap between the two groups: only 29% of the schizophrenic patients were more than one standard deviation outside the control group mean, and only 6% more than two standard deviations outside it. However, the most arresting finding of Andreasen *et al*'s (1990*a*) study was that significant ventricular enlargement was only present in male schizophrenic patients; the distributions for female patients and controls were almost identical.

Jones *et al* (1994) made lateral ventricular area and volume measures in 121 patients meeting RDC criteria (Spitzer *et al*, 1978) for schizophrenia and 67 prospectively ascertained normal volunteers; the controls were subjected to similar exclusion criteria as those of Andreasen *et al* (1990*a*). In this study the patients and controls were not matched for age and sex, but these and other variables including IQ, educational level and ethnicity were recorded and entered as covariates in the analysis. Examination of the raw data revealed evidence of a linear trend towards increased lateral ventricular area and volume in the schizophrenic group; when adjustment was made for the corresponding intracranial area/volume (i.e. when VBR was calculated) this trend became more marked and achieved significance. When further adjustments were made for sex, social class and ethnicity the significance level increased, becoming $P=0.005$ for lateral ventricular area and $P=0.02$ for volume. In this study, however, no evidence of a gender effect was found.

Could heterogeneity within the schizophrenic population be diluting the finding of lateral ventricular enlargement in schizophrenia, so that greater degrees of this would be present in a subgroup of patients? Lewis (1990) reviewed 41 CT scan studies that addressed this issue. Only 1 of 18 studies found evidence for an association with chronicity of illness. A minority (5 of 18 studies) found evidence of a relationship with negative symptoms. The studies were evenly divided on the question of a relationship with poor treatment response. The only associations that Lewis (1990)

found to have more positive than negative replications were presence of tardive dyskinesia (4 of 6 studies) and neuropsychological impairment (11 of 14 studies). The pattern is similar in the two largest studies: Owens *et al* (1985) found no relationship between lateral ventricular size and positive symptoms, negative symptoms or intellectual impairment in 112 chronically hospitalised schizophrenic patients, but there was a significant correlation with presence of tardive dyskinesia. Jones *et al* (1994), in the study already cited, found no association with age at onset, duration of illness, poor premorbid functioning or presence of family history of schizophrenia; a history of obstetric complications was associated with significantly smaller lateral ventricles.

The studies of Andreasen *et al* (1990*a*) and Jones *et al* (1994) place the existence of lateral ventricular enlargement in schizophrenia beyond reasonable doubt. At the same time they emphasise that the differences are small and the overlap with the normal population is great. For example, in Andreasen *et al*'s (1990*a*) study the difference in mean VBR between schizophrenic patients and normals under the age of 50 years (6.49 v. 5.37) was scarcely greater than that between normal women and normal men (5.87 v. 4.83). There is little reason to suspect that the magnitude of the enlargement is being obscured by an association with a particular symptom or clinical subtype of schizophrenia: as Lewis (1990) concluded, "for most clinical variables mooted at one time or another to be related to ventricular enlargement, there is little in the way of convincing replication".

MRI studies

This structural imaging technique gives superior resolution to CT scanning. Its particular advantage, however, lies in its ability to differentiate grey and white matter, allowing the size of particular cortical regions and subcortical structures to be measured. Studies using MRI have been carried out on schizophrenic patients since 1983. The results of several early studies, which typically employed small numbers and unspecified control groups, were reviewed by Coffman & Nasrallah (1986) and Kelsoe *et al* (1988); they yielded conflicting findings with regard to lateral ventricular enlargement, but found suggestions of size reductions of the brain as a whole, or in certain regions such as the frontal lobes.

Subsequent studies have generally been carried out on larger groups, and have almost always utilised prospectively ascertained normal volunteers as controls. In addition, many (though not all) of the studies have matched their groups for age and sex. A number of these studies (Kelsoe *et al*, 1988; Suddath *et al*, 1989, 1990; Andreasen *et al*, 1990*b*; Gur *et al*, 1991; Bornstein *et al*, 1992; DeGreef *et al*, 1992; Zipursky *et al*, 1992) have confirmed the CT scan finding of lateral ventricular enlargement in schizophrenia. However, there have also been a number of exceptions (Smith *et al*, 1987; Johnstone *et al*, 1989; Rossi *et al*, 1990; Young *et al*, 1991; Shenton *et al*, 1992; Harvey *et al*, 1993; Rossi *et al*, 1994).

The findings of these more recent studies with respect to overall brain size, size of individual cortical regions and size of subcortical structures are shown in Table 1. Only studies that used normal volunteers as controls are shown; however, those studies which did not match for age and sex are also included as most corrected for these factors. The studies vary considerably in their MRI methodology, with the earlier studies generally using a single (transverse or coronal) slice, whereas in the most recent studies it has become possible to make volumetric reconstructions from multiple slices. In all the studies, however, regions of interest have had to be identified by drawing round them manually; as yet there is no computerised method for separating grey and white matter. Such technological considerations appear to make little difference to the overall pattern of findings (see Hall *et al*, 1994).

With respect to overall brain size, 3 of 16 studies found a significant reduction in schizophrenia, with one more (DeMyer *et al*, 1988) yielding equivocal evidence of this. One of these studies (Zipursky *et al*, 1992) employed fairly small numbers of patients (22), and in two more (Andreasen *et al*, 1986; Harvey *et al*, 1993) the patient and control groups were not matched for sex (however, the size reductions remained significant when the sex differences were controlled for). It is also interesting to note that the finding of reduced cerebral area made by Andreasen *et al* (1986) was not replicated in a later study by the same group (Andreasen *et al*, 1990*b*). One study (Marsh *et al*, 1994) found a trend towards larger brain size.

A significant reduction in the size of the frontal lobes, or some division thereof, was found in 5 of 14 studies. This number includes the study of Harvey *et al* (1993), in which a reduction in frontal plus anterior parietal lobe volume emerged after controlling for overall brain size and other variables such as sex, age and height. One further study (Raine *et al*, 1992) found significant reductions in two of three left prefrontal and one of three right coronal prefrontal cuts. Another study (DeMyer *et al*, 1988) found a smaller frontal area on one of two transverse cuts, which reached significance (using a one-tailed

Table 1
Magnetic resonance imaging studies in schizophrenia

Study	Sample	Whole brain	Frontal lobe	Temporal lobe	Subcortical structures	Comment
Andreasen *et al* (1986)	38 patients 49 controls	Smaller	Smaller	–	–	Samples age but not sex matched. Whole brain and frontal reductions persisted after controlling for sex, height and weight.
DeMyer *et al* (1988)	24 patients 24 controls	? Smaller right hemisphere	? Smaller	–	–	Samples matched for age and sex. Right hemisphere significantly smaller in one of two cuts. Frontal lobes smaller on one of two cuts.
Kelsoe *et al* (1988)	24 patients 14 controls	Normal	Normal (prefrontal)	Normal	Normal amygdala/ hippocampus	Samples matched for age and sex. Non-blind ratings.
Johnstone *et al* (1989)	21 patients 21 controls	Normal	–	Normal	–	Samples matched for age and sex. Trend towards smaller temporal lobe size.
Suddath *et al* (1989)	17 patients 17 controls	–	Normal (pre-frontal)	Smaller	Smaller amygdala/ hippocampus	Samples matched for age and sex. Temporal lobe size reductions due to smaller amygdala and anterior hippo-campal grey matter.
Uematsu & Kaiya (1989)	40 patients 17 controls	Normal	Normal	–	–	Samples sex matched, not stated if age matched.
Andreasen *et al* (1990*b*)	54 patients 47 controls	Normal	Normal	Normal	–	Samples matched for age and sex. Thalamus normal.
Barta *et al* (1990)	15 patients 15 controls	Normal	–	? Normal	Smaller on left	Samples age and sex matched. Right temporal lobe significantly smaller before correcting for multiple comparisons.
Bogerts *et al* (1990*a*)	34 patients 25 normals	–	–	Normal	Normal hippocampus	Samples matched for age and sex; 7 controls were drawn from radiology files. Left hippocampus smaller in males.
Dauphinais *et al* (1990)[1]	28 patients 28 controls	Normal (excluding temporal lobes)	Normal	Smaller	? Normal hippocampus/ amygdala	Samples matched for age and sex; 5 patients had a history of alcohol abuse. Right hippocampus/amygdala smaller in one of two analyses.
Suddath *et al* (1990)	15 patients 15 controls	–	Normal (grey matter)	Smaller on left	Smaller hippocampus	Control group were non-schizophrenic monozygotic co-twins of patients.
Gur *et al* (1991)	42 patients 43 controls	Normal	–	–	–	Samples matched for age and sex.
Jernigan *et al* (1991)	42 patients 24 controls	Smaller (increased sulcal CSF)	Smaller (inferior)	Smaller (medial)	–	Samples matched for age and sex. Lenticular nucleus larger in patients.
Young *et al* (1991)	31 patients 33 controls	–	Normal	Normal	Normal amygdala and hippocampus	Samples matched for age and sex. Parahippocampal gyrus normal.
Breier *et al* (1992)	44 patients 29 controls	–	Smaller (white matter)	–	Smaller amygdala smaller left hippocampus	Samples matched for age, and sex. Trend towards smaller right hippocampus.
Di Michele *et al* (1992)[2]	25 patients 25 controls	–	–	Smaller	–	Samples matched for age and sex. Reductions more marked on left.
Raine *et al* (1992)	17 patients 19 controls	–	? Smaller	–	–	Samples matched for age and sex. Significant differences between patients and controls on 2 out of 3 left prefrontal cuts and 1 out of 3 right prefrontal cuts.
Shenton *et al* (1992)	15 patients 15 controls	Normal	–	?	Smaller amygdala/ hippocampus on left	Samples matched for age and sex. Smaller superior temporal gyrus on left. Smaller parahippocampal gyri bilaterally.
Zipursky *et al* (1992)	22 patients 20 controls	Smaller (grey matter)	–	–	–	Samples matched for age and sex.

(continued)

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Table 1 *(continued)*

Study	Sample	Whole brain	Frontal lobe	Temporal lobe	Subcortical structures	Comment
Bogerts *et al* (1993)	19 patients 18 controls	-	-	-	Smaller hippocampus	Samples matched for age and sex.
Colombo *et al* (1993)	18 patients 18 controls	-	-	Normal	Normal hippocampus	Samples matched for age and sex.
Harvey *et al* (1993)	48 patients 34 controls	Smaller (grey matter)	Smaller	Smaller	-	Samples age but not sex matched. Reduction in size of temporal lobe not disproportionate to overall cortical reduction.
Kawasaki *et al* (1993*a*)	20 patients 10 controls	Normal	Normal	Normal	Normal hippocampus and amygdala	Samples matched for age and sex. Parahippocampal gyrus smaller on left.
Marsh *et al* (1994)	33 patients 41 controls	Normal	-	-	Smaller hippocampus and amygdala	Samples matched for age and sex. Patients showed tendency to larger whole brain size.
Rossi *et al* (1994)	19 patients 14 controls	-	-	-	Smaller amygdala/ anterior hippocampus on left	Samples age and sex matched.
Schlaepfer *et al* (1994)	46 patients 60 controls	Normal (grey matter)	Smaller (dorsolateral grey matter)	-	-	Samples age and sex matched. Patients also showed smaller inferior parietal area and superior temporal gyrus grey matter.

