Abstract

A central question in schizophrenia research is which brain abnormalities are independent of psychosis and which evolve before and after psychosis begins. This question can be addressed by longitudinal neuroimaging studies beginning in the prodrome, but at present there is only one published study. We reviewed the literature on structural brain imaging in persons with chronic and first episode schizophrenia, nonpsychotic persons at genetic high risk, and persons thought to be at risk for imminent psychosis ("prodromal" persons). Medial temporal lobe (MTL), especially hippocampal, volume alterations are among the most robust brain vulnerabilities for schizophrenia. Because verbal declarative memory (VDM) deficits are prominent and the parahippocampal gyrus (PHG) is considered to be centrally involved with the hippocampus in VDM processing, we analyzed PHG data from a family study of schizophrenia. Patients with schizophrenia and nonpsychotic relatives from "multiplex" families (families with multiple persons with schizophrenia) had significantly smaller right parahippocampal anterior (PHa) volumes than controls. Marginally significant findings were observed for the left PHa. Unexpectedly, relatives from "simplex" families (families with only one person with schizophrenia) had significantly larger PH posterior volumes than controls and did not differ from controls on PHa. Results provide some support for the hypothesis that the vulnerability to schizophrenia includes abnormal volumes of the PHG. These data provide additional support for the hypothesis that some MTL abnormalities in schizophrenia are independent of psychosis, at least in families with presumably high genetic loading. Implications of genetic risk studies for prodromal research are discussed.

Keywords: Schizophrenia, relatives, genetics, MRI, hippocampus, parahippocampal gyrus, verbal declarative memory.


A Review of Medial Temporal Lobe Dysfunction as a Vulnerability Indicator for Schizophrenia Using Structural Magnetic Resonance Imaging

Structural Neuroimaging in Schizophrenia. The etiology and pathophysiology of schizophrenia remain elusive despite more than 300 postmortem and structural neuroimaging studies using computed tomography and magnetic resonance imaging (MRI; Lawrie and Abukmeil 1998; Harrison 1999; McCarley et al. 1999; Wright et al. 2000; Shenton et al. 2001; Liddle and Pantelis 2003). To date, no discrete brain area is unequivocally abnormal, and clinical-pathological correlations have yet to be documented with certainty. However, structural neuroimaging studies consistently indicate enlargement of the third and lateral ventricles, the latter being one of the most consistently replicated biological findings in schizophrenia (Shenton et al. 2001). Of interest is that these structures surround the limbic system, the brain region most associated with emotional behavior and declarative memory (Papez 1937; Squire and Zola-Morgan 1991), functions that are markedly disturbed in schizophrenia (Cirillo and Seidman 2003).

Moreover, the gray matter structures most consistently abnormal on MRI, and meaningfully linked to...
schizophrenic symptoms and cognitive deficits, are the lateral and medial temporal lobe structures (Lawrie and Abukmeil 1998; Nelson et al. 1998; Velakoulis et al. 1999; Heckers 2001; Shenton et al. 2001), findings supported by convergence with neurohistological studies (Harrison 1999; Heckers and Konradi 2002). Meta-analyses of MRI volumetric studies demonstrated that the hippocampus was typically about 6 percent smaller in schizophrenia, bilaterally, with a moderate effect size of approximately 0.40 (Nelson et al. 1998; Wright et al. 2000). Fewer studies have been conducted of the amygdala, yet results are promising, with effect sizes of approximately 0.70 (Wright et al. 2000). Abnormalities found in the cingulate, thalamus, and other subcortical regions anatomically related to the MTL (e.g., the parahippocampal gyrus) have been less often studied and less consistently identified, although there is some support for abnormality in each structure (Wright et al. 2000; Shenton et al. 2001). While structural alterations in schizophrenia appear to be widespread, the most robust abnormalities, to date, center in and around the MTL and the lateral temporal lobe.

The fact that subtle but relatively widespread volumetric abnormalities are common in schizophrenia is now widely accepted (Selemon and Goldman-Rakic 1999). However, the timing and developmental progression of these abnormalities continue to be poorly understood. For example, when do the abnormalities occur (Woods 1998)? In Cannon et al. (this issue), evidence is marshaled that there are “early” (associated with pregnancy and birth complications, and genes) and “late” (associated with neuroregressive events of adolescence: Feinberg 1982) contributions to the neuropathology of schizophrenia. We will review empirical literature relevant to “late” developmental changes in regard to MTL abnormalities.

There are three relatively recent sources of structural neuroimaging data that shed new light on the timing and developmental progression of brain abnormalities in schizophrenia. First, there is a growing body of longitudinal neuroimaging evidence supporting the idea of anatomical brain changes during the course of schizophrenia. This has been demonstrated by various volumetric brain changes in MRI followup studies of first episode (DeLisi et al. 1997; Gur et al. 1998; Lieberman et al. 2001; Wood et al. 2001; Cahn et al. 2002; Ho et al. 2003; Kasai et al. 2003), chronic adult (Mathalon et al. 2001; Wood et al. 2001), and child (Thompson et al. 2001) patients with schizophrenia. However, it remains unclear when these changes begin. Second, cross-sectional studies consistently demonstrate brain abnormalities in either adolescent or adult nonpsychotic relatives of persons with schizophrenia (Seidman 1997; Tsuang et al. 1999a; Seidman and Wencel 2003; Seidman et al., in press). This leads to one inescapable conclusion—that a substantial proportion of brain abnormalities in persons with schizophrenia or with the genetic risk for schizophrenia are independent of psychosis. Moreover, this suggests that certain brain abnormalities may be necessary but not sufficient for the illness. However, this does not clarify whether these abnormalities evolve over time. A third possibility has emerged from a recent paper by Pantelis et al. (2003)—that brain structure is actively changing abnormally during the prodromal period, the period when a person gradually develops a psychotic state. We will review the existing structural MRI literature in studies of persons at high risk (both “clinical” and “genetic”) for schizophrenia to better understand how the brain may be abnormal or changing prior to first acute psychotic illness.

Studies of the Prodrome to Psychosis. To evaluate neurobiological aspects of the transition to psychosis, it is necessary to study persons who are very likely to become ill (clinical high-risk design). A recent strategy, exemplified by the contents of this special issue of the Schizophrenia Bulletin, is to select persons presenting with symptoms putatively suggestive of imminent onset of psychosis (Yung and McGorry 1996; McGorry et al. 2002). To date, only one published study (Pantelis et al. 2003) of such an “ultra high-risk” group has examined the question of whether progressive brain structural changes occur as the prodromal state evolves into frank psychosis. At first assessment, a voxel-based method of analysis demonstrated that in comparison with those individuals not developing a psychotic disorder, those who later manifested psychosis had less gray matter in the right medial temporal, lateral temporal, and inferior frontal cortex and the bilateral cingulate cortex. In a separate region of interest study of this same ultra high-risk group, the prepsychotic individuals had normal hippocampal volumes, which were significantly larger than those of people not developing psychosis, who, like patients with schizophrenia, had significantly smaller hippocampi than controls (Phillips et al. 2002). Thus, substantial amounts of predictive variance were associated with MTL structures. In the voxel-based study, a subgroup of patients were rescanned soon after developing psychosis, or after at least a year if psychosis did not occur. Compared to those individuals who did not develop psychosis, those developing psychosis had a significant reduction in gray matter in the left parahippocampal, fusiform, and orbitofrontal regions (Pantelis et al. 2003).

These striking findings of cortical and paralimbic changes have to be put in context. This is the first study of its kind, but it should be noted that voxel-based measurements were used that have not yet been shown to be comparable to classical morphometry. Moreover, normal compari-
son subjects were not included in this design, and the sample size at followup was small. Type of psychotic disorder (schizophrenia vs. affective psychosis) could not be controlled. These limitations notwithstanding, the neuroimaging study of the prodromal period has been launched and new studies will no doubt be emerging soon. In the meantime, additional clues to prepsychotic brain pathology may be derived from the genetic high-risk brain imaging studies, which have been ongoing for more than 20 years.

Genetic High-Risk Studies of Schizophrenia. Recent perspectives on the etiology of schizophrenia have focused attention on neurobiological vulnerability independent of the psychotic illness (Mednick 1970; Zubin and Spring 1977; Lewis and Murray 1987; Weinberger 1987; Seidman 1997). These studies select child or adult first degree relatives for evaluation ("genetic high-risk design"). The study of biological relatives is a valuable strategy for investigating vulnerabilities to schizophrenia (Tsuang et al. 1999b; Faraone et al. 2001). Abnormalities in relatives may provide clues to the etiology of the illness, suggesting potential genetic effects (Tsuang et al. 1993). Unlike patients with schizophrenia, or those in the prodrome, nonpsychotic relatives are not seeking treatment, are not treated with antipsychotic medications or hospitalized, and are not affected by putative neurotoxic effects of psychosis. Moreover, their risk for a specific form of psychosis (schizophrenia vs. affective psychosis) may be specified by the sampling strategy. Adult relatives who have passed through the peak age of risk for psychosis (20–35) are unlikely to develop schizophrenia and thus may manifest abnormal traits associated with vulnerability and not with psychosis. Child relatives may be studied prior to possible onset of illness, and thus predictors of illness may be derived from long-term followup of outcome.

