Published in final edited form as:
Biol Psychiatry. 2008 March 1; 63(5): 465–474.

Is Gray Matter Volume an Intermediate Phenotype for Schizophrenia? A VBM Study of Patients with Schizophrenia and their Healthy Siblings

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Abstract

Objective: Shared neuropathological characteristics of patients with schizophrenia and their siblings may represent intermediate phenotypes that could be used to investigate genetic susceptibility to the illness. We sought to discover previously unidentified gray matter volume differences in patients with schizophrenia and their siblings using optimized Voxel-Based Morphometry (VBM).

Methods: We studied 169 patients with schizophrenia, 213 of their unaffected siblings, and 212 healthy volunteers from the CBDB/NIMH Genetic Study of Schizophrenia with magnetic resonance imaging (MRI).

Results: Patients with schizophrenia had significant regional gray matter decreases in the frontal, temporal, and parietal cortices compared with healthy volunteers. Their unaffected siblings tended to share gray matter decreases in the medial frontal, superior temporal and insular cortices, but these decreases were not significant after correction for multiple comparisons, even when we looked at a subgroup of siblings with a past history of mood disorder. As an exploratory analysis, we estimated heritability using regions of interest from the VBM analysis, as well as from the hippocampus. Hippocampal volume was significantly correlated within sibling-pairs.

Conclusions: Our findings confirm and extend previous VBM analyses in ill subjects with schizophrenia. Furthermore, these data argue that while siblings may share some regional gray matter decreases with their affected siblings, the pattern of regional differences may be a weak intermediate phenotype for schizophrenia.

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Financial Disclosures: The authors report no competing interests.

INTRODUCTION

A number of risk factors have been implicated in schizophrenia, including family history, lower social class, perinatal and other early developmental insults, and substance abuse (1). Amongst these, family history remains one of the strongest, with an estimated heritability of almost 80% (2). Deviations in brain morphology potentially reflecting genetic risk have been ubiquitous in the literature. Quantitative measures of brain structure using various neuroimaging techniques have a long history as putative intermediate phenotypes (3). Past twin studies have explored the heritability of this phenotype; a process that entails measuring the proportion of variation in this trait (i.e. brain structure) attributable to genetic variation.

The first neuroimaging study to investigate a familial intermediate phenotype of schizophrenia found an increased ventricle to brain ratio (VBR) in patients and their siblings (4). Since then, many twin studies have explored the putative heritability of brain structure using intraclass correlation (ICC), reporting high heritability estimates for total brain volume (94%) (5;6) and lateral ventricular volume (82-85%) (7). Studies of twins discordant for schizophrenia have also found liability-related gray matter volume decreases in whole brain gray matter and frontal lobes (8), polar frontal and dorsolateral prefrontal (DLPFC) (9;10), medial temporal (i.e., the hippocampus) (8;11;12), left medial frontal, and left sensory motor cortices (13), as well as liability-related white matter increases in the orbitofrontal cortex (13). The twin literature in schizophrenia points primarily to a variety of gray matter structural changes that may be heritable.

Investigating non-twin, healthy first-degree relatives represents a complementary approach to formal measures of heritability obtained in twin studies. Siblings who do not have schizophrenia or schizophrenia-spectrum disorder are considered ‘unaffected.’ These studies do not have the power to discern genetic from environmental risk factors as do twin studies, though advantageously lack potential confounders related to the intrauterine disadvantages of MZ twins (14). Region of interest studies have shown that first degree relatives may share regional brain volume abnormalities with their sick siblings in the amygdala-hippocampal complex, thalamus, and the temporal cortices (15-17).

Upon a background of complex and often contradictory structural findings within the volumetric literature, voxel-based morphometry (VBM) offers promise of clarifying the structural deficits in schizophrenia. Voxel-based morphometry performs voxel-wise comparisons of gray and white matter probabilities between groups of subjects. More recent studies have implemented ‘optimized VBM;’ a method described by Good and colleagues (18). A recent review of VBM findings in schizophrenia identified gray matter decreases in the superior temporal, medial temporal, inferior frontal, and medial frontal cortices plus the thalamus as regions most commonly reported to be abnormal, amidst a complex literature (19). The literature is still relatively small, though, and replications are needed to clarify these decreases.

VBM studies of unaffected siblings of patients with schizophrenia, or those at particularly high risk based on genetic background, have had with mixed findings of gray matter deficits (20-23). Borgwardt et. al. found that individuals at high risk who later developed psychosis had reduced gray matter in the right insula, inferior frontal, and superior temporal gyrus compared to those that remained healthy (22). Job et al (2003) report bilateral reductions in the anterior cingulate cortex in first episode patients compared with high risk individuals (20). Job et al (2005) reported density differences in the left temporal cortex and cerebellum over time, but no predictive effects at baseline (21). McIntosh and colleagues (23) found that liability for schizophrenia was related to volume decreases in the VLPFC and DLPFC. Summarizing across these ‘sibling’ VBM studies, the prefrontal and temporal cortices

(primarily the superior temporal gyrus), hippocampus, insula, and cerebellum are regions that may be represent candidate targets for structural intermediate phenotypes in schizophrenia.

To date there has not been an optimized VBM study on a large group of patients with schizophrenia and their first degree/ unaffected siblings. In the present study, we investigated the hypothesis that genetic risk would be reflected in gray matter volume decreases in unaffected siblings. We used optimized VBM to evaluate structural MRI data from the CBDB/ NIMH Genetic Study of Schizophrenia, an ongoing family study aimed at identifying biologic intermediate phenotypes and ultimately risk genes for the illness (24). Based on findings in twins discordant for schizophrenia, we hypothesized that gray matter changes in patients and corresponding but less significant changes in siblings would be identified primarily in the frontal and temporal cortex and medial temporal regions (6;13). We also asked whether there were significant gray matter differences between a subgroup unaffected siblings with a history of mood disorder, namely depression (which made up 27.7% of our sample), and those that had no history of personality or mood disorder at all. In addition, we sought to further clarify the nature of these volume changes in patients and the whole group of siblings in relation to genetic risk by calculating heritability for sibling pairs (one unaffected and one affected), using volumes from the regions of interest identified by the VBM analysis, as well as the hippocampus, based on previous studies implicating this region in liability for schizophrenia (25).

