Structural Brain Imaging in Schizophrenia: A Selective Review

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Structural neuroimaging studies have provided some of the most consistent evidence for brain abnormalities in schizophrenia. Since the initial computed tomography study by Johnstone and co-workers, which reported lateral ventricular enlargement in schizophrenia, advances in brain imaging technology have enabled further and more refined characterization of abnormal brain structure in schizophrenia in vivo. This selective review discusses the major issues and findings in structural neuroimaging studies of schizophrenia. Among these are evidence for generalized and regional brain volume abnormalities, the specificity of anatomic findings to schizophrenia and to men versus women with schizophrenia, the contribution of genetic influences, and the timing of neuroanatomic pathology in schizophrenia. The second section reviews new approaches for examining brain structure in schizophrenia and their applications to studies on the pathophysiology of schizophrenia. The purpose of this paper is to provide a selective review of the major issues and findings germane to structural neuroimaging studies of schizophrenia. In the first section, we review nonspecific abnormalities. Then, we discuss whether certain brain regions or tissue types (e.g., gray vs. white matter) are preferentially affected in schizophrenia, and if such regional patterns are specific to schizophrenia. Finally, we discuss structural neuroimaging studies that address when brain abnormalities might develop in schizophrenia. The second section reviews new approaches for examining brain structure in schizophrenia and their applications to studies on the pathophysiology of schizophrenia. While it is recognized that discrepant findings between structural neuroimaging studies can be attributed in part to methodologic differences, including the sophistication of image acquisition and analysis as well as study design, the reader is referred to other reviews for such discussions (Gur et al 1993; Marsh et al 1996; Pearlson and Marsh 1993; Shenton et al 1997; Woodruff and Lewis 1996).

Part I. Structural Neuroimaging Findings in Schizophrenia

Nonspecific Structural Abnormalities

VENTRICULAR AND SULCAL ENLARGEMENT. Lateral ventricular enlargement is the best replicated anatomic abnormality detected in the brains of patients with...
schizophrenia, both in earlier CT studies and in many MRI investigations (Shenton et al 1997). The consistency of this finding may, in part, reflect the fact that the lateral ventricles are easily and reliably measured. In addition, a number of studies report disproportionately large volumes of the temporal horns, the cortical sulci, and the third and fourth ventricles. Together, these abnormalities provide a context for the observation of relatively widespread volume deficits as well as focal abnormalities in schizophrenia (Table 1), although their significance is unclear.

Despite this, repeated demonstrations of ventricular–sulcal enlargement have been central to the development of hypotheses on the nature of brain dysfunction in schizophrenia.

Leading explanations for the large ventricular and sulcal spaces seen in schizophrenia revolve around whether they are the product of an inherently aberrant developmental process as opposed to an acquired process, yielding excessive reductions in brain tissue relative to normal development and aging. Resolution of this controversy is confounded, in part, because abnormally large ventricles and sulci are both non-selective and nonspecific findings that are associated with a variety of psychiatric conditions as well as multiple congenital, developmental, acquired, and degenerative etiologies (Pearlson and Marsh 1993; Shenton et al 1997). It is also unclear whether ventricular–sulcal enlargement reflects widespread anatomic abnormalities as opposed to pathology in adjacent brain structures, or both. These issues can be addressed through longitudinal imaging studies as well as through examining the relationships between CSF-space volumes and measures of discrete structures, using both traditional morphometric methods as well as more recently developed methods for shape analysis and diffusion imaging (discussed later).

### Table 1. Brain Structural Abnormalities in Schizophrenia Relative to Healthy Control Subjects

<table>
<thead>
<tr>
<th>Observation</th>
<th>Positive findings</th>
<th>Comments/negative studies</th>
</tr>
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<tbody>
<tr>
<td>Increased ventricular size</td>
<td>Johnstone et al 1976; Pearlson et al 1998; Pearlson and Marsh 1993 (review)</td>
<td>Most widely replicated finding in schizophrenia research</td>
</tr>
<tr>
<td>Reduced total brain volume</td>
<td>Andreasen et al 1994b; Shenton et al 1997 (review)</td>
<td>Elkins et al 1995 (meta-analysis)</td>
</tr>
<tr>
<td>Decreased total gray matter</td>
<td>Zipursky et al 1992, 1998; Lauriello et al 1997; Lim et al 1996a, 1996b; Harvey et al 1993</td>
<td>Effect weak and not significant; Pearson et al 1997b; Buchanan et al 1993 or only in HASC regions; Schlaepfer et al 1994</td>
</tr>
<tr>
<td>Frontal neocortical reductions</td>
<td>Buchanan et al 1998</td>
<td>Imaging nonreplications Wible et al 1995</td>
</tr>
<tr>
<td>Broca’s area and perhaps DLPFC</td>
<td>McGilchrist 1993; Donnino et al 1996; Pearlson et al 1998</td>
<td>Few or no neuropathology studies; no imaging nonreplications</td>
</tr>
<tr>
<td>Parietal neocortical reductions</td>
<td>McGilchrist 1993; Donnino et al 1996; Pearlson et al 1998</td>
<td>Few or no neuropathology studies; no imaging nonreplications</td>
</tr>
<tr>
<td>Central gray/basal ganglia</td>
<td>Jernigan et al 1991; Andreasen et al 1994a</td>
<td>Imaging nonreplications for thalamus–Shenton et al 1997 (review); Wolkin et al 1998; Basal ganglia abnormalities related to neuroleptic treatment–Chakos et al 1994</td>
</tr>
</tbody>
</table>
A second important aspect of ventricular enlargement in schizophrenia is that the range for ventricular–sulcal size overlaps considerably with the normal population and does not appear to be bimodally distributed (Daniel et al 1991). Thus, ventricular–sulcal abnormalities are present in schizophrenic patients as a group relative to control populations, but ventricular size in a given patient may fall within the normal range. This observation suggests that neuroanatomic findings in schizophrenia are graded phenomena that affect all patients (Cardno and Farmer 1995; Goldberg and Weinberger 1995). By contrast, disease subtypes, at least based on this measure, are not apparent (Tsuang and Faraone 1995). It is unclear whether this also applies to focal abnormalities (Marsh et al 1999a).

**Regional Brain Structural Abnormalities in Schizophrenia**

**FOCAL GRAY MATTER ABNORMALITIES.** Identified patterns of gray matter volume abnormalities in schizophrenia suggest that the entire cortex is affected (Harvey et al 1993; Lim et al 1996a, 1996b; Shenton et al 1997; Zipursky et al 1992, 1998), although the generally small volume difference from normal (approximately 5%) does not always reach statistical significance in comparisons with healthy control populations (Pearlson 1997a). Within the context of these widespread volume deficits, volumes in specific frontal, temporal, and parietal cortical subregions appear to be disproportionately smaller (generally 10% to 15%) (Daniel et al 1991; Shenton et al 1997; Sullivan et al 1998a). However, like the widespread abnormalities, the significance of focal cortical volume deficits in schizophrenia remains unknown. Further, it is unclear whether all patients with schizophrenia demonstrate the same anatomic findings, if focal changes are specific to the disease, or if there are subgroups of schizophrenia with distinct clusters of particular volume abnormalities that involve discrete neuroanatomic circuits. Also unknown is whether the observed changes are the consequence of a single disease process occurring during a critical period, or if specific cells, regions, or components of a distributed system (such as those sharing a common enzyme, unusually sensitive to anoxia, or needing a particular growth factor) are affected.

Temporal lobe abnormalities in schizophrenia have been investigated in over 50 MRI studies (Shenton et al 1997), of which over 75% report differences from controls. Such differences are reported in medial temporal lobe (hippocampus, amygdala, and entorhinal or parahippocampal cortex), or in various subdivisions of the superior temporal gyrus. Of nearly 10 MRI studies that measured superior temporal gyrus volume in schizophrenia, the majority reported volume reductions in schizophrenia (Barta et al 1990; Flaum et al 1995a; Marsh et al 1997; Menon et al 1995; Schlaepfer et al 1994; Shenton et al 1992; Zipursky et al 1994), while two found no differences relative to control values (Kulynych et al 1995; Vito et al 1995). Shenton and co-workers (1997) note that superior temporal gyrus measures in the negative reports were comprised of combined gray and white matter volumes, which may have obscured detection of group differences from control subjects if the pathology is confined to gray matter.

