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MRI Brain Volume Abnormalities in Young, Nonpsychotic Relatives of Schizophrenia Probands are Associated with Subsequent Prodromal Symptoms

Beng-Choon Ho, MRCPsych
Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City, Iowa, USA

Abstract

Schizophrenia is characterized by subtle but well-replicated total and regional (frontal and temporal) brain tissue volume deficits. Studies of individuals at-risk for developing schizophrenia suggest that the onset of brain volume decrement may closely pre-date overt manifestations of schizophrenia, making brain volume abnormalities potential predictors for early identification. In an ongoing longitudinal morphometric MRI study of young, nonpsychotic first- or second-degree relatives of schizophrenia probands, we compared brain volumes in 46 relatives who are still within age range for developing schizophrenia against comparison groups of 46 schizophrenia patients and 46 healthy volunteers without family history of schizophrenia. Relatives had similar brain volume abnormalities as schizophrenia patients albeit less severe. Relatives had significantly larger whole brain, frontal, temporal and parietal gray matter (GM) volumes than patients. Relatives also had significantly smaller frontal GM volumes than healthy volunteers. Both relatives and patients had significantly larger whole brain WM (specifically parietal WM) volumes compared to healthy volunteers. Abnormally greater WM volumes in relatives and patients are suggestive of genetically-mediated dysmaturation of the age-expected myelination during adolescence through mid adulthood. On prodromal symptoms assessed in relatives one year after MRI brain scans, initial GM deficits as well as larger WM volumes correlated significantly with greater severity of subsequent prodromal symptoms. Together with previous genetic high-risk studies of adolescent or young adult relatives, these findings indicate that premorbid MRI brain abnormalities may be of predictive value for the early identification of schizophrenia.

Keywords

Schizophrenia; Genetics; Magnetic resonance imaging; Prevention; Prodrome; White Matter

Introduction

Schizophrenia is perhaps the most enigmatic and devastating brain disorder. Even though schizophrenia patients experience severe symptoms and impairment, their microscopic and macroscopic brain abnormalities are relatively subtle (Harrison 1999; Shenton et al. 1997). Compared to healthy volunteers, brain volumes in schizophrenia patients are reduced by 1–2% for the whole brain and frontal lobes, between 4–6% reductions in temporal lobe structures

Address for correspondence: Dr. Beng-Choon Ho, Department of Psychiatry, W278 GH, University of Iowa Carver College of Medicine, 200 Hawkins Drive, Iowa City, IA 52242, Phone: 319/384-9400, Fax: 319/353-8656, Email: beng-ho@uiowa.edu.

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(including the hippocampus, amygdala, anterior superior temporal gyrus) (Wright et al. 2000). Although the etiology and pathogenesis of schizophrenia are still not well understood, family studies indicate that the causes of schizophrenia are primarily genetic (Sullivan et al. 2003). Twin studies have estimated heritabilities of around 80%. Prevalence of schizophrenia among relatives is higher than the general population (1%), and diminishes with decreased degree of relatedness to the schizophrenia proband – from 48% in monozygotic twins, to 17% dizygotic twins, 13% off springs, 9% full siblings and down to 2% in first cousins. Besides higher rates of schizophrenia, relatives who do not manifest the disorder are more likely to have similar, but less severe, neuroanatomical, electrophysiological, neurocognitive and behavioral deficits seen in schizophrenia probands (Keshavan et al. 2005).

There are now fairly substantial numbers of in vivo anatomical neuroimaging studies on nonpsychotic relatives of schizophrenia probands (see summary in Table 1). Brain volumes in unaffected relatives are intermediate between schizophrenia probands and healthy controls with no family history of schizophrenia. These volume abnormalities are in similar brain regions as the deficits observed in schizophrenia. Diminished amygdala-hippocampus volumes have been the most frequently reported abnormalities among nonpsychotic relatives.

However, as seen in Table 1, most studies have comprised of older adult relatives who are for most part unlikely to develop schizophrenia. To the best of our knowledge, there are only five independent samples in the literature that examined MRI brain volume deficits in nonpsychotic, young relatives who are still in the age range at-risk for developing schizophrenia. Focusing on adolescent or young adult relatives has advantages over studies involving older adult relatives. As volumetric abnormalities in nonpsychotic relatives are partly related to shared genetic vulnerability to schizophrenia, studying brain development of adolescent or young adult relatives who are still in age range at-risk will likely lead to better understanding of the neurodevelopmental etiology of schizophrenia. Since younger samples are likely to contain subjects who will develop schizophrenia in future, and if adequate numbers of the high-risk subjects are followed-up, such genetic high-risk studies can address the issue of whether brain volume abnormalities are present in predisposed individuals before the clinical manifestations of schizophrenia. Brain volume abnormalities together with other biomarkers of increased susceptibility may aid in early identification of schizophrenia and the eventual secondary and primary prevention of the disorder.

To achieve these long term goals, we have begun studying adolescent or young adult first- or second-degree relatives of schizophrenia probands who have been carefully screened for the absence of psychotic disorders. In this report, we compared high-resolution MRI brain volumes of at-risk relatives obtained at intake into the study against two comparison groups of schizophrenia probands and healthy volunteers without family history of schizophrenia. Based on previous studies (Table 1), we hypothesized that these relatives will have gray matter (GM) and white matter (WM) volume deficits that are intermediate between the two comparison groups. In this study, we further assessed the relationships between initial MRI brain volumes and follow-up ratings of prodromal symptoms. We hypothesized that brain volume deficits will be associated with greater severity of prodromal symptoms among relatives.

