

# Neuroimaging of schizophrenia: structural abnormalities and pathophysiological implications

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**Abstract:** Schizophrenia, once considered a psychological malady devoid of any organic brain substrate, has been the focus of intense neuroimaging research. Findings reveal mild but generalized tissue loss as well as more selective focal loss. It is unclear whether these abnormalities reflect neurodevelopmental or neurodegenerative processes, or some combination of each; current evidence favors a preponderance of neurodevelopmental abnormalities. The pattern of brain abnormalities is also influenced by environmental and genetic risk factors, as well as by the course (and possibly even treatment) of this illness. These findings are described in this article.

**Keywords:** schizophrenia, brain imaging, magnetic resonance imaging

## Introduction

Schizophrenia is a major mental disorder most often characterized by functional impairment and by the presentation, persistence, and severity of symptoms (Table 1). It is considered as a brain disorder (Jones and Buckley 2003; McClure and Lieberman 2003). Although its fundamental pathobiology remains elusive, neuroimaging studies provide compelling evidence of (subtle) abnormalities of cerebral structure and function in patients with schizophrenia (McCarley et al 1999; Wright et al 2000; Flashman and Green 2004). This article reviews our understanding of the nature and extent of structural brain abnormalities in schizophrenia.

## The origins of schizophrenia: pathophysiological speculations

An argument has raged back and forth as to whether the brain abnormalities in schizophrenia are either neurodegenerative or neurodevelopmental in origin (Weinberger and Marengo 2003). The neurodevelopmental view held ascendancy until several recent studies which have now provided evidence of progressive brain deterioration (DeLisi et al 1997; Vita et al 1997; Matheron et al 2001; Thompson et al 2001; Cahn et al 2002; Ho, Andreasen, et al 2003; Sporn et al 2003). Current theories concerning the origins of schizophrenia suggest these structural neuroimaging changes are evidence of a neurodevelopmental basis for schizophrenia, arising from early noxious events (intra utero and perhaps also in early childhood/adolescence) that are either genetic or environmental or involve some combination of the two types of events (Buckley et al 2003; Weinberger and Marengo 2003). While this neurodevelopmental model has held ascendancy in conceptualizing the onset and cause(s) of schizophrenia, there is also evidence of progressive brain changes (neurodegenerative processes) in some patients with schizophrenia. There is evidence

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**Table 1** Core characteristics of schizophrenia

- Delusions
  - Persecutory
  - Referential
  - Guilt
  - Religious
  - Nihilism
  - Somatic
  - Bizarre
- Hallucinations
  - Auditory
  - Visual
  - Somatic
  - Olfactory
- Thought disorder
  - Loosening of association
  - Neologisms
  - Word salad
- Negative symptoms
  - Apathy
  - Avolition
  - Amotivation
  - Neglect
  - Alogia
- Cognitive impairment
  - Memory
  - Attention and concentration
- Impairment of insight into illness
- Functional impairment
  - Vocational
  - Social
  - Interpersonal

NOTE: There is no single, pathognomonic feature of schizophrenia. The constellation of symptoms is otherwise not attributable to mood disorder, substance abuse, or any organic brain disorder.

that these changes are present (to a similar extent and magnitude) in first-episode schizophrenia patients. A summary of recent neuroimaging findings in populations with first-episode schizophrenia is provided in Table 2. More recent, neuroimaging studies have tracked the course of these brain changes and they show a deterioration in brain structure with compelling evidence now of loss of cortical tissue and progressive ventricular enlargement (DeLisi et al 1997; Mathalon et al 2001; Ho, Andreasen, et al 2003;

**Table 2** Overview of structural neuroimaging abnormalities in schizophrenia

- Generalized
  - Cortical tissue loss
  - Lateral ventricular enlargement
  - Third ventricle enlargement
- Regional
  - Smaller thalamus
  - Enlarged caudate nucleus
  - Smaller temporal lobes
  - Reversed cerebral asymmetries

Kasai et al 2003b; Sporn et al 2003). These findings have led some to recast the neurodevelopment versus neurodegeneration dichotomy essentially as a two-stage pathogenic trajectory (Church et al 2002; McClure and Lieberman 2003). In such a schema, it is proposed that some noxious event causes initial neurodevelopmental cortical impairment. This impaired cortical substrate confers susceptibility thereafter to the later emergence of neurodegenerative processes. Thus, this may represent an interactive process between neurodevelopmental vulnerability and progressive deterioration with neurotoxicity (Mathalon, Rapoport, et al 2003). The emergence of early-onset dementia in patients with Down's syndrome provides the prototype for this pathogenic model. In this regard, a recent study by Teipel and colleagues (2003) reported substantial hippocampal and corpus callosal loss in nondemented patients with Down's syndrome. It is plausible that a neurodevelopmental–neurodegenerative interaction such as this may also account for the pattern of brain changes seen in schizophrenia.