**HETEROMODAL NEOCORTICAL VOLUME DEFICITS IN SCHIZOPHRENIA.** Recent reviews implicate pathology of heteromodal association cortex (HASC) in schizophrenia (Pearlson et al 1996; Ross and Pearlson 1996). HASC is a highly organized and interconnected neocortical system comprised of the planum temporale (PT), the dorsolateral prefrontal cortex (DLPFC), Broca’s area, and the inferior parietal lobule (IPL) (Mesulam 1985). As discussed by Ross and Pearlson (1996), several neurodevelopmental features of HASC suggest that its component regions may be especially vulnerable to disruptions in neuronal function or connectivity during brain development, which are also implicated in schizophrenia. First, HASC regions mature at differential rates relative to other brain regions. For example, the late prenatal and early postnatal phases are critical early periods in HASC development, whereas other brain regions mature earlier in fetal development. Therefore, a noxious process occurring during one of these phases might affect ongoing events such as neuronal and oligodendrogial differentiation, myelination, and astrocytic proliferation in HASC regions whereas another area that matures relatively earlier, such as primary motor cortex, would be “protected.” Secondly, the development of HASC regions is protracted, extending into early adult life. For example, Brodmann area 22 has a longer developmental process than area 17. In addition, differentiation of HASC areas is highly dependent on callosal fibers, i.e., corticocortical connections. This may be related to the thicker subplate seen in HASC regions relative to other cortical areas. Rakic (1988) postulated that this thick subplate exists to receive developing callosal fibers, and in turn, plays a critical role in gyral formation.

Specific studies of HASC regions are few, given the need for complex image analysis methods such as cortical parcellation and 3D-rendering techniques to identify sulcal/gyral delineation boundaries. Reports of reversed normal asymmetry of PT surface area in schizophrenia (Barta et al 1997; Petty et al 1995) are consistent with the hypothesis of specific HASC involvement. By contrast, there are no morphometric differences between schizophrenia patients and controls on measures of anatomically
adjacent cortex, i.e., Heschl’s gyrus, which consists of unimodal (primary) sensory cortex rather than HASC and serves as an “internal control” region (Petty et al. 1995). More recently, Buchanan and colleagues (1998) tested the HASC hypothesis using cortical sub-parcellation (Barta et al. unpublished data, 1999) and cortical “paint” techniques (Ross and Pearlson 1996) applied to the frontal lobe. Patients with schizophrenia showed selective gray matter volume deficits in the right and left inferior prefrontal cortex, which contains Broca’s area. There were no group differences in other prefrontal regions except for a trend for left DLPFC volume reduction. Schlaepfer and co-workers (1994) also reported disproportionate reduction of bilateral DLPFC regions. However, in first-episode schizophrenic patients, Nopoulos and co-workers (1995) reported reduced gray matter volumes only in the frontal lobe measure. In the only frontal lobe study comparable to Buchanan and co-workers (1998), Wible and colleagues (1995) failed to detect group differences between patients and control subjects.

Findings from studies on other HASC regions, e.g., the inferior parietal lobule, are equivocal, for reasons similar to those discussed for the frontal lobe. Generally, investigators have used somewhat thick (e.g., 1 cm) slices to examine this region, without careful delineation of parcelated sub-regions or use of 3-D outlining techniques. Schlaepfer and colleagues (1994), however, found specific gray matter deficits in inferior parietal lobule. Two recent abstracts add information on abnormalities in this region. Donnino and co-workers (1996) examined 15 chronic male schizophrenics compared to gender-matched normal control subjects using thin (1.5 mm coronal) SPGR slices. Like Pearlson and co-workers (1998), they reported reversal in the schizophrenia group of the normal male control pattern of left greater than right volume asymmetry. Donnino and co-workers (1996) found this largely due to asymmetry reversals in the IPL; Pearlson and colleagues (1998) assessed IPL exclusively.

**THALAMIC ABNORMALITIES.** The thalamus is an important node within the neural circuits implicated in schizophrenia. Only a few quantitative MRI investigations have examined the thalamus, in part because of difficulties measuring the structure reliably. For the small number of studies conducted to date, findings are mixed. Some report volume reductions (Andreasen et al. 1994a; Buchsbaum et al. 1996; Corey-Bloom et al. 1995), as have neuropathologic studies (Pakkenberg 1990, 1992). Other studies found no differences in thalamic measures between patients and control subjects (Portas et al. 1998; Wolkin et al. 1998). In Portas and co-workers (1998), thalamic volumes in schizophrenic patients, but not control subjects, were correlated with prefrontal white matter and lateral ventricular volumes. Given that the thalamus is an anatomically heterogeneous structure comprising many different nuclei, it is possible that its abnormal regions may be difficult to detect with available MRI methods. Parcellation of the thalamus into its various subcomponents, if possible, might address whether certain nuclei (e.g., the medial dorsal nucleus, which is connected to heteromodal regions) are disproportionately affected in schizophrenia.

**ABNORMAL ASYMMETRIES IN SCHIZOPHRENIA.** Many structures are normally lateralized in the human brain, with surface areas or volumes being consistently larger in one or the other hemisphere, on occasion in

<table>
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<tr>
<th>Brain region</th>
<th>Positive studies</th>
<th>Negative studies/comments</th>
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<tr>
<td>Petalia (cerebral “torque”)</td>
<td>Luchins et al 1979, 1982</td>
<td>Luchins studies were with CT</td>
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<td></td>
<td>Bilder et al 1994</td>
<td>Early measures were linear or area; later studies using volume measures are more valid</td>
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<tr>
<td></td>
<td>Bullmore et al 1995</td>
<td></td>
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<tr>
<td>Planum temporale (and lateral sulcus)</td>
<td>Petty et al 1995</td>
<td>Kulynych et al 1996; Bartley et al 1993</td>
</tr>
<tr>
<td></td>
<td>Barta et al 1997</td>
<td>Review of methodologic problems in various studies in Barta et al 1995</td>
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<td></td>
<td>Kwon et al 1999</td>
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<td></td>
<td>Hoff et al 1992</td>
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<tr>
<td>Anterior cingulate cortex</td>
<td>Albanese et al 1995</td>
<td>Neuropathologic study, small sample size</td>
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<tr>
<td>Assorted cortical regions</td>
<td>Bilder et al 1994</td>
<td>Occipitoparietal, premotor and prefrontal asymmetries examined by Bilder, heteromodal association cortex by Tien; prefrontal and temporal by Turetsky</td>
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<tr>
<td></td>
<td>Tien et al 1996</td>
<td></td>
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<tr>
<td></td>
<td>Turetsky et al 1995</td>
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<tr>
<td>Inferior parietal lobule</td>
<td>Pearlson et al 1998</td>
<td>First carefully controlled documentation of this asymmetry on MRI</td>
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conjunction with lateralized functions such as language. A variety of studies have demonstrated the absence or reversal of such normal cerebral structural asymmetries in schizophrenia (see Table 2). Such investigations are prompted by the presence of quantitative differences between the volumes of structures in the right versus left cerebral hemispheres that are normally apparent as early as the second trimester of prenatal development (Chi et al 1977b). In schizophrenia, disruptions in normal patterns of asymmetry are thought to reflect abnormalities in fetal brain development (see Barta et al 1997; Pearlson et al 1995b). Crow argues that such disturbed brain asymmetries are a “key to the etiology of schizophrenia” (Crow 1990a, 1990b, 1995a, 1995b, 1997, 1998; Crow et al 1989a, 1989b). Crow hypothesizes that one human gene comprising an asymmetry or cerebral dominance factor that is essential to the evolution of human language and hand dominance also “contributes substantially to the predisposition to psychosis.” Crow’s hypothesis also suggests that processes related to asymmetries also influence gender differences in schizophrenia by interacting with normal differences in the rate of asymmetry development between genders.