Experimental/Materials and Methods

Subjects

The 138 subjects in this study comprised of 46 first- (N=30) or second-degree relatives of schizophrenia probands, 46 schizophrenia patients and 46 healthy controls with no family history of schizophrenia. After complete description of the study to subjects, written informed consent was obtained.

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Relatives were ascertained either through 1) schizophrenia patients who have participated in research studies or have received psychiatric treatment at the University of Iowa Health Care, or 2) advertisements in local newspapers or mental health advocacy groups. Inclusion criteria for relatives were age between 13 to 28 years and having at least one first- or second-degree relative with schizophrenia. Family history of schizophrenia was further verified using Family History-Research Diagnostic Criteria (FH-RDC) (Andreasen et al. 1977), which has well-established reliability and validity. Relatives were interviewed using the SCID (Structured Clinical Interview for DSM-IV), and were excluded if they had a primary psychotic disorder (schizophrenia, schizophreniform disorder, schizoaffective disorder, or delusional disorder), or if they met criteria for substance abuse or dependence currently or within the past year. None of the relatives had schizophrenia-spectrum (schizotypal, schizoid or paranoid) personality disorders. Thirty-five relatives had no lifetime history of any psychiatric disorders. In the remaining 11 relatives, diagnoses included: major depressive disorder (6), depressive disorder, not otherwise specified (1), attention deficit hyperactivity disorder (2), panic disorder (1) and generalized anxiety disorder (1).

Schizophrenia patients and control subjects were selected from neuroimaging studies conducted at the Department of Psychiatry University of Iowa. These two comparison groups were of equivalent gender composition (M:F ratio=20:26) and age range (13 to 28 years) as relatives. Patients were evaluated using a semi-structured interview instrument, Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al. 1992), from which schizophrenia diagnosis meeting DSM-III-R or DSM-IV criteria was based. Thirty of the 46 patients are participants in the Iowa Longitudinal of Recent-Onset Psychoses (Flaum et al. 1992). Mean age of illness onset was 18.3 years (SD=4.8). These patients were still early in their course of illness (Mean duration of illness=2.4 years (SD=3.1), and have had minimal prior antipsychotic treatment (Median duration of treatment=3.0 months (25–75% interquartile range=23)). Healthy controls were evaluated using an abbreviated version of the CASH to exclude subjects with current or past psychiatric illnesses and substance misuse. FH-RDC was also used to assess the absence of family history of schizophrenia in healthy controls. Additional exclusion criteria for all subjects in this study were: neurological disorders, mental retardation, unstable medical conditions or contraindications for magnetic resonance imaging.

All patient subjects and healthy controls in this report were unrelated and were derived from independent families. The 46 relatives were ascertained from 34 independent families: 21 families each contributed 1 relative subject, 4 families each contributed 1 relative subject and 1 schizophrenia proband, 7 families contributed 2 relatives subjects each, 1 family 3 relatives subjects and the last family 4 relatives subjects.

MRI image acquisition and processing

All subjects underwent a high resolution anatomical MR imaging protocol on a 1.5 T GE CVMRI scanner (General Electric Medical Systems, Milwaukee, Wis). This protocol acquired multimodal scans of the whole brain consisting of T1 and T2 weighted sequences. The T1 sequence was obtained as a 3D volume in the coronal plane using a spoiled GRASS sequence with the following parameters: TE = 6 ms, TR = 20 ms, flip angle = 30°, FOV = 160×160×192 mm, matrix = 256×256×124, NEX=2. The T2 images were acquired using a 2D fast spin-echo sequence in the coronal plane with the following parameters: TE = 85 ms, TR = 4800 ms, slice thickness/gap = 1.8/0.0 mm, FOV = 160×160 mm, matrix = 256×256, NEX = 3, number of echoes = 8, number of slices = 124.

After the MR scans were acquired, the images were transferred to our Image Processing Lab for processing using an automated, highly reliable image analysis pipeline. Detailed descriptions of image analysis methods have been provided elsewhere (Andreasen et al. 1996; Harris et al. 1999; Magnotta et al. 2003; Magnotta et al. 2002). In brief, T1 weighted

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images were aligned horizontally along the interhemispheric fissure in the axial and coronal views and vertically along the anterior commissure (AC) and posterior commissure (PC). Talairach parameters that define the bounding box for the brain as well as the AC and PC points were selected. These parameters define the piecewise linear scaling of the Talairach grid onto the current brain of interest. The T2-weighted images were then co-registered to the AC-PC aligned T1 weighted images. These images were warped into standardized stereotaxic Talairach atlas space (Talairach and Tournoux 1988) to generate automated measurements of frontal, temporal, parietal, and occipital lobes, cerebellum, and subcortical regions (Andreasen et al. 1996). To further classify tissue volumes into gray matter (GM), white matter (WM) and CSF, we employed a discriminant analysis method of tissue segmentation based on automated training class selection that utilized data from the T1 and T2 sequences (Harris et al. 1999). This method identifies the range of values that characterized GM, WM, and CSF in the multispectral MRI data (10–70 for CSF, 70–190 for GM, and 190–250 for WM). Each voxel was given an intensity value based on the weights assigned by the discriminant functions. This reflected the relative combination of GM, WM, and CSF in a given voxel and allows us to correct for partial volume (Harris et al. 1999). Intraclass correlations for this automated tissue segmentation analysis ranged from 0.97 to 0.98.