METHODS

Subjects

All subjects were recruited as part of the CBDB/NIMH Genetic Study of Schizophrenia [NIH Study ID NCT00001486] described in detail elsewhere (26). In brief, subjects included 169 patients with schizophrenia-spectrum disorders (SCZ), 213 of their unaffected siblings (SIB), and 212 healthy volunteers (i.e. normal controls, or NC) (Table 1). All patients were on antipsychotic medications at the timing of scan acquisition. Exclusionary criteria for the Sibling Study is described in detail elsewhere (26). Patients were included if they had a schizophrenia spectrum disorder, which included patients with schizophrenia, schizoaffective disorder, Psychosis NOS, or schizoid personality disorder (see supplementary material, Table 1). Siblings were included if they had a past history of mood (~ 37 %) or personality (5 %) disorder, leaving a majority with no history (~ 58%). Subjects were excluded if they had a past history of drug or alcohol abuse. Medication and family representation are detailed in supplemental material. All scans from subjects with available, usable structural imaging data free of visible artifact, distortion, incomplete acquisition, or evidence of neurological abnormality, were processed for the whole-brain VBM analysis. Differences in demographic means between each diagnostic group were tested using an ANOVA in SPSS version 13.0 (27) (Table 1).

Structural image processing and analyses

Image acquisition and data processing software have been described in previous studies from this group (28). Customized template creation was based on a sample of 100 healthy volunteers, 100 unaffected siblings, and 100 patients with schizophrenia or schizoaffective disorder taken from our study sample. They were matched for age (NC mean = 35.6 (± standard deviation 9.97), SIB = 36.27(±9.17), SCZ = 36.18 (±9.54); $p>.05$).

We used optimized VBM performed in SPM2, including the non-uniformity correction option (18;29). Modulated images were smoothed using a 6mm FWHM isotropic Gaussian kernel for the small volume extractions for ICC calculation, and 10mm for the whole brain VBM analysis. We used a smaller smoothing kernel for the ICC calculation so that the extracted regions would better represent the gray matter volume present in that region.

The images were analyzed using the General Linear Model as implemented in SPM2. For the across-group analysis, we used an analysis of covariance model with diagnostic group as factor, age, gender, and IQ as covariates of interest, and total gray matter volume and second-order polynomial age expansions as covariates of no interest. Voxel-by-voxel t-tests were computed across the whole brain to determine global differences in gray matter volumes based on diagnosis, contrasting SCZ vs. NC, SCZ vs. SIB, and SIB vs. NC. In addition, we examined sibling subgroups broken down by past history of a major depressive episode since this represented the largest uniform diagnostic subgroup (SIBpast, n = 44) and those with no past history (SIBnopast, n = 128). Both SIBpast and SIBnopast were contrasted with SCZ and NC. Significant voxels (thresholded at .05 FWE corrected, cluster (k) > 5 contiguous voxels) are reported in Talairach spaceas in prior reports (30).

We masked the gray matter decreases of SIB vs. NC with SCZ vs. NC to identify overlap in voxel-wise variation in gray matter. This method identifies voxels that are significantly different in both contrasts (NC>SIB, NC>SCZ) ($p< 0.001$ uncorrected), i.e. a conjunction analysis. Since the findings from the NC>SIB analysis were seen only at the exploratory threshold of $p<.001$ uncorrected, we used that threshold for the conjunction analysis. We then extracted regional volume measures from this masked analysis using a 2mm sphere around the peak voxels and plotted the regional gray matter volumes across diagnosis to visualize the distribution across the three groups.

Finally, gray matter volumes from these regions as well as the hippocampus were extracted from the 6mm smoothed gray matter images in patients and their unaffected sibling pair using automatic ROI's from the Wakeforest University Pickatlas (WFU) (www.fmri.wfubmc.edu) (31). In addition we extracted volumes from Brodmann's area 17 to serve as a negative control for an intermediate phenotype, as gray matter volume in patients and unaffected siblings has not been identified as abnormal in this region by previous VBM studies (19). For ICC calculations, data from 116 sibling pairs were imported into Statistica 6 for Windows (http://www.statsoft.com/) and analyzed using the Variance Components and Mixed Model ANOVA module, with a significance level of $p<.05$ (for more detail, see supplemental material).

To test for confounds of drug ingestion in patients, we did a post-hoc analysis to look at medication effects on brain structure. We ran a multiple regression with a constant in SPM2 in the patients that had chlorpromazine equivalents (n = 79), regressing out effects of age, gender, years of education, mean gray matter volume, and IQ and testing for a linear relationship between medication and regional gray matter volume.

RESULTS

We first contrasted gray matter in SCZ vs. NC using an ANCOVA. A widespread distribution of significant gray matter decreases was found in patients compared with healthy volunteers (FWE $p<.05$, cluster size > 5) (Table 2, Figure 1). The most robust differences in regional gray matter were observed in the superior and inferior frontal, the medial prefrontal, the insular, left superior temporal, and the inferior parietal cortices, the medial thalamus and the posterior cerebellum. There were also increases in gray matter in SCZ compared with NC in the medial cerebellum, globus pallidus, left inferior temporal cortex, right middle temporal gyrus, left precentral gyrus, left anterior cingulate, and orbitofrontal cortex (Table 3).