The planum temporale (PT), a brain region on the superior surface of the temporal lobe involved in language processing, is notable for its size differences between the left and right sides (the normal pattern is left > right). As PT asymmetry develops in utero, disruptions in the usual pattern suggests a process involving abnormal neurodevelopment (Chi et al 1977a). In addition to serving as a potential indicator of abnormal development, the PT is of particular interest in schizophrenia because it is comprised of heteromodal association cortex, as discussed earlier. Barta and co-workers (1995) developed a novel method for measuring the surface area of the PT that accurately follows the surface contours of the region. Applying this method, Petty and colleagues (1995) demonstrated a reversal in schizophrenia of the usual PT asymmetry; a finding not attributable to handedness differences. This initial finding was then replicated in a second, expanded sample (Barta et al 1997). In the second study, there was a complete reversal of the normal PT surface area asymmetry in both men and women schizophrenic subjects. However, others have not detected such PT asymmetry reversals using different MRI measurement methods, as reviewed by Barta and co-workers (1995).

**DISTURBED CONNECTIVITY.** Recent discussions have focused on disturbed connectivity between different brain regions in schizophrenia (Liddle 1997; Woodruff et al 1997). Tien and co-workers (1996) applied factor analysis procedures to cortical and subcortical regional brain volume measures from MRI data in normal and schizophrenia subjects. Basal ganglia, heteromodal cortical gray, and medial temporal lobe factors were present in both groups. The factor structure observed in normal subjects showed a high degree of bilateral symmetry, which was disrupted in the schizophrenia group. Across hemispheres, the disruption was most pronounced in medial and lateral temporal lobes structures, including entorhinal cortex and anterior and posterior superior temporal gyri. There was a significant correlation between the basal ganglia factor and the heteromodal cortical gray factor in the normal group that was not present in the schizophrenia group. Within the hemispheres, left posterior superior temporal gyrus did not load onto any factor in the schizophrenic group. Thus, several brain regions seem affected in schizophrenia, including temporo-limbic and HASC areas, with relationships between groups of regions also being abnormal. Wible and colleagues (1995) similarly found correlations between prefrontal and temporal cortical volumes in schizophrenia that differed markedly from volumetric associations seen in the healthy control group.

**CLINICOPATHOLOGICAL CORRELATES OF REGIONAL STRUCTURAL ABNORMALITIES.** Functional brain abnormalities are also demonstrated in schizophrenia, (see reviews by Gur and Pearlson 1993; Liddle 1997). Among the brain regions showing demonstrable functional abnormalities in schizophrenia, e.g., DLPFC (Weinberger 1987), Broca’s area (McGuire et al 1993), superior temporal gyrus (Woodruff 1997), and thalamus (Silbersweig et al 1996), all manifest significant structural abnormalities on either MRI or neuropathology (e.g., Akbarian et al 1995; Andreasen 1997; Barta et al 1990; Buchanan et al 1998; Pakkenberg 1992; Shenton et al 1992). It is unknown what relationship the structural and functional abnormalities bear to one another and which, if either, is primary. Some hypothesize that brain abnormalities in schizophrenia involve alterations in or altered correlations between regional patterns of brain function (Chua et al 1995; Liddle 1997). For example, Woodruff and co-workers (1997) reported that schizophrenics were characterized by an abnormally lateralized temporal cortex response to perception of speech. They suggested that this change was the functional equivalent of the previously reported structural abnormality (i.e., reversed asymmetry of planum temporale surface area) (Barta et al 1997; Petty et al 1995).

While none of the clinical symptoms seen in schizophrenia are pathognomonic for the disease, they are striking, and it is reasonable to ask whether they are related to underlying brain changes. To address this question, one needs to distinguish putative disease subtypes (e.g., paranoid) from the severity of a specific
symptom (e.g., thought disorder), from overall disease severity (e.g., number of hospitalizations). Attempts to link global brain changes of schizophrenia to specific symptom groups have generally failed (Pearlson et al 1989), although volumes of some brain regions have been associated with the severity of positive symptoms. For example, several groups report that superior temporal gyral volume reductions are related to positive symptoms (Fllaum et al 1995a; Marsh et al 1997). Reduced medial temporal volumes have also been associated with more severe clinical symptoms, including positive symptoms (Bogerts et al 1993; Goldberg et al 1993) and disrupted logical memory (Goldberg et al 1993). Reduced mesial temporal and temporal neocortical volumes were associated in a study by Nestor and colleagues (1993) with poorer scores on verbal memory, abstraction, and categorization. More specific findings include associations between smaller anterior superior temporal gyrus volumes and the severity of auditory hallucinations (Barta et al 1990) and smaller posterior superior temporal gyrus volumes and the severity of formal thought disorder (Barta et al 1997; Menon et al 1995; Shenton et al 1992). Mathalon and co-workers (1997) noted that rate of MRI volume loss over 4 years correlated with BPRS severity at baseline and follow-up. In particular, positive symptoms predicted loss of anterior superior temporal, frontal, and parietal (i.e., HASC) gray matter.

The work of Carpenter and co-workers suggests that deficit symptoms, which are more enduring relative to positive symptoms, may be more likely to show associations with brain structural abnormalities (e.g., Buchanan and Gold 1996). Three CT studies found higher rates of persistent unemployment (a presumed surrogate for severity of negative symptoms and/or cognitive impairment) among schizophrenic patients with ventricular enlargement (Katsanis et al 1991; Pearlson et al 1985; Vita et al 1991). A fourth CT study found that increased volume of the sylvian fissure predicted unemployment over a 4-year follow-up (van Os et al 1995). Using MRI, Harvey and colleagues (1993) found an association between unemployment and reduced volume of the anterior cerebral cortex and increased volume of sulcal fluid in schizophrenia. Others reported a relationship between negative symptom severity and larger left-hemisphere and total CSF volumes (Gur et al 1994; Mozley et al 1994).

Although many clinical and demographic variables have been found to correlate with everyday functional independence among patients with schizophrenia, their relative contributions remain unclear. A presumed link of deficit symptoms to dysfunction or structural change in the prefrontal and parietal cortex is certainly plausible (Weinberger 1987). However, Buchanan and colleagues (1993), using global gray and white matter MRI measures, found that right and left prefrontal volumes were actually smaller in nondeficit patients. By contrast, pilot data from Ventura and co-workers (1997) showed that severity of the deficit syndrome in schizophrenia correlated with lower total frontal lobe and hippocampal volumes. In a longitudinal analysis, Mathalon and co-workers (1997) reported an association between reductions in prefrontal gray matter and third ventricular expansion with negative symptoms.

Clearly, there are wide gaps in our understanding of the links between symptoms in schizophrenia and underlying brain changes. While it is logical that symptoms such as hallucinated voices or disturbed language could be produced by structural or functional deficits in language circuits, evidence for this remains suggestive rather than conclusive. Since the original report by Barta and colleagues (1990), which related superior temporal gyral volumes to psychotic symptom severity, several studies tie positive symptoms, particularly hallucinations and thought disorder, to structural changes in superior temporal gyrus. The finding from Mathalon and colleagues (1997), mentioned previously, suggests a potential explanation for the paradox, how can (inherently changing) positive symptoms be associated with (fixed) structural deficits? (Roth and Pfefferbaum 1992). While not consistently demonstrated, it is possible that positive symptom severity relates to the magnitude of a dynamic process involving progressive brain atrophy.

**Specificity of Identified Brain Abnormalities to Schizophrenia**

**ANATOMIC DIFFERENCES BETWEEN MEN AND WOMEN WITH SCHIZOPHRENIA.** The prevalence rates of schizophrenia in men versus women are about equal, but there are substantial gender differences in the age of onset, treatment response, and overall course of schizophrenia (Goldstein 1995). Whether these clinical differences are reflected in anatomic differences between men and women with schizophrenia remains unclear. Accordingly, investigation of the neuropathology of schizophrenia requires attention to the normal gender differences in brain anatomy (Marsh et al 1996; Pearlson and Pulver 1994).