Another important consideration is whether specific brain regions are involved in schizophrenia or whether there is global involvement. Some have argued that schizophrenia is a disorder of neural dysconnectivity (Andreasen 1999) and that the brain changes reflect widespread failure of neural connections. The post-mortem disturbances in cortical synaptic formation, as well as mitochondrial abnormalities that may underlie cell membrane (phospholipid) development, are consistent with this view of schizophrenia (Davis and Haroutunian 2003). As I review herein neuroimaging findings from studies in schizophrenia, I will attempt to evaluate the relevance for each of these aspects of our understanding of schizophrenia.

## Methodological considerations

In advance of reviewing available studies, some consideration is necessary of the methodological issues that prevail in this literature. First, structural neuroimaging research in schizophrenia is a mammoth undertaking. There are several important technical issues that affect both the quality of the study and its comparability with other schizophrenia imaging studies. These are listed in Table 3.

Methodological issues related to clinical aspects of schizophrenia are also of importance. Diagnosis is a major consideration. This may be most clear in patients with chronic illness. On the other hand, well characterized schizophrenia occurring early in childhood tends to a severe and more progressive illness associated with more

**Table 3** Methodological and patient population considerations in brain imaging studies of schizophrenia

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- Technical parameters
    - Scanner type and strength (1.5T vs 3T)
    - Image sequence
    - Slice thickness
    - Post-processing techniques
    - Atlas or reference points for anatomical demarcation
    - Procedure used to determine measurements (automated vs semiautomated vs receiver operated)
  - Illness parameters
    - Accuracy of diagnosis
    - Stage of illness (prodromal, first episode, multipisode, chronic-refractory)
    - Comorbidities (eg, substance abuse, medical illness)
    - Medications (antipsychotic naive or medicated, choice of medication)
  - Patient population parameters
    - Age
    - Gender composition
    - Matching to control subjects
    - Extent of patient attrition in longitudinal studies
- 

pronounced brain changes (Thompson et al 2001). Comorbid substance abuse can also be a major confounder in neuroimaging studies. Patients with alcohol comorbidity exhibit a more complex pattern of brain abnormalities during neuroimaging studies (Mathalon, Pfefferbaum, et al 2003). While many studies specifically exclude patients with recent substance abuse, it may well be the case that patients with substantial substance abuse early on in their illness are still included. Additionally, although other aspects of the prior history such as head injury may go undetected, these may still be of direct relevance to the brain imaging examination (Buckley et al 1993). It is also becoming more apparent that the medications patients take can affect the measurements of brain structures, especially in the basal ganglia (Arango et al 2003; Lang et al 2004).

It is also important to appreciate that imaging research requires large patient samples. This is particularly relevant for studies examining symptomatic or genetic correlates of brain abnormalities. Additionally, since so much more information is gleaned from sequential MRI assessments, studies that are able to retain their patient population across time are particularly helpful. The attrition of subjects from longitudinal studies makes this very difficult research indeed.

## Historical context

Johnstone and colleagues (1976) first demonstrated brain abnormalities on CT scans in patients with schizophrenia. This finding of enlarged ventricles is still the most consistent

and reproducible finding in neuroimaging studies of schizophrenia (McCarley et al 1999). Cortical sulcal prominence, a less presumptive term than either cortical atrophy or hypoplasia, is another early finding for CT that was again confirmed as a reproducible finding in subsequent MRI studies (Friedman et al 1991; McCarley et al 1999; Flashman and Green 2004). However, it soon became apparent that these abnormalities were subtle in extent and were neither universally reproducible across studies nor specific to schizophrenia alone (Table 4). As alluded to above, patient characteristics (age, sex, chronicity of illness, site – eg, state facility versus veterans' hospitals) exert a powerful influence on the prevalence and pattern of the observed brain abnormalities (for discussion, see Lauriello et al 1997; McCarley et al 1999) (Table 3). These factors are critical to take into account when evaluating the available literature. A succinct review of this literature is provided here.