The ANCOVA comparing SCZ vs. SIB revealed significant gray matter decreases in the patients when compared to their healthy siblings (FWE $p<.05$) (Table 4, Figure 1). These decreases in patients were in the fronto-polar cortex (superior and middle frontal gyri, BA 10), inferior frontal gyrus, right pre- and post-central gyrus, left middle temporal gyrus, right medial

parietal cortex, left prestriate cortex, right ventrolateral nucleus of the thalamus and the right ventral cerebellum. In addition, the ANCOVA comparing SCZ vs. SIBnopast revealed similar significant gray matter decreases in the patients, namely in the left and right superior and middle frontal gyri (BA 9 and 10), left inferior frontal gyrus (BA 45), and the right ventrolateral nucleus of the thalamus. Peaks unique to this subgroup with no past psychiatric history were in the left insula, right superior temporal gyrus (BA 22) and right parietal cortex (BA 40) (Table 4). The ANCOVA comparing SCZ vs. SIBpast revealed similar frontal cortical regions as the combined group and the no past depression group, with the addition of left and right BA 46, the left middle frontal gyrus (BA 6), the right precentral gyrus (BA 6), the right thalamus, and the right superior temporal gyrus (BA 22) (Table 4). In all three analyses the patients had two large clusters of increased gray matter in the cerebellum (bilateral culmen, $p<.001$ FWE, k=40,690, 28, −53, −38), and the left lateral globus pallidus (lentiform nucleus, $p<.000$ FWE, k=9,661, −18, −3 −3) compared to the unaffected siblings.

The ANCOVA comparing SIB vs. NC revealed several focal gray matter decreases in the SIB when compared to NC, but these did not survive correction across the whole brain. At an exploratory threshold ($p<.001$, uncorrected) (Table 2), these decreases were in the medial frontal cortex, the right anterior cingulate, the inferior temporal gyrus, the parahippocampal gyrus, right hippocampus, left putamen, and left cerebellum. The ANCOVA comparing SIBpast vs. NC revealed no suprathreshold voxels for increases or decreases, even at an uncorrected threshold at $p<.001$. The ANCOVA comparing SIBnopast vs. NC resulted in the same clusters listed from the SIB vs. NC analysis above, such that there was no significant contribution of mood disorder history on the gray matter decreases compared with healthy controls. SIBs had increased gray matter compared to NC at an exploratory threshold ($p<.001$, uncorrected) in the right inferior frontal cortex (BA 45 and BA 9), right parahippocampal gyrus, right inferior frontal gyrus, and right precuneus (Table 3).

The masked analysis revealed regions that were commonly decreased in the SCZ and SIB when compared with NC (Table 2, Figure 1). These were the left medial frontal polar cortex, paracingulate cortex, left inferior frontal gyrus, left insula, and left superior temporal gyrus. The most significant differences lay in the left medial frontal gyrus, left insula, and left superior temporal gyrus. These volumes were extracted as described and plotted in Figure 2.

The ICC calculations within gray matter regions of interest, as well as calculated p-values are listed in Table 5. The left hippocampus, right hippocampus, and bilateral hippocampus had significant intra-class correlation coefficients within sib-pairs. The three regions implicated in the masked analysis were not significantly correlated within sib-pairs. In addition, the ICC analysis was not significant within Brodmann's area 17.

DISCUSSION

We report the results of the largest optimized VBM study to our knowledge addressing gray matter changes in patients with schizophrenia (and related psychoses) and their siblings. Our findings confirm previous VBM analyses of gray matter in patients with schizophrenia. The analysis of siblings compared with healthy controls revealed trends for decreases and increases in the siblings. The masked analysis showed some shared gray matter decreases between patients and their unaffected siblings in the left medial frontal, left superior temporal, and left insular cortices. In our analysis of heritability, we found these three regions were not significantly correlated within the 116 sibling pairs. Interestingly, when we calculated ICCs for the hippocampal region in an exploratory analysis, we found significant correlations within sibling pairs. In general, brain structure is highly heritable and siblings may share regional gray matter variation (4;5;9), however it is difficult to determine how much of this is genetically mediated by risk genes for schizophrenia.

Gray Matter Changes Specific to Schizophrenia

Our ANCOVA comparing patients with schizophrenia to healthy volunteers was largely consistent with previous VBM (19) and ROI studies (32). Patients with schizophrenia had highly significant decreases in the frontal cortex, primarily the bilateral medial frontal cortex and inferior frontal gyri, consistent with other VBM studies (19). Frontal cortex ROI analyses have shown similar evidence for gray matter volume changes in the prefrontal and medial frontal cortices (32). There were significant insular decreases in patients with schizophrenia, consistent with studies showing volume changes in the insula (33-36). These data may support a re-evaluation of the role the insula may play in schizophrenia, though this region may be subject to artifact in VBM previously mentioned.

Patients with schizophrenia also had significant decreases in the medial thalamus and pulvinar compared to the healthy volunteers, consistent with some (37;38), but not all previous reports (39-41). This discrepancy may be caused by issues specific to imaging (39). for instance lack of sensitivity in this region and tissue classification issues (40). Smaller changes have been reported in the post-mortem brain (42), though not replicated in others (43), making it a difficult finding to interpret in schizophrenia.