1. Includes patients from DeLisi *et al* (1988).
2. Includes patients from Rossi *et al* (1990).

t-test) for the right hemisphere only. As above, an initial positive finding by Andreasen *et al* (1986) was not subsequently replicated by the same group (Andreasen *et al*, 1990*b*).

A significant reduction in the size of the temporal lobes was found in 6 of 14 studies. This includes one study (Suddath *et al*, 1990) in which a difference was found for the left temporal lobe only. One further study (Johnstone *et al*, 1989) found a trend towards smaller size. In many of these studies temporal lobe subcortical nuclei, i.e. the hippocampus and amygdala, have been a particular focus of interest and have sometimes, but not always, accounted for the overall size reductions. A reduction in the size of one or both structures has been found in 8 of 14 studies: bilaterally (five studies) or on the left side only (three studies). One further study (Dauphinais *et al*, 1990) had equivocal results, finding the right hippocampus/ amygdala to be significantly smaller compared to one of two control groups. Two studies (Shenton *et al*, 1992; Kawasaki *et al*, 1993*a*) also found reductions in the size of an associated limbic structure, the parahippocampal gyrus, but another (Young *et al*, 1991) found this structure to be not significantly different from normal.

This overall pattern of MRI findings is reflected in the study of Suddath *et al* (1990) where 15 schizophrenic patients were compared with an arguably ideal control group made up of their non-schizophrenic monozygotic twins; this study also used volumetric reconstruction and was methodologically superior in other aspects of MRI technology (see Hall *et al*, 1994). On comparison of prefrontal and temporal grey and white matter volumes, the only significant difference found was for the volume of grey matter in the left temporal lobe, which was less in the patients ($P<0.002$). Further analysis revealed that this was due to a significant volume reduction in the left hippocampus ($P=0.006$); there was also a significant size reduction in the right hippocampus ($P=0.01$). No significant differences were found for the amygdala. The volume of the hippocampus was smaller in the affected twin than the unaffected twin in 14 of the cases on the left and 13 of 15 cases on the right. The differences in hippocampal size (together with lateral ventricular enlargement, which was also found) enabled the affected twin to be identified by visual inspection of the scans in 12 of 15 cases.

In the MRI studies to date there has been relatively little emphasis on clinical correlates of the abnormalities found, and it is only the temporal lobe findings that are numerous enough to permit a critical evaluation. In the main, these have found no

association between chronicity of illness and overall temporal lobe size (Kelsoe *et al*, 1988; Dauphinais *et al*, 1990; Young *et al*, 1991; Kawasaki *et al*, 1993*a*), size of temporal lobe grey matter (Zipursky *et al*, 1992), or size of the hippocampus and/or amygdala (Suddath *et al*, 1990; Young *et al*, 1991; Kawasaki *et al*, 1993*a*; Marsh *et al*, 1994). However, one study (DeLisi *et al*, 1991) found an inverse relationship between temporal lobe volume and chronicity. A similar lack of association has been found between various temporal lobe parameters and related variables such as poor outcome (Johnstone *et al*, 1989; Harvey *et al*, 1993), age of onset (Kelsoe *et al*, 1988; Suddath *et al*, 1990; Jernigan *et al*, 1991; Kawasaki *et al*, 1993*a*) and poor premorbid adjustment (Harvey *et al*, 1993). Neuropsychological test impairment has been found to be uncorrelated with temporal lobe size in several studies (Johnstone *et al*, 1989; DeLisi *et al*, 1991; Seidman *et al*, 1994). One study found equivocal evidence of an association (Di Michele *et al*, 1992), and another (Nestor *et al*, 1993) found a correlation between performance on a variety of tasks and size of the parahippocampal gyrus and posterior superior temporal gyrus bilaterally. No studies have found evidence of a relationship with negative symptoms (Young *et al*, 1991; Zipursky *et al*, 1992; Kawasaki *et al*, 1993*a*). The findings with respect to positive symptoms are more complicated: three studies found no association between overall temporal lobe size or volume of temporal lobe grey matter and global measures of positive symptoms (Young *et al*, 1991; Zipursky *et al*, 1992; Kawasaki *et al*, 1993*a*), but one study (Bogerts *et al*, 1993) found an inverse correlation for subcortical temporal lobe structures. Two studies (Barta *et al*, 1990; Shenton *et al*, 1992) found a correlation between size of the superior temporal gyrus and presence of auditory hallucinations and formal thought disorder respectively.

In summary, there is no consistent evidence from MRI studies for a global reduction in brain size in schizophrenia, and only a minority of studies have pointed to a focal reduction in the size of the frontal lobes. However, the numbers of positive and negative replications are approximately equal for the finding of reduced temporal lobe size, and when the hippocampus and amygdala (and perhaps also the parahippocampal gyrus) are specifically considered this turns into a slight majority in favour of reduced size. A reasonable conclusion might therefore be that, while not yet established beyond reasonable doubt, it is likely that any brain substance abnormality in schizophrenia will be found to be localised to the temporal lobe, where it will be predominantly subcortical and perhaps also predominantly left-sided. In line with the CT finding of lateral ventricular enlargement, there is little to suggest that abnormality will be more marked in any particular subgroup of patients.

Neuropathological abnormalities

While accepting that the brain appeared macroscopically normal in schizophrenia, Kraepelin (1913) interpreted a variety of abnormalities found at the microscopic level by Alzheimer, Niss and others as evidence of severe and widespread cortical disease. A number of further early studies added to the list of abnormalities, but at the same time they raised doubts as to whether the findings were consistent from case to case (see Kirch & Weinberger, 1986). Ultimately, a careful review of all the studies of this era by David (1957) indicated compellingly that many of the reported abnormalities were artefacts, or minor and widely scattered, or non-specific changes, for instance related to agonal events.

The renewal of interest in the brain in schizophrenia has been accompanied by the appearance of a number of contemporary post-mortem studies. Such studies face many potential methodological pitfalls, especially when, as had by now become clear, any abnormalities are likely to be subtle and quantitative rather than qualitative in nature. As noted by Benes (1988), in these circumstances selection of controls becomes an important consideration. Matching needs to be close, especially for sex. Volume or area estimations have to be scrupulous. The cause of death, the duration of the agonal period, the post-mortem delay, the amount of time spent in fixative and numerous other factors can all introduce systematic bias and need to be comparable in patient and control groups. It is also noteworthy that several post-mortem studies have utilised series of schizophrenic brains collected earlier this century, when clinical information was liable to have been partial and inaccurate. Even though it has sometimes proved possible to apply diagnostic criteria to the case notes, it is quite possible that accessory diagnoses such as mental handicap, alcohol abuse or brain injury would not always have been recorded.

The literature on the neuropathological findings in schizophrenia has become quite large and has been reviewed several times (Kirch & Weinberger, 1986; Lantos, 1988; Roberts, 1991; Bogerts, 1993; Shapiro, 1993). Continuing the present review's emphasis on replicability, only abnormalities that have been examined for in more than one study are included here. Following Roberts (1991), three main avenues of investigation can be distinguished. These are studies of overall brain size, studies of the size of

basal ganglia and limbic system structures, and studies of histological changes.

Overall brain size

This has been examined in four studies. Brown *et al* (1986) compared 41 patients meeting Feighner criteria for schizophrenia with 29 controls consisting of patients with affective psychosis. The patients and controls were matched for age, but there were considerable differences in sex distribution. It was found that fixed brain weight was significantly less for the schizophrenic brains, which were 6% lighter. However, there was no difference in fresh brain weight.

Pakkenberg (1987) compared the brains of 29 schizophrenic patients and 30 age- and sex-matched controls. Fixed brain weight was found to be significantly (8%) lighter in the schizophrenic group. In this study no diagnostic criteria were used and it should be noted that 18 of the schizophrenics, but none of the controls, were described as being demented without further clarification.

Bruton *et al* (1990) compared 48 patients meeting Feighner criteria for schizophrenia with 48 age- and sex-matched normal controls. No difference in fresh brain weight was found, but there was a significant (4.5%) reduction in fixed brain weight. There was also a significant (4.5%) reduction in the length of the brain, which was considered to be a possibly more reliable measure of brain shrinkage than brain weight. The authors then went on to 'purify' their samples by excluding all patients and controls in whom there was evidence of moderate Alzheimer-type changes, cerebrovascular pathology or focal structural abnormality. When this was done, differences in fixed brain weight and brain length of comparable magnitude remained. (Although the authors did not provide significance figures for their 'purified' sample, they included their raw data. An analysis of covariance on 38 'purified' cases yields a difference in fixed brain weight that borders on significance ($P=0.055$) and a difference for brain length that is highly significant ($P=0.002$). Age and sex are significant determinants of brain weight ($P=0.047$ and 0.002 respectively), but these factors do not influence brain length.)

Heckers *et al* (1991) compared the brains of patients meeting DSM–III criteria for schizophrenia with normal controls, individually matched for age and sex. In a similar way to Bruton *et al* (1990), they excluded any pairs where one member showed cerebrovascular or severe senile changes; this left 23 pairs. Both fresh and fixed brain weights did not differ significantly between the patients and controls, with the volumes of the hemispheres, cortex and white matter being virtually identical.

Size of basal ganglia and limbic system structures

The relevant studies in this area are summarised in Tables 2 and 3. In the basal ganglia, a smaller internal segment of the globus pallidus was found in two studies (Bogerts *et al*, 1985, 1990*b*): in both of these, the samples were not sex matched and the diagnosis of schizophrenia was made according to ICD–9 (World Health Organization, 1977) rather than by means of a criterion-based approach. Two studies (Brown *et al*, 1986; Pakkenberg, 1990) did not replicate this finding, and one (Heckers *et al*, 1991)

Table 2
Post-mortem studies of basal ganglia structures in schizophrenia

Study	Sample	Diagnostic criteria	Caudate nucleus	Putamen	Globus pallidus	Nucleus accumbens	Comment
Bogerts *et al* (1985)	13 patients 9 controls	None	Normal	Normal	Smaller (internal segment)	Normal	Samples age but not sex matched. Comparisons not blind.
Brown *et al* (1986)	41 patients 29 controls	Feighner	Normal	Normal	Normal	–	Samples age but not sex matched. Control group consisted of patients with affective disorder. Trend towards smaller medial globus pallidus.
Bogerts *et al* (1990*b*)	18 patients 21 controls	None	Normal	Normal	Smaller (internal segment)	Normal	Samples age but not sex matched. Patients diagnosed according to ICD–9.
Pakkenberg (1990)	12 patients 12 controls	DSM–III	–	–	Normal	Smaller	Samples age and sex matched; 18 patients 'demented'.
Heckers *et al* (1991)	23 patients 23 controls	DSM–III	Larger corpus striatum		Larger	–	Samples age and sex matched. Increased striatal and pallidal size equivocal on left.