Children at risk for schizophrenia and nonpsychotic adult relatives manifest electrophysiological, neurocognitive, symptomatic, and behavioral abnormalities, usually to a milder degree than patients with frank psychosis (Olin and Mednick 1996; Seidman 1997; Faraone et al. 2001). A similar pattern is emerging from neuroimaging studies (Seidman 1997; Tsuang et al. 1999a; Seidman and Wencel 2003; Seidman et al., in press). Recent MRI studies have identified structural abnormalities in prepsychotic individuals (Lawrie et al. 2001), while a number of MRI studies in nonpsychotic relatives have also demonstrated abnormalities in brain structures found to be abnormal in schizophrenia. Individuals from the genetic high-risk studies who are teenagers or young adults (Keshavan et al. 1997; Lawrie et al. 1999; Schreiber et al. 1999; Lawrie et al. 2001; Keshavan et al. 2002a), or older nonpsychotic relatives (Seidman et al. 1997, 1999, 2002; Cannon et al. 1998, 2002; Sharma et al. 1998, 1999; Staal et al. 1998; Chua et al. 2000; O'Driscoll et al. 2001; Harris et al. 2002; Steel et al. 2002; Van Erp et al. 2002; Marcelis et al. 2003), typically past the peak age for onset of schizophrenia, manifest a number of structural brain abnormalities (table 1). While some studies have negative results (Staal et al. 2000; Marcelis et al. 2003; Schulze et al. 2003), the most consistent volumetric abnormalities to date are in MTL structures, especially in the hippocampal-amygdala region (table 1). This suggests that MTL abnormalities may reflect preexisting vulnerability to the illness. The fact that structural abnormalities in the hippocampus have shown no significant changes in volume in followup studies of patients with first episode schizophrenia (Delisi et al. 1997; Gur et al. 1998; Lieberman et al. 2001; Wood et al. 2001; Kasai et al. 2003) emphasizes the prepsychotic-vulnerability component of hippocampal abnormality.

MTL Memory System. The findings from genetic high-risk studies are consistent with schizophrenia patients' MRI-measured abnormalities, particularly in the hippocampus. Postmortem studies have also demonstrated subtle anomalies in limbic structures, most consistently in the hippocampus (Harrison 1999), including reduced neuronal size and reduced levels of synaptic proteins (Benes 1999; Harrison 1999; Weinberger 1999). The hippocampus and, more broadly, the MTL, are considered to be important in schizophrenia, especially because of their role in learning and memory, and emotion (Papez 1937; Squire and Zola-Morgan 1991). Some laterized temporal lobe abnormalities have been observed in schizophrenia, often left-sided (Shenton et al. 1992), and some researchers have proposed that this pattern reflects a genetic, neurodevelopmental vulnerability (Crow et al. 1989).

Verbal declarative or "explicit" memory (the conscious recollection of words, stories, or events) is one of the most robustly impaired neurocognitive functions in schizophrenia (Heinrichs and Zakzanis 1998; Aleman et al. 1999; Cirillo and Seidman 2003). Verbal declarative memory is commonly impaired in diseases affecting the MTL memory system, particularly the left hippocampus and PHG (Squire and Zola-Morgan 1991; Eichenbaum 1994). These findings suggest that MTL abnormalities, especially left-sided ones (because the left hemisphere is specialized for language), and verbal memory deficits could be associated as vulnerability indicators. At least two studies have demonstrated this association (O'Driscoll et al. 2001; Seidman et al. 2002) in adult, nonpsychotic relatives of persons with schizophrenia.

Is the PHG Also a Vulnerability Indicator for Schizophrenia? It is already clear that VDM deficits and structural abnormalities in the amygdala-hippocampal
## Table 1. Structural MRI studies of nonpsychotic first degree relatives of persons with schizophrenia compared with normal controls

<table>
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<th>Study</th>
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<th>MRI field strength and slice thickness</th>
<th>Region of interest measured</th>
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<tr>
<td><strong>Adolescents at risk</strong></td>
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<tr>
<td>Keshavan et al. (1997, 2002a)(^1)</td>
<td>17 offspring of SZ (8M, 9F; 13–22 years old); 22 normal controls (11M, 11F; 9–22 years old)</td>
<td>1.5T, 5-mm slices</td>
<td>Amyg.-hipp. complex, dorsolateral prefrontal cortex</td>
<td>Sig. ↓ amyg.-hipp. complex volumes in offspring of SZ compared to controls; sig. ↑ leftward asymmetry of the anterior amyg.-hipp. complex in offspring of SZ compared to controls</td>
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<td>Schreiber et al. (1999)</td>
<td>15 offspring of SZ (11.7–18.9 years old); 15 controls (11.5–19.1 years old).</td>
<td>1.5T, 1.5-mm slices</td>
<td>Corpus callosum, prefrontal diameter, total sagittal diameter, frontal and temporal lobes; amyg.-hipp. complex, lateral and third ventricles</td>
<td>Sig. ↓ right amyg.-hipp. complex volumes in the offspring of SZ compared to controls; sig. ↑ leftward asymmetry of the anterior amyg.-hipp. complex in offspring of SZ compared to controls</td>
</tr>
<tr>
<td>Lawrie et al. (1999, 2001)(^2)</td>
<td>147 offspring of SZ (74M, 73F); 34 first episode SZ (22M, 12F), 36 controls (17M, 19F); 16–25 years old</td>
<td>1.0T, 5-mm slices</td>
<td>Whole brain; prefrontal and temporal lobes, amyg.-hipp. complex; caudate, lenticular nuclei; thalamus; lateral, third, and fourth ventricles.</td>
<td>Sig. ↓ amyg.-hipp. complex and thalamic volumes in offspring of SZ compared to controls; sig. ↑ amyg.-hipp. complex volumes and sig. ↓ lenticular nuclei in offspring to SZ; offspring of SZ with psychotic symptoms had sig. ↓ brains than offspring of SZ without psychotic symptoms</td>
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<td><strong>Adults at risk</strong></td>
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<td>Staal et al. (1998)(^3)</td>
<td>32 same-sex siblings discordant for SZ (24M, 8F), 32 normal controls (24F, 8F)</td>
<td>1.5T, 1.2-mm slices</td>
<td>Thalamus, total brain, intracranium</td>
<td>Thalamic volume in sig. ↓ SZ than in their siblings or controls and sig. ↓ in non-psychotic siblings compared to controls</td>
</tr>
<tr>
<td>Cannon et al. (1998)(^5)</td>
<td>63 SZ, 12 SZA (40M, 35F); 60 nonpsychotic full siblings (27M, 33F); 56 normal controls (25M, 31F); All subjects age 40.</td>
<td>1.0T, 5-mm slices</td>
<td>Cortical gray matter, white matter, sulcal and ventricular CSF</td>
<td>Sig. ↓ cortical gray matter volume and sulcal ↑ CSF in SZ and their non-psychotic siblings (primarily in frontal and temporal lobes) compared to controls; sig. ↓ white matter ↑ ventricular CSF in SZ.</td>
</tr>
<tr>
<td>Study</td>
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<td>Sharma et al. (1998)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>29SZ (18M, 11F); 55 nonpsychotic first degree relatives (24M, 31F); 39 normal controls (20M, 19F).</td>
<td>1.5T, 1.5-mm slices</td>
<td>Whole brain, cortical grey matter, temporal lobe, lateral ventricles, cerebellum</td>
<td>Sig. T lateral ventricles in SZ than in their relatives or normal controls; sig. T lateral ventricles inSZ than their nonpsychotic siblings inSZ; sig. T bilateral amygdala, hippocampus volumes in relatives compared to controls.</td>
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<tr>
<td>Seidman et al. (1997)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>28 nonpsychotic first degree relatives (24M, 31F); 39 controls (20M, 19F).</td>
<td>1.5T, 3-mm slices</td>
<td>Whole brain, cerebral, cortex grey and white, basal ganglia, hippocampus, amygdala, thalamus, brain stem, lateral ventricles, cerebellum</td>
<td>Cerebral asymmetry between SZ and obligate carriers lacked normal brain asymmetry in prefrontal, sensorimotor, and occipitoparietal cortical regions; nonobligate carriers lacked asymmetry in occipitoparietal region.</td>
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<tr>
<td>Sharma et al. (1999)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>26 SZ (17M, 10F); 53 nonpsychotic first degree relatives (28M, 27F); 35 normal controls (24M, 15F).</td>
<td>1.5T, 1.5-mm slices</td>
<td>Cerebral asymmetry in SZ and obligate carriers inSZ than in controls; and sig. T cerebral volumes inSZ than in controls; sig. T whole brain and lateral ventricle volumes inSZ than in non-psychotic siblings or controls.</td>
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<tr>
<td>Chua et al. (2000)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>27SZ (17M, 10F); 53 same-sex siblings discordant for SZ (24M, 8F); 32 matched controls (24M, 8F).</td>
<td>1.5T, 1.2-mm slices</td>
<td>Corpus callosum</td>
<td>No significant differences in intracranial, whole brain, lateral and third ventricles, frontal lobe, caudate nucleus, amygdala, hippocampus, parahippocampal gyri, cerebellum.</td>
</tr>
<tr>
<td>O'Driscoll et al. (2001)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>20 nonpsychotic first degree relatives of SZ; 14 controls (18-50 years old).</td>
<td>1.5T, 1-mm slices</td>
<td>Amygdala-anterior hippocampus volumes in relatives than in controls.</td>
<td>Sig. T third ventricle volume inSZ and nonpsychotic siblings than in controls; sig. T cerebellar volume inSZ than in controls; sig. T caudate, fornix, lateral ventricle volumes inSZ than nonpsychotic siblings or controls. (No sig. differences in the hippocampus or parahippocampal gyri).</td>
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</table>
Table 1. Structural MRI studies of nonpsychotic first degree relatives of persons with schizophrenia compared with normal controls—Continued