Assessment of prodromal symptoms at follow-up

After the initial evaluation, a single rater interviewed the relatives at 6-monthly intervals for prodromal symptoms using the Scale of Prodromal Symptoms (SOPS) (Miller et al. 1999). The SOPS provides systematic assessment for the presence and severity of prodromal symptoms. Each of the 19 symptom items is rated on a 7-point ordinal scale (0=Absent, 6=Extreme). The items are further grouped into 4 symptom domains (i.e. Psychotic (5 items), Negative (6 items), Disorganized (4 items) and General (4 items)), which have good construct validity (Hawkins et al. 2004). Domain scores are the sum of individual item ratings within each symptom domain. Total SOPS score is the sum of the 19 symptom ratings. In this report, we present data from the last available SOPS ratings.

Statistical analysis

To reduce type I error, the analyses were conducted in stages. We first performed one joint omnibus multivariate regression test, which assessed the main effects of group membership (healthy controls with no family history of schizophrenia versus relatives of schizophrenia probands versus schizophrenia patients) simultaneously on all 4 primary MRI regions of interest (ROIs) (i.e. whole brain GM, whole brain WM, whole brain CSF and lateral ventricles). A Bonferroni-corrected alpha of .05/4=.0125 was used to control for multiple comparisons. To evaluate which primary ROI and which group contributed to the significant joint omnibus test, we followed up with univariate analyses of covariance (ANCOVA) assessing main effects of group, and with pair-wise group contrasts using the independent sample t statistic on each of the 4 primary ROI. Intracranial volume, age and gender were entered as covariates in the joint omnibus test and univariate ANCOVAs. Pair-wise independent group t-tests compared least-square group means adjusted for these covariates.

For the secondary ROIs (frontal, temporal, parietal, and occipital GM volumes and WM volumes), group differences in brain volumes were tested using ANCOVAs. In each general linear model, the respective secondary ROI was the dependent measure. Intracranial volume, age and gender were entered as covariates and grouping as the independent factor in each model. Similarly, pair-wise independent group t-tests compared least-square means of the secondary ROIs. All tests were 2-tailed. Analyses of secondary ROIs as well as all follow-up analyses of primary ROIs were deemed statistically significant at the $p \leq .05$ level.

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Given the skewed distribution in total SOPS score (toward low ratings), we used Spearman partial correlations to analyze the relationships between MRI brain volumes and follow-up prodromal symptoms in relatives. Intracranial volume and age were entered as covariates in these correlation analyses.

Results

Relatives, patients and control subjects were comparable with respect to age (Means=19.9 years (SD=4.1), 20.8 years (SD=4.5) and 20.9 years (SD=3.5) respectively) and parental socioeconomic status (modified Hollingshead scale (Hollingshead and Redlich 1958) Means=2.7 (SD=0.6), 2.9 (SD=0.7) and 2.7 (SD=0.4) respectively) ($F \leq 1.57$, df=2,137, $p \geq 0.21$).

MRI brain volumes in young, non-psychotic relatives

The joint omnibus test assessing all 4 primary ROIs simultaneously found a significant main group effect ($F=7.11$, df=6,260, $p<0.0001$). Least square means for these primary ROIs broken down by comparison groups are summarized in Table 2. There were statistically significant main effects of group on whole brain GM, whole brain WM, whole brain CSF and lateral ventricles ($F \geq 4.45$, df=2,137, $p \leq 0.01$). Compared to patients, relatives had significantly larger whole brain GM volumes and smaller whole brain CSF and lateral ventricles ($T \geq 3.33$, df=90, $p \leq 0.001$). Whole brain WM volumes did not differ significantly between relatives and patients ($T=0.26$, df=90, $p=0.79$). Compared to control subjects, relatives as well as patients had significantly larger whole brain WM volumes ($T \geq 2.42$, df=90, $p \leq 0.02$). Relatives had smaller whole brain GM volumes than controls; this approached but did not achieve statistical significance ($T=1.74$, df=90, $p=0.08$). Whole brain CSF and lateral ventricles did not differ significantly between relatives and controls ($T \leq 0.55$, df=90, $p \geq 0.58$). Patients had significantly smaller whole brain GM and larger whole brain CSF and lateral ventricles than controls ($T \geq 3.09$, df=90, $p \leq 0.002$).

Least square means for the secondary ROIs broken down by comparison groups are summarized in Table 3. There were statistically significant main effects of group on frontal, temporal and parietal GM volumes ($F \geq 12.67$, df=2,137, $p \leq 0.0001$), but not for occipital GM. Post hoc pair-wise group comparisons indicate that relatives had significantly smaller frontal GM volumes than controls, and significantly larger frontal GM volumes than patients ($T=2.08$ or 3.97 respectively, df=90, $p \leq 0.04$). Temporal, parietal and occipital GM volumes among relatives were also intermediate between controls and patients, but did not differ significantly from controls ($T \leq 1.39$, df=90, $p \geq 0.17$). Compared to patients, relatives subjects had significantly larger temporal and parietal GM volumes as well ($T \geq 3.97$, df=90, $p \leq 0.0001$).