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Table 3
Post-mortem studies of limbic system structures in schizophrenia

Study	Sample	Diagnostic criteria	Hippocampus	Amygdala	Parahippocampal gyrus	Comment
Bogerts *et al* (1985)	13 patients 9 controls	None	Smaller	Smaller	Smaller	Samples age but not sex matched. Comparisons not blind.
Brown *et al* (1986)	41 patients 29 controls	Feighner	–	–	Smaller	Samples age but not sex matched. Control group consisted of patients with affective disorder.
Falkai & Bogerts (1986)/Falkai *et al* 1988)	13 patients 11 controls	None	Smaller	–	Smaller (entorhinal cortex)	Samples age but not sex matched. Patients diagnosed according to ICD-9.
Jeste & Lohr (1989)	13 patients 9 leuco-tomised controls 16 normal controls	DSM-III	Normal	–	–	Patients and normal controls age and sex matched. Half of sample did not meet DSM-III criteria.
Altshuler *et al* (1990)	12 patients 17 suicides 10 controls	DSM-III	Normal	–	Smaller	Samples not matched for age or sex. Parahippocampal gyrus reduction due to significant difference between patients and controls on right only.
Bogerts *et al* (1990*b*)	18 patients 21 controls	None	Smaller	–	–	Samples age but not sex matched. Patients diagnosed according to ICD-9.
Heckers *et al* (1990*a*)	18 patients 18 controls	DSM-III	–	–	Normal	Samples age and sex matched.
Heckers *et al* (1990*b*)	20 patients 20 controls	DSM-III	Normal	Normal	–	Samples age and sex matched.
Pakkenberg (1990)	12 patients 12 controls	DSM-III	–	? Normal	–	Samples age and sex matched. Only 5 patients and 5 controls available for analysis.
Benes *et al* (1991)	14 patients 9 controls	Feighner	Normal	–	–	Samples age matched, sex distributions not specified.

found the whole globus pallidus to be increased in size. Size reductions of the caudate nucleus and putamen have not been found. A smaller nucleus accumbens was found in one study (Pakkenberg, 1990) but not in two others (Bogerts *et al*, 1985, 1990*b*).

As regards the limbic system, only one finding, that of reduced size of the parahippocampal gyrus, has been consistently replicated, being reported in four out of five studies. The hippocampus has been found to be smaller in schizophrenic patients in three of seven studies (Bogerts *et al*, 1985, 1990*b*; Falkai & Bogerts, 1986); once again all the positive findings are in studies that failed to use criterion-based diagnosis and did not match for sex.

Histological studies

The most investigated finding of this type is that of hippocampal pyramidal cell disarray. This was first reported by Scheibel & Kovelman (1981; Kovelman & Scheibel, 1984). They compared the left hippocampus in ten clinically diagnosed schizophrenic patients and eight age-matched controls and found a disturbance of the normal orderly palisade-like arrangement of the pyramidal cells and irregularity of their dendritic domains. In a later study the same group (Altshuler *et al*, 1987) found no significant difference in the degree of hippocampal cell disarray between seven schizophrenic patients and six controls. Recently, this group (Conrad *et al*, 1991) has examined a further (overlapping) series of 11 patients and 7 controls (age matched, not sex matched and using no diagnostic criteria). This time they found significantly more hippocampal pyramidal cell disarray overall ($P=0.039$), but disorganisation was also common in the controls and there was a large variation in both groups. Three other studies that examined hippocampal cell orientation in schizophrenic patients and controls (Christison *et al*, 1989; Benes *et al*, 1991; Arnold, 1994) all failed to replicate the finding.

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Other histological claims for schizophrenia that have been investigated in more than one study include:

(a) Reduced cell numbers in the hippocampus (Falkai & Bogerts, 1986). This was partially replicated by Jeste & Lohr (1989) who found significant reductions in two of four cortical subregions in leucotomised schizophrenic patients compared to normal controls; however, there were no differences from leucotomised controls. Benes *et al* (1991) and Arnold (1994) found no significant differences in cell numbers in any subregion of the hippocampus.

(b) Reduced cell numbers in the entorhinal cortex (part of the parahippocampal gyrus). This was initially observed by Jakob & Beckmann (1986) and was replicated by Falkai *et al* (1988); however, it was not found in the study of Arnold (1994).

(c) Reduced hippocampal cell size. This was reported by Bogerts *et al* (1985), replicated by Benes *et al* (1991) and partially replicated by Arnold (1994) who found smaller cell size in one of the four hippocampal cortical subregions.

(d) Disturbed cytoarchitecture in the entorhinal cortex. This was also first noted by Jakob & Beckmann (1986). Arnold *et al* (1991) found similar changes in all of six leucotomised or lobotomised schizophrenic patients, but not in any of 16 controls, three of whom had also had similar neurosurgical procedures.

The post-mortem studies of schizophrenia do not permit a definite answer to the question of reduced overall brain size in schizophrenia, and the two most meticulous studies have had contradictory findings. If present, this abnormality could be a reflection of loss of brain substance or a correlate of lateral ventricular enlargement, or both since the two are not mutually exclusive. With respect to specific neuropathological findings, the most consistent of these is reduction in size of the parahippocampal gyrus. There seems to be no convincing evidence for size reductions of basal ganglia or limbic subcortical nuclei, and in particular the claims for reduced hippocampal size have not been found in methodologically rigorous studies. The leading candidate for histological abnormality, hippocampal cell disarray, cannot be regarded as robust and is at best a relative rather than an absolute phenomenon. Other histological findings, particularly those of cell loss and disorganisation in the parahippocampal/entorhinal cortex, are perhaps best regarded as intriguing but not firmly established as yet.

Functional brain abnormality in schizophrenia

Resting studies

Functional imaging was first applied to schizophrenia by Ingvar & Franzen (1974). Using a crude technique to measure regional cerebral blood flow, they compared 15 normal individuals (actually abstinent alcoholics), 11 patients with dementia and two groups of schizophrenic patients, one consisting of nine relatively old, chronically hospitalised patients and the other of 11 younger patients. It was found that whereas the demented patients showed significantly reduced cerebral blood flow in all areas, both of the schizophrenic groups had flow rates that were only slightly, and not significantly, lower than the controls. However, there were suggestions of a changed regional pattern of flow in both groups of schizophrenic patients, with a reversal of the normal pattern of greater flow in anterior as compared to posterior regions; this became known as hypofrontality.

Over 30 further functional imaging studies have been carried out on schizophrenic patients. Unfortunately, while these have been marked by considerable increases in technological sophistication, this has not always been accompanied by corresponding increases in sample sizes: several studies have based their conclusions on examinations of between four and ten patients. In order to reduce the 'noise' introduced by early, small-scale and sometimes poorly described studies, the investigations that will be reviewed here comprise, first, those that have included 12 or more schizophrenic patients (and control numbers approaching this) and, secondly, those that have been communicated in reasonably detailed form with full presentation of data (e.g. not as an abstract or a brief report). Studies in which scanning was carried out during performance of a vigilance task (typically the Continuous Performance Test) are included here rather than in the next section, since these did not compare resting and activation conditions, and also because such tasks are not usually considered to be tests of frontal function.

The findings of these studies are summarised in Tables 4 and 5. Only 4 of 20 studies found statistically significant reductions in overall cerebral blood flow/metabolism. One of these studies (Wolkin *et al*, 1988) was small, employing only 13 patients and eight controls, and another (Mathew *et al*, 1982) only found significant reductions in 11 of 16 cortical regions examined. One study (Paulman *et al*, 1990) found significantly increased general cerebral blood flow.

Table 4
Functional imaging studies in schizophrenia: regional cerebral glucose metabolism studies

Study	Numbers	Medication	General reduced metabolism	Hypofrontality	Comment
Buchsbaum *et al* (1984)	16 patients 13 controls	Drug free	No	Yes	Anterior: posterior ratio 1.02 in patients v. 1.08 in controls.
Farkas *et al* (1984)	13 patients 11 controls	Some drug free	No	?	No significance figures presented.
DeLisi *et al* (1985)	21 patients 21 controls	Drug free	No	Yes	Anterior: posterior ratio 1.04 in patients v. 1.11 in controls.
Gur *et al* (1987)	12 patients 12 controls	Drug free	?	No	General reductions, but not significant.
Volkow *et al* (1987)	18 patients 12 controls	All treated	No	Yes	Both patients and controls showed lower metabolism in frontal compared to occipital regions.
Cohen *et al* (1987)	16 patients 27 controls	Drug free	No	Yes	Scanning performed while subjects carried out a vigilance task.
Wiesel *et al* (1987)	20 patients 10 controls	Drug free	No	No	Patients showed significantly lower flow in left temporal region.
Wolkin *et al* (1988)	13 patients 8 controls	Drug free	Yes	Yes	Anterior: posterior ratio 1.04 in patients v. 1.11 in controls.
Szechtman *et al* (1988)	17 patients 10 controls	Some drug free	-	No	Patients showed hyperfrontality.
Buchsbaum *et al* (1990)	13 patients 18 controls	Drug free	-	Yes	Scanning performed while subjects carried out a vigilance task. Anterior: posterior ratios 1.10 and 1.07 (r and l) in patients v. 1.15 and 1.11 (r and l) in controls.
Buchsbaum *et al* (1992)	18 patients 20 controls	Drug naive	-	?	Scanning performed while subjects carried out a vigilance task. Anterior: posterior ratios significantly lower for patients in 3 of 6 frontal regions.
Siegel *et al* (1993)	70 patients 30 controls	Drug free	No	No	Anterior: posterior ratios 1.03 in patients v. 1.06 in controls, but this was due to high occipital rather than low frontal metabolism.

r = right; l = left.