<table>
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<tr>
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<th>MRI field strength and slice thickness</th>
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<tbody>
<tr>
<td>Steel et al. (2002)</td>
<td>6 SZ (2M, 4F); 6 of their obligate carrier siblings (2M, 4F); 6 of their nonpsychotic noncarrier siblings (3M, 3F).</td>
<td>1.0T, 1.88-mm slices</td>
<td>Whole brain; third, fourth, and lateral ventricles; prefrontal and temporal lobes; caudate nuclei; lentiform nuclei; thalamic nuclei; amyg.-hipp. complex</td>
<td>Sig. ↑ whole-brain and cortical structure volumes in carrier and non-carrier than in SZ siblings; sig. ↓ ventricles in carriers than in their SZ siblings; sig. ↓ amyg.-hipp. complex volume in carriers and SZ than in their non-carrier siblings.</td>
</tr>
<tr>
<td>Cannon et al. (2002)</td>
<td>64 SZ or SZA (32M, 32F); 51 of their nonpsychotic full siblings (22M, 29F); 54 controls with no family history of psychosis (23M, 31F). All subjects 40 years old.</td>
<td>1.0T, 5-mm slices</td>
<td>Cortical gray matter, CSF</td>
<td>Fetal hypoxia correlated with ↓ gray matter volume and ↑ bilateral CSF in patients and siblings, mostly in temporal lobe; fetal hypoxia correlated with sig. ↑ ventricular volume in patients.</td>
</tr>
<tr>
<td>Van Erp et al. (2002)</td>
<td>60 SZ, 12 SZA (39M, 33F); 58 nonpsychotic siblings (25M, 33F); 53 controls with no family history of psychosis (24M, 29F). All subjects 40 years old.</td>
<td>1.5T, 1.3-mm slices</td>
<td>Hippocampus</td>
<td>SZ patients had sig. ↓ bilateral hippocampus than controls and their siblings. Siblings had sig. ↓ bilateral hippocampus than controls. Fetal hypoxia correlated with ↓ hippocampus in SZ patients only.</td>
</tr>
<tr>
<td>Seidman et al. (2002)</td>
<td>45 nonpsychotic first degree relatives from simplex (n = 28) or multiplex (n = 17) families, 18 SZ; 48 controls, 20–68 years old.</td>
<td>1.5T, 3-mm slices</td>
<td>Hippocampus</td>
<td>Sig. ↓ left hippocampus in relatives (especially multiplex relatives) than in controls; no sig. difference in hipp. volumes between SZ and their nonpsychotic relatives.</td>
</tr>
<tr>
<td>Harris et al. (2002)</td>
<td>6 SZ (5M, 1F); their nonpsychotic biological parents including 1 parent in each family with ancestral SZ history; 6 controls (5M, 1F).</td>
<td>1.5T, 1.5- or 1.7-mm slices</td>
<td>Hippocampus</td>
<td>Sig. ↑ hippocampal volume in parents with ancestral SZ family history than in SZ.</td>
</tr>
<tr>
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<tr>
<td>Schulze et al.</td>
<td>35 multiplex SZ; 63 nonpsychotic relatives; 31 SZ without psychosis in family; 33 of their nonpsychotic relatives; 68 controls 17-70 years old.</td>
<td>1.5T, 1.5-mm slices</td>
<td>Hippocampus</td>
<td>Sig. ↓ left hipp. volume in all SZs; hipp. volume not sig. ↓ in any SZ relatives.</td>
</tr>
<tr>
<td>Marcelis et al.</td>
<td>31 SZ (15M, 16F); 32 nonpsychotic relatives (14M, 18F); 27 controls. 18-55 years old.</td>
<td>1.5T, 3-mm slices</td>
<td>Whole-brain voxel-based morphometry</td>
<td>Sig. ↓ cerebellum and fusiform gyrus and sig. ↑ superior temporal gyrus volume in relatives compared to controls. SZ sig. ↓ in fronto-limbic areas, superior frontal gyrus, insula, inferior frontal gyrus, cingulate gyrus, and paracentral gyrus, and sig. ↑ in putamen and pallidum than relatives. No reported difference in hippocampus.</td>
</tr>
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</table>

Note.—↑ = increased; ↓ = decreased; amyg.-hipp/complex = amygdala-hippocampal region (not separated); CSF = cerebrospinal fluid; F = female; M = male; MRI = magnetic resonance imaging; sig. = statistically significant difference; SZ = persons with schizophrenia; SZA = persons with schizoaffective disorder. "Multiplex" denotes a family with two or more persons with schizophrenia; "simplex" is a family with one person with schizophrenia.

1 Keshavan et al. (2002) includes subjects reported in Keshavan et al. (1997).
2 Lawrie et al. (2001) includes subjects reported in Lawrie et al. (1999).
3 Staal et al. (1998) and Staal et al. (2000) use the same subjects.
4 Cannon et al. (1998), Cannon et al. (2002) and Van Erp et al. (2002) use essentially the same sample.
5 Sharma et al. (1998), Sharma et al. (1999) and Chua et al. (2000) use essentially the same sample.
6 Seidman et al. (1999) includes subjects reported in Seidman et al. (1997).
7 Seidman et al. (2002) enlarged the sample reported in Seidman et al. (1997,1999), adding relatives from multiplex families and additional controls.
8 "Multiplex" denotes a family with two or more persons with schizophrenia; "simplex" is a family with one person with schizophrenia.
An MRI Morphometric Family Study of the PHG

In this article, we focus on the hypothesis that the PHG is volumetrically altered in adult, nonpsychotic relatives of persons with schizophrenia and that this alteration, like the finding of a smaller hippocampus in relatives of persons with schizophrenia, is associated with VDM deficit (Seidman et al. 2002). As noted above, we report elsewhere that the PHG (as a whole) is volumetrically reduced in patients with schizophrenia from families with multiple ill members (Goldstein et al., submitted). In this study, we further parcelle the PHG into anterior and posterior components and evaluate the effect of hemisphere.

Our prior work suggests that VDM (Faraone et al. 1995, 1999) and hippocampal volume (Seidman et al. 2002) might represent genetic markers of vulnerability to schizophrenia. Most researchers agree that a single-gene theory is untenable, even if that theory allows for many different single-gene variants (McCue et al. 1983; Gottesman and McCue 1990; Tsuang et al. 1999b). The multifactorial model of schizophrenia has found some, although not complete, support (McCue et al. 1983; Faraone and Tsuang 1985; Gottesman and McCue 1990; Tsuang et al. 1999b).

In accordance with the multifactorial model, the amount of impairment in relatives should increase with their genetic loading for schizophrenia. Supporting this hypothesis, verbal memory impairment and smaller left hippocampal volume were significantly different in nonpsychotic persons from "multiplex" families (containing two first degree relatives with schizophrenia) compared to persons from "simplex" families (containing one first degree relative with schizophrenia; Faraone et al. 2000; Seidman et al. 2002). Other investigators have found similar results assessing neurological signs (Griffiths et al. 1998). This type of model does not prove genetic influences but is consistent
with the hypothesis. Altered hippocampal volume could also reflect pregnancy or birth complications (Lewis and Murray 1987; Cannon et al. 1993; Stefanis et al. 1999; Van Erp et al. 2002), which could be more severe in multiplex than in simplex relatives.