We found significantly decreased gray matter volume in the superior and middle temporal gyri, but not in the medial temporal gyri. Decreased volume in the superior temporal gyrus is one of the most consistently found morphometric abnormalities in patients with schizophrenia (44-46) and has been found both in ROI (32) and a majority, but not all VBM studies (19; 34). Our study did not reveal grossly abnormal volume in the hippocampus of patients with schizophrenia. Findings of abnormality in the medial temporal cortex extend from VBM studies (reviewed by (19)) to manually drawn ROI analyses on MRI (reviewed by (32)), post-mortem studies (reviewed by (47)), and genetic studies (reviewed by (48)). While found more often in MRI studies (49) than in postmortem studies (47), hippocampal volume decrease in patients is not the only region were such discrepancies exist (50), and a lack of decreased gross volume does not exclude abnormalities at the subcellular level in patients. To clarify whether diagnostic subtype affected this finding (51), we performed an analysis looking at gray matter variation in a subgroup of patients with only schizophrenia compared with those that had broader spectrum psychosis, and found no significant differences in the results, or a finding of hippocampal decrease in these subgroups (data available upon request). We also found no relationship between gray matter volume and chlorpromazine equivalent dosage (see supplemental material). It is likely that our lack of finding of hippocampal decrease is due to methodological limitations; especially considering that another overlapping analysis, using subcortical segmentation, did find hippocampal volume decreases (Goldman et al., in submission).

The most significant region in which patients had increased gray matter relative to the controls was the bilateral globus pallidus. Other regions of increased gray matter are discussed more in detail in supplemental material. Enlargement of basal ganglia volumes in patients with schizophrenia was originally described in MRI studies by DeLisi et al and Jernigan et al in 1991 (52), and may vary with antipsychotic drug treatment. This is inconclusive in post-mortem studies (53; 54). However, most MRI studies have found increased caudate volumes in patients with schizophrenia (reviewed in (32)). Some have concluded that such changes reflect an iatrogenic effect of antipsychotic treatment (55). Data from our group would suggest the same (see Goldman et al. in submission).

Gray Matter Changes Specific to Siblings

Overall, the gray matter decreases in the unaffected siblings when compared with healthy controls were small compared to differences found in their affected siblings. No regions were

significantly increased or decreased (FWE). Some studies looking at genetic liability for schizophrenia have failed to find any differences in healthy relatives of patients, though their samples have been smaller (56;57). Overall, the regions in which we see tendencies for volume decreases in unaffected siblings are qualitatively consistent with the liability literature (9;58). For instance, findings of decreased gray matter in the superior temporal gyrus and medial frontal cortex have been found in both studies of high risk subjects that later transitioned to schizophrenia (22), unaffected siblings (59), and siblings from multiply-affected families (58). The anterior cingulate and medial frontal cortex have also been reported to be decreased in the Edinburg high risk group (20). Temporal lobe decreases have been reported from density measurements in those at risk for schizophrenia (21), as well as volume decreases in siblings with fetal hypoxia (17), the latter demonstrating possible gene-environment interactions affecting the temporal cortices. Our sibling group had medial temporal lobe decreases in the parahippocampal and hippocampal cortices. The hippocampus and hippocampalamygdala complex have been reported to be a vulnerability indicator for schizophrenia (15;16). In addition, the insula has been reported to be decreased in subjects at high risk (22). Our unaffected siblings also had trends for decreases in the cerebellum compared to controls, similar to Job et al., 2005 (21). In general, our sibling decreases are supported by the liability literature, but should be interpreted with caution in light of the lack of significance.

There were unique gray matter volume increases that reached a trend for significance ($p < .001$ uncorrected, $k > 5$) in the right inferior frontal cortex, with clusters in BA 9 and BA 45, as well as a small region in the right parahippocampal gyrus, the right inferior temporal gyrus, and the right precuneus. In support of our findings, increases of bilateral parahippocampal gyrus volume (60) and temporal lobe volumes (though middle temporal) have been reported in unaffected relatives of schizophrenia (59). The largest increases compared with healthy controls were in BA 9 and BA 46 in the right inferior frontal cortex. These regions were also significantly increased ($p < .05$ FWE corrected) when compared with patients with schizophrenia, in the combined group, as well as the past history and no past history subgroups (Table 4). More regional decreases in the prefrontal cortex have been reported in siblings in one study (23), though overall frontal lobe decreases are more common (reviewed in (61)). Increased gray matter in siblings or high-risk subjects compared to healthy controls are measures not always reported in liability studies (9;57), though Seidman et al. (1977) found increased cerebral volume in a small group of relatives (62). These increases could represent a protective or compensatory phenomenon in unaffected family members, though this is highly speculative.

Sibling and Patient overlap: ICC Analysis

Our masked analysis revealed that there were shared gray matter decreases in the left superior temporal gyrus, left medial frontal gyrus, and left insula between siblings and patients, but these were not significant. We extracted these regions and calculated ICC, but they were not significantly correlated between sibling pairs. Cortical gray matter variations in these regions, at least as measured by optimized VBM, may be only weakly related to genetic risk for schizophrenia. If the volumes of these regions are affected by genetic factors, other factors would seem to be obscuring these effects. For example, future studies could investigate other cortical regions of interest in unaffected non-twin siblings.

There is an apparent conundrum presented by the competing observations of increased gray matter volume in our three regions (SIB > SCZ) against non-significant ICC in the setting of smaller areas of shared gray matter reductions (NC > SIB, SCZ). We think this is an important issue to address, because an exploratory analysis using λ_s suggests significant familiality in these three regions (data upon request). Hopefully, future experiments using some combined methodological approach to heritability and a larger sample may solve this paradox.

Sibling and Patient overlap: ICC Analysis within the Hippocampus

The hippocampus had significant heritability values between sibling pairs, arguing for genetic effects on the volume of this region. Hippocampal volume changes measured with MRI are not specific to schizophrenia, as they are also seen in dementia (63;64), depression (65;66), and post-traumatic stress disorder (67;68). However, several "risk" genes for schizophrenia have been shown to affect hippocampal structure (28;30). Moreover, the hippocampus has been tagged as a key region under genetic control from various family studies (15;25), though a recent imaging study of monozygotic twins did not find liability related density changes in the limbic cortex (13). Despite this, the significant ICC values for sibling pairs reported here may still reflect heritability of gray matter volume in the hippocampus, though we are not able to measure whether or not this heritability is related to schizophrenia and can only posit such relationship based on other studies showing similar results in twins (8;12).