There were significant main effects of group on temporal, parietal and occipital WM volumes (Table 3; $F \geq 3.30$, df=2,137, $p \leq 0.04$), but not for frontal WM. Relatives had significantly larger parietal WM volumes than controls ($T=3.15$, df=90, $p=0.002$). Frontal, temporal and occipital WM volumes did not differ significantly between relatives and controls ($T \leq 1.76$, df=90, $p \leq 0.08$). Patients had significantly larger temporal, parietal and occipital WM volumes ($T \geq 2.42$, df=90, $p \leq 0.02$) but not for frontal WM ($T=1.19$, df=90, $p=0.23$) than controls. Lobar WM volumes also did not differ significantly between relatives and patients ($T \leq 1.78$, df=90, $p \geq 0.08$).

Because other psychiatric disorders (e.g. major depressive disorder and attention deficit hyperactivity disorder) have also been associated with brain volume deficits, the analyses were repeated after excluding relatives with Axis I disorders. Restricting the relatives sample to only those 35 relatives without any psychiatric disorders did not change the results reported above (details available upon request). Furthermore, to account for potential confounds that may have

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arisen from correlations of brain volume among family members, we re-ran the analyses with family clustering as an additional covariate. The family clustering covariate was entered as a class variable with 14 levels (1 to 13 coded for the 13 families that contributed at least 2 family members to the study sample; the 14th level was for all remaining unrelated subjects). Again, inclusion of family clustering covariate did not change the results reported above (details available upon request).

Relationships between intake MRI brain volumes and follow-up prodromal symptoms

Thirty-five relatives had SOPS ratings at follow-up assessment. The mean duration between MRI brain scan and last available follow-up SOPS ratings was 1.08 years (SD=0.80). Mean total SOPS score was 2.8 (SD=7.1; Median=0, 25th–75th interquartile range=2). Most subjects either had no prodromal symptoms (N=19) or had prodromal symptoms that were no greater than 'Mild' severity (N=13) (Figure 1). If present, prodromal symptoms were predominantly from the Negative or General symptom domains. The only relative subject who endorsed psychotic symptoms has developed probable schizophrenia at follow-up assessment.

The associations between MRI brain volumes and the SOPS total scores one year later are summarized in Figure 2 and Figure 3. Greater severity in SOPS total score correlated significantly with smaller total, frontal, temporal and parietal GM volumes (Figure 2; Spearman $r \leq -0.35$, df=33, $p \leq 0.04$). Greater severity in SOPS total score was also significantly associated with larger total, frontal and temporal WM volumes (Figure 3; Spearman $r \geq 0.35$, df=33, $p \leq 0.05$).

Discussion

In this study, we examined MRI brain volumes of nonpsychotic, adolescent or young adult relatives of schizophrenia probands who were still within the age range at-risk for developing schizophrenia. Brain volumes in these young, unaffected first- or second-degree relatives were intermediate between those of schizophrenia patients and healthy volunteers without family history of schizophrenia. Compared to patients, at-risk relatives had significantly larger whole brain GM as well as larger frontal, temporal and parietal GM volumes. Compared to healthy volunteers, relatives also had significantly smaller frontal GM volumes, and (at a trend level) smaller whole brain GM. Whole brain WM (specifically parietal WM) volumes were significantly larger in relatives compared to healthy volunteers. WM volumes did not differ significantly between relatives and patients. Relatives had significantly smaller whole brain CSF volumes and lateral ventricles than patients, but these did not differ from healthy volunteers. More interestingly, on prodromal symptoms assessed approximately one year after MRI brain scans, these brain volume abnormalities in adolescent or young adult relatives (i.e. smaller GM as well as larger WM volumes) correlated significantly with greater severity of prodromal symptoms.

In general, our findings are consistent with previous MRI studies from five independent samples (Pittsburgh, Edinburgh, Ulm, Bethesda and Orangeburg/New York) of genetic high-risk individuals still within the age range for developing schizophrenia (DeLisi et al. 2006; Gogtay et al. 2003; Job et al. 2003; Job et al. 2005b; Job et al. 2006; Keshavan et al. 1997; Keshavan et al. 2002b ; Lawrie et al. 1999; Lawrie et al. 2001; Lawrie et al. 2002; Rajarethinam et al. 2004; Schreiber et al. 1999). Even though these young relatives do not have psychotic disorders, they have volume deficits in similar brain regions as schizophrenia patients - albeit less severe. As a group, unaffected relatives have global as well as regional (primarily fronto-temporal) GM brain volume deficits. Unlike our study, most previous studies have examined smaller brain regions, especially structures in the medial temporal lobe. The most consistently

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reported abnormalities in young relatives of schizophrenia probands have been smaller hippocampus, amygdala and parahippocampus gyrus when compared to healthy volunteers with no family history. Additionally, larger third ventricles (Keshavan et al. 1997; Lawrie et al. 2001), smaller thalamus (Lawrie et al. 1999), smaller anterior cingulate (Job et al. 2003), smaller superior temporal gyrus (Rajarethinam et al. 2004) have also been reported. In this study, relatives subjects did not differ significantly from healthy controls on temporal lobe GM volume even though these were intermediate between the other 2 comparison groups. Since our brain volume measures were only at the lobar level, our study may not have been sensitive enough to detect volume deficits within the smaller medial temporal structures. Despite this limitation, we still found smaller frontal GM volumes in relatives, which is consistent with the Gogtay et al study where siblings of childhood-onset schizophrenia patients also had smaller frontal GM and total GM than healthy controls (Gogtay et al. 2003). Using a novel and potentially more sensitive MR imaging technique of diffusion weighted imaging, DeLisi et al found nonpsychotic young relatives of schizophrenia probands had increased apparent diffusion coefficients suggestive of volume reductions in the left parahippocampal, lingual, superior frontal and middle frontal gyri (DeLisi et al. 2006).