Based on this model, we tested a number of hypotheses. First, we predicted that PHG volumes would be significantly different in relatives than in normal controls and that they would be smaller in multiplex as compared to simplex relatives. Second, we predicted that left PHG volume and verbal memory would be correlated significantly and positively because of the more specialized role of the left hemisphere for VDM (Squire and Zola-Morgan 1991). Third, we hypothesized that PHG volumes would be smaller in patients with schizophrenia than in their nonpsychotic relatives or in controls.

**Methods**

**Subjects.** Subjects for this study were the same as those used in a previous study of the hippocampus (Seidman et al. 2002), with the exception that we included all patients with schizophrenia that received MRI of the PHG (Goldstein et al., submitted). Subjects (45 nonpsychotic first degree relatives of probands with schizophrenia, 48 normal controls, and 88 patients with schizophrenia) were 20 to 68 years of age, had at least an eighth-grade education, spoke English as their first language, and had an estimated IQ above 70. Exclusion criteria were (1) substance abuse within the past 6 months, (2) head injury with documented cognitive sequelae or loss of consciousness greater than 5 minutes, (3) neurologic disease, and (4) medical illness that impairs neurocognitive function.

After describing the study, we obtained written informed consent, including permission from the patients with schizophrenia (the probands) for us to contact their relatives. DSM–III–R (American Psychiatric Association 1987) diagnoses in patients were established using the Schedule for Affective Disorders and Schizophrenia (SADS; Spitzer and Endicott 1978) or the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger et al. 1994) and a systematic review of the medical record. Substance use was assessed through a semistructured interview to determine quantity, frequency, and duration of use (Faraone et al. 1995). Blindness of assessments was maintained among psychotic, neuropsychological, and MRI data.

**Relatives.** Relatives were free of psychosis during their lifetime. There were 28 simplex (16 siblings, 7 offspring, 5 parents) and 17 multiplex (16 siblings, 1 offspring) relatives from 34 unique families. Twenty-six families provided a single relative, three families had three relatives, and five families had two relatives. All available relatives were interviewed to determine whether the family was simplex or multiplex. Relatives were interviewed with the Structured Clinical Interview for DSM–III–R (Spitzer et al. 1987) or DIGS for Axis I disorders and the Structured Interview for DSM–III Personality Disorders (Stangl and Zimmerman 1983). Fifty-six percent had nonpsychotic diagnoses, mainly Axis I disorders such as past major depressive disorder (MDD) or substance abuse. One had schizotypal personality disorder. Three relatives had received psychotropic medication (1 antianxiety and 2 antidepressant medication). In previous work we demonstrated that these potential confounds did not significantly affect brain volumes (Seidman et al. 1999, 2002) or neuropsychological dysfunction (Faraone et al. 1995, 1999).

We also analyzed a subset of 18 (of 45) relatives (8 males, 10 females) from the 13 families who had a proband with schizophrenia who had received an MRI. This sample included 1 father, 2 mothers, 13 siblings (6 sisters, 7 brothers), and 2 daughters of patients. Nine families had one, three families had two, and one family had three nonpsychotic relatives. Thirteen were from multiplex and five were from simplex families.

**Patients with schizophrenia.** Eighty-eight patients with schizophrenia received an MRI, 40 simplex and 48 multiplex, who have been described elsewhere in detail (Goldstein et al., submitted; Seidman et al., submitted). Eighteen of the 88 participating patients had a first degree relative who had an MRI. These included 10 males and 8 females from 13 families (4 simplex, 9 multiplex). The nine multiplex families included five with two ill members and four with one ill member.

**Normal controls.** Forty-eight controls came from unrelated families acquired through advertisements in the catchment areas of the hospitals from which the patients had been ascertained. Our goal was to acquire controls who were demographically similar to patients and relatives. Controls underwent a screening process like the one used for other subjects, except (as in previously published studies with this control sample; Goldstein et al. 1999, 2001, 2002; Seidman et al. 1999, 2002) they were screened for current psychopathology using a short form of the Minnesota Multiphasic Personality Inventory (MMPI–168; Vincent et al. 1984) rather than interviewed. We excluded potential controls if they had a personal or family history of psychosis or psychiatric hospitalization or had MMPI elevations above 70 on the clinical scales. Controls were also administered the substance use section of the SADS. We did not screen for a lifetime history of psychopathology or neuropsychological dysfunction. In choosing a control group, we attempted to balance two competing sources of bias. Unscreened controls frequently have rates of psychopathology and neuropsychological dys-
function above the population expectation (Shastel et al. 1991; Buckley et al. 1992). Thus, they can obscure the effects of interest. However, excessive screening of controls can exaggerate the effects of interest (Tsuang et al. 1988). The data we collected from tests having extensive normative data provide some indication of the “normalcy” of our controls. The mean score for controls on the Wide Range Achievement Test—Revised (WRAT-R; Jastak and Jastak 1985) reading subtest was 105.6 (SD = 11.1), well within the normal range.

Neuropsychological Measures. The Vocabulary and Block Design tests of the Wechsler Adult Intelligence Scale—Revised (Wechsler 1981) estimated current intelligence (Brooker and Cyr 1986), and the Reading test of the WRAT—R estimated intellectual potential (Kremen et al. 1996). Handedness was determined by questionnaire (Annett 1970). VDM was assessed with the Logical Memory Stories test of the Wechsler Memory Scale—Revised (Wechsler 1987). Data consisted of raw scores at immediate and 30-minute delayed recall.

MRI Procedures

MRI image acquisition and morphometric analysis. Subjects received a brain MRI close to the time of their neuropsychological testing. MRI was obtained at the Massachusetts General Hospital (MGH) on a General Electric 1.5 Tesla Signa Scanner (Milwaukee, WI). Image acquisitions included a conventional sagittal scout, a coronal T2-weighted sequence to rule out gross pathology, and a coronal volumetric T1-weighted spoiled gradient echo imaging sequence for morphometric analysis, using the following parameters: pulse sequence = 3D-Spoiled Gradient Recall (SPGR), Time to Relaxation (TR) = 40 ms, Time to Echo (TE) = 8 ms, flip angle = 50°, field of view = 30 cm, slice thickness = 3.0 mm, number of slices = 60 contiguous, coronal images of the entire brain, matrix = 256 × 256, number of excitations = 1. Measurement of brain images was conducted at the MGH Center for Morphometric Analysis by the team of scientists that developed the system.

Images were positionally normalized to overcome variations in head position by imposing a standard three-dimensional brain coordinate system on each scan using the midpoints of the descensions of the anterior and posterior commissures and the midsagittal plane at the level of posterior commissure as points of reference for rotation and translation (Filipek et al. 1989, 1994).

Gray-white matter segmentation was performed on each T1-weighted, normalized, 3D coronal scan using a semiautomated intensity contour algorithm for external border definition and signal intensity histogram distributions for demarcation of gray-white borders (Kennedy et al. 1989). Regions of interest for this study included total cerebral volume and PHG (anterior and posterior). Prior to measurement of the PHG, volumetric morphometry was undertaken by methods employed in our previous study of the hippocampus (figure 1, upper left and right). To measure the PHG, we applied the parcellation system of Caviness et al. (1996) to the entire neocortex (figure 1, lower half) as we had with a sample of patients with schizophrenia (Goldstein et al. 1999).

Anatomical definition. The parahippocampal gyri are medial, inferior, cortical structures that, along with the cingulate gyri, compose a considerable portion of the lim-3

bic system (figure 2 contains a schematic representation). The PHG is strongly connected with other limbic structures, especially the amygdala and hippocampus, buried deep within the temporal lobe. The posterior part of PHG merges with the cingulate and lingual gyri caudally. The anterior end of the PHG curves on itself, forming a medially defined node called the uncus. The PHG has been described as “paralimbic” (Mesulam 1985), acting as a kind of bridge from the limbic system to the neocortex. Most of the inputs to the hippocampus arrive from the entorhinal cortex (figure 3 contains a representation of PHG white matter). Along with the perirhinal cortex, the entorhinal cortex, which overlaps with the rostral part of the PHG, projects strongly to the hippocampus and receives projections from unimodal and polymodal areas in the frontal, temporal, and parietal lobes (Rosene and Van Hoesen 1987; Nolte 1999).

Parcellation procedure (Caviness et al. 1996; Center for Morphometric Analysis 2002). The PHG comprises the PHa (anterior portion) and the PHp (posterior portion). The anterior border of the PHa is plane B, which approximates the posterior end of the temporal pole. Its posterior border is the coronal plane at the level of the lateral geniculate nucleus. Its lateral border is the collateral sulcus, while medially it borders the hippocampus. The entorhinal cortex is a part of the PHa parcellation unit. The anterior border of the PHp is immediately posterior to the coronal plane that passes through the lateral geniculate nucleus (i.e., the posterior border of the PHa). Its posterior border is the coronal plane N at the level of the anterior-most tip of the calcarine fissure in the retrosplenial area, which approximates the zone of transition between the PHG and the lingual gyri (figure 2). Its lateral and medial borders are the same as the PHa’s. Surrounding areas of the temporal cortex parcellation units are shown in figure 1 (lower right) and schematically in figure 2.