Limitations

There are limitations to VBM, including sensitivity to methodological choices in normalization, smoothing kernel and template (29;69). In this study, we paid close attention to these issues, using a custom template which could for instance reduce ventricle-related artifact. However, the size of the smoothing kernel can affect which results reach significance, and while we attempted to choose a moderate kernel, it may have contributed to false-negatives, especially in the sibling group as the findings might be expected to be small relative those of patients verses controls. Further discussion of study limitations is included as supplemental material.

Conclusions

Our whole brain VBM study replicated previous work showing regional gray matter volume abnormalities in patients with schizophrenia compared with healthy volunteers. Furthermore, our evaluation of gray matter volume in sibling pairs demonstrated that while some areas appear heritable (e.g., the hippocampus), others do not share as much gray matter variation as one might expect (e.g., the superior temporal gyrus, medial frontal gyrus and the insula). While evidence for functional brain neuroimaging intermediate phenotypes have been found within the frontal and temporal cortices (25;70), gray matter regional volume changes may not fully characterize the deficit to make it an intermediate phenotype for schizophrenia, or they may simply be in very specific regions. Possible explanations for this discrepancy include strong environmental factors impacting on these regional gray matter changes or the influence of compensatory mechanisms. After all, unaffected siblings, while not always free of major mental illness, remain free of schizophrenia. Their affected siblings, on the other hand, experience factors that could impact on measures of brain volume that are related to clinical state (i.e. antipsychotic medication, metabolic and nutritional factors, or smoking). Further investigation using healthy sibling pairs or twins may prove useful for the identification and clarification of structural intermediate phenotypes in schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the staff of the Clinical Brain Disorders Branch Sibling Study of Schizophrenia and all participating families. We thank M. Weirich and staff for subject recruitment. In addition, we wish to thank Aaron Goldman and Brad Zoltick for contributions relating to the structural archive, and Joshua W. Buckholtz for helpful comments during manuscript preparation. This work was supported by grants from the NIMH intramural program.

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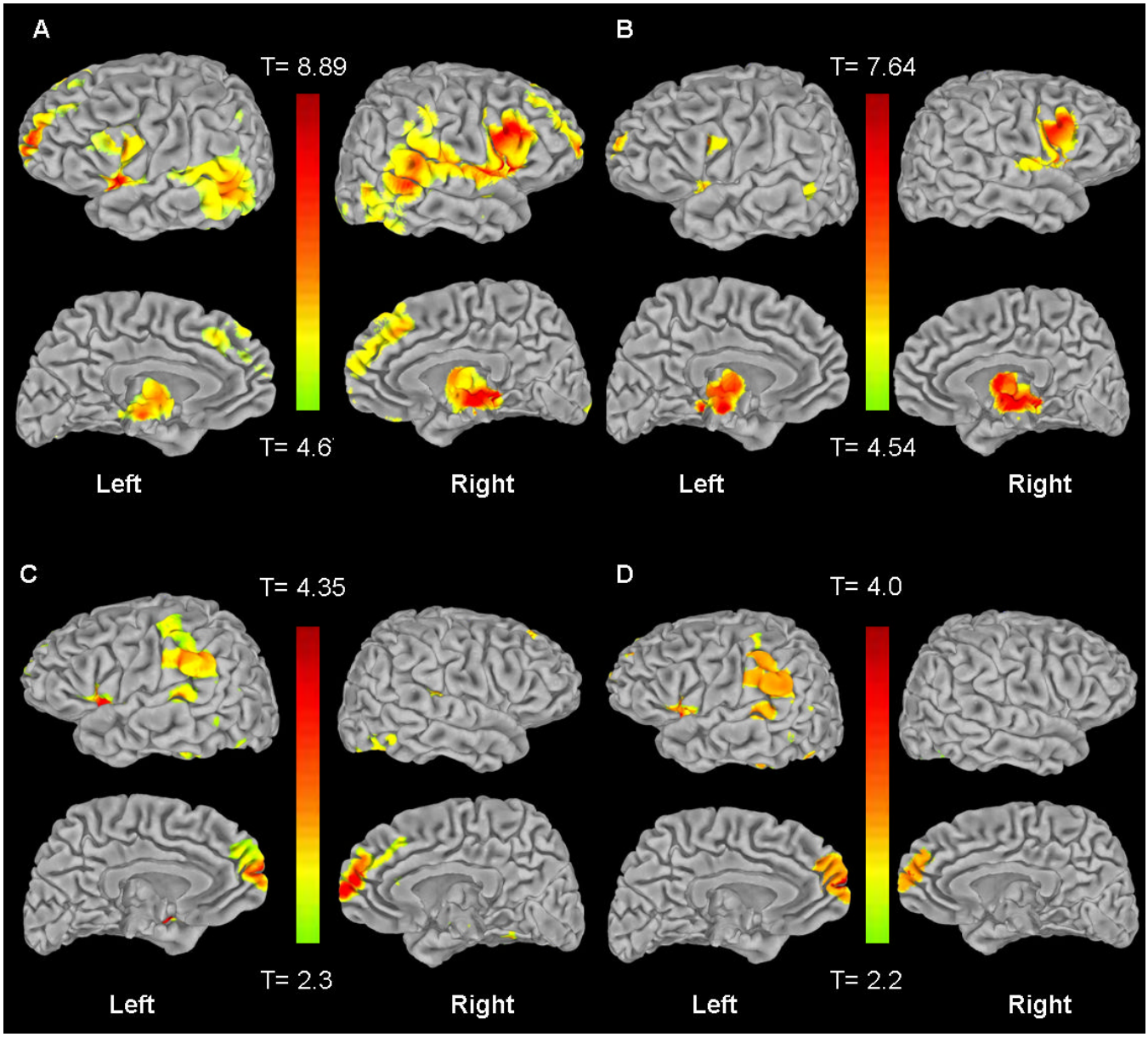

Figure 1.