While GM volume deficits in our young nonpsychotic relatives are consistent with previous studies, the finding of enlarged WM volumes was not predicted initially. To the best of our knowledge, this is the first study reporting enlarged WM volumes in nonpsychotic adolescent or young adult relatives of schizophrenia probands. Previous studies examining WM abnormalities in nonpsychotic relatives involved relatives who were already in their 30s to 40s, and have found either smaller WM volumes (McIntosh et al. 2006) or no difference (Cannon et al. 1998; McIntosh et al. 2005; Schneider-Axmann et al. 2006; Staal et al. 2000). Our observation of significantly larger parietal WM volumes among relatives is unlikely to be a chance finding since schizophrenia patients in this study also had significantly greater whole brain, temporal, parietal and occipital WM volumes than healthy volunteers. More importantly, both GM deficits as well as WM enlargements in relatives were associated with greater everity of subsequent prodromal symptoms. Taken together, enlarged WM volumes in relatives subjects are likely to be of relevance to the pathogenesis of schizophrenia.

Although a recent meta-analysis estimated a 1% reduction in whole brain WM volume among schizophrenia patients (Wright et al. 2000), patient-control MRI volumetric studies have reported conflicting findings: no significant group differences in WM volumes (e.g. (Gur et al. 1999; Gur et al. 2000; Zipursky et al. 1992), regional WM reductions (e.g. (Buchsbaum et al. 1998; Marsh et al. 1997) as well as WM enlargements (e.g. (Highley et al. 2003; Shenton et al. 1992; Wible et al. 1995) in schizophrenia patients. That both unaffected relatives and schizophrenia patients in our study had larger WM volumes in the posterior (temporal, parietal and occipital lobes) but not the anterior (frontal lobe) portions of the brain than healthy volunteers may be related to aberrant WM maturation during adolescence and early adulthood. Unlike GM brain volume, WM volume continues to increase during adolescence in a back-to-front wave (Giedd et al. 1999; Paus et al. 1999; Pfefferbaum et al. 1994; Sowell et al. 1999; Sowell et al. 2002). During early to mid-adulthood, WM volumes plateau during the fifth decade of life with the frontal lobe being the last to mature (Mathalon et al. 2001; Sowell et al. 2003). Schizophrenia patients do not show this normal age-related expansion in WM volume (Bartzokis et al. 2003). In fact, schizophrenia patients may actually start out having abnormally enlarged WM brain volumes during adolescence and early adulthood (Bartzokis et al. 2003). Because patients do not show the normal age-related WM volume expansion during early to mid-adulthood, patient-control differences in WM volumes become increasingly more evident with age such that WM volume reductions are most marked by the fifth decade of life (Bartzokis et al. 2003). Thus, our finding of enlarged WM volumes in nonpsychotic relatives and in schizophrenia patients, all of whom were either adolescents or still in their early twenties, may be related to dysmaturation in myelination.

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The underlying basis for these brain volume deficits observed in young nonpsychotic relatives of schizophrenia probands are not well understood. A plausible and often cited explanation is that these less severe morphometric abnormalities are primarily due to the genetic factors of schizophrenia, and with additional contributions from yet unknown environmental effects that relatives and schizophrenia probands share (Seidman and Wencel 2003). That schizophrenia susceptibility genes have major influences on these intermediary brain volume abnormalities in nonpsychotic relatives is supported by indirect evidence from several lines of investigations: schizophrenia is a genetic disorder (Kendler and Robinette 1983; Sullivan et al. 2003), subtle but well-replicated global and regional brain volume deficits are a core feature of schizophrenia (Honea et al. 2005; Pantelis et al. 2005; Steen et al. 2006; Vita et al. 2006; Wright et al. 2000), and brain volume is a heritable trait (Narr et al. 2002; Pfefferbaum et al. 2004; Thompson et al. 2001). In line with the prevailing concept of schizophrenia as a neurodevelopmental disorder (Murray and Lewis 1987; Weinberger 1987), it has been further postulated that aberrant synaptic pruning, programmed cell death and/or synaptic plasticity affecting schizophrenia patients (Feinberg 1982) may also have similar but less severe effects on reducing fronto-temporal brain volumes in nonpsychotic relatives (Keshavan et al. 1997). With recent advances in the complex genetics of schizophrenia (Harrison and Weinberger 2005) and the current interest in genotype-phenotype association studies (Ho et al. 2005b), this hypothetical relationship between schizophrenia susceptibility genes and brain structural and functional abnormalities in nonpsychotic relatives are now beginning to be tested more directly (Hall et al. 2006; McIntosh et al. 2007). Of particular interest would be genes whose products mediate neurobiological processes involved in late maturational events of synaptic remodeling and myelination.