Also detailed in Tables 4 and 5 are the findings concerning hypofrontality in schizophrenia. It should be pointed out that the definition of hypofrontality has differed across the studies. Some studies have measured flow/metabolism in all anterior regions, others have measured prefrontal cortex rates only, and others have subdivided the prefrontal cortex further, e.g. into dorsolateral and ventromedial or superior, middle and inferior levels. The earlier studies tended to use the frontal: occipital ratio as the measure of hypofrontality, whereas the majority of more recent studies have used absolute flow/metabolism values with or without correction for mean total brain or hemisphere rates. According to any of these definitions, 10 of 27 studies have found statistically significant hypofrontality. In two further studies hypofrontality was found but this was considered to be artefactual. Mathew *et al* (1988) found a significantly reduced anterior: posterior ratio in 108 patients compared to 108 controls, but this difference was due to significantly higher flows in temporal and occipital regions. The study of Siegel *et al* (1993), which incorporated the patients of Buchsbaum *et al* (1990) and Buchsbaum *et al* (1992), found as in these earlier studies a significantly reduced frontal: occipital ratio in schizophrenic patients, but once again this was reflective of high occipital cortical activity rather than low frontal cortical activity. Two studies found a tendency to hyperfrontality (Szechtman *et al*, 1988; Ebmeier *et al*, 1993). In most cases the differences between patients and controls have been small (of the order of 4–6% in the studies of Buchsbaum and co-workers) and none of the studies have documented a reversal of a hyperfrontal to hypofrontal pattern in schizophrenia; three studies (Paulman *et al*, 1990; Rubin *et al*, 1991; Andreasen *et al*, 1992) in fact found lower flow in frontal than occipital regions in both schizophrenic patients and controls.

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Table 5
Functional imaging studies in schizophrenia: regional cerebral blood flow studies

Study	Numbers	Medication	General reduced metabolism	Hypofrontality	Comment
Mathew *et al* (1982)	23 patients 18 controls	Some drug free	Yes	No	Significant reductions in 11 of 16 areas examined.
Ariel *et al* (1983)	29 patients 22 controls	Most treated	Yes	Yes	Anterior:posterior difference 0.3 s.d. in patients v. 0.8 s.d. in controls.
Gur *et al* (1983)	15 patients 25 controls	All treated	No	No	-
Gur *et al* (1985)	19 patients 19 controls	Drug free	No	No	-
Kurachi *et al* (1985)	16 patients 20 controls	All treated	No	Yes	Patients also showed increased flow in temporal regions.
Weinberger *et al* (1986)	20 patients 25 controls	Drug free	No	?	Patients showed significantly reduced prefrontal flow, but this disappeared when differences in end-tidal pCO_2 were controlled for.
Geraud *et al* (1987)	51 patients 36 controls	Some drug free	No	Yes	-
Dousse *et al* (1988)	27 patients 27 controls	Most treated	Yes	No	-
Mathew *et al* (1988)	108 patients 108 controls	Some drug free	-	No	Anterior:posterior ratios significantly lower in patients, but this due to high occipital flow rather than low frontal flow.
Paulman *et al* (1990)	40 patients 31 controls	Half drug free	No	No	Patients showed significantly increased general flow. Patients showed significantly more frontal and temporal perfusion deficits on visual inspection. Both patients and controls showed lower flow in frontal compared to occipital regions.
Sagawa *et al* (1990)	53 patients 32 controls	All treated	-	Yes	-
Warkentin *et al* (1990)	17 patients 17 controls	Some drug free	No	No	-
Rubin *et al* (1991)	19 patients 7 controls	Most drug free	No	No	Both patients and controls showed lower flow in frontal compared to occipital regions.
Andreasen *et al* (1992)	36 patients 15 controls	13 drug naive 23 drug free	-	No	Both patients and controls showed lower flow in frontal compared to occipital regions.
Tamminga *et al* (1992)	12 patients 12 controls	All drug free	-	No	Significant reductions in flow found in hippocampus and anterior cingulate cortex.
Ebmeier *et al* (1993)	20 patients 20 controls	All drug free or drug naive	-	No	Patients showed trend towards hyperfrontality.

This lack of uniformity in the findings does not appear to be related to differences in treatment status among the studies: it can be seen from Tables 4 and 5 that hypofrontality was found in only 6 of 15 studies carried out on drug-free or drug-naive patients. In a review of this topic, Waddington (1990) also concluded that there was little reason to suspect a systematic effect of neuroleptic treatment on the findings. Nor does it seem to be a function of the scanning technique used: from Tables 4 and 5 it is clear that there are positive and negative findings in both the flow and metabolism studies; and the findings are similarly divided in studies using the two main techniques, ^{133}Xe inhalation and PET (see Andreasen *et al*, 1992). There are a number of other factors that affect cerebral blood flow/metabolism

and might conceivably differ between schizophrenic patients, for example autonomic arousal and end-tidal pCO_2; the possible role of these cannot be systematically examined, although studies that have corrected for them have generally not found any influence on their results (the study of Weinberger *et al* (1986) is one of the few exceptions).

The possible clinical correlates of hypofrontality have been investigated in a considerable number of studies. The findings with respect to chronicity are unclear: only one study (Mathew *et al*, 1988) found direct evidence of a correlation, and in this study the measure used (anterior:posterior ratio) was not considered to reflect hypofrontality. One study (Geraud *et al*, 1987) found that hypofrontality was evident in chronic patients but not chronic patients undergoing an acute exacerbation. Another (Warkentin *et al*, 1990) similarly found that acutely exacerbated patients became more hypofrontal as they improved with treatment. However, several studies (Mathew *et al*, 1982; Buchsbaum *et al*,1984; DeLisi *et al*, 1985; Bajc *et al*, 1989; Sagawa *et al*, 1990) found no relationship with chronicity and/or number of hospitalisations. More studies have found evidence for an association between hypofrontality and presence of negative symptoms (Kurachi *et al*, 1985; Volkow *et al*, 1987; Wolkin *et al*, 1992; Ebmeier *et al*, 1993). Weisel *et al* (1987) found that 'autism' scores correlated with reduced metabolism in frontal but also several other areas. Andreasen *et al* (1992) had findings pointing in the same direction, but no formal analysis of resting frontal flows was made (there was a significant association between negative symptoms and degree of increase of frontal flow during the activation part of the study). However, Paulman *et al* (1990) found no correlations with either negative or positive symptoms and any area. The studies of Seigel *et al*, (and the previous ones of Buchsbaum *et al* 1990, 1992), found no relationship between their anterior:posterior ratios and negative or positive symptoms (this index, as with the study of Mathew *et al* (1988), was considered not to reflect hypofrontality). Only a few studies have examined the relationship between hypofrontality and neuropsychological task impairment under resting conditions. Paulman *et al* (1990) found that low left frontal flow was associated with impairment on a variety of tasks, not just frontal ones. Sagawa *et al* (1990) found a correlation between a frontal task and absolute left inferior frontal flow and also some evidence of correlations between right frontal flow and performance on non-frontal tasks. However, Cohen *et al* (1987) found no relationship between hypofrontality and a test of sustained attention.

With negative findings outnumbering positive by nearly two to one, hypofrontality cannot be regarded as a robust finding in schizophrenia. Here, though, there are grounds for appeal against a verdict of non-replication. There are strong suggestions that hypofrontality (especially when measured in terms other than anterior:posterior ratio) is a function of deficit schizophrenia, particularly as characterised by presence of negative symptoms and possibly also in relation to cognitive impairment.

Studies combining functional imaging with task activation

When normal individuals perform cognitive tasks, the pattern of regional cerebral blood flow shows changes corresponding to areas of neuronal activation. There are also areas of deactivation when some tasks are performed (e.g. Friston *et al*, 1991). Schizophrenic patients are known to perform poorly on many cognitive tasks (e.g. Chapman & Chapman, 1973; McKenna, 1994), and so it is possible that this impairment will be reflected in a lesser degree of activation of relevant brain areas on functional imaging. One area of particularly poor neuropsychological test performance in schizophrenia is executive function (Goldberg *et al*, 1987; Shallice *et al*, 1991), which is of course associated with prefrontal cortex activation (e.g. Friston *et al*, 1991). Another, it has recently emerged, is memory (e.g. McKenna *et al*, 1990; Saykin *et al*, 1991); the functional imaging correlates of this cognitive activity also involve the prefrontal cortex among other sites (Shallice *et al*, 1994).

The first study to investigate the possibility of task-related hypofrontality in schizophrenia was carried out by Weinberger *et al* (1986). They examined cerebral blood flow in 20 schizophrenic patients and 25 age- and sex-matched controls; functional imaging was carried out both at rest and during performance of the Wisconsin Card Sorting Test, a prototypical frontal/executive task. The schizophrenic patients performed more poorly than the controls on this task, as anticipated. It was also found that their neuropsychological impairment was mirrored in a significantly smaller increase in blood flow to the prefrontal cortex. No such differences were found using a non-executive task involving number matching. The authors were able to establish that the degree of failure of prefrontal cortex activation correlated with the severity of the impairment in task performance, and that the differences between patients and controls were not attributable to drug treatment. However, when they 'zeroed' the blood flow changes by subtracting the activation produced by the control

task (which itself produced significant changes in regional blood flow) from that produced by the executive task, the finding became equivocal: the overall analysis of variance across patients and controls became insignificant, although a *post-hoc* test of the difference in prefrontal flow between the groups remained significant. A subsequent study comparing a new cohort of 16 schizophrenic patients with the same control group (Weinberger *et al*, 1988) had almost exactly similar findings.

Subsequent studies of this type are shown in Table 6. Four of the seven studies replicated the finding of Weinberger *et al* (1986). One of these (Lewis *et al*, 1992) did not employ a resting condition and so could be considered an incomplete test of the hypothesis. In another study (Andreasen *et al*, 1992), which employed groups of neuroleptic-naive and neuroleptic-free patients, analysis of variance indicated significant differences among the groups in the left medial frontal region, but *post-hoc* tests revealed that only the drug-naive patients showed a significant failure to activate. In both these studies, in contrast to the original study of Weinberger *et al* (1986), there was no correlation between executive test performance and degree of prefrontal activation in the patients. There have also been two negative findings (Busatto *et al*, 1994; Gur *et al*, 1994). Another study (Kawasaki *et al*, 1993*b*) failed to find any differences between patients and controls in the dorsolateral prefrontal cortex, and so was felt by the authors not to replicate the original finding of Weinberger *et al* (1986). However, they did find a significant failure of activation in the left medial prefrontal cortex, although only on one of two cuts.