Normal gender differences in brain anatomy (sexual dimorphisms) include differences in total brain volume, brain weight, regional brain size, and patterns of asymmetry that are well established in both animal and human studies (see Table 3 and reviews by Marsh and Casper 1998; Pearlson and Pulver 1994). Despite controversy regarding their magnitude, there are also normal gender differences in cognition that have been recognized for many years (Heller 1993; Maccoby and Jacklin 1974). Whether normal sexual dimorphisms in neuroanatomy
interact with hormones to modulate differences in cognition is unknown (Schlaepfer et al. 1995). In addition, how the patterns of volumetric differences in schizophrenia are influenced by normal gender effects, over and above disease related effects, remains unclear.


Further evidence suggests that the rates and timing of gray and white matter pruning, and hence longitudinal neurodevelopmental patterns, also differ among male and females (Aboitiz et al. 1996; Benes et al. 1994).

Using MRI in a cross-sectional study, Pfefferbaum and co-workers (1994) demonstrated that intracranial volumes increased between the ages of 3 to 10 years in a sample of males and females ranging in age from 3 months to 30 years, with cortical gray matter volumes peaking in both boys and girls around age 4 and declining thereafter. Cortical white matter volumes increased to age 20, with cerebrospinal fluid volume staying constant. By contrast, Giedd and co-workers (1996) did not find age-related brain developmental differences in corpus callosum in a cross-sectional MRI sample of healthy 4 to 18 year-olds. More recently, high-resolution diffusion-weighted MRI sequences (see Part II for discussion for this technique) have been developed to investigate white matter maturation in animal models and, for example, the effects of sex hormones on the rat brain (Prayer et al. 1997). Initial data suggest that white matter maturation accelerates with estrogen treatment, but is delayed by testosterone. The role of estrogen effects in brain development is corroborated by evidence that antiestrogens inhibit myelination in animal models (Guttinger et al. 1993). In rodents, there are also sex steroid effects on amygdala, hippocampus, and prefrontal cortex (MacLusky et al. 1987). These gender differences occur in neocortical and limbic regions, where they are likely associated with gender-related cognitive dimorphisms. In addition, gender differences occur in hypothalamic regions in association with reproductive differences.

Given the evidence for schizophrenia as a disorder of abnormal brain development, i.e., (Weinberger 1987), an

Table 3. Anatomic Imaging Studies Contrasting Normal Male and Female Neuroanatomy

<table>
<thead>
<tr>
<th>Observation</th>
<th>Study</th>
<th>Comment</th>
</tr>
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<tbody>
<tr>
<td>Female brain is smaller in weight and volume</td>
<td>Dekaban 1978; Breedlove 1994; Schlaepfer et al 1995</td>
<td>Not fully accounted for by larger male body height + weight</td>
</tr>
<tr>
<td>Female brain is less asymmetric, e.g., in planum temporale (PT) (where most males have left &gt; right asymmetry)</td>
<td>Geschwind and Levitsky 1968; Witelson and Kigas 1992; Diamond 1991; McGlone 1980; Kertesz et al 1990</td>
<td>Women have greater neuronal density in PT; Witelson et al 1995</td>
</tr>
<tr>
<td>Female brain myelinates and prunes earlier</td>
<td>Benes 1989; Geschwind and Galaburda 1985</td>
<td>Frontal lobe and amygdala + hippocampus differ most markedly</td>
</tr>
<tr>
<td>Female brain ages differently</td>
<td>Murphy et al 1996; Raz et al 1997; Cowell et al 1994</td>
<td>Sexually dimorphic nucleus of preoptic area and bed nucleus of the stria terminals of hypothalamus</td>
</tr>
<tr>
<td>Areas related to reproductive behavior differ</td>
<td>Allen et al 1989; Swaab and Fliers 1985</td>
<td>Prefrontal and lateral temporal cortical</td>
</tr>
<tr>
<td>Language regions (Broca’s, dorsolateral prefrontal cortex, PT) are proportionately larger in females</td>
<td>Schlaepfer et al 1995; Harasty et al 1997</td>
<td>Inferior parietal lobule</td>
</tr>
<tr>
<td>Visuospatial areas are proportionately larger in males</td>
<td>Pearlson et al 1998</td>
<td>Primate gender differences in CC closely related to development of cerebral asymmetries; de Lacoste and Woodward 1988</td>
</tr>
<tr>
<td>Corpus callosum (CC) size and shape differ</td>
<td>Witelson 1989; Allen and Gorski 1992; Pearlson et al 1998; Raine et al 1990, Andreasen et al 1990</td>
<td>CHEDULE</td>
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additional unresolved issue is whether a developmental disorder could differentially affect males and females. Outside of the Fragile-X syndrome and other sex chromosome-based disorders, the answer appears to be positive. For example, in dyslexia, Kaufmann and Galaburda (1989) and Humphreys and colleagues (1990) found that males showed only microdysgenesis whereas females showed both microdysgenesis and myelinated scars. This suggests that males with dyslexia are affected only during neuronal migration while female brains may be “disturbed” during migration as well as postmigration, including postnatal development. In schizophrenia, structural differences that distinguish schizophrenia from healthy brains also appear to be regions with predictable neurodevelopmental outcomes, i.e., normal brain asymmetries and sexual dimorphisms. Evidence for disruption of asymmetries and sexually dimorphic features in schizophrenic brains suggests that different patterns of anatomic abnormalities will be apparent in men versus women with schizophrenia.

Few neuropathologic studies in schizophrenia have explicitly examined gender differences and fewer still CT or MRI studies comparing men and women with schizophrenia have considered structures other than the ventricular system (Table 4). Many studies are limited by small and/or unequal sample sizes and additional confounds, such as poorly matched samples. In addition, a majority of studies have included only or mostly male subjects (Nopoulos et al 1997a). Others argue that apparent gender differences in brain structure “evaporate if confounds such as socioeconomic status and race are controlled” (Harvey et al 1991; Lewis 1992). However, in a recent analysis that accounted for these confounds (Pearlson et al 1997b), comparisons of schizophrenic patients to healthy controls on MRI-derived measures of superior temporal gyrus, medial temporal structures, and global brain measures, sex-by-diagnosis interactions were evident for temporo-limbic structures (right and left amygdala and a trend for left entorhinal cortex). Thus, these data suggest disease-related gender differences in neocortical and temporo-limbic anatomy in schizophrenia. Whether such gender differences in brain anatomic abnormalities are also linked to the well-established gender differences in onset, course and outcome of schizophrenia is not known.

**GENETIC COMPARISONS.** A high prevalence of various biologic abnormalities and of schizophrenia spectrum disorders in the first-degree relatives of schizophrenia patients suggests that a proportion of clinically unaffected first-degree relatives carry one or more pathologic genes for the disorder (Cannon et al 1994; Kremen et al 1994; Shedlack et al 1997; Wickham and Murray 1997). However, the identity and role of gene(s) and gene products in schizophrenia remains unknown (Wickham and Murray 1997). One possibility is that the putative gene(s) influence cortical migration or development (Ross and Pearlson 1996). Thus, if structural brain abnormalities in schizophrenia patients are genetically transmitted, they could function as a major biologic marker for transmission of the schizophrenia genotype, as well as reflecting environmental etiologies (Cannon et al 1994; Wickham and Murray 1997). As candidate genes for schizophrenia and bipolar disorder become evident, brain imaging studies will become extremely important for clarifying these relationships between genotype and phenotype. Biologic markers such as structural brain abnormalities might allow
identification of phenocopies and homogeneous subtypes and clarification of the relationship of the genotype to the neural phenotype. Such data, which highlight genetic influences, are a useful counterpoint to discordant monozygotic twin studies, which emphasize environmental factors (Suddath et al 1990). Finally, studies focusing on a single generation (e.g., sib-pair designs) control better for possible age and family environment confounds.