Statistical maps of the entire brain showing gray matter volume reductions in: A. SCZ compared with NC (at a threshold of p<.05 FWE corrected, cluster size > 5), B. SCZ compared to SIB (at a threshold of p<.05 FWE corrected, cluster size > 5), C. SIB compared with NC (at a threshold of p<.001 uncorrected, cluster size > 5),. D. SIB compared with NC, only results that overlap with SCZ are shown (at a threshold of p<.001 uncorrected, cluster size >5, small volume corrected with patient decreases). Thresholded images have been transformed from MNI space into Talairach space and converted to T-scores, which were projected onto the pial surface of a representative standard surface ; the range is shown in the corresponding color bars. The lateral surface is in the top row of each section, and the medial surface is shown below the lateral.

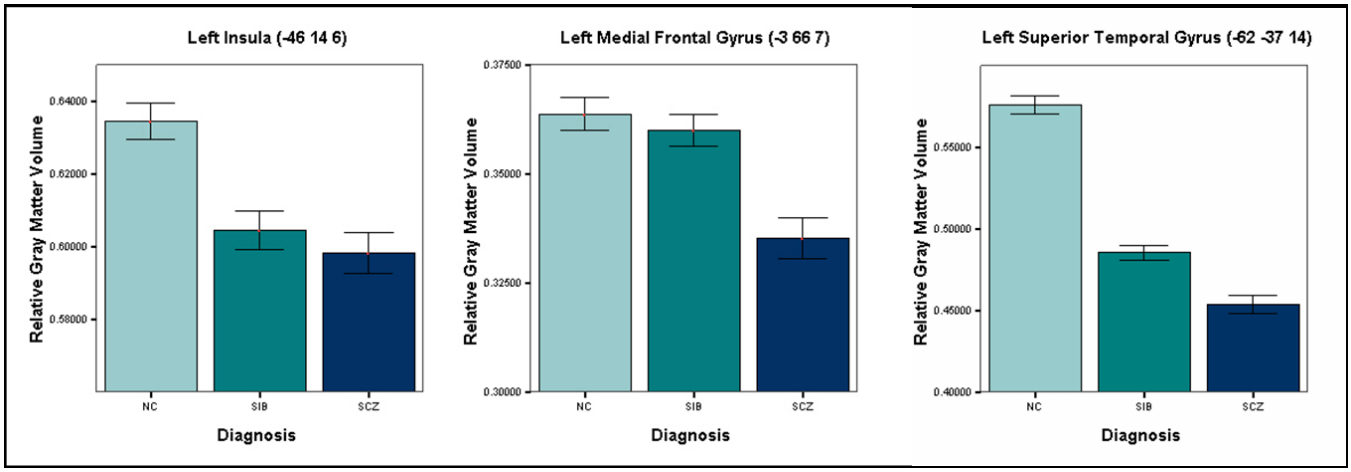

Figure 2.

Mean differences in regional gray matter volume in regions identified by the masked analysis. The left insula, left medial temporal gyrus, and left superior temporal gyrus (sphere of 2mm around listed coordinate) were decreased in SCZ compared with NC, were decreased in SIB compared to NC, and were decreased in SCZ relative to SIB ($p<.001$, all p values at voxel level, uncorrected, 1 standard error shown with the error bars). Measures for regional volume have been extracted from the significant cluster and transformed into percentage volume relative to class total gray matter, while controlling for confounding variables such as age and gender.

Table 1

Group demographics for VBM Analysis

Demographics (Means +/− SD) **Variable**	**SCZ (n=169)**	**SIB (n=213)**	**NC (n=212)**	**NC vs. SCZ**	**SCZ vs. SIB**	**NC vs. SIB**
Age	(36.39, 9.46)	(36.5, 9.75)	(33.31, 9.86)	0.00*	0.88	0.00*
Gender (% male)	78.2%	41.8%	48.6%	0.00*	0.00*	0.18
Education (years)	(14.41, 2.23)	(16, 2.48)	(16.89, 2.82)	0.00*	0.00*	0.00*
Mean WAIS-full scale IQ	(94.89, 11.18)	(106.4, 12.73)	(107.69, 11.72)	0.00*	0.00*	0.28
Handedness	(71.09, 57)	(73.36, 54.65)	(78.25, 49.58)	0.09	0.45	0.33
Relative Gray matter volume (mm^3)	(0.73, .06)	(0.73, .06)	(0.74, 0.06)	0.08	0.9	0.09
Positive Syndrome Score	(12.79, 5.69)	(7.06, .32)	(7.06, .35)	0.00*	0.00*	0.89
Negative Syndrome Score	(19.52, 9.40)	(8.45, 3.46)	(8.14, 2.8)	0.00*	0.00*	0.33
No Past or Present Diagnosis	0%	57.80%	85.40%			

* Significant at p<.05 in ANOVA comparison of means, SPSS

Table 2

Summary of the results obtained by voxel-wise wtatistical analysis of the GM Maps of decreases in SCZ and SIB compared with NC. Only the peak voxels are listed. Left is defined as “L” and Right is defined as “R”.