One reason for the lack of uniformity of these findings might be the imaging techniques used. These have been either ^{133}Xe inhalation, which is relatively insensitive, or single photon emission computed tomography (SPECT), which measures the progressive extravascular accumulation of a tracer and hence provides only an indirect measure of changes in regional blood flow. The fragility of the effect when it has been found could also reflect the use, in every study, of an essentially unselected group of schizophrenic patients. By no means all schizophrenic patients show neuropsychological deficits: for

Table 5
Functional imaging studies in schizophrenia with neuropsychological task activation

Study	Numbers	Medication	Neuropsychological task	Finding	Comment
Rubin *et al* (1991)	19 patients 7 controls	Most drug naive	Executive	Reduced frontal activation on left	Differences significant for left inferior prefrontal region plus trend for left superior prefrontal region.
Andreasen *et al* (1992)	13+23 patients 15 controls	13 drug naive 23 drug free	Executive	Reduced frontal activation on left, but only in drug-naive group	No diagnostic criteria given! Both patient groups also showed reduced activation in right parietal region.
Berman *et al* (1992)	10 patients 10 controls	All treated	Executive	Reduced frontal activation	Controls were non-schizophrenic monozygotic co-twins of patients. Activation lower in affected co-twin in all 10 cases.
Lewis *et al* (1992)	25 patients 25 controls	Most treated	Executive	Reduced frontal activation on left	No resting condition employed. Patients also showed increased 'activation' in left temporal and occipital regions.
Kawasaki *et al* (1993*b*)	10 patients 10 controls	All treated	Executive	No differences in dorsolateral prefrontal regions. Significant reduction in medial prefrontal region on left in 1 of 2 slices	Results interpreted as negative by authors.
Busatto *et al* (1994)	10 patients 10 controls	All treated	Memory	No differences in frontal or temporal regions	Patients performed significantly more poorly than controls on the memory task.
Gur *et al* (1994)	18 patients 18 controls	All but one untreated	Memory (verbal and non-verbal tasks)	No regionally specific differences	Significant task – region interactions for both patients and controls.

example, Bentham *et al* (unpublished) found that between 44 and 74% of a sample of acute and chronic schizophrenic patients showed normal executive function depending on the test used, and McKenna *et al* (1990) found that slightly over 50% of a similar patient group scored in the normal range on a memory test. Normal or near-normal prefrontal activation in a majority of patients with intact neuropsychological performance could therefore swamp a significant failure to activate by the minority showing task deficits. In such circumstances a decisive test of the hypothesis of task-activated hypofrontality in schizophrenia might be a study that used a very sensitive functional imaging technique and which selected patients who showed clear evidence of a specific deficit in executive or memory function.

Recently, a study that fulfils these requirements has been carried out. Liddle, Frith and co-workers (Liddle *et al*, 1994; Frith *et al*, 1995) examined the pattern of brain activation using the executive task of verbal fluency, in which subjects have to generate words in a given category. The samples consisted of six normal individuals and three groups of six medicated chronic schizophrenic patients. The schizophrenic groups were selected according to their performance on a standard verbal fluency task: the first group showed normal performance, the second showed impaired performance and the third was quantitatively normal but included more than five unusual or erroneous words. Six PET scans lasting 2 min each were carried out on each patient: two of these were during performance of a verbal fluency task and the other four incorporated control tasks that allowed the specific executive components of the task to be separated from the effects of speaking and using the semantic lexicon.

The normal subjects showed a pattern of activation in the left dorsolateral prefrontal cortex and deactivation in the superior temporal cortex bilaterally, as found previously (Friston *et al*, 1993). Taken together, the schizophrenic patients showed no failure of activation in the left prefrontal region, but instead a trend towards greater activation. This effect was most marked in the impaired subgroup of patients. However, the patients did differ from the controls, in that they showed a lack of deactivation (and if anything a tendency towards increased activation) in the superior temporal cortex on the left. Here, all three groups of schizophrenic patients showed a very similar pattern.

Hypofrontality in schizophrenia has proved difficult to establish under resting conditions, although the phenomenon shows more promise under conditions of cognitive task activation. However, the first study that has directly compared patients with and without evidence of the relevant neuropsychological deficits appears to have thrown the hypofrontality hypothesis into doubt. According to Frith, Liddle and co-workers, schizophrenic patients exhibit as much if not more prefrontal activation than controls during performance of an executive task.

Conclusion

It is evident, perhaps always has been, that any brain pathology in schizophrenia is subtle rather than gross, and takes the form of quantitative differences that must be isolated against a background of often wide normal variation rather than the presence of some easily recognisable lesion. To make matters worse, schizophrenia is a heterogeneous disorder clinically and one which many believe will ultimately be found to be aetiologically heterogeneous as well. These facts conspire to make any abnormality difficult to demonstrate in the first place, and virtually guarantee that its replication will not be a straightforward matter. In these circumstances it is the balance of evidence that becomes the deciding factor. Does this favour the acceptance of any structural or functional brain abnormality in schizophrenia?

Easily the most consistently replicated brain abnormality in schizophrenia is structural, and takes the form of lateral ventricular enlargement. This finding has had many more positive than negative replications and has surmounted the important methodological hurdle of being demonstrable in studies using rigorously representative population controls. Lateral ventricular enlargement has also been documented in a post-mortem study (Crow *et al*, 1989) that employed the same 'purified' series of brains as the study of Bruton *et al* (1990). It has also been found to be present in some of the MRI studies, with the failure to find it in all of them perhaps merely reflecting the emergent fact that large sample sizes are necessary to demonstrate the abnormality unequivocally (particularly when non-medical control groups are used).

Nevertheless, it is clear that the degree of enlargement is small and that a large majority of schizophrenic patients will have lateral ventricles that are within the normal range. The studies of Andreasen *et al* (1990*a*) and Jones *et al* (1994) also indicate that uncertainties and unresolved questions remain, for example whether or not ventricular enlargement is only present in male schizophrenic patients. Lateral ventricular enlargement does not appear to be associated with any aspect of the clinical picture and seems to emerge, as Jones *et al* (1994) concluded, as a risk factor or trait marker for schizophrenia rather than something that is of direct causal relevance.

If not of direct aetiological significance in schizophrenia, the importance of lateral ventricular enlargement may be that it indexes structural pathology elsewhere in the brain. The available CT scan studies offer few clues to the site or sites of this, but one post-mortem study has pointed to a localisation in the left temporal lobe. Crow *et al* (1989), in the study mentioned above, found that lateral ventricular enlargement in schizophrenia was largely restricted to the temporal horns, in contrast to that seen in Alzheimer's disease which was generalised. Furthermore, significant enlargement was only present on the left side; on the right side the difference between patients and controls was negligible. These findings have been corroborated to some extent in a recent MRI study of the ventricular system in schizophrenia (Degreef *et al*, 1992).

Such a view is of course consistent with the MRI studies of brain substance in schizophrenia: using consistency across studies as a criterion, the case for size reductions is strongest in the temporal lobe; the hippocampus and amygdala are particularly implicated; and there is a noticeable tendency for abnormality to be found more often on the left side. It is also consistent with the general tenor of post-mortem studies which, even if the case for hippocampal and amygdala abnormalities is discounted as inconclusive, have suggested temporal lobe pathology in the form of size reductions and cellular disorganisation of the parahippocampal gyrus. However, before these findings are accepted as a convergence of evidence, a lesson from the CT scan literature should perhaps be borne in mind that, paradoxically, the larger the study, the smaller the differences that are found. With the relatively small numbers and conflicting findings of the currently available MRI and post-mortem studies not everyone would consider the null hypothesis to be disproved just yet.

The rather surprising conclusion to be drawn from a considerable number of functional imaging studies is that a technique which is sensitive enough to register differences when the eyes are opened and closed, reveals no differences between schizophrenic patients and normal individuals. In particular, hypofrontality, or more precisely hypofrontality under resting conditions, does not seem to characterise schizophrenia as a disorder: positive findings are greatly outnumbered by negative ones and the two largest studies, one of them by a group including the staunchest advocates of hypofrontality over the years, seem if anything to point to the decidedly less interesting finding of hyperoccipitality. Nevertheless, there are two qualifications to this conclusion that leave the concept of hypofrontality in schizophrenia some room for manoeuvre.

One possibility is that functional imaging abnormalities are associated not with schizophrenia but with certain schizophrenic symptoms. In the studies that have examined the clinical correlates of resting hypofrontality, an association with negative symptoms has been a fairly consistent finding. In the most recent of these studies, Wolkin *et al* (1992) found a marked negative correlation between right dorsolateral prefrontal cortex metabolism and scores on a negative symptom scale, but no other symptom scores.

This work has been replicated and extended by Liddle and co-workers. Liddle *et al* (1992) made detailed clinical ratings on 30 stable chronic schizophrenic patients and then performed a pixel-by-pixel analysis correlating their resting PET scan appearances with scores for positive, negative and disorganisation symptoms. Negative symptoms were significantly negatively correlated with flow in widespread areas of the prefrontal cortex, particularly on the left side. There was also a negative correlation with flow in the left parietal association cortex and a positive correlation with flow in the heads of the caudate nuclei bilaterally. Positive symptoms (delusions and hallucinations) showed positive correlations with the left temporal and frontal regions, and negative correlations with a number of right hemisphere regions. Disorganisation symptoms (formal thought disorder and inappropriate affect) showed a complex pattern of positive and negative correlations that included circumscribed areas within the prefrontal cortex. Subsequently, Dolan *et al* (1993) combined the 30 patients of Liddle *et al* (1992) with 40 patients meeting diagnostic criteria for major depression who had undergone PET scanning on the same machine. The patients were divided into those showing the symptom of poverty of speech, which is common to both schizophrenia and depression. This revealed that patients showing this symptom had significantly lower flow in the left dorsolateral prefrontal cortex. Analysis of variance indicated that poverty of speech was predictive of low left prefrontal flow independent of diagnosis. Persuasive though these findings are, it is clear that they are not without complexities and it should also be pointed out that as yet no study has shown significantly lower prefrontal flow/metabolism in schizophrenic patients with negative symptoms compared to normal individuals.

It is also possible that, as a disorder, schizophrenia is associated with a subtle form of hypofrontality that only becomes apparent when the prefrontal cortex is challenged with a cognitive task. However, the available group studies combining functional imaging with neuropsychological task activation have had both positive and negative findings, and when positive some qualification to the conclusion has

invariably been required. In these circumstances, it might be anticipated that the finding could be made more robust by arranging more favourable conditions for its appearance. Contrary to expectations, however, the studies of Liddle, Frith and co-workers (Liddle *et al*, 1994; Frith *et al*, 1995), which employed the most sensitive functional imaging technique, highly sophisticated methodology and groups of patients with and without evidence of executive deficits, seem to indicate no evidence of task-activated hypofrontality, but instead a decoupling of the normal reciprocal patterns of activity in the frontal and temporal lobe. This finding should only be regarded as preliminary, and the findings of this review would certainly suggest that it needs to be replicated several times before it can be accepted. Nevertheless, it suggests that schizophrenia may be characterised not by any simple focal reductions in regional brain activity, but rather by complex alterations in the normal reciprocal patterns of activation between anatomically related areas of the cerebral cortex.