Twin studies of healthy control populations emphasize the role of heritability of total brain and sulcal volumes, and show similar, but smaller, effects for ventricular volumes (Pfefferbaum et al 1997; Reveley et al 1982). Studies of nonschizophrenic siblings of patients with schizophrenia show ventricular volumes intermediate between those of patients and control subjects (DeLisi et al 1986; Weinberger et al 1981). In monozygotic twins discordant for schizophrenia, the schizophrenic twin has larger ventricles while ventricular size is intermediate between that of the schizophrenia patients and normal controls in the unaffected twin (Reveley et al 1982, 1984). Shihabuddin and co-workers (1996) assessed lateral ventricular enlargement and frontoparietal atrophy on CT in one large family containing multiple cases of schizophrenia. Shihabuddin hypothesized that these changes may be associated with a schizophrenia-related gene and denote a susceptibility to schizophrenia-related conditions. Frangou and co-workers (1997) initially suggested that planum temporale volume asymmetry in patients with schizophrenia, and their first-degree relatives, did not differ from those of normal control subjects. However, a later study (Barta et al 1997) showed that schizophrenia patients differ in asymmetry of the planum temporale surface area but not in the volume of the underlying gray matter. Cannon and colleagues (1997) contrasted MRI measures from schizophrenia patients and their unaffected siblings; the schizophrenia patients had increased CSF, especially in the frontal lobes and left hemisphere. In a small pilot study (Seidman et al 1997), there was increased ventricular size and reduced volumes of gray matter and right amygdala in the nonschizophrenic sisters of schizophrenia patients relative to female control subjects. Sharma and co-workers (1998) examined families multiply affected with schizophrenia. Ventricular volume in the MRI scans of schizophrenia patients was larger than those of first-degree relatives and control subjects.

Wickham and Murray (1997) argue that questions of biologic vulnerability markers can be usefully addressed via sibling comparisons. Presumed obligate genetic carriers (e.g., nonschizophrenic individuals who have parents and children with schizophrenia) are of particular interest to researchers. Sharma and co-workers (1998) compared MRI scans of patients from families multiply affected with schizophrenia to many of their first-degree relatives and to group-matched normal control subjects. Male schizophrenics had larger lateral ventricles than normal control subjects, but the schizophrenia patients had smaller total brain volumes and larger lateral ventricles compared to nonaffected age- and gender-matched siblings. Structural brain measures in siblings were no different than those in the healthy control subjects, but presumed obligate carriers showed similar lateral ventricular enlargement to schizophrenia patients. Sharma argued that nonschizophrenic relatives could manifest similar brain changes to schizophrenia patients, especially relatives who are presumed carriers of the schizophrenia gene.

Other than the ventricles, relatively few anatomic regions have been investigated in this context. Dauphinais and co-workers (1990) reported smaller temporal lobe size in nonschizophrenic siblings. Dickey and colleagues (1997) preliminarily explored structural brain abnormalities in schizotypal personality disorder (SPD). Although SPD commonly appears in family members of schizophrenics, the Dickey sample was recruited through local advertisements. Many of the same structural abnormalities previously reported to occur in the brains of patients with schizophrenia (for example, reduced gray matter volume of the posterior superior temporal gyrus and whole-brain gray matter), though, were also found by Dickey in SPD. Silverman and co-workers (1998) found that the ventricular-brain ratio in the schizophrenic patients was similar to that of their siblings with SPD, but differed from family members without schizophrenia-related disorders.

**COMPARISON DISORDERS.** In the absence of a definitive pathologic feature, none of the reported structural abnormalities is pathognomonic for schizophrenia. Comparison of brain abnormalities in schizophrenia to those present in other neuropsychiatric conditions that also exhibit brain structural abnormalities provides one approach for discerning normal patterns as well as those that are unique to schizophrenia versus some other condition, e.g., Alzheimer’s disease, epilepsy, mood disorders, alcoholism, or Parkinson’s disease (Marsh et al unpublished data, 1999; Sullivan et al 1998b). Potentially more revealing are comparisons of schizophrenia to disorders that share clinical phenomena with schizophrenia, as these may reveal clinicopathologic correlations that are either specific to schizophrenia or merely common to the presence of certain clinical signs. Neurologic disorders with schizophrenia-like illness and more overt neuropathology than idiopathic schizophrenia may further improve the likelihood of detecting abnormalities and clinicopathologic relationships, which are salient to the schizophrenic syndrome. Here, we discuss two candidate disorders for such comparisons: bipolar disorder and epilepsy.
**Bipolar Disorder.** Bipolar disorder (BP) is a common disorder with a lifetime prevalence of 1.5%. Psychotic symptoms frequently occur, and, in the absence of additional history, the clinical syndrome of acute mania can be indistinguishable from an acute schizophrenic episode (Carlson and Goodwin 1973). In addition, many patients with schizophrenia experience depression or other affective symptoms. These shared clinical features of schizophrenia and bipolar disorder have led some to suggest that there is a continuum of pathology between bipolar disorder and schizophrenia (see Crow 1990b; Taylor 1992).

Separate structural and functional imaging studies comparing control subjects to bipolar disorder or to schizophrenia subjects implicate many of the same brain regions in both conditions, including the frontal lobe, basal ganglia, and temporal lobe structures (see reviews and comments by Pearlson and Schlaepfer 1995a, 1997c; Soares and Mann 1997). However, it is also important to note that many earlier neuroimaging studies on bipolar disorder included mixed samples of patients with bipolar type I and type II syndromes, major depression, early as well as late onset syndromes, and psychotic versus nonpsychotic features, for example. By contrast, the study criteria for studies on schizophrenia have tended to be more selective (see Pearlson and Schlaepfer 1997). Nonetheless, despite the clinical heterogeneity of studies on bipolar disorder, certain anatomic findings have emerged. Like schizophrenia, these include generalized changes such as increased ventricle size and sulcal widening, and localized volume abnormalities such as reduced amygdala and/or anterior temporal lobe volumes (Altshuler et al 1991; Hauser et al 1989; Pearlson et al 1997b; Strakowski et al 1993), and subgenual cingulate volumes (Drevets et al 1997). A more recent MRI study suggests amygdalar enlargement in bipolar disorder (Altshuler et al 1998). In contrast to studies of schizophrenia, MRI studies of bipolar disorder also reveal an increased frequency of subcortical white matter hyperintensities (Aylward et al 1994; Brown et al 1992; Dupont et al 1990; reviewed by Marsh et al 1996).

Few studies have directly compared brain abnormalities in schizophrenia to those in bipolar disorder. Those carried out so far seem to suggest that regional changes in schizophrenia consist of disturbances in normal asymmetries and changes in entorhinal cortex volumes, whereas bipolar disorder subjects show an increased frequency of subcortical white matter hyperintensities and perhaps cingulate changes (Aylward et al 1994; Drevets et al 1997; Noga et al 1995). Recently, Lim and colleagues (unpublished data, 1999) showed that global cerebral gray matter reductions in patients with bipolar disorder were intermediate between those of schizophrenia and controls, along with a similar pattern of cortical deficits to schizophrenia, i.e., maximal reductions in prefrontal cortex and superior temporal regions. These findings support the hypothesis that HASC regions are preferentially affected in schizophrenia.

**Epilepsy.** The occurrence of transient psychotic symptoms or prolonged interictal schizophrenia-like syndrome in some patients with epilepsy has led to hypotheses that epilepsy may serve as a useful model for investigating the neuropathology of schizophrenia (Engel and Rocha 1992; Scheibel 1991; Slater et al 1963). Although epilepsy and ictal psychotic phenomena are related to recurrent paroxysmal electrophysiologic events, this hypothesis suggests that the occurrence of chronic interictal schizophrenia-like illness represents additional brain disease, i.e., structural pathology, not directly related to seizure generation. In particular, brain abnormalities specific to psychosis or negative symptoms should be over and above the abnormalities seen in epilepsy without these symptoms. Accordingly, comparisons of patients with epilepsy plus schizophrenia-like syndromes (E+SCZ) to patients with idiopathic schizophrenia enables identification of converging brain abnormalities or critical nodes that are specific to the schizophrenic syndrome, rather than epiphenomena.