## Qualitative and generalized brain abnormalities: neurodevelopmental anomalies

The availability of high resolution MRI and the capacity for sequential imaging has been a real advantage in exploring the relative effect of neurodevelopmental versus neurodegenerative processes in schizophrenia. Although the brain changes are subtle, several studies have reported high rates of neurodevelopmental abnormalities on MRI examination. These include corpus callosal agenesis, cavum septum pellucidum, and hypoplasias/heterotopias, which are thought to be of etiopathologic significance (Andreasen et al 1990; DeLisi et al 1993; O'Callaghan et al 1995; Woodruff et al 1995; McCarley et al 1999; Lieberman et al in press). Several groups have described failure of fusion of the leaflet separating the lateral ventricles, cavum septum pellucidum (CSP), in patients with schizophrenia. Estimates vary widely (2%–58% in imaging studies); when only large CSP was considered in one study this abnormality was still found in some 20% of patients (Nopoulos et al 1997). Dysgenesis or agenesis of the corpus callosum, whether evident qualitatively or through measurement, has been observed in a minority of patients (Woodruff et al 1995). Other findings that can be seen on qualitative evaluation include porencephalic cysts, micro- and macrogyria, white matter heterotopias (gray matter neurons that are developmentally misplaced within cortical white matter tracts), and the so-called unidentified bright objects (UBOs), probably related to microvascular ischemia. Many of these findings are of

**Table 4** Neuroimaging studies: representative recent structural MRI studies in patients with first-episode schizophrenia

Reference	Nr of patients/controls	Imaging focus	Findings
Bagary et al 2003	30/30	Magnetic transfer imaging, whole brain MRI	Diffuse gray and white matter tissue loss
Cahn et al 2002	34/36	Volumetric analysis, whole brain	7.7% lateral ventricular volume increase, 1.2% whole brain volume decrease over 1 year; associated with poorer outcome
Ho, Alicata, et al 2003	156	Volumetric analysis, whole brain	Mean DUP of 74 weeks; DUP unrelated to brain or neurocognitive abnormalities
Job et al 2002	34/36	Voxel based morphometrics, whole brain	Gray matter volume reductions in cingulate, frontal, and temporal lobe structures
Kasai et al 2003b	13–15/14	Volumetric analysis, STG and hippocampus	Progressive volume reduction of 9.6% in gray matter in posterior STG and of 8.4% in anterior STG over 1.5 years in first-episode schizophrenia
Keshavan et al 2002	31/31	Volumetric analysis, corpus callosum	Selective regional reductions in corpus callosum
Kim et al 2003	25/25	Volumetric analysis, STG	Anterior and posterior STG decrements associated with positive and negative symptoms, respectively
Kubicki et al 2002	16 and 16 <sup>a</sup> /18	Voxel-based morphometrics, whole brain MRI	Less STG reduction in bipolar vs schizophrenia patients
Smith et al 2003	33/19	Hippocampus	Hippocampal fissure dilation, associated with poor educational achievement
Sumich et al 2002	16/16	Volumetric analysis, temporal lobe	Reductions in hippocampus (bilateral) and in planum temporale (left)

<sup>a</sup> Sixteen patients with first-episode schizophrenia and 16 patients with first-episode affective psychosis.

**Abbreviations:** DUP, duration of untreated psychosis; STG, superior temporal gyrus.

putative causal significance. Additionally, some of these are normal morphologic variants that appear to be overrepresented in schizophrenia (Smith et al 2003).

## Generalized brain involvement in schizophrenia: is it global or does it follow a distinct pattern?

There is now convincing evidence of generalized (rather than just selective) brain pathology in schizophrenia (Wright et al 2000). Studies report diffuse cortical loss of tissue, with gray matter being more selectively affected (Zipursky et al 1992; Harvey et al 1993; Lieberman et al 1993; Schlaepfer et al 1994; Kulynych et al 1995; Lim et al 1996; Bagary et al 2003; Zhou et al 2003). Bagary and colleagues (2003) have recently applied magnetic resonance transfer imaging to study these gray–white matter changes in schizophrenia. In a first-episode sample, they found magnetization transfer signal loss especially in the frontal cortex that did not appear to be associated with volume loss. There is also recent use of diffusion tensor imaging (DTI), which has the capacity to show subtle changes in white matter structure and orientation (Frumin et al 2002). Such

technical developments are important because of the subtlety and complexity of brain changes in schizophrenia. Wang and colleagues (2004) conducted a study of DTI of the cingulate gyrus in patients with schizophrenia. Amid renewed interest in phospholipid abnormalities and deficits in myelination in schizophrenia, DTI has emerged as a usual neuroimaging approach to visualize white matter track pathology. Wang and colleagues (2004) report a reduction of left–right asymmetry in patients, as well as DTI deficits (so-called lower fractional anisotropy: meaning less or less integral white fibers which therefore create a lower mathematical “signal”). This is yet another study showing brain asymmetries in schizophrenia. Tim Crow, a leading British schizophrenia researcher, believes that these asymmetries are key to understanding the pathology of schizophrenia, which he says relates to altered development in the region of the brain subserving language (Crow 1989).