While shared genetic factors and aberrant neurodevelopment may be the underlying basis for intermediary brain volume abnormalities in unaffected young relatives of schizophrenia probands, there is now increasing evidence that such abnormalities ascertained using morphometric MR imaging may also be pertinent biomarkers useful for the early identification of schizophrenia. In our study, GM volume deficits and larger WM volumes in young relatives subjects assessed at intake correlated significantly with greater severity of prodromal symptoms a year later. Although limited by small sample size, short follow-up duration and the absence of prodromal symptom ratings at baseline assessment, these associations between brain volume abnormalities and prodromal symptoms are intriguing. And as we enroll more subjects into our study, and as we continue our longitudinal assessments of these relatives, initial GM volume deficits and greater WM volumes may prove to be indicators of future development of schizophrenia.

Studying such a genetic high-risk population of nonpsychotic, young relatives, who are still within age range for developing schizophrenia, is a potentially fruitful research strategy from the standpoint of early identification of schizophrenia (Johnstone et al. 2005; Keshavan et al. 2005). By contrasting the neurodevelopmental trajectories between young relatives who go on to develop schizophrenia against relatives who remain well, we can better appreciate the early manifestations of schizophrenia which, in turn, could lead to early identification and intervention. However, such a longitudinal study of young relatives is relatively inefficient since a large sample is needed to obtain a sufficient numbers of schizophrenia subjects. Nevertheless, convergent findings from genetic high-risk studies and from clinical high-risk samples identified through having at-risk mental states (Falloon 1992; McGlashan and Johannessen 1996; McGorry et al. 1996) suggest that such a longitudinal study of young relatives is feasible, and can aid in the development of multi-stage screening programs for early identification of schizophrenia. In the Edinburgh high-risk study, longitudinal reductions in temporal and cerebellar gray matter densities prior to overt clinical symptoms of schizophrenia appear to have good predictive power in identifying young relatives who went on to develop schizophrenia (Job et al. 2005a; Job et al. 2006). These premorbid medial temporal lobe

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changes in genetic high-risk subjects are consistent with findings from the clinical high-risk or prodromal studies (Borgwardt et al. 2007; Pantelis et al. 2003), where ultra high-risk subjects who subsequently developed psychotic disorders had smaller baseline hippocampus, parahippocampus gyrus, and superior temporal gyrus volumes as well as longitudinal reductions in parahippocampus and fusiform gyri (Pantelis et al. 2003).

Thus, structural brain volume abnormalities, especially longitudinal medial temporal lobe volume reductions, have predictive validity in at-risk individuals. Its predictive value will likely further improve when combined with other known clinical risk factors (e.g. prodromal symptoms, poor scholastic test scores) and biological/genetic risk factors (e.g. endophenotypic traits and genetic allelic variations) into more sophisticated, multifactorial and multi-stage screening programs for the early detection of schizophrenia (Ho et al. 2005a).

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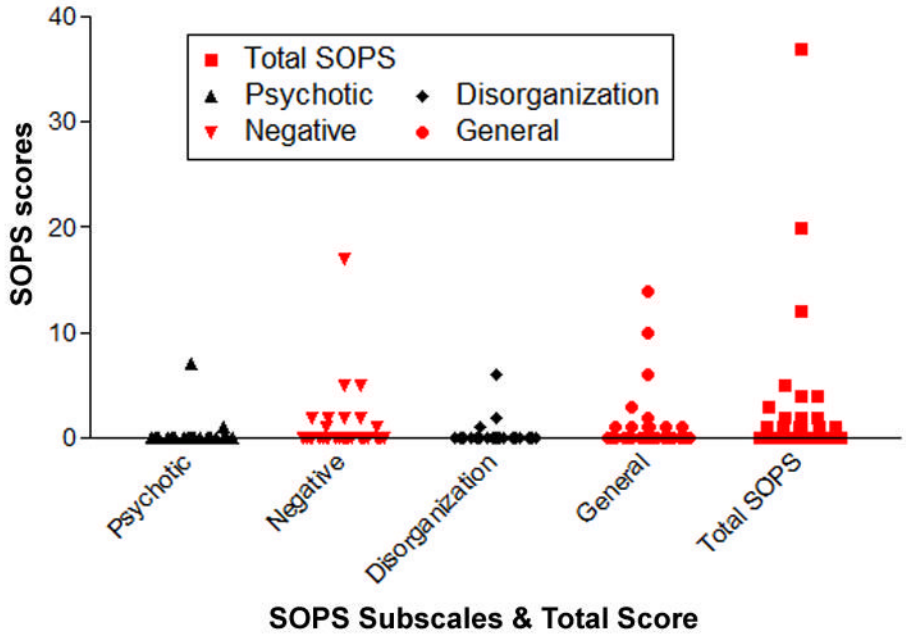

Figure 1.
Severity of prodromal symptoms in 35 young, nonpsychotic relatives of schizophrenia probands assessed using the Scale of Prodromal Symptoms (SOPS) on average one year after MRI brain scan.