Many commentaries and investigations on the relationship between E+SCZ and schizophrenia have focused on the role of temporal lobe pathology and temporal lobe epilepsy (TLE) in the occurrence of the schizophrenic syndrome (Mace 1993; Sachdev 1998; Trimble 1991). In part, this bias is because E+SCZ occurs most commonly (though not exclusively) in patients with localization-related epilepsy of temporal lobe origin (the most common site for localized seizure foci). Furthermore, samples were limited to patients with TLE, the clinical characterizations of patients with E+SCZ tended to focus on the presence of psychotic symptoms (which, as above, may be clinicopathologically related to temporal lobe processes), and brain regions outside the temporal lobe were not examined. However, the hypotheses on the relationship between epilepsy and schizophrenia are important historically in that they influenced the theoretical basis for focusing anatomic investigations of schizophrenia on specific brain regions, namely the lateral and medial temporal lobe (e.g., Barta et al 1990; Suddath et al 1990). Yet, the prevailing hypotheses on relationships between epilepsy and schizophrenia did not evolve along with advances in imaging technology and evidence from MRI of widespread cortical abnormalities in schizophrenia.

Despite speculation on the importance of left temporal pathology in E+SCZ, the neuroimaging data, albeit limited, has not been compelling in this regard. At the least, neuroimaging and neuropathologic studies comparing E+SCZ to schizophrenia tend to implicate extratemporal, and possibly, subcortical abnormalities as common factors.
The Timing of Neuroanatomic Pathology in Schizophrenia

EVIDENCE FOR ABBRENT NEURODEVELOPMENT IN SCHIZOPHRENIA. Despite the usual onset of schizophrenia in adolescence or early adulthood, a prevailing hypothesis suggests that schizophrenia develops as a result of a disruption in normal brain development that is then clinically manifest later in life when inter-related neural systems mature (Jakob and Beckmann 1986; Jones and Lewis 1992; Weinberger 1987; Weinberger et al 1988). Support for this hypothesis is derived from epidemiologic evidence of an increased incidence of perinatal insults and obstetrical complications in the schizophrenic population (Jones et al 1998; Kendell et al 1996), the presence of mild somatic defects suggestive of an ectodermal developmental etiology (Green et al 1994), and documentation of premorbid neurobehavioral abnormalities during infancy and childhood in individuals who go on to develop schizophrenia (Cannon et al 1997; Pilowsky et al 1993; Weinberger et al 1988).

Several MRI studies report an excess of gross structural abnormalities in schizophrenia, such as cavum septum pellucidum and callosal agenesis, that reflect abnormal brain development (e.g., Nopoulos et al 1997b; Nopoulos et al 1995). Quantitative MRI studies also provide data that is consistent with abnormal brain development in schizophrenia, such as reversed cerebral asymmetries or aberrant sulcal/gyral morphology (Barta et al 1997; Bullmore et al 1995; Kikinis et al 1994). The neuropathologic evidence of abnormal cytoarchitecture, gyral patterns, and neural migratory patterns in postmortem brains of schizophrenic patients is also compelling (Akbarian et al 1995; Arnold et al 1997; Jakob and Beckmann 1986), although these findings have not been consistently replicated. Further supporting the hypothesis that anatomic abnormalities are present before the clinical onset of illness are cross-sectional MRI studies that, in general, fail to demonstrate correlations of brain abnormalities with duration of illness and age of illness onset (see Marsh et al 1996).

MRI studies on patients with childhood-onset schizophrenia (first psychotic symptoms before age 12 years) provide an opportunity to test whether there are different anatomic abnormalities associated with psychotic phenomenology in a population that has not yet undergone adolescent cerebral maturational processes. Recent MRI studies on such cases by the NIMH Child Psychiatry Group provide insights in this regard. Frazier and colleagues (1996) reported that basal ganglia were larger, attributable to prior treatment with conventional neuroleptics and that lateral ventricles were (nonsignificantly) larger compared to normal age-matched controls. The same group reported that these early-onset patients did not differ from controls in whole-brain adjusted temporal lobe volumes, except for larger superior temporal gyri (Jacobsen et al 1998). At 2-year follow-up, schizophrenic subjects showed significantly greater decreases in bilateral superior temporal gyrus and left hippocampus volumes than did healthy subjects. Decline in right posterior superior temporal gyrus volume was associated with worse positive symptoms at both baseline and follow-up. Thus, at initial assessment, portions of the superior temporal gyrus were larger in patients relative to control subjects, but progressive tissue loss was seen with ongoing illness (Jacobsen et al 1998). Also, ongoing ventricular increases were seen in schizophrenics compared to control subjects (Rapport et al 1997). In a subset of these patients, no differences were observed between controls and schizophrenics in planum temporale area or asymmetry (Jacobsen et al 1998). However, the method used had not previously distinguished adult-onset schizophrenics from control subjects on this measure. The frequency of an enlarged cavum septum pellucidum was higher in the patient group compared to control subjects (Nopoulos et al 1998).

It may be hard to generalize from these findings, as childhood onset schizophrenia is rather rare with an atypical presentation of the disorder, much as in the case of childhood-onset Huntington’s disease, which may involve a variant neuropathology. In addition, the NIMH sample is itself a treatment-resistant subset from within...
childhood-onset schizophrenia, again suggesting that generalizability from this sample may be limited. However, these interesting findings offer some support for (perhaps ongoing) developmental anomalies.

Other studies have examined brain abnormalities in adults with chronic schizophrenia who had an early age of illness onset (i.e., preadolescent and adolescent) (Lim et al 1996a; Marsh et al 1997) and compared these findings to schizophrenic patients with a more typical age onset of schizophrenia in young adulthood (Marsh et al 1999). These MRI studies show similar patterns of brain abnormalities (widespread reductions in cortical gray matter and temporolimbic abnormalities) in both patient groups, despite their clinical differences in onset age, clinical course, and response to neuroleptic medications. Thus, these data in adults are suggestive of similar processes in early onset versus later onset groups, although such cross-sectional analyses cannot address whether disparate processes were present earlier.

EVIDENCE FOR NEURODEGENERATIVE DISEASE PROCESSES IN SCHIZOPHRENIA. A competing hypothesis on the nature of schizophrenia (see DeLisi 1997) is that the clinical onset of schizophrenia is followed by an active and ongoing neurodegenerative process. If a progressive process in schizophrenia persists into adulthood, identification of the underlying pathophysiology, and whether it is restricted to a subset of patients, is extremely important; an appealing aspect of this hypothesis is that it more readily offers the potential for therapeutic interventions that stave off or even abort the disease process.

Several brain imaging studies have addressed the issue of progressive brain changes in schizophrenia, but there are conflicting findings in both longitudinal and cross-sectional studies. Longitudinal CT (Illowsky et al 1988) and MRI (Vita et al 1988) studies showed no accelerated atrophy compared to control subjects. Lim and co-workers (1996a), in a cross-sectional study using an age-regression model, found no evidence for accelerated brain change in schizophrenia. However, other MRI studies (DeLisi et al 1995; Hoffman et al 1991; Kemali et al 1989; Mathalon et al 1997; Turetsky et al 1995; Woods et al 1990) show small decreases in brain volume in schizophrenic patients over time. By contrast, progressive changes have not been detected in follow-up studies of first-episode cases (Jaskiw et al 1994; Vita et al 1994).

It is possible that deterioration occurs only in a subgroup of schizophrenic patients. Historically, pneumoencephalography studies found progressive ventricular enlargement in schizophrenic patients with a deteriorating course (Haug 1962). In schizophrenic patients rescanned 2 to 3 years after initial assessment, approximately 50% of patients resembled healthy control subjects, but the remainder had more than 5 times the rate of total ventricular enlargement of the control subjects (Nair et al 1997). Recently, an analysis of CT-derived measures of ventricular size from 53 schizophrenic patients scanned an average of 5 years apart (Davis et al 1998) showed marked longitudinal increases in ventricular size in the “Kraepelian” patients (about 40% of the sample), compared both to non-Kraepelian schizophrenic patients and to elderly normal control subjects. These data suggest that neurodegenerative processes are specific to the Kraepelian subgroup, which was defined on the basis of chronic dependence on others for life necessities, chronic unemployment, and symptom chronicity. Another promising lead is the observation that elderly, chronic institutionalized schizophrenic patients develop a non-Alzheimer type dementia (Barak et al 1997; Purohit et al 1993). Examination of such individuals using quantitative anatomic measures is important to determine if this is the rule in schizophrenia, when the process begins, and whether those with prominent deficit symptoms are at high risk.