One possibility is that the diffuse loss is related to distinct neural systems, of which the frontotemporal interconnections predominate. Pearlson and colleagues (1996) have suggested that the brain changes in schizophrenia result from diffuse involvement of (phylogenetically older)

heteromodal association cortex of frontal, temporal, and subcortical regions. Buchanan and colleagues (2004) recently examined these relationships in 44 patients with schizophrenia. They found that patients had smaller inferior prefrontal cortex volume than normal controls. In addition, they showed a reversal of the normal asymmetry of the inferior parietal cortex. Surprisingly, however, temporal lobe volumes did not differ between patients and normal controls.

Another prevailing notion in structural neuroimaging of schizophrenia is that schizophrenia is a disorder of neural dysconnectivity (Andreasen, Flashman, et al 1994; Andreasen 1999). To this end, abnormalities within the cortico-striato-thalamo-cortical circuit have been suggested in schizophrenia. Diminished volumes of thalamus, striatum, and cortical gray matter have been described in neuroleptic-naïve patients with schizophrenia (Lim et al 1996). Myelinated fibers connecting these information-processing centers have been reported to be swollen and to have impaired integrity on DTI and magnetic transfer imaging (Bagary et al 2003). Garver and colleagues (2004) have sought to evaluate the effects of antipsychotic drugs and of antipsychotic response upon volumetric change of both cerebral white matter and gray matter associated with thalamus, striatum, and cerebral cortex. Patients who had responded had significant increases in thalamic and striatal volumes, together with decreases in white matter volume as compared with poor responders. Companion DTI in these patients documented increased “integrity” (partial normalization) of the impaired myelinated connections among the information-processing centers. Cortical gray matter increases were found only in patients treated with atypical antipsychotics. The authors speculated that patients who experienced antipsychotic responses during treatment appear to have partial restoration of integrity of myelinated connections among critical subcortical information-processing centers, together with enhancement of thalamic and striatal volumes. This is an interesting study showing the evolution of this work as well as the complex interactions between disease and medication (see *Treatment response and brain abnormalities*).

Studies addressing cortical surface patterns in schizophrenia are difficult to interpret, since there is such great intersubject variation (Kulynych et al 1997; Kubicki et al 2002). Also, detailed knowledge of normal anatomy of cortical gyral patterns is at a rudimentary level. Nevertheless, several studies have reported abnormalities of surface pattern in schizophrenia (Kikinis et al 1994; Kulynych et al 1997; Kubicki et al 2002; White et al 2003). It has been reported

that folding is less complex in the left hemisphere of gyral patterns between patients and compared with normal individuals. On the other hand, others have found diffuse cortical dysmorphology in schizophrenia, which is most pronounced in male patients. Sallet and colleagues (2003) report on a large, well conducted MRI study of cortical surface morphology wherein they found a 3%–4.5% reduction in gyrification index (GI) – a measure of cortical folding – in both hemispheres. This reduction in GI is more prominent on the left side. The lack of differences in brain volume between patients and controls in this study is surprising. However, this strengthens the findings from this study, since the evaluation of cortical morphology is complicated by partial volume effects, incomplete measurements across brain segments, and underlying volumetric reductions. It is not clear, however, whether the associations with clinical subtypes (disorganized subtype had most GI reduction, paranoid subtype had least) have any real relevance, even though the statistical strength of these reported associations is robust. White and colleagues (2003) found reduced cortical thickness and less curvature in sulci (with greater curvature in gyri) in patients with early-onset schizophrenia.

## Ventricular enlargement

In broad terms, ventricular enlargement has been observed more often than not in most studies, but the size of this effect is small and, more speculatively, does not appear to be confined to a subgroup of patients. Associations between ventricular enlargement and illness chronicity have been observed but these lack any consistency to support earlier assertions that these CT abnormalities represented visual proof of the dementia of dementia praecox. In a similar manner, Crow’s Type I/Type II symptom and causal model of schizophrenia, which predicted more brain abnormalities in patients with chronic illness and with predominantly negative symptoms, was not borne out in subsequent studies. While ventricular enlargement is a replicable finding, it is not generalized. There is evidence for third, but not fourth, ventricular enlargement. Additionally, lateral ventricular enlargement shows some regional specificity. Studies have reported that the left temporal horn is selectively enlarged in schizophrenia (and also, but to a lesser extent, in affective disorder) (Crow 1989; Degreef et al 1992; McCarley et al 1999). Degreef and colleagues (1992) found that ventricular enlargement was most pronounced in the frontal and temporal horns (bilaterally), with enlargement of the

temporal horns associated with the presence of positive symptoms. Morphometrics (the scientific study of form and shape) has been applied in neuroimaging research in schizophrenia. A study using morphometrics reported prominent, gender-specific abnormalities of ventricular shape in male patients with schizophrenia which were localized to the foramen of Munro and the proximal portion of the temporal horn of the lateral ventricular system (Buckley et al 1999).