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References

ALTSHULER, L. L., CONRAD, A., KOVELMAN, J. A., *et al* (1987) Hippocampal pyramidal cell orientation in schizophrenia: a controlled neurohistologic study of the Yakovlev Collection. *Archives of General Psychiatry*, **44**, 1094–1098.

———, CASANOVA, M. F., GOLDBERG, T. E., *et al* (1990) The hippocampus and parahippocampus in schizophrenic, suicide and control brains. *Archives of General Psychiatry*, **47**, 1029–1034.

AMERICAN PSYCHIATRIC ASSOCIATION (1980) *Diagnostic and Statistical Manual of Mental Disorders* (3rd edn) (DSM-III). Washington, DC: APA.

ANDREASEN, N. C., NASRALLAH, H. A., DUNN, V., *et al* (1986) Structural abnormalities in the frontal system in schizophrenia. *Archives of General Psychiatry*, **43**, 136–144.

———, SWAYZE, V. W., FLAUM, M., *et al* (1990*a*) Ventricular enlargement in schizophrenia evaluated with computed tomographic scanning. *Archives of General Psychiatry*, **47**, 1008–1015.

———, EHRARDT, J. C., SWAYZE, V. W., *et al* (1990*b*) Magnetic resonance imaging of the brain in schizophrenia: the pathophysiologic significance of structural abnormalities. *Archives of General Psychiatry*, **47**, 35–44.

———, REZAI, K., ALLIGER, R., *et al* (1992) Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia. *Archives of General Psychiatry*, **49**, 943–958.

ARIEL, R. N., GOLDEN, C. J., BERG, R. A., *et al* (1983) Regional cerebral blood flow in schizophrenics. *Archives of General Psychiatry*, **40**, 258–263.

ARNOLD, S. E. (1994) Investigations of neuronal morphology and the neuronal cytoskeleton in the hippocampal region in schizophrenia. *Neuropsychopharmacology*, **10**, 634S.

———, HYMAN, B. T., VAN HOESEN, G. W., *et al* (1991) Some cytoarchitectural abnormalities of the entorhinal cortex in schizophrenia. *Archives of General Psychiatry*, **48**, 625–632.

BAJC, M., MEDVED, V., BASIC, M., *et al* (1989) Cerebral perfusion inhomogeneities in schizophrenia demonstrated with single photon emission computed tomography and ^{99m}Tc-hexamethylpropyleneamineoxime. *Acta Psychiatrica Scandinavica*, **80**, 427–433.

BARTA, P. E., PEARLSON, G. D., POWERS, R. E., *et al* (1990) Auditory hallucinations and smaller superior temporal gyral volume in schizophrenia. *American Journal of Psychiatry*, **147**, 1457–1462.

BEBBINGTON, P. & KUIPERS, L. (1988) Social influences on schizophrenia. In *Schizophrenia: the Major Issues* (eds P. Bebbington & P. McGuffin), pp. 201–225. Oxford: Heinemann/Mental Health Foundation.

BENES, F. M. (1988) Post-mortem structural analyses of schizophrenic brain: study designs and the interpretation of data. *Psychiatric Developments*, **6**, 213–226.

———, SORENSEN, I. & BIRD, E. D. (1991) Reduced neuronal size in posterior hippocampus of schizophrenic patients. *Schizophrenia Bulletin*, **17**, 597–608.

BERMAN, K. F., TORREY, E. F., DANIEL, D. G., *et al* (1992) Regional cerebral blood flow in monozygotic twins discordant and concordant for schizophrenia. *Archives of General Psychiatry*, **49**, 927–934.

BOGERTS, B. (1993) Recent advances in the neuropathology of schizophrenia. *Schizophrenia Bulletin*, **19**, 431–445.

———, MEERTZ, E. & SCHOENFELDT-BAUSCH, R. (1985) Basal ganglia and limbic system pathology in schizophrenia: a morphometric study of brain volume shrinkage. *Archives of General Psychiatry*, **42**, 784–791.

———, ASHTARI, M., DEGREEF, G., *et al* (1990*a*) Reduced temporal limbic structure volumes on magnetic resonance imaging in first episode schizophrenia. *Psychiatry Research: Neuroimaging*, **35**, 1–13.

———, FALKAI, P., HAUPTS, M., *et al* (1990*b*) Post-mortem volume measurements of limbic system and basal ganglia structures in chronic schizophrenics. *Schizophrenia Research*, **3**, 295–301.

———, LIEBERMAN, J. A., ASHTARI, M., *et al* (1993) Hippocampus–amygdala volumes and psychopathology in chronic schizophrenia. *Biological Psychiatry*, **33**, 236–246.

BORNSTEIN, R. A., SCHWARTZKOPF, S. B., OLSON, S. C., *et al* (1992) Third-ventricle enlargement and neuropsychological deficit in schizophrenia. *Biological Psychiatry*, **31**, 954–961.

BREIER, A., BUCHANAN, R. W., ELKASHEF, A., *et al* (1992) Brain morphology and schizophrenia. *Archives of General Psychiatry*, **49**, 921–926.

BROWN, R., COLTER, N., CORSELLIS, J. A. N., *et al* (1986) Postmortem evidence of structural brain changes in schizophrenia: differences in brain weight, temporal horn area, and parahippocampal gyrus compared with affective disorder. *Archives of General Psychiatry*, **43**, 36–42.

BRUTON, C. J., CROW, T. J., FRITH, C. D., *et al* (1990) Schizophrenia and the brain: a prospective post-mortem study. *Psychological Medicine*, **20**, 285–304.

BUCHSBAUM, M. S., DELISI, L. E., HOLCOMB, H. H., *et al* (1984) Anteroposterior gradients in cerebral glucose use in schizophrenia and affective disorders. *Archives of General Psychiatry*, **41**, 1159–1166.

———, NUECHTERLEIN, K. H., HAIER, R. J., *et al* (1990) Glucose metabolic rate in normals and schizophrenics during the continuous performance test assessed by positron emission tomography. *British Journal of Psychiatry*, **156**, 216–227.

———, HAIER, R. J., POTKIN, S. G., *et al* (1992) Fronto-striatal disorder of cerebral metabolism in never-medicated schizophrenic patients. *Archives of General Psychiatry*, **49**, 935–942.

BUSATTO, G. F., COSTA, D. C., ELL, P. J., *et al* (1994) Regional cerebral blood flow (rCBF) in schizophrenia during verbal memory activation: a ^{99m}Tc-HMPAO single photon emission tomography (SPET) study. *Psychological Medicine*, **24**, 463–472.

CHAPMAN, L. J. & CHAPMAN, J. P. (1973) *Disordered Thought in Schizophrenia*. New York: Appleton-Century-Crofts.

CHRISTISON, G. W., CASANOVA, M. F., WEINBERGER, D. R., *et al* (1989) A quantitative investigation of hippocampal pyramidal cell size, shape, and variability of orientation in schizophrenia. *Archives of General Psychiatry*, **46**, 1027–1032.

COFFMAN, J. A. & NASRALLAH, H. A. (1986) Magnetic brain imaging in schizophrenia. In *The Neurology of Schizophrenia* (eds H. A. Nasrallah & D. R. Weinberger), pp. 251–266. Amsterdam: Elsevier.

COHEN, R. M., SEMPLE, W. E., GROSS, M., *et al* (1987) Dysfunction in a prefrontal substrate of sustained attention in schizophrenia. *Life Sciences*, **40**, 2031–2039.

COLOMBO, C., ABBRUZZESE, M., LIVIAN, S., *et al* (1993) Memory functions and temporal–limbic morphology in schizophrenia. *Psychiatry Research: Neuroimaging*, **50**, 45–56.

CONRAD, A. J., ABEBE, T., AUSTIN, R., *et al* (1991) Hippocampal pyramidal cell disarray in schizophrenia as a bilateral phenomenon. *Archives of General Psychiatry*, **48**, 413–417.

CRAWLEY, J. C., CROW, T. J., JOHNSTONE, E. C., *et al* (1986) Dopamine D2 receptors in schizophrenia studied in vivo. *Lancet*, *ii*, 224–225.

CROW, T. J., BALL, J., BLOOM, S. R., *et al* (1989) Schizophrenia as an anomaly of development of cerebral asymmetry: a post-mortem study and a proposal concerning the genetic basis of the disorder. *Archives of General Psychiatry*, **46**, 1145–1150.

DAUPHINAIS, I. D., DELISI, L. E., CROW, T. J., *et al* (1990) Reduction in temporal lobe size in siblings with schizophrenia: a magnetic resonance imaging study. *Psychiatry Research: Neuroimaging*, **35**, 135–147.

DAVID, G. B. (1957) The pathological anatomy of the schizophrenias. In *Schizophrenia: Somatic Aspects* (ed. D. Richter), pp. 93–130. Oxford: Pergamon.

DAY, R. (1981) Life events and schizophrenia: the "triggering" hypothesis. *Acta Psychiatrica Scandinavica*, **64**, 97–122.

DEGREEF, G., ASHTARI, M., BOGERTS, B., *et al* (1992) Volumes of ventricular system subdivisions measured from magnetic resonance images in first-episode schizophrenic patients. *Archives of General Psychiatry*, **49**, 531–537.

DELISI, L., BUCHSBAUM, M. S., HOLCOMB, H. H., *et al* (1985) Clinical correlates of decreased anteroposterior gradients in positron emission tomography (PET) of schizophrenic patients. *American Journal of Psychiatry*, **142**, 78–81.

———, DAUPHINAIS, I. & GERSHON, E. S. (1988) Perinatal complications and reduced size of brain limbic structures in familial schizophrenia. *Schizophrenia Bulletin*, **14**, 185–191.

———, HOFF, A. L., SCHWARTZ, J. E., *et al* (1991) Brain morphology in first-episode schizophrenic-like patients: a quantitative magnetic resonance imaging study. *Biological Psychiatry*, **29**, 159–175.

DEMYER, M. K., GILMOR, R. L., HENDRIE, H. C., *et al* (1988) Magnetic resonance image in schizophrenic and normal subjects: influence of diagnosis and education. *Schizophrenia Bulletin*, **14**, 21–32.

DI MICHELE, V., ROSSI, A., STRATTA, P., *et al* (1992) Neuropsychological and clinical correlates of temporal lobe anatomy in schizophrenia. *Acta Psychiatrica Scandinavica*, **85**, 484–488.

DOLAN, R. J., BENCH, C. J., LIDDLE, P. F., *et al* (1993) Dorsolateral prefrontal cortex dysfunction in the major psychoses; symptom or disease specificity? *Journal of Neurology, Neurosurgery and Psychiatry*, **56**, 1290–1294.

DOUSSE, M., MAMO, H., PONSIN, J. C., *et al* (1988) Cerebral blood flow in schizophrenia. *Experimental Neurology*, **100**, 98–111.