Patients with Schizophrenia (Significant at .05 FWE corrected, cluster size > 5)										**Sibling**										**Sibling- Masked with SCZ decreases at FEW corrected, P<.05**									
Anatomical Region	**MNI Label for peaks**	**FWE[a]**	**FDR**	**T**	**Z**	**p**	**x**	**y**	**z**	**MNI Label for peaks**	**FEW**	**FDR**	**T**	**Z**	**p[a]**	**x**	**y**	**z**	**MNI Label for peaks**	**FEW**	**FDR**	**T**	**Z**	**p[a]**	**x**	**y**	**z**
Medial Frontal Cortex	L Frontal Pole	0.000	0.000	7.89	7.58	0.000	-28	62	13	Medial Frontal Pole	0.995	0.124	2.60	2.79	0.003	0	65	-5	L Medial Frontal Gyrus, BA 10	0.055	0.120	3.88	3.84	0.000	-3	66	7
	R Superior Frontal Gyrus	0.000	0.000	6.56	6.38	0.000	30	63	1	R Anterior Cingulate	1.000	0.211	2.43	2.42	0.008	1	29	14	R Paracingulate sulcus	0.326	0.120	3.28	3.26	0.001	1	60	9
	L Medial Frontal Gyrus, BA9	0.000	0.000	6.01	5.87	0.000	-2	52	41																			
	L Medial Frontal Gyrus, BA6	0.000	0.000	5.97	5.83	0.000	-4	35	40																			
	R Medial Frontal Gyrus	0.000	0.000	5.79	5.66	0.000	7	47	50																			
	L Medial Frontal Gyrus, BA10	0.013	0.000	4.89	4.82	0.000	-2	65	9																			
	L Superior Frontal Gyrus	0.000	0.000	5.67	5.55	0.000	-17	42	49																			
Lateral Frontal Cortex	R Inferior Frontal Gyrus, BA 45	0.000	0.000	7.62	7.34	0.000	52	18	3										L Inferior Frontal Gyrus	0.283	0.120	3.34	3.31	0.000	-58	-46	-20
	R Inferior Frontal Gyrus	0.003	0.000	5.26	5.17	0.000	54	11	32																			
	R Postcentral Gyrus, BA2	0.003	0.000	5.25	5.15	0.000	58	-25	47																			
OrbitoFrontal Cortex	L Rectal Gyrus, BA11 (medial orbital)	0.001	0.000	5.52	5.41	0.000	-3	32	-26																			
Insular Cortex	L Insula	0.000	0.000	8.89	Inf	0.000	-41	13	-6										L Insula	0.166	0.120	3.53	3.51	0.000	-46	14	6
																			L Insula	0.189	0.120	3.49	3.46	0.000	-34	15	-6
Temporal Cortex	L Superior Temporal Gyrus	0.000	0.000	7.07	6.84	0.000	-60	-49	6	L Inferior Temporal Gyrus	0.350	0.022	3.74	3.71	0.000	-58	-46	-23	L Superior Temporal Gyrus	0.244	0.120	3.39	3.37	0.000	-64	-37	14
	L Fusiform Gyrus	0.001	0.000	5.54	5.42	0.000	-57	-48	-23	R Parahippocampal Gyrus	0.796	0.049	3.30	3.28	0.001	31	-51	-7									
	L Lingual Gyrus	0.011	0.000	4.93	4.85	0.000	-20	-84	-10	R Inferior Temporal Gyrus	0.883	0.062	3.19	3.17	0.001	48	-68	-17									
										L Parahippocampal Gyrus	0.901	0.065	3.16	3.14	0.001	-28	-58	-5									
Parietal Cortex	L Inferior Parietal Lobe	0.008	0.000	5.02	4.94	0.000	-48	-52	52																			
Occipital Cortex	R Middle Occipital Gyrus, BA19	0.000	0.000	5.88	5.75	0.000	54	-70	6																			
	L Inferior Occipital Gyrus, BA17	0.004	0.000	5.17	5.08	0.000	-18	-94	-16																			
	R Inferior Occipital Gyrus	0.006	0.000	5.10	5.01	0.000	23	-99	-4																			
Subcortical	R Thalamus	0.000	0.000	7.35	7.10	0.000	4	-20	-1	L Putamen	0.043	0.016	4.39	4.34	0.000	-31	-4	-7									
										R Hippocampus	0.997	0.133	2.77	2.76	0.003	45	-22	15									
Cerebellum	L Cerebellum (posterior, uvulva)	0.003	0.000	5.22	5.12	0.000	-32	-84	-36	L Cerebellum	0.933	0.074	3.09	3.07	0.001	-36	-76	-50									
	R Cerebellum(posterior)	0.009	0.000	4.99	4.91	0.000	35	-85	-35	L Cerebellum	0.999	0.160	2.63	2.62	0.004	-7	-85	-44									

[a] Statistical threshold used for inclusion. FWE-corrected for patient decreases and p- uncorrected for sibling and conjunction analysis.

Table 3

Summary of the results obtained by voxel-wise statistical analysis of the gray matter maps of increases in SCZ compared with NC listed rostal to caudal. Below that are results of the analysis of gray matter increases in SIB compared with NC. Patients results are significant ($p<.05$ FWE corrected, $k > 5$), and sibling results are not significant, trends shown at $p<.001$ uncorrected, $k > 5$ for comparison with their affected siblings.

Group	MNI Label	FWE	FDR	T	Z	p	x	y	z
SCZ	R Orbitofrontal Cortex	0.002	0.000	5.37	5.27	0.000	28	50	−7
	L Orbitofrontal Cortex	0.000	0.000	5.87	5.74	0.000	−16	40	−13
	R Orbitofrontal Cortex	0.001	0.000	5.56	5.44	0.000	18	38	−15
	Anterior Cingulate	0.000	0.000	5.85	5.72	0.000	−6	27	−5
	L Globus Pallidus	0.000	0.000	7.65	7.37	0.000	−13	4	−2
	R Globus Pallidus	0.000	0.000	6.46	6.28	0.000	12	4	−4
	L Precentral Gyrus, BA 6	0.028	0.000	4.71	4.64	0.000	−41	−4	41
	L Inferior Temporal Gyrus	0.002	0.000	5.35	5.24	0.000	−49	−14	−27
	R Middle Temporal Gyrus	0.000	0.000	5.66	5.54	0.000	50	−32	−19
	R Medial Cerebellum	0.000	0.000	10.0	Inf	0.000	20	−64	−24
SIB	R Inferior Frontal Gyrus, BA 45	0.937	0.505	3.39	3.37	0.000	49	15	18
	R Inferior Frontal Gyrus, BA 9	0.739	0.505	3.64	3.61	0.000	61	8	24
	R Parahippocampal Gyrus	0.742	0.505	3.64	3.61	0.000	26	−22	−25
	R Inferior Temporal Gyrus	0.101	0.467	4.38	4.33	0.000	51	−29	−20
	R Precuneus	0.906	0.505	3.45	3.42	0.000	12	−55	36