## Regional brain abnormalities

There is evidence for brain changes in most, but not all, regions selectively reported in imaging studies. This is mostly prominent for the frontotemporal regions, the thalamus, and the caudate nucleus (see sections below). However, an area of intense research has been to determine whether these focal/regional abnormalities are independent of or in excess of more generalized cortical tissue loss. Available evidence favors the latter assumption. Studies addressing the brain regions that are most affected in schizophrenia are reviewed below.

## Temporal lobes

Since the publication of the earliest imaging studies in schizophrenia (Johnstone et al 1989; Suddath et al 1989), there has been an enduring focus on examining for temporal lobe (gray and white matter) abnormalities. Several studies report generalized temporal lobe reduction, selective reductions in discrete structures, and subtle focal asymmetries. Increasing technology has rendered this analysis more complex with the sampling issues, technical variation, definition of tissue boundaries, and variable statistical power. The preponderance of evidence suggests a loss of temporal lobe volume in schizophrenia of an order of approximately 8% with comparable (or even slightly larger) reductions when the amygdala or parahippocampal gyrus are considered alone (Wright et al 2000; Csernansky et al 2002). There is some evidence, but by no means conclusive, that these losses show a predilection for the left hemisphere. Studies report asymmetries within temporal lobe structures, the planum temporale, Heschl's gyrus, and the superior temporal lobe gyrus (DeLisi et al 1994; Kulynych et al 1995; Barta et al 1997; McCarley et al 1999; Kesa et al 2003). Barta and colleagues (1997) have shown reversed planum temporale asymmetry in schizophrenia, with the right planum temporale surface area being greater so that gray matter volume is reduced in patients relative to controls. This results from substantial loss in thickness of

planum temporale gray matter in the right hemisphere of patients with schizophrenia. They have also shown that smaller superior temporal lobe volume is associated with auditory hallucinations in schizophrenia (Barta et al 1990). Shenton and colleagues (1992) reported similar associations for thought disorder in patients with schizophrenia. Recently, Kasai and colleagues (2003a) have reported substantial decreases in gray matter volume in the left Heschl's gyrus and left planum temporale among first-episode schizophrenia patients who were imaged twice over a 1.5-year span. Importantly, this pattern was not seen among the psychotic control group of first-episode affective psychoses. Turetsky and colleagues (2003) have examined whether the anterior temporal lobe deficits observed in imaging studies might be associated with impairments in olfactory function in patients with schizophrenia. Among 52 patients, they found evidence that reduction in anterior ventromedial (but not entorhinal) temporal lobe volume was related to olfactory dysfunction. Csernansky and colleagues (1998, 2002) noted shape changes in the hippocampus in patients with schizophrenia that was not attributable to focal tissue loss in the hippocampus.

## Frontal lobes

The frontal lobes have also been the subject of extensive structural imaging research. Andreasen and colleagues (1986, 1990), in a seminal study, showed marked frontal lobe decrements on MRI. Many subsequent studies, but not all, have noted a modest (6%–8%) volumetric reduction. The complexity of the gyral pattern in the frontal cortex has made standardization of subregions difficult, and different researchers have applied disparate criteria to determine the boundaries for this region. More recently, Roth and colleagues (2004) examined the relationships between apathy in patients with schizophrenia and structural and cognitive brain changes. They observed that only patients with high apathy scores exhibited decrements in frontal lobe volume.

## Caudate nucleus

An accumulating literature also points to abnormalities in caudate and related regions that may be related to treatment effects. Jernigan and colleagues (1991) reported caudate nucleus enlargement in patients with schizophrenia but its meaning was unclear until later studies found that caudate size depended on whether patients were receiving treatment with typical or atypical antipsychotic medications (Breier et al 1992; Chakos et al 1994; Keshavan et al 1994, 2002).

It was noted that the caudate volume decreased in patients who were changed from treatment with typical antipsychotics to clozapine therapy. This effect has also been observed (although is less pronounced) with other atypical antipsychotics. Dazzan and colleagues (2004) investigated the effect of antipsychotic medications on brain structure in 90 patients at their first psychotic episode. Of these, 50 patients were taking typical neuroleptics, 16 were taking atypicals, and 24 were drug-free. These results highlighted that, in comparison to drug-free subjects, those on typical neuroleptics showed larger gray matter volume of basal ganglia and smaller gray matter volume of the right insula and bilateral precuneus. In contrast, patients taking only atypical neuroleptics, compared with drug-free subjects, showed larger gray matter volume of the thalamus (bilaterally). This study illustrated that even the short-term use of typical neuroleptics is associated with basal ganglia and cortical volume changes. Lang and colleagues (2004) reported on a study where patients were switched from either older antipsychotics or risperidone to olanzapine. The effect on brain structures of switching from older drugs to olanzapine was greater than for the switch from risperidone to olanzapine. Putamen and globus pallidus volumes were significantly reduced in switching from older drugs to olanzapine. In an outpatient sample of patients with a longer duration of illnesses, Arango and colleagues (2003) also found a differential effect of medication treatment and response associated with structural abnormalities. Patients with larger, more preserved, brain volume were more likely to respond to clozapine. This was not true for patients who were treated with haloperidol.