Reliability. In 16 blindly segmented brains, intra-class correlation coefficients (ICCs) were 0.93 for total cerebral volume (Seidman et al. 2002). As previously reported, the brains of 10 subjects were completely par-
Figure 1. Images depicting the method of PHG parcellation

(A) A coronal slice approximately midway from front to back of the brain, five slices posterior to the anterior commissure, near the anterior portion of the thalamus. (B) The same slice segmented in the coronal plane, highlighting the hippocampus on the right side of the brain. (C) A parcellated coronal slice depicting the parahippocampal gyrus anterior (PHA) in relation to the hippocampus (hipp.) and the amygdala (amyg.). (D) An enlarged image of a parcellated coronal slice (C) depicting PHA in relation to other temporal lobe regions, including the INS (insula), H1 (Heschl's gyrus), the PP (planum polare), the T2P (middle temporal gyrus, posterior), and the TFp (temporal frontal cortex, posterior). Interiorly is shown the white matter of the PHG, within which the perforant path is a principal fiber connection between the entorhinal cortex and the dentate gyrus.

1 PHG identification is achieved using a cross-referencing tool (Caviness et al. 1996), which allows visualization of the structure in three coregistered cardinal views (coronal, axial, and sagittal). (A) A coronal slice approximately midway from front to back of the brain, five slices posterior to the anterior commissure, near the anterior portion of the thalamus. (B) The same slice segmented in the coronal plane, highlighting the hippocampus on the right side of the brain. (C) A parcellated coronal slice depicting the parahippocampal gyrus anterior (PHA) in relation to the hippocampus (hipp.) and the amygdala (amyg.). (D) An enlarged image of a parcellated coronal slice (C) depicting PHA in relation to other temporal lobe regions, including the INS (insula), H1 (Heschl's gyrus), the PP (planum polare), the T2P (middle temporal gyrus, posterior), and the TFp (temporal frontal cortex, posterior). Interiorly is shown the white matter of the PHG, within which the perforant path is a principal fiber connection between the entorhinal cortex and the dentate gyrus.

cellated into 48 parcellation units in the left and right hemispheres (Goldstein et al. 1999). Intrarater reliability for PHA was good (0.92), as was intrarater reliability (ICC = 0.88). ICCs were originally poor for PHp (0.11) because of outliers in Goldstein et al. (1999), but after additional discussion and training, reliability improved considerably with a second set of 10 brains (ICC = 0.81). Intrarater reliability was also good for PHp (0.93).

Volumetric analysis. The volume of each structure was calculated by multiplying the number of voxels assigned to that structure on each slice, by the slice thickness and summing across all slices in which the structure appeared.

Data Analysis. Primary comparisons were made among controls, relatives from simplex and multiplex families,
Figure 2. Drawings of (A) a sagittal section of the left side of the brain representing the hippocampus and parahippocampal gyrus anterior; and (B) an axial slice of the PHa and PHp in medial relation to temporal, frontal, and occipital cortices (from cortical parcellation system, Caviness et al. 1996)  

1 (A) The hippocampus is superior to the parahippocampal gyrus anterior (PHa) and posterior (PHp), which are shaded. Other regions shown are (A) FP (frontal pole), F1 (superior frontal gyrus), FMC (frontal medial cortex), PAC (paracingulate gyrus), CGa (cingulate gyrus, anterior), CGp (cingulate gyrus, posterior), SC (subcallosal cortex), and OP (occipital pole). (B) The PHa and PHp are medial to temporal lobe structures. Also shown (a = anterior, p = posterior) are FP (frontal pole), FMC (frontal medial cortex), FOC (frontal orbital cortex), SC (subcallosal cortex), LG (lingual gyrus), TP (temporal pole), TFa and TFp (temporal frontal cortex), T3a and T3p (inferior temporal gyrus), TOF (temporal occipital fusiform cortex), TO3 (inferior temporal gyrus, temporoccipital part), OF (occipital fusiform gyrus), OLj (lateral occipital cortex, inferior division), and OP (occipital pole).

...and patients with schizophrenia from simplex and multiplex families. Some families yielded more than one subject. Random effects regression models for clustered data account for the potential error in the estimation of standard errors of parameter estimates resulting from covariances in brain volumes between family members (Cnaan et al. 1997). These clustered data regression models provide consistent estimates of means and standard errors under weak assumptions about the population distribution of the data. A random effect for each family was used to account for clustering within families, and SAS PROC MIXED was used for estimation. Analyses included tests of overall group effects (4 df) and selected pairwise comparisons between groups of relatives and patients with each other and with controls (each 1 df). In testing for PHG group differences, total cerebral volume and potential confounds (i.e., age, sex, handedness, ethnicity, parental education, reading ability, and past alcohol and drug abuse) were used as covariates in the analyses. Selected analyses were performed excluding all relatives (n = 11; multiplex, n = 5, simplex, n = 6) with a lifetime diagnosis of Major Depressive Disorder (MDD). Pearson and Spearman correlations were used to measure associations between PHp and PHa and verbal memory. Cohen’s $d$ was calculated to estimate effect sizes using absolute volumes. Demographic characteristics were tested by one-way analysis of variance for continuous factors and Pearson’s chi-squared statistic for categorical factors. Statistical significance was $p < 0.05$ (2-tailed).

Results

Demographic and Clinical Characteristics in Patients, Relatives, and Controls. Groups did not differ significantly on age, parental education, ethnicity, handedness, or past alcohol use (table 2). There were significant differences by sex, education, estimated IQ, and past drug use, and there were marginally significant differences in single word reading ability ($p < 0.10$).

Effects of Group Status on Brain Volumes. There were no significant differences for total cerebrum in any contrast (table 3 contains volumetric data and overall test of group differences and table 4 contains pairwise comparisons).
There were marginal group differences for left PHa volume, in that patients ($p = 0.094$) and relatives ($p = 0.060$) from multiplex families had smaller volumes than controls. Multiplex relatives had significantly smaller volumes than simplex relatives. This difference was no longer significant after excluding relatives with MDD. Effect sizes for absolute volume differences were generally small (table 5 contains effect sizes).

For right PHa volume, patients and patients from multiplex families had significantly smaller volumes than controls. Relatives had smaller right PHa volumes than controls, largely accounted for by relatives from multiplex families. Multiplex and simplex relatives did not significantly differ. After relatives with MDD were excluded, multiplex relatives had significantly smaller volumes than controls, whereas simplex relatives did not differ significantly from controls or from multiplex relatives. Neither patients nor nonpsychotic relatives from simplex families differed significantly from controls on right PHa. Effect sizes were modest for differences between multiplex relatives and controls.

There were significant group differences for left PHp volume, as relatives had larger volumes than controls. Relatives from simplex families had significantly larger volumes than did controls. Multiplex and simplex relatives did not significantly differ. These effects did not change when the 11 subjects with MDD were excluded from analysis. The relatives from simplex families accounted for significantly larger volumes in the combined group of relatives compared with the combined group of patients. Effect sizes were large. There were significant group differences for right PHp volume. Simplex relatives had larger right PHp volumes than controls. Multiplex relatives had marginally signifi-
<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls</th>
<th>Multiplex</th>
<th>Simplex</th>
<th>Relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 48)</td>
<td>(n = 48)</td>
<td>(n = 40)</td>
<td>(n = 17)</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Age at MRI</td>
<td>40.5 (10.8)</td>
<td>44.3 (9.0)</td>
<td>44.9 (10.4)</td>
<td>39.6 (10.5)</td>
</tr>
<tr>
<td>Years of parental education</td>
<td>12.1 (2.3)</td>
<td>12.1 (2.4)</td>
<td>11.9 (2.9)</td>
<td>11.7 (2.1)</td>
</tr>
<tr>
<td>Years of subject education</td>
<td>15.1 (2.2)</td>
<td>12.4 (2.3)</td>
<td>12.6 (2.4)</td>
<td>12.2 (2.2)</td>
</tr>
<tr>
<td>IQ estimate&lt;sup&gt;1&lt;/sup&gt;</td>
<td>112.9 (13.0)</td>
<td>95.6 (16.2)</td>
<td>98.8 (16.0)</td>
<td>107.9 (18.6)</td>
</tr>
<tr>
<td>WRAT-R reading</td>
<td>105.6 (11.1)</td>
<td>96.5 (17.9)</td>
<td>102.3 (16.4)</td>
<td>99.2 (12.9)</td>
</tr>
<tr>
<td>Past drug use&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.27 (0.63)</td>
<td>0.35 (0.70)</td>
<td>0.95 (1.22)</td>
<td>0.53 (0.87)</td>
</tr>
<tr>
<td>Past alcohol use&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.95 (0.80)</td>
<td>0.80 (1.11)</td>
<td>1.30 (1.44)</td>
<td>1.29 (1.21)</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>56.3</td>
<td>66.7</td>
<td>67.5</td>
<td>41.2</td>
</tr>
<tr>
<td>Ethnicity (% Caucasian)</td>
<td>91.7</td>
<td>80.0</td>
<td>82.5</td>
<td>94.1</td>
</tr>
<tr>
<td>Handedness (% right)</td>
<td>91.7</td>
<td>83.0</td>
<td>77.5</td>
<td>88.2</td>
</tr>
</tbody>
</table>

Note.—MRI = magnetic resonance imaging; SD = standard deviation; WRAT-R = Wide Range Achievement Test—Revised.