The largest study to date addressing this question is that of DeLisi (1997), which reported on 50 young, first-episode schizophrenic patients who were followed since first clinical onset and 20 control subjects. Annual scans where obtained from 4 or more years and slopes of change in measured brain regions were calculated. No differences were found for total temporal lobe or hippocampus/amygdala volumes. Schizophrenic patients were characterized by decreased hemisphere sizes, right cerebellum area, isthmus of the corpus callosum area, and of left lateral ventricle (on coronal but not axial slices). Gur and co-workers (1998) rescanned 40 schizophrenics (20 first-episode) at a mean of 30 months. Patients were distinguished by frontal lobe volume decreases. Various volume reductions correlated with positive and negative symptoms in a complex manner, differing between first-episode and previously-treated schizophrenia and further complicated by medication effects.

There are well-documented precedents for neurodevelopmental conditions with an adult neurodegenerative outcome, e.g., Alzheimer disease in Down syndrome (Raz et al 1995). If schizophrenia exemplifies this type of condition, then this awareness would be an important advance in our understanding of the disorder. Existing evidence suggests that at least a subset of patients with schizophrenia manifest degenerative changes, but there are problems with such studies. These include generally small patients and control samples, mainly cross-sectional design, relatively brief follow-up times, inclusion of substance abusers, and selection of unrepresentative age spans of schizophrenic subjects relative to the lifetime span of the illness.
Part II. Advances in Structural Neuroimaging Methodology

MRI continues to provide the best methodology for examining the anatomic details of the brain in the living subject. Most of the structural imaging studies on schizophrenia described in Part I examined abnormalities in the size (either area or volume) of the total brain, or of various brain regions, or structures such as specific lobes, ventricles, gyri, or nuclei. The computerized approaches for obtaining these measures have become quite advanced, with improved image acquisition and image contrast, and 3-dimensional surface rendering enabling the refined measurement of very specific structures or regions, e.g., entorhinal cortex or the inferior parietal lobule. Other computerized methods are used to obtain separate estimates of the volumes of gray matter, white matter, and CSF for a given region (Reiss et al 1998). While these investigations of the relative sizes of different brain structures in schizophrenia have been unequivocally informative, the data provided are limited to the global characteristics of a structure and the methods have overall been extremely labor intensive. In addition, even in disease states, the extent of normal variation attributable to aging, gender, total brain size, handedness, race, body size, and perhaps, socioeconomic status (Gur and Pearlson 1993; Marsh et al 1996) may obscure the recognition of pathology. Thus, additional morphometric methods that provide biologically meaningful information are necessary to complement the traditional measures of structural size and for integration with clinical and functional studies.

Advances in Image Analysis Approaches

STEREOLOGY. Stereological techniques, based on the Cavalieri principle, have traditionally been used in histologic and pathologic studies to obtain accurate and unbiased measures of the number of objects (e.g., neurons) in an anatomically defined volume (Howard and Reed 1998). These techniques form the usual basis for estimating volumes for regions of interest (ROIs) from structural neuroimaging data. The Cavalieri principle is based on a theory that the volume of any structure can be estimated by cutting it into thin parallel slices, measuring the cross-sectional area of the structure in each slice, summing these areas, and multiplying the sum by the slice thickness. The accuracy of the measurement is thus a function of the thinness of the slices: thick slices yield less precise estimates than thinner ones. In earlier imaging studies, thicker image slices, variable orientation of the head in the scanner, reduced image contrast (and hence the clarity of brain structural margins), and scanning sequences that imaged only a limited portion of the brain all profoundly affected volume estimates. Gradual improvements in imaging technology now enable collection of MRI data that samples the entire brain in very thin slices and can be reoriented in a standardized fashion along the 3-D axis, thereby minimizing these confounding influences. More sophisticated imaging hardware has also facilitated the efficient acquisition of small isotropic voxels (e.g., 1 mm³) that reduce error when image data are reoriented and resliced against standardized landmarks (Stievenart et al 1993).

POINT COUNTING. Many volumetric measurements of brain structures from MRI data typically involve tracing the edges of region of interest (ROI) on a series of images. This edge-tracing approach is extremely laborious, especially with newer acquisition sequences that include an increased number of thinner slices. To reduce the effort involved in volumetric measurements but still maintain anatomic accuracy, several studies have substituted point counting methods as opposed to edge tracing for delineating ROIs. Point counting refers to a method in which a 3-D grid is superimposed on the image data (Hyman et al 1998). Specialized software can be used to display a series of cross-sectional images of the brain that are overlaid with the regular, 3-D grid of points. After denoting whether grid points intersect the ROI, software algorithms calculate the true volume of the structure in physical units and substantially reduce the time devoted to image analysis.

CORTICAL “PAINT” TECHNIQUES. Many morphometric imaging studies have been limited by the inability to measure accurately and reliably structures in which gyral patterns are highly convoluted or variable when viewed from a single 2-D orientation. Earlier MRI studies subdivided, or parcellated, the brain into its functional or anatomic subregions using standardized geometrically defined algorithms, (e.g., Zipursky et al 1992). More recently, novel software tools have been developed to enable 3-D tracing of complex cortical regions, such as the prefrontal cortex and its superior, middle, inferior, and orbital subregions (Ross and Pearlson 1996). These methods for parcellating brain regions may also enhance our ability to detect specific structure–function relationships. One approach uses a “paint” method (Ross and Pearlson 1996), which allows for demarcation of specific gyri by “painting” the region of interest on a 3-D rendering of the cortical surface. With this method, the rater views a 3-D surface rendered image of the brain along with the three orthogonal views (coronal, axial, and sagittal). Such a method enables visualization of entire lobes or brain regions as well as subregions. After identifying the sulcal landmarks for a given region and their course over the brain’s curvature, the sulcal landmarks for each demarcated region are each “painted” a different color on the
3-D representation of the brain. These colors are then depicted on each set of orthogonal views and define the set of voxels used to calculate the gray and white matter components of the region of interest. When applied to analyses of frontal lobe structures in schizophrenia compared to control subjects (Buchanan et al. 1998), schizophrenic patients, showed significant reductions in total prefrontal volume, as well as selective volume reductions in inferior prefrontal gray matter bilaterally and total prefrontal white matter. The greater anatomic precision provided by the “paint” technique may account for the inconsistent results from earlier MRI studies using anatomic landmarks on a 2-D image slices to define prefrontal cortical regions (see Marsh et al. 1996; Wible et al. 1995).

**IMAGE AVERAGING AND AUTOMATED PARCELLATION.** Image averaging and automated parcellation techniques (Andreasen et al. 1996) provide an alternative to traditional manually based morphometric techniques or the “paint” techniques described above. Image averaging techniques, which have been adapted from functional neuroimaging approaches, rely on the standardized stereotaxic coordinate system proposed originally by Talairach and Tournoux (1988) to define, or parcellate, brain regions. Using specialized computer software and specific anatomic anchor points, the raw image data are mapped onto the standardized coordinate space so that all images are coregistered in the 3-D grid. In effect, the brain image data are “normalized” to the grid, which defines over 1000 3-D volumes that theoretically map to the same neuroanatomic regions across subjects. Comparisons can be either pixel-wise or across parcellated regions. A main advantage of these techniques is that the entire brain can be evaluated simultaneously. In addition, the method is more automated and thus more efficient than manual morphometric measurements. By contrast, the manual sulcal-based methods delineate brain subdivisions more accurately, require advanced knowledge of neuroanatomy, and can be associated with reduced reliability over time. Thus, the automated methods may be more appropriate for estimating volumes of larger structures, such as cerebral lobes, the cerebellum, and ventricles, or in combination with a limited degree of nonautomated image processing.