## Thalamus

There has been much interest in thalamic volume in the light of the theory of neural dysconnectivity in schizophrenia. Subtle decrements in thalamic volume have also been reported which are consistent with the fundamental role of the thalamus as a cortical–subcortical relay station and with findings of thalamic hypometabolism in schizophrenia. In a study that used a bounding box approach to create an average thalamus, Andreasen, Arndt, and colleagues (1994) reported a reduction in thalamic volume in schizophrenia. Kemether and colleagues (2003) recently performed high resolution MRI examining substructure volumes of the thalamus in 41 patients with schizophrenia. The most pronounced volume decrements were seen in the mediodorsal and pulvinar nuclei of the thalamus. This was not attributable to a medication effect, since the same pattern

was seen among a subsample of 15 patients in this study who had never been treated with antipsychotic medications. In another analysis from the same study, these volume losses were associated with the ventricular enlargement (Gaser et al 2004). Although conclusions from correlation analyses should be limited, the authors asserted that these thalamic losses may in part explain the extent of ventricular enlargement in schizophrenia. In a complementary study from Japanese investigators, decreased volume of the anterior portion of the internal capsule was seen among 53 patients with schizophrenia, which the authors attributed to a possible effect upon adjacent thalamic structures (Zhou et al 2003).

## Corpus callosum

There is an extensive but largely confusing literature documenting an array of size and shape changes in the corpus callosum in patients with schizophrenia (Woodruff et al 1995; Wright et al 2000; Keshavan et al 2002). A landmark-based analysis of midsagittal structures in 14 patients and 14 normal controls reported focal displacement, reduced thickness of the corpus callosum, and displacement of adjacent upper brain stem structures in schizophrenia (DeQuardo et al 1996). Thus far, it has been difficult to image the corpus callosum in detail and to synthesize findings across studies (many of which are of small sample size).

## Cerebellum

The cerebellum has been a recent focus of research because of the proposed disruption of cortico-cerebellar-thalamic-cortical networks that might lead to cognitive dysmetria in schizophrenia (Andreasen 1999). In general, however, the preponderance of studies do not find cerebellar abnormalities in schizophrenia. However, a few studies have shown selective cerebellar hypoplasia (Aylward et al 1994). Ho and colleagues (2004) showed smaller cerebellar volume in first-episode schizophrenia patients who exhibited cerebellar neurological soft signs. Structural imaging finds of cerebellar abnormalities in schizophrenia are scant.

## Clinical correlates of structural brain abnormalities in schizophrenia

### Gender-specific findings

Structural brain abnormalities occur more frequently and are more pronounced in male patients with schizophrenia

(Kulynych et al 1995; O'Callaghan et al 1995; Frazier et al 1996; Lim et al 1996; McCarley et al 1999; Weinberger and Marenco 2003). This is in accordance with epidemiologic observations and also with the belief that male patients with schizophrenia are more likely to express neurodevelopmental process(es) (Jones and Buckley 2003).

## Symptoms

Association with symptoms, however, is more complex. Temporal lobe abnormalities have been associated with positive symptoms (Barta et al 1990; Shenton et al 1992; Turetsky et al 1995; Ho, Andreasen, et al 2003; Kim et al 2003; Flashman and Green 2004). Similarly, negative symptoms of schizophrenia have been shown to be associated with subtle tissue decrements in the frontal lobes (Andreasen et al 1990; Breier et al 1992; Buchanan et al 1993; Turetsky et al 1995; Lim et al 1996; Chua et al 1997; Ho, Andreasen, et al 2003; Flashman and Green 2004; Roth et al 2004). These are difficult to interpret because of the methodologic issues of imaging, often small samples, and the inherent risk of Type I error when correlations are sought between anatomic structures and multiple clinical measures (Turetsky et al 1995; Sallet et al 2003). Additionally, in the absence of longitudinal assessments, studies are difficult to replicate, since they rely upon symptom complexes that may not be stable over time. Narr and colleagues (2003) report on a highly complicated but very interesting study from an international (US–UK) collaborative group. The findings of more progressive cerebrospinal fluid (CSF) increases in patients with schizophrenia who are younger is consistent with emerging evidence that brain changes in schizophrenia are not static. The authors argue that cortical tissue loss is more subtle and, therefore, while they report CSF increases they cannot discount accompanying cortical volume reductions. This may well be so, but the tissue volume reductions are estimated at about 5% and have been generally reproducible in modern MRI studies. The authors, by way of explanation, provide an account of the differences between their computational landmark-based morphometrics and other voxel-based morphometric approaches. The effects of age and gender upon CSF volume and cortical gray matter changes are carefully teased out here. Young male patients with schizophrenia are most affected; this is consistent with other gender-specific findings (see above). In another 5-year follow-up study, Milev and colleagues (2003) found that persistence of auditory hallucinations over 5 years of care was associated with smaller temporal lobe volumes bilaterally.