<sup>1</sup> IQ estimate derived from vocabulary and block design age scale scores (Brooker and Cyr 1986).

<sup>2</sup> Substance abuse ratings: 0 = never/occasional use; 1 = recreational (episodic) use; 2 = regular use; 3 = abuse (for a period of 6 months to 5 years); 4 = sustained abuse (for greater than 5 years).
Table 3. Parahippocampal gyrus volumes and verbal memory scores in controls, patients with schizophrenia, and relatives of persons with schizophrenia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n = 48)</th>
<th>Multiplex Patients (n = 48)</th>
<th>Simplex Patients (n = 40)</th>
<th>Multiplex Relatives (n = 17)</th>
<th>Simplex Relatives (n = 28)</th>
<th>Overall 5-Group Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>F test (df = 4) p</td>
</tr>
<tr>
<td>MRI measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cerebral exterior</td>
<td>1,073.1 (101.2)</td>
<td>1,070.6 (140.7)</td>
<td>1,082.9 (93.1)</td>
<td>1,104.5 (93.2)</td>
<td>1,067.4 (99.6)</td>
<td>0.69 (0.617)</td>
</tr>
<tr>
<td>Left parahippocampal gyrus anterior</td>
<td>2.6 (0.6)</td>
<td>2.5 (0.5)</td>
<td>2.7 (0.7)</td>
<td>2.3 (0.5)</td>
<td>2.8 (0.8)</td>
<td>2.27 (0.141)</td>
</tr>
<tr>
<td>Right parahippocampal gyrus anterior</td>
<td>3.0 (0.7)</td>
<td>2.8 (0.6)</td>
<td>2.9 (0.7)</td>
<td>2.5 (0.5)</td>
<td>2.9 (0.8)</td>
<td>2.90 (0.085)</td>
</tr>
<tr>
<td>Left parahippocampal gyrus posterior</td>
<td>1.7 (0.4)</td>
<td>1.5 (0.4)</td>
<td>1.6 (0.4)</td>
<td>1.9 (0.4)</td>
<td>2.3 (0.6)</td>
<td>9.06 (0.003)</td>
</tr>
<tr>
<td>Right parahippocampal gyrus posterior</td>
<td>1.4 (0.4)</td>
<td>1.4 (0.4)</td>
<td>1.5 (0.4)</td>
<td>1.7 (0.4)</td>
<td>1.9 (0.5)</td>
<td>6.79 (0.008)</td>
</tr>
<tr>
<td>Verbal memory measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logical memory immediate recall</td>
<td>28.4 (5.7)</td>
<td>17.1 (6.7)</td>
<td>24.6 (9.0)</td>
<td>22.1 (6.5)</td>
<td>27.8 (6.8)</td>
<td>11.46 (0.001)</td>
</tr>
<tr>
<td>Logical memory delayed recall</td>
<td>25.0 (6.4)</td>
<td>12.3 (7.4)</td>
<td>20.4 (8.7)</td>
<td>19.4 (7.4)</td>
<td>24.9 (7.4)</td>
<td>12.26 (0.001)</td>
</tr>
</tbody>
</table>

Note. — MRI = magnetic resonance imaging; SD = standard deviation.
1 Unadjusted absolute brain volumes in cubic centimeters.
2 High numbers are better scores for each of the logical memory variables.
3 Analyses controlled for age, sex, ethnicity, handedness, parental education, reading ability, past alcohol and drug use, and total cerebral exterior (except for group comparison of total cerebral exterior, which was not used as a covariate).
4 Verbal memory data from control subjects, simplex relatives, and multiplex relatives was reported previously (Seidman et al. 2002)

Effects of Group Status on Verbal Memory Performance. There were significant impairments on immediate and delayed verbal memory performance compared to controls in all patients, the multiplex patients, the simplex patients, and the total relatives sample, largely accounted for by the significant impairments in the multiplex relatives (Faraone et al. 2000). Simplex relatives were not significantly impaired compared to controls, whereas the multiplex relatives were significantly impaired when contrasted with simplex relatives (Faraone et al. 2000). The total patient sample performed significantly worse than the total sample of relatives. Effect sizes were large.

Relationship of VDM and Parahippocampal Volumes in Relatives and Controls. We fit clustered regression models for immediate and delayed verbal memory, with left and right anterior and posterior parahippocampal volumes included as predictors. Other covariates included sex, group (relatives, controls), the interaction between sex and group, handedness, ethnicity, parental education, and IQ. There were no significant associations between the brain volumes and VDM scores in comparisons of relatives versus controls.

To help in understanding the magnitude of the relationship between parahippocampal volumes and residual verbal memory scores in the subgroups of relatives and controls, we calculated Pearson correlations, partialing out age, sex, WRAT reading score, and total cerebral exterior. Correlations were generally weak (r < 0.25), and none were statistically significant. However, for the multiplex relatives only, there were moderately strong correlations between PHa and VDM (r = 0.41–0.50; tables 6 and 7). Results were virtually identical using Spearman's rank-order correlation.

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Discussion

We found partial support for our hypotheses regarding parahippocampal volumes as a manifestation of vulnerability to schizophrenia, observed mainly with participants from the families with multiply affected ill members. Patients with schizophrenia and first degree nonschizophrenic relatives from multiplex families had significantly smaller right PHa volumes than controls. Marginally significant findings were observed for the left PHa for the same subjects. However, the picture became more complex with the subjects from the simplex families. Unexpectedly, simplex relatives had significantly larger PHp volumes than controls and did not differ from controls on PHa. Simplex patients did not significantly differ from controls on any PHG measure. These results suggest that the nature of the schizophrenia sample has important ramifications for measures of brain volumes. In this case, it appears that patients from multiplex schizophrenia families have more severe effects on brain structure, a finding we have explored more extensively on a large number of brain regions (Goldstein et al., submitted).

The results with VDM were more consistent than the neuroimaging results in that, as expected (Cirillo and Seidman 2003), patients from both multiplex and simplex families were significantly impaired on VDM. As we have demonstrated previously with a slightly larger sample of relatives (Faraone et al. 2000), the largest effect on VDM is found among relatives from multiplex families, and this association appears to hold for the patients as well. However, the overall association between verbal memory function and PHG volumes was not significant, although the relationship was roughly as strong in the multiplex subjects with PHa region as it had been with the left hippocampal area in a previous study (approximate $r = 0.40-0.50$; Seidman et al. 2002). While the results overall are not as consistently robust as those in our study of hippocampal abnormalities with the same samples of relatives, they are generally consistent with the hypothesis that increased genetic liability to schizophrenia affects brain structure and function.

It is apparent that the multiplex relatives—none of whom had ever been psychotic and who are comparable to controls on age, parental education, ethnicity, and handedness—have abnormal MTLs. These subjects, who come from families with unusually heavy loading of mental illness, have significant verbal memory problems, despite having normal-range IQs (Faraone et al. 2000). The structural brain and cognitive abnormalities cannot be attributed to differences in premorbid cognitive (reading) ability or substance abuse, because these were controlled in the analyses. Moreover, the findings remained largely consistent when analyses were performed on a reduced sample of persons excluded for MDD, consistent with previous studies (Seidman et al. 2002). This pattern is consistent with MTL damage or dysfunction, and it appears that this characteristic includes both the hippocampus and the PHa. The fact that the only strong association between VDM and brain volumes in this study was with the PHa, as it was with the left hippocampus, suggests that both components of the MTL are contributing to impaired verbal memory in multiplex relatives.

The finding of significantly larger PHp volumes in simplex relatives was unexpected. While the implications of this finding are unclear, increases in size may reflect either an abnormality or a compensatory mechanism. Other groups have found larger volumes in the MTL in patients with schizophrenia and similar trends in their unaffected relatives (Peter Falkai, oral and written personal communication, December 2002; Harris et al. 2002).