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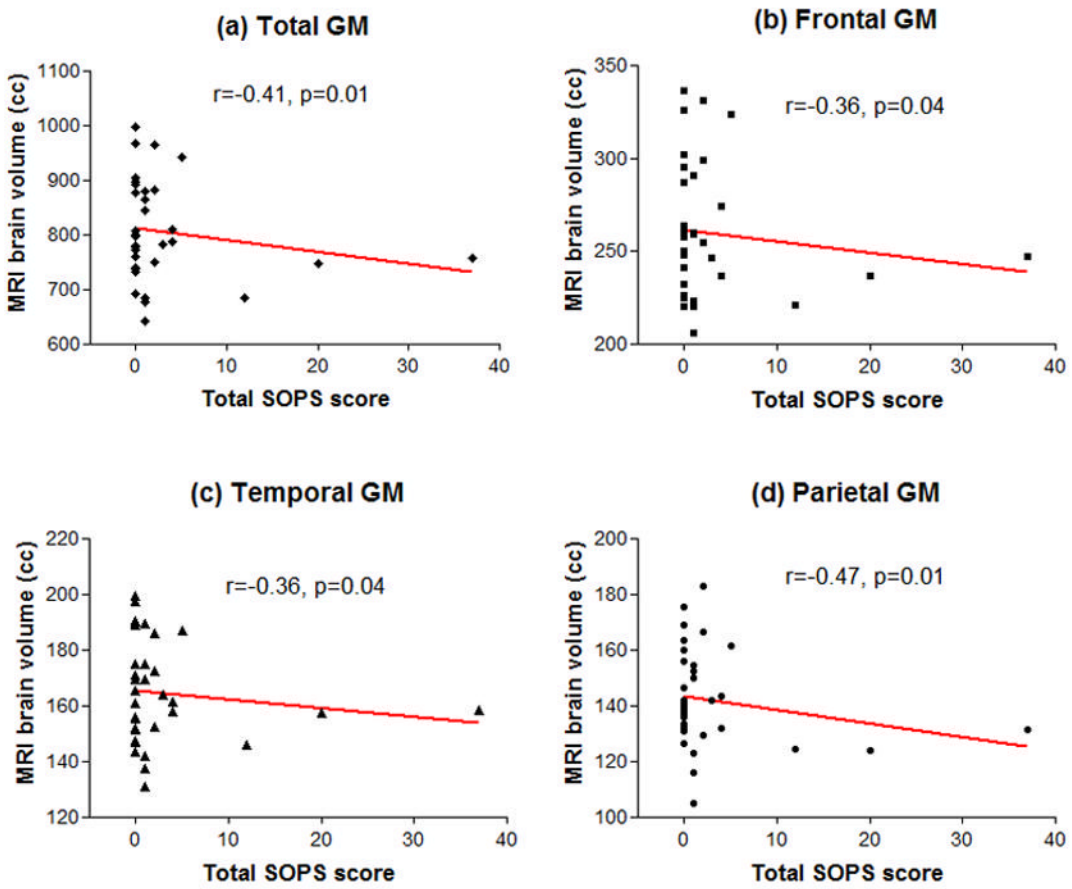

Figure 2.

Relationships between initial MRI brain gray matter (GM) volumes and severity of subsequent prodromal symptoms (total score on the Scale of Prodromal Symptoms): (a) Total whole brain GM (b) Frontal Lobe GM (c) Temporal Lobe GM (d) Parietal Lobe GM

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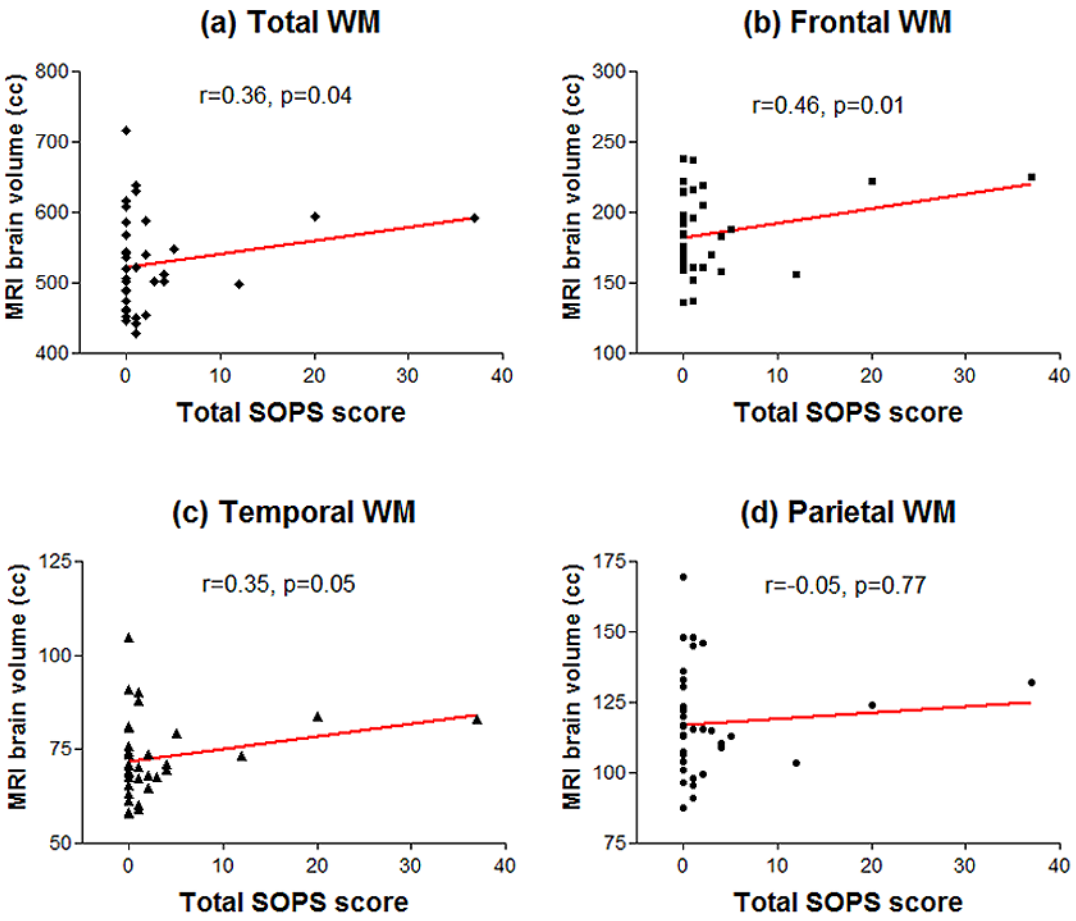