## Genes and brain abnormalities

Genetic influences on brain abnormalities in schizophrenia have also been extensively studied (Suddath et al 1990; Frangou et al 1997; Lawrie et al 1999; McCarley et al 1999; Stefanis et al 1999; Siedman et al 2003; Tepest et al 2003). Several studies of high-risk families report a pattern of structural abnormalities in relatives that is broadly similar to, but less pronounced than that of affected probands (Frangou et al 1997; Johnstone et al 2002; Siedman et al 2003). The seminal MRI study of monozygotic twins discordant for schizophrenia showed that twins affected with schizophrenia had ventricular enlargement and temporal lobe abnormalities that were not seen in their normal co-twins (Suddath et al 1990). These findings have been extended and replicated (Siedman et al 2003). The interaction between genes and environment has also been studied. It has been found that the genetic effects may relate to cortical pathology, while ventricular enlargement may be related to obstetric complications.

The Edinburgh high-risk study has elegantly addressed this “graded effect” of genetic risk (Lawrie et al 1999). Asymptomatic offspring from high-risk families had smaller temporal lobe structures than control individuals. The offspring who went on to show psychotic symptoms also had smaller whole brain volumes than the nonpsychotic offspring (Lawrie et al 1999; Johnstone et al 2002). Siedman and colleagues (2003) also show a strong relationship between genetic loading for schizophrenia and temporal lobe abnormalities. Tepest and colleagues (2003) also report subtle deformations of hippocampal shape as well as volume reductions in patients and in their “unaffected” relatives when compared with normal controls. Tepest and colleagues (2004) also measured thalamus volume and shape in patients and healthy siblings to study the changes as a marker of genetic vulnerability for schizophrenia in 13 pairs of patients with schizophrenia and their unaffected siblings from families with multiple affected members, in 12 patients with schizophrenia from families without another affected member, and in 10 healthy controls. Thalamus volume and shape were compared using large-deformation high-dimensional brain mapping. The researchers observed a decrease in thalamic volume (6%), covaried for total cerebral volume, in the schizophrenia subjects without affected members in their families. In patients from families that were multiply affected by the illness, the investigators also found a minor decrease of the volume (2%). Healthy family members showed no volume reduction of the thalamus. These findings contrast with the finding in the hippocampus,

wherein hippocampal volume and shape were changed in healthy and ill members from multiply affected families in a similar way to those in schizophrenic patients from families without a history of the illness. There is even evidence of more subtle (but nevertheless similar) abnormalities in the brains of patients who are genetically at high risk for developing schizophrenia. Two recent sequential MRI studies in ultra high-risk patient groups provide preliminary evidence of reduction in temporal lobe structures in patients who convert from high risk to actual schizophrenia (Lawrie et al 2001; Pantelis et al 2003). Another genetic variant of schizophrenia is schizotypal personality disorder (SPD). Recently, Dickey and colleagues (2003) failed to replicate their earlier finding of smaller left superior temporal gyrus volume in SPD patients. They did, however, find greater temporal gyrus asymmetry in patients who also had a family history of mental illness. Siever and Davis (2004) highlight the degree of overlap in psychophysiological deficits (eg, impaired sensory gating, prepulse inhibition deficits, poor performance on attention tasks, and overall similarity of brain structure changes – more attenuated findings except for relative preservation of frontal lobe volume in SPD) between chronic schizophrenia and SPD. They suggest a model wherein social and cognitive deficits predominate as the clinical expression of genetic vulnerability that selectively affects frontal and temporal lobe structures. The extent, then, to which patients are “spared” and go on to develop SPD rather than schizophrenia depends on the extent of modifying factors (eg, frontal reserve capacity, general intelligence) and the extent of the individual’s risk factors and the proposed genetic–environmental interactions.

Another approach in studying the genetic influence upon brain structure in schizophrenia is to study genetic phenocopies of schizophrenia (McDonald and Murphy 2003). Velocardiofacial syndrome (VCFS) is the prototype, as it is associated with high rates of psychosis. Brain changes, similar to but more attenuated than those in schizophrenia have been observed in VCFS; a recent DTI study showed white matter changes in this condition (Barnea-Goraly et al 2003).