A growing literature attesting to widespread brain alterations in schizophrenia (Selemon and Goldman-Rakic 1999; Shenton et al. 2001) suggests that it is unlikely that a focally acting pathologic process produces uniform brain volume reductions in specific regions in schizophrenia. Consistent with this, we previously reported some cortical gray matter structures to be somewhat larger than in controls, as well as significant volume reductions (Goldstein et al. 1999). One possibility is that these patterns are caused by some developmental mechanism reflecting brain plasticity. Increases in volume may reflect abnormal cell migration or inefficient pruning of cells (Feinberg et al. 1999). One possibility is that these patterns are caused by some developmental mechanism reflecting brain plasticity. Increases in volume may reflect abnormal cell migration or inefficient pruning of cells (Feinberg et al. 1999). Alternatively, the posterior PHG may develop in some compensatory manner that has a protective effect, either against the likelihood of psychosis, or for more efficient verbal memory function. Although these interpretations are speculative, the study of protective (as well as risk) factors warrants further investigation.

The absence of a significant difference in parahippocampal volumes between multiplex relatives (mainly siblings) and patients with schizophrenia is important. This finding is very similar to our study of hippocampal size supporting the idea that a smaller MTL is a primary vulnerability to schizophrenia. To date, longitudinal studies of first episode patients with schizophrenia have not demonstrated significant change in hippocampal volumes over time (Delisi et al. 1997; Gur et al. 1998; Lieberman et al. 2001; Wood et al. 2001; Kasai et al. 2003). To our knowledge, most investigators have not longitudinally assessed the PHG, with the exception of Pantelis et al. (2003). Their observation of reduction in left PHG volume over time is intriguing and requires replication. The fact that all three genetic high-risk studies (Keshavan et al. 1997, 2002a; Lawrie et al. 1999, 2001; Schreiber et al. 1999) and the only clinical high-risk study (Pantelis et al.
Table 4. Statistical pairwise comparisons of parahippocampal gyrus volumes and verbal memory scores in controls, patients with schizophrenia, and relatives of persons with schizophrenia, $p$ values\textsuperscript{1}

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients vs. controls</th>
<th>Multiplex patients vs. controls</th>
<th>Simplex patients vs. controls</th>
<th>All relatives vs. controls</th>
<th>Multiplex relatives vs. controls</th>
<th>Simplex relatives vs. controls</th>
<th>Multiplex vs. Simplex Relatives</th>
<th>All Patients vs. All Relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI measures\textsuperscript{1}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cerebral exterior</td>
<td>0.805</td>
<td>0.652</td>
<td>0.982</td>
<td>0.199</td>
<td>0.357</td>
<td>0.225</td>
<td>0.851</td>
<td>0.211</td>
</tr>
<tr>
<td>Left parahippocampal gyrus anterior</td>
<td>0.260</td>
<td>0.094</td>
<td>0.820</td>
<td>0.303</td>
<td>0.060</td>
<td>0.567</td>
<td><strong>0.020</strong></td>
<td>0.968</td>
</tr>
<tr>
<td>Right parahippocampal gyrus anterior</td>
<td><strong>0.044</strong></td>
<td><strong>0.032</strong></td>
<td>0.155</td>
<td><strong>0.017</strong></td>
<td><strong>0.016</strong></td>
<td>0.118</td>
<td><strong>0.308</strong></td>
<td>0.0500</td>
</tr>
<tr>
<td>Left parahippocampal gyrus posterior</td>
<td>0.500</td>
<td>0.366</td>
<td>0.788</td>
<td><strong>0.004</strong></td>
<td>0.100</td>
<td><strong>0.001</strong></td>
<td><strong>0.128</strong></td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Right parahippocampal gyrus posterior</td>
<td>0.585</td>
<td>0.970</td>
<td>0.380</td>
<td><strong>0.003</strong></td>
<td>0.053</td>
<td><strong>0.002</strong></td>
<td><strong>0.198</strong></td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>Verbal memory measures</td>
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<tr>
<td>Logical memory immediate recall</td>
<td><strong>0.001</strong></td>
<td><strong>0.001</strong></td>
<td><strong>0.050</strong></td>
<td><strong>0.117</strong></td>
<td><strong>0.032</strong></td>
<td>0.938</td>
<td><strong>0.018</strong></td>
<td><strong>0.017</strong></td>
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<tr>
<td>Logical memory delayed recall</td>
<td><strong>0.001</strong></td>
<td><strong>0.001</strong></td>
<td><strong>0.040</strong></td>
<td>0.192</td>
<td><strong>0.049</strong></td>
<td>0.861</td>
<td><strong>0.037</strong></td>
<td><strong>0.005</strong></td>
</tr>
</tbody>
</table>

Note.—MRI = magnetic resonance imaging.

\textsuperscript{1} All analyses controlled for age, sex, ethnicity, handedness, parental education, reading ability, past alcohol and drug use, and total cerebral exterior. Degrees of freedom $= 1$ for all pairwise comparisons. $p$ values in bold are statistically significant at $p < 0.05$. 
have found MTL abnormalities (i.e., smaller volumes) suggests that MTL abnormalities are present by early adolescence. Others have demonstrated significant reductions in N-acetyl-aspartate (NAA) in the hippocampi of unaffected adult siblings of patients with schizophrenia (Callcott et al. 1998), suggesting that the abnormalities involve neuronal integrity.

It is not yet clear whether the etiology of these abnormalities reflects genes, environment, or some interaction of these factors. In the study by Van Erp et al. (2002), the data appear to best fit a model in which genes and environment (as indexed by fetal hypoxia) combine to yield the smallest hippocampi in patients with schizophrenia. Because the nonpsychotic siblings in that study also had smaller hippocampi compared to controls (but significantly larger than those of the patients) and did not show a significant influence of fetal hypoxia on hippocampal size, it is reasonable to assume that their hippocampal size was caused largely by genetic vulnerability.

The finding of smaller PHAs and hippocampi in multiplex compared with simplex relatives is consistent with some genetic models. The distribution of impairment among families is consistent with multifactorial models of familial transmission. Presumably, multiplex families harbor more schizophrenia genes than simplex families, putting relatives at greater risk for both schizophrenia and genetically related deficits. Our results, however, do not address the genetic versus environmental causes of MTL deficits given the inferential limitations of family studies that do not include twin or adoptive relatives (Cannon et al. 1993; Tsuang et al. 1999b). Nor do our data rule out other etiologies affecting MTL in nonpsychotic relatives, such as perinatal brain injury (Stefanis et al. 1999) or effects of psychosocial stress on the hippocampus (McEwen and Magarinos 1997)—etiologies that could interact with genetic vulnerability. This latter occurrence has been shown to be plausible in a twin study of posttraumatic stress disorder, in which smaller hippocampi were a risk factor for the development of subsequent stress-related psychopathology (Gilbertson et al. 2002).

The MTL abnormalities in nonpsychotic relatives could originate from subtle brain injuries similar to those occurring in schizophrenia (Suddath et al. 1990), caused by obstetric complications (OCs; McNeil 1995) or viruses (Torrey and Peterson 1974). There is some support for slightly elevated rates of OCs in nonpsychotic relatives of patients with schizophrenia (Sacker et al. 1996; Cannon et al. 2000; Rosso et al. 2000). We also cannot rule out the possibility of later-occurring alterations in developmental processes such as abnormal synaptic pruning or myelination that could account for the abnormal MTL (Cannon et al., this issue). However, consistent with occurrence of
earlier abnormal brain development, children at risk for schizophrenia show signs of neurological, cognitive, and social-affective maladjustment as early as the preschool years (Olin and Mednick 1996). These facts tend to support the hypothesis of abnormal MTL development from early childhood. Recent studies demonstrating abnormal hippocampal fissure size in schizophrenia point to MRI measures that indicate abnormal early brain development (Smith et al. 2003).

The nature of the subtle memory problems observed in the relatives suggests several points worthy of followup research. Unlike patients with schizophrenia (Seidman et al. 1998) or patients with amnestic disorders (Squire and Zola Morgan 1991), the relatives do not have abnormal rates of forgetting compared with controls (Faraone et al. 1995, 1999, 2000). Thus, their memory deficits suggest defects in the acquisition or retrieval, rather than storage, of information (Cirillo and Seidman 2003). Such difficulties have been linked to posterior hippocampus and other associated structures such as the PHG (Schacter and Wagner 1999), as well as the prefrontal cortex (Wagner 1999). Further research, especially in the prodromal phase, is needed to evaluate the shift from subtle encoding impairments to more severe encoding, storage, and retrieval deficits and to link these with possible brain changes.

Our results must be interpreted in light of some limitations. It would have been optimal to diagnose controls in the same way as relatives and patients. Nevertheless, the groups were comparable on many demographic factors. Although we did not administer an extensive family history diagnostic interview to the controls, the absence of this information would not bias the findings. This mitigates against the idea that the control group is “supernormal.” Because we controlled for alcohol and drug use, and a measure of cognitive (reading) ability, these factors cannot account for volumetric differences between groups. Moreover, the results were comparable after excluding relatives with MDD.