Figure 3.
Relationships between initial MRI brain white matter (WM) volumes and severity of subsequent prodromal symptoms (total score on the Scale of Prodromal Symptoms): (a) Total whole brain WM (b) Frontal Lobe WM (c) Temporal Lobe WM (d) Parietal Lobe WM

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Table 1

Family studies of magnetic resonance imaging brain volumes in schizophrenia grouped into studies involving young relatives who are still within age range at-risk for developing schizophrenia versus older relatives

Young Relatives	Older Relatives
(Keshavan et al. 1997)	(Suddath et al. 1990)
(Lawrie et al. 1999)	(Noga et al. 1996)
(Schreiber et al. 1999)	(Seidman et al. 1997)
(Lawrie et al. 2001)	(Cannon et al. 1998)
(Keshavan et al. 2002a)	(Staal et al. 1998)
(Lawrie et al. 2002)	(Seidman et al. 1999)
(Gogtay et al. 2003)	(Sharma et al. 1999)
(Job et al. 2003)	(Dickerson et al. 1999)
(Rajarethinam et al. 2004)	(Chua et al. 2000)
(Job et al. 2005a)	(Staal et al. 2000)
(Job et al. 2006)	(O'Driscoll et al. 2001)
(DeLisi et al. 2006)	(Vogeley et al. 2001)
	(Baare et al. 2001)
	(Cannon et al. 2002)
	(Harris et al. 2002)
	(McDonald et al. 2002)
	(Seidman et al. 2002)
	(Steel et al. 2002)
	(Van Erp et al. 2002)
	(Marcelis et al. 2003)
	(Schulze et al. 2003)
	(Tepest et al. 2003)
	(McIntosh et al. 2004)
	(McIntosh et al. 2005)
	(McDonald et al. 2006)
	(McIntosh et al. 2006)
	(Schneider-Axmann et al. 2006)
	(Goghari et al. 2007)

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Table 2

Comparison of MRI primary brain regions of interest (least square mean volumes (SD)) between control subjects with no family history of schizophrenia, relatives of schizophrenia probands and schizophrenia patients

Primary Regions of Interest	Controls (N=46)	Relatives (N=46)	Patients (N=46)	Group [a] $F_{2,137}$ (p)	Pair-wise Group Comparison [b] T_{90} (p)		
					Relatives v Controls	Relatives v Patients	Controls v Patients
Whole Brain Gray Matter	802.8 (32.5)	790.0 (33.5)	762.7 (37.2)	15.68 (<.0001)	.08	.0003	<.0001
Whole Brain White Matter	499.2 (31.8)	515.8 (29.0)	517.7 (35.7)	4.45 (.01)	.02	.79	.008
Whole Brain CSF	89.9 (32.0)	85.1 (32.1)	110.6 (35.0)	7.58 (.0008)	.58	.0005	.002
Lateral ventricles	11.8 (4.4)	11.9 (7.4)	16.8 (7.9)	7.79 (.0006)	.90	.001	.0006

[a] Main effects of group membership (covariates of intracranial volume, age and gender)

[b] Independent sample t-tests

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Table 3

Comparison of MRI secondary brain regions of interest (least square mean volumes (SD)) between control subjects with no family history of schizophrenia, relatives of schizophrenia probands and schizophrenia patients

Secondary Regions of Interest	Controls (N=46)	Relatives (N=46)	Patients (N=46)	Group [a] $F_{2,137}$ (p)	Pair-wise Group Comparison [b] T_{90} (p)		
					Relatives v Controls	Relatives v Patients	Controls v Patients
Lobar Gray Matter							
Frontal	261.0 (14.9)	253.8 (16.2)	240.1 (17.3)	19.20 (<.0001)	.04	.0001	<.0001
Temporal	164.3 (6.8)	162.1 (7.0)	155.7 (8.6)	15.75 (<.0001)	.17	.0001	<.0001
Parietal	139.0 (8.5)	138.6 (7.7)	131.2 (8.3)	12.67 (<.0001)	.80	<.0001	<.0001
Occipital	74.2 (6.9)	72.6 (6.3)	71.4 (6.4)	2.05 (.13)	.24	.42	.05
Lobar White Matter							
Frontal	178.5 (15.4)	180.6 (15.2)	182.6 (17.0)	0.65 (.52)	.52	.59	.23
Temporal	69.9 (7.1)	71.5 (5.2)	73.9 (6.3)	4.59 (.01)	.23	.08	.003
Parietal	109.9 (8.7)	116.0 (9.8)	114.6 (9.0)	5.47 (.005)	.002	.46	.02
Occipital	46.1 (5.0)	48.0 (4.7)	48.8 (5.4)	3.30 (.04)	.08	.48	.01

[a] Main effects of group membership (covariates of intracranial volume, age and gender)

[b] Independent sample t-tests