EBMEIER, K. P., BLACKWOOD, D. H. R., MURRAY, C., *et al* (1993) Single-photon emission computed tomography with ^{99m}Tc-exametrazine in unmedicated schizophrenic patients. *Biological Psychiatry*, **33**, 487–495.

FALKAI, P. & BOGERTS, B. (1986) Cell loss in the hippocampus of schizophrenics. *European Archives of Psychiatry and Neurological Sciences*, **236**, 154–161.

———, ——— & ROZUMEK, M. (1988) Limbic pathology in schizophrenia: the entorhinal region – a morphometric study. *Biological Psychiatry*, **24**, 515–521.

FARDE, L., WIESEL, F.-A., HALL, H., *et al* (1987) No D2 receptor increase in PET study of schizophrenia. *Archives of General Psychiatry*, **44**, 671–672.

———, ———, STONE-ELANDER, S., *et al* (1990) D2 dopamine receptors in neuroleptic-naive schizophrenic patients: a positron emission tomography study with [^{11}C]raclopride. *Archives of General Psychiatry*, **47**, 213–219.

FARKAS, T., WOLF, A. P., JAEGER, J., *et al* (1984) Regional brain glucose metabolism in chronic schizophrenia: a positron emission transaxial tomographic study. *Archives of General Psychiatry*, **41**, 293–300.

FRISTON, K. J., FRITH, C. D., LIDDLE, P. F., *et al* (1991) Investigating a network model of word generation with positron emission tomography. *Proceedings of the Royal Society of London B*, **244**, 101–106.

———, ———, ———, *et al* (1993) Functional connectivity: the principal component analysis of large (PET) data sets. *Journal of Cerebral Blood Flow and Metabolism*, **15**, 5–14.

FRITH, C. D., FRISTON, K. J., HEROLD, S., *et al* (1995) Regional brain activity in chronic schizophrenic patients during the performance of a verbal fluency task: evidence for a failure of inhibition in left superior temporal cortex. *British Journal of Psychiatry*, in press.

GERAUD, G., ARNE-BES, M. C., GUELL, A., *et al* (1987) Reversibility of hemodynamic hypofrontality in schizophrenia. *Journal of Cerebral Blood Flow and Metabolism*, **7**, 9–12.

GOLDBERG, T. E., WEINBERGER, D. R., BERMAN, K. F., *et al* (1987) Further evidence for dementia of prefrontal type in schizophrenia? A controlled study of teaching the Wisconsin Card Sorting Test. *Archives of General Psychiatry*, **44**, 1008–1014.

GOTTESMAN, I. I. (1991) *Schizophrenia Genesis: the Origins of Madness*. New York: Freeman.

GUR, R. E., SKOLNICK, B. E. & GUR, R. C. (1983) Brain function in psychiatric disorders I: regional cerebral blood flow in medicated schizophrenics. *Archives of General Psychiatry*, **40**, 1250–1254.

———, GUR, R. C., SKOLNICK, B. E., *et al* (1985) Brain function in psychiatric disorders III: regional cerebral blood flow in unmedicated schizophrenics. *Archives of General Psychiatry*, **42**, 329–334.

———, RESNICK, S. M., ALAVI, A., *et al* (1987) Regional brain function in schizophrenia I: a positron emission tomography study. *Archives of General Psychiatry*, **44**, 119–125.

———, MOZLEY, P. D., RESNICK, S. M., *et al* (1991) Magnetic resonance imaging in schizophrenia. *Archives of General Psychiatry*, **48**, 407–412.

———, JAGGI, J. L., SHTASEL, J., *et al* (1994) Cerebral blood flow in schizophrenia: effects of memory processing on regional activation. *Biological Psychiatry*, **35**, 3–15.

HALL, L. D., HERROD, J., CARPENTER, T. A., *et al* (1994) Magnetic resonance imaging in schizophrenia: a review of clinical and methodological issues. In *Schizophrenia: Exploring the Spectrum of Psychosis* (eds R. J. Ancill, S. Halliday & J. Higenbottam), pp. 115–135. Chichester: Wiley.

HARVEY, I., RON, M. A., DU BOULAY, G., *et al* (1993) Reduction of cortical volume in schizophrenia on magnetic resonance imaging. *Psychological Medicine*, **23**, 591–604.

HECKERS, S., HEINSEN, H., HEINSEN, Y., *et al* (1990*a*) Morphometry of the parahippocampal gyrus in schizophrenics and controls: some anatomical considerations. *Journal of Neural Transmission*, **80**, 151–155.

——, ——, ——, *et al* (1990*b*) Limbic structures and lateral ventricle in schizophrenia: a quantitative postmortem study. *Archives of General Psychiatry*, **47**, 1016–1022.

——, ——, ——, *et al* (1991) Cortex, white matter, and basal ganglia in schizophrenia: a volumetric postmortem study. *Biological Psychiatry*, **29**, 556–566.

HERITCH, A. J. (1990) Evidence for reduced and dysregulated turnover of dopamine in schizophrenia. *Schizophrenia Bulletin*, **16**, 605–615.

HIETALA, J., SYVALATHI, E., VAORIO, K., *et al* (1994) Striatal D2 dopamine receptor characteristics in neuroleptic-naive schizophrenic patients studied with positron emission tomography. *Archives of General Psychiatry*, **51**, 116–123.

HIRSCH, S. R. & LEFF, J. P. (1975) *Abnormalities in Parents of Schizophrenics*. London: Oxford University Press.

INGVAR, D. H. & FRANZEN, G. (1974) Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. *Acta Psychiatrica Scandinavica*, **50**, 425–462.

JAKOB, H. & BECKMANN, H. (1986) Prenatal developmental disturbances in the limbic allocortex in schizophrenics. *Journal of Neural Transmission*, **65**, 303–326.

JERNIGAN, T. L., ZISOOK, S., HEATON, R. K., *et al* (1991) Magnetic resonance imaging abnormalities in lenticular nuclei and cerebral cortex in schizophrenia. *Archives of General Psychiatry*, **48**, 881–890.

JESTE, D. V. & LOHR, J. B. (1989) Hippocampal pathologic findings in schizophrenia. *Archives of General Psychiatry*, **46**, 1019–1024.

JOHNSTONE, E. C., CROW, T. J., FRITH, C. D., *et al* (1976) Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *Lancet*, *ii*, 924–926.

——, OWENS, D. G. C., CROW, T. J., *et al* (1989) Temporal lobe structure as determined by nuclear magnetic resonance in schizophrenia and bipolar affective disorder. *Journal of Neurology, Neurosurgery and Psychiatry*, **52**, 736–741.

JONES, P. B., HARVEY, I., LEWIS, S. W., *et al* (1994) Cerebral ventricle dimensions as risk factors for schizophrenia and affective psychosis. *Psychological Medicine*, **24**, 995–1011.

KAWASAKI, Y., MAEDA, Y., URATA, K., *et al* (1993*a*) A quantitative magnetic resonance imaging study of patients with schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*, **242**, 268–272.

——, ——, SUZUKI, M., *et al* (1993*b*) SPECT analysis of regional cerebral blood flow changes in patients with schizophrenia during the Wisconsin Card Sorting Test. *Schizophrenia Research*, **10**, 109–116.

KELSOE, J., CADET, J. L., PICKAR, D., *et al* (1988) Quantitative neuroanatomy in schizophrenia. *Archives of General Psychiatry*, **45**, 533–541.

KIRCH, D. G. & WEINBERGER, D. R. (1986) Anatomical neuropathology in schizophrenia: post-mortem findings. In *Handbook of Schizophrenia, Vol. 1, The Neurology of Schizophrenia* (eds H. A. Nasrallah & D. R. Weinberger), pp. 325–348. Amsterdam: Elsevier.

KOVELMAN, J. A. & SCHEIBEL, A. B. (1984) A neurohistological correlate of schizophrenia. *Biological Psychiatry*, **19**, 1601–1621.

KRAEPELIN, E. (1913) *Dementia Praecox and Paraphrenia* (trans. R. M. Barclay, 1919). Edinburgh: Livingstone.

KURACHI, M., KOBAYASHI, K., MATUSBARA, R., *et al* (1985) Regional cerebral blood flow in schizophrenic disorders. *European Neurology*, **24**, 176–181.

LANTOS, P. (1988) The neuropathology of schizophrenia: a critical review of recent work. In *Schizophrenia: the Major Issues* (eds P. Bebbington & P. McGuffin), pp. 73–89. Oxford: Heinemann/Mental Health Foundation.

LEFF, J. (1991) Schizophrenia in the melting pot. *Nature*, **353**, 693–694.

LEWIS, S. W. (1990) Computerised tomography in schizophrenia 15 years on. *British Journal of Psychiatry*, **157** (suppl. 9), 16–24.

——, FORD, R. A., SYED, G. M., *et al* (1992) A controlled study of ^{99m}Tc-HMPAO single-photon emission ima[illegible] in chronic schizophrenia. *Psychological Medicine*, **22**, 27[illegible]

LIDDLE, P. F., FRISTON, K. J., FRITH, C. D., *et al* [illegible]2) Patterns of cerebral blood flow in schizophrenia. *British Journal of Psychiatry*, **160**, 179–186.

——, HEROLD, S., FLETCHER, P., *et al* (1994) A PET study of word generation in schizophrenia. *Schizophrenia Research*, **11**, 168.

MARSH, L., SUDDATH, R. L., HIGGINS, N., *et al* (1994) Medial temporal lobe structures in schizophrenia: relationship of size to duration of illness. *Schizophrenia Research*, **11**, 225–238.

MARTINOT, J. L., PERON-MAGNAN, D., HURET, J. D., *et al* (1990) Striatal D2 dopaminergic receptors assessed with positron emission tomography and ^{76}Br bromospiperone in untreated schizophrenic patients. *American Journal of Psychiatry*, **147**, 44–50.

——, PAILLERE-MARTINOT, M. L., LICH, C., *et al* (1991) The estimated density of D2 striatal dopamine receptors in schizophrenia. A study with ^{76}Br bromolisuride. *British Journal of Psychiatry*, **158**, 346–351.

MATHEW, R. J., DUNCAN, G. C., WEINMAN, M. L., *et al* (1982) Regional cerebral blood flow in schizophrenia. *Archives of General Psychiatry*, **39**, 1121–1124.

——, WILSON, W. H., TANT, S. R., *et al* (1988) Abnormal resting regional blood flow patterns and their correlates in schizophrenia. *Archives of General Psychiatry*, **45**, 542–549.

MCGUFFIN, P., ASHERSON, P., OWEN, M., *et al* (1994) The strength of the genetic effect: is there room for an environmental influence in the aetiology of schizophrenia. *British Journal of Psychiatry*, **164**, 593–599.