It is possible that the unexpected finding of a larger PHp in relatives from simplex families could result from some artifact of measurement. For example, it could theoretically be a function of the location of the lateral geniculate nucleus, which acts as a boundary between PHa and PHp. We consider this unlikely because the overall volume of the simplex relatives is large relative to the other groups and PHG volume is independent of the lateral geniculate. If this putative measurement error were operative, we would expect a larger PHp and a smaller PHa. Another possibility is lower reliability of measurement of PHp. Because this is one of only a few studies that have measured anterior and posterior PHG, replication is necessary.

Table 6. Correlations between anterior parahippocampal gyral volumes and verbal memory performance in controls and relatives of patients with schizophrenia

<table>
<thead>
<tr>
<th>Memory variables</th>
<th>Controls (n = 48)</th>
<th>Simplex Relatives (n = 28)</th>
<th>Multiplex Relatives (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PHa</td>
<td>PHa</td>
<td>PHa</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
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<tr>
<td>Logical memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>0.21</td>
<td>0.06</td>
<td>-0.11</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>0.16</td>
<td>0.01</td>
<td>-0.23</td>
</tr>
</tbody>
</table>

Note.—PHa = anterior parahippocampus; WRAT-R = Wide Range Achievement Test-Revised.

Table 7. Correlations between posterior parahippocampal gyral volumes and verbal memory performance in controls and relatives of patients with schizophrenia

<table>
<thead>
<tr>
<th>Memory variables</th>
<th>Controls (n = 48)</th>
<th>Simplex Relatives (n = 28)</th>
<th>Multiplex Relatives (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PHp</td>
<td>PHp</td>
<td>PHp</td>
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<tr>
<td></td>
<td>Left</td>
<td>Right</td>
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<tr>
<td>Logical memory</td>
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</tr>
<tr>
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<td>0.22</td>
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<td>0.20</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>0.19</td>
<td>-0.06</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Note.—PHp = posterior parahippocampus; WRAT-R = Wide Range Achievement Test-Revised.

1 Pearson correlations of residualized memory scores (adjusted for age, sex, WRAT-R reading and total cerebral exterior) with absolute brain volumes (none were significant at p < 0.05).
Studies of adult relatives of schizophrenia that investigate susceptibility indicators of schizophrenia are limited by the fact that many of these individuals have crossed the typical age of risk for onset of this illness—that is, late adolescence. In this study, approximately two-thirds of the nonpsychotic relatives were over the age of 35. That is, they had passed through the peak ages of risk for schizophrenia. Thus, the abnormalities identified in such adult nonpsychotic relatives help identify trait abnormalities that cannot be caused by psychosis per se but do not indicate which abnormalities may predict the psychosis. Adolescent offspring of parents with schizophrenia represent an attractive high-risk population for study because having one parent with schizophrenia entails about 10 to 15 percent risk of developing the illness, and having two parents with schizophrenia increases the risk to close to 40 percent (Erlenmeyer-Kimling et al. 1997). Among young offspring at high risk for schizophrenia, impairments in attention and short-term verbal memory have been found to be possible predictors of adult psychotic disorders (Erlenmeyer-Kimling 2001). These observations highlight the importance of examining child and adolescent subjects.

Three genetic high-risk studies (Keshavan et al. 1997, 2002a; Lawrie et al. 1999, 2001; Schreiber et al. 1999) have investigated whether structural brain alterations are present in predisposed individuals before the typical period of age of risk. These research groups observed significant reductions in the MTL in young relatives at risk for schizophrenia. Abnormalities were observed mainly in the left amygdala-hippocampal region in the Pittsburgh (Keshavan et al. 2002a) and Edinburgh (Lawrie et al. 2001) studies. However, genetic high-risk designs are limited by the low conversion rate and the potentially long period before conversion. Thus, studies of prodromal adolescents may offer good alternative samples. Reports from the Melbourne clinical high-risk psychosis study (see Yung and McGorry 1996 for a description of the Melbourne strategy) have also identified limbic system abnormalities in high-risk individuals; areas of abnormality included the hippocampus, the PHG, and the anterior cingulate cortex (Phillips et al. 2002; Pantelis et al. 2003; Yücel et al. 2003).

This study did not address whether other brain regions, such as the dorsolateral prefrontal cortex (DLPFC), are vulnerability indicators. In the Pittsburgh study, structural changes in prefrontal volumes were not observed using region of interest–based methods. This is not very surprising given that structural MRI studies of the DLPFC in schizophrenia have yielded equivocal findings (Wible et al. 1995; Gur et al. 1998; Baare et al. 1999; Goldstein et al. 1999). This contrasts with consistent demonstration of cognitive impairments (Deakin et al. 1997; Diwadkar et al. 2001) and reduced activation in at least one functional MRI study indicative of prefrontal dysfunction among offspring at risk for schizophrenia (Keshavan et al. 2002b). Reduced neuronal viability as evidenced by reductions of NAA has been observed using proton (1H) magnetic resonance spectroscopy (MRS) in the prefrontal cortex in adolescent offspring of persons with schizophrenia (Keshavan et al. 1997). Phosphorus (31P) MRS studies have shown reduced membrane phospholipid metabolism in the prefrontal cortex in high-risk offspring (Klemm et al. 2001; Keshavan et al. 2003). Furthermore, using an automated voxel-based analysis, researchers in the Melbourne high-risk study (Pantelis et al. 2003) identified prefrontal (including DLPFC) abnormalities in preschizophrenic individuals.

Genetic and clinical high-risk studies can each reveal important insights into neurobiological alterations that may underlie the risk for schizophrenia (Cannon et al., this issue). The study of the adolescent period seems most relevant to understanding the descent into psychosis, with the ultimate goal of preventing or ameliorating the illness. An important issue to consider in studies of adolescents is the marked developmental variability in brain structure and function in these age ranges and therefore the importance of appropriate age and sex matching. Larger longitudinal studies will allow us to prospectively examine the utility of the observed alterations for predicting the emergence of psychopathology in these individuals, as has been shown in the Melbourne and Edinburgh studies. The Edinburgh study, which combines genetic and prodromal designs, in part because of its large sample size, allows early assessment before symptomatic persons receive medication and yields a reliable estimate of genetic factors.

In conclusion, this study’s PHG results provide additional support for the hypothesis that expressions of the liability to schizophrenia include volumetrically altered MTL and inefficient VDM. Because both genetic factors and OCs have been suggested as risk factors for schizophrenia and for hippocampal dysfunction (Jones and Murray 1991; Cannon et al. 1993; Tsuang and Faraone 1995; Buka et al. 1999; Van Erp et al. 2002), it is important to investigate the possibility that independent or interactive aspects of these causes may result in MTL abnormalities in relatives. This work also helps to differentiate between vulnerability factors and those associated with psychosis per se, an important distinction for improved treatment and prevention of schizophrenia (Tsuang et al. 1999c; McGorry et al. 2002).

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Acknowledgments

Preparation of this article was supported in part by grants from the Stanley Medical Research Institute, the National Association for Research in Schizophrenia and Depression (NARSAD), the Mental Illness Neuroscience Discovery (MIND) Institute, and National Institute of Mental Health (NIMH) Grant MH 56956 to Dr. Jill M. Goldstein; NARSAD to Dr. Nikos Makris; and (NIMH) Grant MH 63951 to Dr. Larry J. Seidman; (MIND) Institute, and National Institute of Mental Health (NARSAD), the Mental Illness Neuroscience Discovery Association for Research in Schizophrenia and Depression, the Stanley Medical Research Institute, the National Institute of Mental Health Grant MH 63951 to Dr. Larry J. Seidman; National Institute of Mental Health Grant MH 56956 to Dr. Jill M. Goldstein; NARSAD to Dr. Nikos Makris; and (NIMH) Grant MH 63951 to Dr. Larry J. Seidman; National Institute of Mental Health Grant MH 56956 to Dr. Jill M. Goldstein; NARSAD to Dr. Nikos Makris; and a NARSAD Distinguished Investigator Award and NIMH Grants MH 43518 and 46318 to Dr. Ming T. Tsuang. This work was presented, in part, at the Society of Biological Psychiatry, May 11, 2000.

We thank the following people for their contributions to this project: Mimi Braude, Deborah Catt, Joanne Donatelli, Dr. Elizabeth Hoge, Jennifer Holtzinger, Lynda Jacobs, Dr. William Kremen, Dr. Genichi Matsuda, Camille McPherson, Catherine Monaco, James Myers, Dr.
John Pepple, Anne Shore, Dr. Rosemary Toomey, Jason Tourville, Dr. Michael Ward, Dr. Heidi Wencel, Judith Wides, and Dr. Andrew Worth. We especially thank Jennifer Koch for technical assistance in manuscript preparation.

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