Table 4

Summary of the results obtained by voxel-wise statistical analysis of the gray matter maps of decreases in SCZ compared with SIB, SIBpast, and SIBnopast. Only peak findings that reached our threshold for significance are listed (FWE p<.05, cluster size > 5). Findings are listed rostral to caudal.

Sibling Subgroup	MNI Label	FWE [a]	FDR	T	Z	p	x	y	z
All (SIB)	L Superior Frontal Gyrus, BA 10	0.000	0.000	6	5.86	0.000	−27	62	14
	R Middle Frontal Gyrus, BA 10	0.021	0.000	4.68	4.61	0.000	33	62	3
	R Inferior Frontal Gyrus	0.000	0.000	6.58	6.39	0.000	56	16	22
	L Inferior Frontal Gyrus	0.000	0.000	5.7	5.58	0.000	−53	14	24
	L Inferior Frontal Gyrus, BA 47	0.001	0.000	5.49	5.38	0.000	−43	13	−4
	R Precentral gyrus	0.028	0.000	4.62	4.55	0.000	60	3	28
	R Thalamus (ventrolateral nucleus)	0.000	0.000	7.64	7.36	0.000	12	−10	6
	R Postcentral gyrus	0.008	0.000	4.92	4.84	0.000	65	−29	37
	L Middle Temporal Gyrus, BA 21	0.015	0.000	4.77	4.7	0.000	−61	−48	4
	L Prestriate	0.019	0.000	4.72	4.65	0.000	−16	−94	−15
	R Cuneus	0.011	0.000	4.85	4.78	0.000	21	−99	−6
Past Depression (SIBpast)	L Superior Frontal Gyrus, BA 10	0.003	0.000	5.48	5.28	0.000	−29	65	15
	R Superior Frontal Gyrus, BA 10	0.033	0.000	4.90	4.76	0.000	37	60	−1
	R Middle Frontal Gyrus, BA 46	0.006	0.000	5.34	5.15	0.000	49	50	12
	L Middle Frontal Gyrus, BA 46	0.017	0.000	5.07	4.91	0.000	−54	33	18
	L Middle Frontal Gyrus, BA 9	0.008	0.000	5.24	5.07	0.000	−44	33	38
	R Inferior Frontal Gyrus, BA 9	0.000	0.000	6.71	6.37	0.000	60	16	24
	L Inferior Frontal Gyrus	0.000	0.000	5.89	5.65	0.000	−55	13	25
	L Middle Frontal Gyrus, BA 6	0.003	0.000	5.36	5.17	0.000	−52	7	47
	R Superior Temporal Gyrus, BA 22	0.000	0.000	6.54	6.22	0.000	63	1	2
	R Precentral Gyrus, BA 6	0.021	0.000	5.02	4.87	0.000	64	−8	39
	R Thalamus	0.013	0.000	5.13	4.97	0.000	8	−16	0
	R Thalamus	0.005	0.000	5.35	5.17	0.000	11	−33	−1
No Past (SIBnopast)	L Middle Frontal Gyrus, BA 10	0.000	0.000	6.30	6.09	0.000	−29	66	14
	R Superior Frontal Gyrus, BA 10	0.006	0.000	5.24	5.12	0.000	35	65	1
	R Middle Frontal Gyrus, BA 10	0.014	0.000	5.04	4.92	0.000	37	63	11
	R Middle Frontal Gyrus, BA 9	0.002	0.000	5.53	5.38	0.000	44	39	40
	R Middle Frontal Gyrus, BA 9	0.000	0.000	6.32	6.10	0.000	58	14	33
	L Inferior Frontal Gyrus, BA 45	0.002	0.000	5.48	5.34	0.000	−55	14	23
	L Insula	0.002	0.000	5.48	5.34	0.000	−42	12	−5
	R Superior Temporal Gyrus, BA 22	0.003	0.000	5.44	5.30	0.000	62	−2	3
	R Thalamus (ventrolateral nucleus)	0.000	0.000	7.24	6.93	0.000	13	−8	6
	R Inferior Frontal Gyrus, BA 40	0.021	0.000	4.95	4.85	0.000	48	−36	57

[a] Significant at .05 FWE corrected, cluster size > 5

Table 5

Summary of ICC results from ROI analysis of mean gray matter volumes between 116 sibling pairs.

Components of Variance (ICC)					
ROI	**MS_F**	**MS_E**	**F**	**ICC (η^2)**	**p**
L Hippocampus	0.000593	0.004971	14.961	0.106	0.0001**
R Hippocampus	0.000519	0.004036	16.032	0.114	0.0000**
Bilateral Hippocampus	0.002236	0.016196	17.152	0.121	0.0000**
L BA 17	−0.000045	0.007798	0.3315	0.000	0.56531
R BA 17	−0.000073	0.008935	0.0389	0.000	0.84364
L Superior Temporal Gyrus*	−0.000062	0.007201	0.0005	0.000	0.98145
L Insula*	0.000006	0.005472	1.1314	0.001	0.28856
L Medial Frontal Gyrus*	−0.000030	0.003597	0.0366	0.000	0.84831

* 2 mm region of interest used from masked analysis, see coordinates in Figure 2

** significant at p<.05