The role and biologic significance of image averaging methods in structural imaging analyses of schizophrenia remains uncertain. This is because interpretations of signal intensity values from MRI data are based on their anatomic location (e.g., white versus gray matter), as opposed to functional imaging studies that measure cerebral activity throughout the brain. Another issue is that coregistration (normalization) of structural MRI data to a uniform grid may actually obscure disease-related structural abnormalities or even normal anatomic variability under investigation. This issue is particularly germane to studies on schizophrenia. Nonetheless, as with other approaches, image averaging techniques appear to provide a novel and useful tool for the study of brain morphology in schizophrenia provided the limitations of the method are also taken into account. Recent reports using image averaging techniques to compare schizophrenic subjects to control subjects support evidence for widespread abnormalities involving cortical volume reductions and ventricular enlargement as well as major white matter tracts (Wolkin et al. 1998). An earlier study using this method highlighted evidence for signal intensity reductions in the thalamus and its white matter connections (Andreasen et al. 1994a).

**SHAPE ANALYSIS.** The objective of shape analysis is to examine and quantify focal characteristics (or descriptors) of a structure that are independent of variations in size, which reflects more global features of a structure. In shape analysis, mathematical models of image analysis are used to evaluate evidence of neuropathologic change, such as morphological distortion of a boundary, a feature that would not be apparent in a volumetric measure. For the hippocampal boundary, comparisons might include measures of the number and size of concavities within the boundary, the length of the boundary, the shape of contours within the boundary, or the topological relationships between various regions on the boundary to one another or to a neighboring structure (Gonzalez and Wintz 1987). The internal characteristics of a structure, represented by pixels within the defined boundary, can also be analyzed for changes in texture (variations in signal intensities) or compactness (pixel density for a given region), along with the usual measures of area or volume. In combination, this information can be used to test specific models of disease pathology. For example, if the neuropathology of schizophrenia is related to a disturbance in neuronal migration, there would be a decrease in the size of a structure without concomitant change in shape characteristics if the migratory disturbance is generalized. However, if abnormal development were selective to specific regions of the hippocampus, for example, such focal changes would affect the configuration or shape of the hippocampus on MRI. Earlier MRI studies using quantitative shape analysis techniques (Casanova et al. 1990a, 1990b) suggested nonspecific disease-related distortions of the temporal and prefrontal lobes in schizophrenia. However, these studies did not use high-resolution MRI acquisition techniques, which reduce the confounding effects of MRI partial voluming on shape analysis. The newer image acquisition and analytic techniques, which enable consistent 3-D realignment of the brain data against specified anatomic landmarks, should also permit more meaningful analyses of corpus callosum abnormalities in
SURFACE AREA, THICKNESS, AND MEAN CURVATURE. Surface area measurements provide another approach for obtaining information on brain structure that may have greater biologic relevance than size measurements alone and will also be useful for integration with functional neuroimaging data. In the case of cortical structures, separate estimates of cortical thickness and surface area, which both contribute to estimates of cortical volume, may provide information that has different implications. Specifically, measures of surface area devoted to a particular function, e.g., motor activity, may be indicative of the relative portion of the brain devoted to the related task. Using a tessellation approach for deriving surface area of the planum temporale, Petty and co-workers (1995) and Barta and colleagues (1997) showed reversal of the usual pattern of left greater than right hemispheric asymmetry in schizophrenia. Disturbances in measures of cortical thickness, which normally vary regionally, would indirectly reflect disruptions in the cortical columns. Differences in surface areas, but similar thickness, suggest that fewer cortical columns are devoted to the region in the patients with less surface area. Conversely, similar surface areas for a given region, along with differences in the degree of thickness, suggest that similar amounts of the brain are devoted to a region, but that the development within the cortex between the groups was perhaps different. Measures of mean curvature of the brain surface may provide method for assessing the extent and character of convolutions on the brain’s surface, thereby serving as an index of normal versus abnormal brain development (van Essen 1997).

Diffusion Tensor Imaging

MR diffusion imaging, a recently developed extension of MRI technology, provides an approach for mapping and quantifying white matter connections between brain regions (Mori and van Zijl 1995; Prichard 1998; van Zijl et al 1994; Westin et al 1997). MR diffusion measures on solutions were first described by Stejskal and Tanner (1965) and imaging was first performed in vivo by Le Bihan (1990). The basic principles of diffusion imaging involve setting MRI parameters to use the net flow of water to generate image contrast. Under circumstances where the mobility of water is unrestricted, e.g., a still bowl of water, there is no directional preference and water displacement in the x-, y-, and z-directions is equal, a condition of isotropic diffusion. Anisotropic diffusion occurs when there are structural limitations, e.g., as imposed by organized fibers (such as axonal fibrils) that are arrayed predominantly in one direction (Beaulieu and Allen 1994).

Quantification in diffusion imaging is based on the diffusion constant, referred to as the apparent diffusion coefficient (ADC). The ADC, calculated for each image voxel, is based on the gradient amplitude and duration of the magnetic field used during image acquisition. When ADCs are orientation-dependent, as for brain tissue and white matter in particular, in vivo diffusion is described with six different diffusion constants, which are generally ordered in a tensor. A tensor is an array of numbers. In order to get information on directionality in three dimensions, tensors are measured for each voxel using six different magnetic field orientations. Linear algebraic operations are then performed on the tensors to derive anisotropy indices. Differences in anisotropy represent relative differences in diffusional amplitude or rate, thereby providing information on axonal density and the directionality of neural structures. Thus, differences in anisotropy may correspond to variation in the number or coherence of fibers within regions, and may be used to contrast subjects in healthy versus diseased states.

Initial studies on healthy control subjects using dimensional diffusion imaging studies demonstrate greater alignment of fiber tracts in the right hemispheric anterior internal capsule as compared to this same region on the left (Peled et al 1997). Initial analyses using diffusion tensor images for studies on schizophrenia report lower diffusion anisotropy in the white matter of the prefrontal cortex in patients relative to controls subjects (Buchsbaum et al 1998). Using 18-FDG PET in the same subjects, there was also evidence for lower correlation coefficients between metabolic rates in the prefrontal cortex and the striatum in the patients relative to control subjects, suggesting convergent evidence for aberrant frontostriatal connectivity in schizophrenia. A more recent report using diffusion tensor imaging showed reduced white matter anisotropy, particularly in the corpus callosum, in schizophrenic men relative to age-matched healthy control men (Lim et al 1998). These findings might be explained by disordered fibers within the bundles or reduced bundle number in the corpus callosum.

Summary

In this review, we discussed the general neuroanatomic findings from structural neuroimaging studies of schizophrenia. We also addressed issues related to the specificity of these findings in terms of gender differences in brain abnormalities in schizophrenia, observations in clinically unaffected relatives, and comparisons with other neuropsychiatric disorders. The relationships of these structural...
neuroimaging findings to the neurodevelopmental and neurodegenerative hypotheses of schizophrenia were also discussed. Finally, we reviewed newer methods of structural image acquisition, processing, display, and analysis, and their applications in research on schizophrenia.

Structural imaging methodologies have proven to be powerful tools enabling the recognition of fundamental brain abnormalities in schizophrenia. To date, these include evidence for widespread deficits in cortical gray matter volumes, regional reductions in heteromodal association cortex and temporolimbic structures, and nonspecific increases in ventricular size, thereby implicating dysfunction of neural circuits involving cortical, thalamic, basal ganglia, and limbic structures in the pathogenesis of the illness. Presumably, the identified patterns of regional change are related to characteristic symptoms of the disorder, although there are still no consistently demonstrated clinicopathologic correlates. The emerging evidence that affected neocortical regions comprise components of the heteromodal neocortical association network may provide a framework for further investigating the otherwise elusive brain structure–function relationships. Furthermore, the converging role of heteromodal regions in both the expression of neuroanatomic gender differences and in normal cerebral asymmetries suggests that disruption of these cortical areas in schizophrenia may be important to the clinical expression of the disease, including clinical differences between men and women with schizophrenia. The continued development of techniques for investigating the brain will ensure that structural neuroimaging will remain a strong contender in helping to address questions related to the origin and mechanism of brain alterations in schizophrenia.

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