MCKENNA, P. J. (1994) *Schizophrenia and Related Syndromes*. Oxford: Oxford University Press.

——, TAMLYN, D., LUND, C. E., *et al* (1990) Amnesic syndrome in schizophrenia. *Psychological Medicine*, **20**, 967–972.

NESTOR, P. G., SHENTON, M. E., MCCARLEY, R. W., *et al* (1993) Neuropsychological correlates of MRI temporal lobe abnormalities in schizophrenia. *American Journal of Psychiatry*, **150**, 1849–1855.

OWENS, D. G. C., JOHNSTONE, E. C., CROW, T. J., *et al* (1985) Lateral ventricular size in schizophrenia: relationship to the disease process and its clinical manifestations. *Psychological Medicine*, **15**, 27–41.

PAKKENBERG, B. (1987) Post-mortem study of chronic schizophrenic brains. *British Journal of Psychiatry*, **151**, 744–752.

—— (1990) Pronounced reduction of total neuron number in mediodorsal thalamic nucleus and nucleus accumbens in schizophrenics. *Archives of General Psychiatry*, **47**, 1023–1028.

PAULMAN, R. G., DEVOUS, M. D., GREGORY, R. R., *et al* (1990) Hypofrontality and cognitive impairment in schizophrenia: dynamic single-photon tomography and neuropsychological assessment of schizophrenic brain function. *Biological Psychiatry*, **27**, 377–399.

PILOWSKY, L. S. (1992) Understanding schizophrenia. *British Medical Journal*, **305**, 327–328.

——, COSTA, D. C., ELL, P. J., *et al* (1994) D2 dopamine receptor binding in the basal ganglia of antipsychotic-free schizophrenic patients: ^{123}IBZM single photon emission tomography (SPET) study. *British Journal of Psychiatry*, **164**, 16–26.

RAINE, A., LENCZ, T., REYNOLDS, G., *et al* (1992) Evaluation of structural and functional prefrontal deficits in schizophrenia. *Psychiatry Research: Neuroimaging*, **45**, 123–137.

RAZ, S. & RAZ, N. (1990) Structural brain abnormalities in the major psychoses: a quantitative review of the evidence from computerised imaging. *Psychological Bulletin*, **108**, 93–108.

——, RAZ, N. & BIGLER, E. D. (1988) Ventriculomegaly in schizophrenia: is the choice of controls important? *Psychiatry Research*, **24**, 71–77.

ROBERTS, G. W. (1991) Schizophrenia: a neuropathological perspective. *British Journal of Psychiatry*, **158**, 8–17.

RON, M. A. & HARVEY, I. (1990) The brain in schizophrenia. *Journal of Neurology, Neurosurgery and Psychiatry*, **53**, 725–726.

ROSSI, A., STRATTA, P., D'ALBENZIO, L., *et al* (1990) Reduced temporal lobe areas in schizophrenia. *Biological Psychiatry*, **27**, 61–68.

———, ———, MANCINI, F., *et al* (1994) Magnetic resonance imaging findings of amygdala–hippocampus shrinkage in male patients with schizophrenia. *Psychiatry Research*, **52**, 43–53.

RUBIN, P., HOLM, S., FRIBERG, L., *et al* (1991) Altered modulation of prefrontal and subcortical brain activity in newly diagnosed schizophrenia and schizophreniform psychosis: a regional cerebral blood flow study. *Archives of General Psychiatry*, **48**, 987–995.

SAGAWA, K., KAWAKATSU, S., SHIBUYA, I., *et al* (1990) Correlation of regional cerebral blood flow with performance on neuropsychological tests in schizophrenic patients. *Schizophrenia Research*, **3**, 241–246.

SAYKIN, A. J., GUR, R. C., GUR, R. E., *et al* (1991) Neuropsychological function in schizophrenia: selective impairment in memory and learning. *Archives of General Psychiatry*, **48**, 618–624.

SCHEIBEL, A. B. & KOVELMAN, J. A. (1981) Disorientation of the hippocampal pyramidal cell and its processes in the schizophrenic patient. *Biological Psychiatry*, **16**, 101–102.

SCHLAEPFER, T. E., HARRIS, G. J., TIEN, A. Y., *et al* (1994) Decreased regional cortical gray matter volume in schizophrenia. *American Journal of Psychiatry*, **151**, 842–848.

SEEMAN, P. (1987) Dopamine receptors and the dopamine hypothesis of schizophrenia. *Synapse*, **1**, 133–152.

SEIDMAN, L. J., YURGELIN-TODD, D., KREMEN, W. S., *et al* (1994) Relationship of prefrontal and temporal lobe MRI measures to neuropsychological performance in chronic schizophrenia. *Biological Psychiatry*, **35**, 235–246.

SHALLICE, T., BURGESS, P. W. & FRITH, C. D. (1991) Can the neuropsychological case-study approach be applied to schizophrenia. *Psychological Medicine*, **21**, 661–673.

———, FLETCHER, P., FRITH, C. D., *et al* (1994) Brain regions associated with acquisition and retrieval of verbal episodic memory. *Nature*, **368**, 633–635.

SHAPIRO, R. M. (1993) Regional neuropathology in schizophrenia: where are we? Where are we going. *Schizophrenia Research*, **10**, 187–239.

SHENTON, M. E., KIKINIS, R., JOLESZ, F. A., *et al* (1992) Abnormalities of the left temporal lobe and thought disorder in schizophrenia. *New England Journal of Medicine*, **327**, 604–612.

SIEGEL, B. V., BUCHSBAUM, M. S., BUNNEY, W. E., *et al* (1993) Cortical–striatal–thalamic circuits and brain glucose metabolism in 70 unmedicated male schizophrenic patients. *American Journal of Psychiatry*, **150**, 1325–1336.

SMITH, G. N. & IACONO, W. G. (1986) Lateral ventricular size in schizophrenia and choice of control group. *Lancet*, *i*, 1450.

SMITH, R. C., BAUMGARTNER, R. & CALDERON, M. (1987) Magnetic resonance imaging studies of the brains of schizophrenic patients. *Psychiatry Research*, **20**, 33–46.

SPITZER, R. L., ENDICOTT, J. & ROBINS, E. (1978) *Research Diagnostic Criteria for a Selected Group of Functional Disorders*. New York: Biometric Research, New York State Psychiatric Institute.

SUDDATH, R. L., CASANOVA, M. F., GOLDBERG, T. E., *et al* (1989) Temporal lobe pathology in schizophrenia: a quantitative magnetic resonance imaging study. *American Journal of Psychiatry*, **146**, 464–472.

———, CHRISTISON, G. W., TORREY, E. F., *et al* (1990) Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. *New England Journal of Medicine*, **322**, 789–794.

SZECHTMAN, H., NAHMIAS, C., GARNETT, S., *et al* (1988) Effect of neuroleptics on altered cerebral glucose metabolism in schizophrenia. *Archives of General Psychiatry*, **45**, 523–532.

TAMMINGA, C. A., THAKER, G. K., BUCHANAN, M., *et al* (1992) Limbic system abnormalities identified in schizophrenia using positron emission tomography with fluorodeoxyglucose and neocortical alterations with deficit syndrome. *Archives of General Psychiatry*, **49**, 522–530.

TORREY, F. C. (1992) Are we overestimating the genetic contribution to schizophrenia? *Schizophrenia Bulletin*, **18**, 159–170.

TUNE, L. E., WONG, D. F. & PEARLSON, G. D. (1992) Elevated dopamine D2 receptor density in 23 schizophrenic patients: a positron emission tomography study with [^{11}C]N-methylspiperone. *Schizophrenia Research*, **6**, 147.

UEMATSU, M. & KAIYA, H. (1989) Midsagittal cortical pathomorphology of schizophrenia: a magnetic resonance imaging study. *Psychiatry Research*, **30**, 11–20.

VAN HORN, J. D. & MCMANUS, I. C. (1992) Ventricular enlargement in schizophrenia: a meta-analysis of studies of the ventricle : brain ratio (VBR). *British Journal of Psychiatry*, **160**, 687–697.

VOLKOW, N. D., WOLF, A. P., VAN GELDER, P., *et al* (1987) Phenomenological correlates of metabolic activity in 18 patients with chronic schizophrenia. *American Journal of Psychiatry*, **144**, 151–158.

WADDINGTON, J. L. (1990) Sight and insight: regional cerebral metabolic activity in schizophrenia visualised by positron emission tomography, and competing neurodevelopmental perspectives. *British Journal of Psychiatry*, **156**, 615–619.

WARKENTIN, S., NILSSON, A., RISBERG, J., *et al* (1990) Regional cerebral blood flow in schizophrenia: repeated studies during a psychotic episode. *Psychiatry Research: Neuroimaging*, **35**, 27–38.

WEINBERGER, D. R., TORREY, E. F., NEOPHYTIDES, A. N., *et al* (1979) Lateral cerebral ventricular enlargement in schizophrenia. *Archives of General Psychiatry*, **36**, 735–739.

———, BERMAN, K. F. & ZEC, R. F. (1986) Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia: I. Regional cerebral blood flow evidence. *Archives of General Psychiatry*, **43**, 114–124.

———, ——— & ILLOWSKY, B. P. (1988) Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia: III. A new cohort and evidence for a monoaminergic mechanism. *Archives of General Psychiatry*, **45**, 609–615.

WIESEL, F. A., WIK, G., SJOGREN, G., *et al* (1987) Regional brain glucose metabolism in drug free schizophrenic patients and clinical correlates. *Acta Psychiatrica Scandinavica*, **76**, 628–641.

WOLKIN, A., ANGRIST, B., WOLF, A., *et al* (1988) Low frontal glucose utilization in chronic schizophrenia: a replication study. *American Journal of Psychiatry*, **145**, 251–253.

———, SANFILIPO, M., WOLF, A. P., *et al* (1992) Negative symptoms and hypofrontality in chronic schizophrenia. *Archives of General Psychiatry*, **49**, 959–965.

WONG, D. F., WAGNER, H. N., TUNE, L. E., *et al* (1986) Positron emission tomography reveals elevated D2 dopamine receptors in drug-naive schizophrenics. *Science*, **234**, 1558–1563.

WORLD HEALTH ORGANIZATION (1977) *The Ninth Revision of the International Statistical Classification of Diseases, Injuries and Causes of Death* (ICD-9). Geneva: WHO.

YOUNG, A. H., BLACKWOOD, D. H. R., ROXBURGH, H., *et al* (1991) A magnetic resonance imaging study of schizophrenia. *British Journal of Psychiatry*, **158**, 158–164.

ZIPURSKY, R. B., LIM, K. O., SULLIVAN, E. V., *et al* (1992) Widespread cerebral gray matter volume deficits in schizophrenia. *Archives of General Psychiatry*, **49**, 195–205.

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