### Minor physical anomalies and neuroimaging

Minor physical anomalies (MPAs) are commonly found in elevated frequency among patients with schizophrenia, providing evidence to support the neurodevelopmental hypothesis (Buckley et al 2003). Dean and colleagues (2004) examined the relationship between the presence of minor

physical anomalies and brain morphology (MRI) in 60 first-episode psychosis patients, divided into two groups (high and low MPA groups each with 30 patients). In comparison with the low MPA group, patients with high MPAs showed larger gray matter volume of basal ganglia (bilateral), thalamus (bilateral), inferior temporal gyrus (right), lingual gyrus (bilaterally), and cuneus (right). They also showed smaller gray matter volume at the level of the lobulus paracentralis (bilaterally), with extension anteriorly into the dorsal frontal gyrus, posteriorly into the precuneus, and inferiorly into the cingulate gyrus (left). The authors concluded that high MPA frequency was associated with gray matter volume changes on MRI even in first-episode psychosis.

### Treatment response and brain abnormalities

Response to neuroleptic treatment has also been examined in relation to neuroimaging abnormalities (Friedman et al 1991; Lieberman et al 1992; Kikinis et al 1994; Ho, Andreasen, et al 2003). Kolakowska and colleagues (1985) reported that cortical atrophy on CT was associated with poor treatment outcome. Lieberman and colleagues (1993), in a first episode of schizophrenia study, found that a global index of brain abnormalities chiefly reflecting ventricular enlargement (but not any cortical and temporal lobe pathology) predicted treatment response. In contrast, Friedman and colleagues (1991) reported that prefrontal sulcal prominence was inversely related to clozapine response. They postulated that this tissue loss resulted in diminished response to clozapine owing to a decrement in frontal serotonergic receptors. Neuroimaging studies have shown that typical neuroleptics may increase volume, metabolism, and relative blood flow in the basal ganglia, and that these actions can be reverted or not apparent with atypical antipsychotics (Liddle and Pantelis 2003). Effects of medication on the basal ganglia have been described above. The different effects of neuroleptics upon brain structure remain poorly understood. Patients at their first psychotic episode represent an ideal sample to investigate differential effects of neuroleptics on brain structure, as the study described earlier (Dazzan et al 2004) illustrates. Interesting findings have also emerged from a comparative study of olanzapine and haloperidol in first-episode schizophrenia during which patients receive sequential neuroimaging assessments (Lieberman et al in press). Over the course of 1 year, patients on haloperidol showed a divergent pattern on MRI compared with patients being

treated with olanzapine, with patients treated with haloperidol showing loss of gray and white cortical matter, as well as enlarged ventricular volume. The possible “sparing” of progressive brain changes in patients treated with olanzapine is a noteworthy and intriguing finding. Patients treated with olanzapine also had greater improvement in cognitive function over the first year of treatment. Ho, Andreasen, and colleagues (2003) also found worsening of brain changes in patients who were receiving treatment with first-generation antipsychotics compared with patients on newer, second-generation agents. The therapeutic implications of such studies for the selection of second-generation antipsychotic medications over first-generation antipsychotics are important and compelling. This is also of therapeutic interest because many researchers believe that failure to intervene early (and aggressively) when schizophrenia first begins may result in the illness running a more unfavorable long-term course (Harrigan et al 2003). The findings from first-episode brain imaging underscore this notion, since even at the earliest stages of illness there is evidence of prominent brain changes. The recent seminal study by Thompson and colleagues (2001) is a good example and it showed progressive cortical tissue loss in childhood schizophrenia. A summary of representative first-episode brain imaging studies is given in Table 4. Additionally, there is some, albeit preliminary, evidence that second-generation antipsychotic medications may help “recovery” of brain cells (ie, stimulate neurogenesis), an effect that is not seen with older, first-generation medications (Wake et al 2002). Taken collectively, these observations provide the context for early intervention studies seeking to evaluate the prodrome of schizophrenia (Pantelis et al 2003) and seeking to avert/abort/delay the onset of schizophrenia (McGlashan et al 2003).

## Concluding remarks

There is now compelling evidence from neuroimaging studies that schizophrenia is a brain disease. Abnormalities, albeit subtle in magnitude and variable in extent across studies, are now reported in virtually every brain region; global deficits, lateral ventricular enlargement, and frontotemporal deficits are the most pronounced. It is still unclear as to the relationship of these changes to associations with illness and clinical variables, and these brain changes have yet to directly affect clinical care. Even though the observations of structural changes and progressive tissue loss on neuroimaging are provocative, they are not yet of clinical or diagnostic relevance.

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