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The Contributions of Disease and Genetic Factors towards Regional Cortical Thinning in Schizophrenia: The UCLA Family Study

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Abstract

Objective—Cortical thickness reductions in prefrontal and temporal cortices have been repeatedly observed in patients with schizophrenia. However, it remains unclear whether regional variations in cortical thickness may be attributable to disease-related or genetic-liability factors.

Method—The structural magnetic resonance imaging data of 48 adult-onset schizophrenia patients, 66 first-degree non-psychotic relatives of schizophrenia patients, 27 community comparison (CC) probands and 77 CC relatives were examined using cortical pattern matching methods to map and compare highly localized changes in cortical gray matter thickness between groups defined by biological risk for schizophrenia.

Results—Schizophrenia patients showed marked cortical thinning primarily in frontal and temporal cortices when compared to unrelated CC probands. Results were similar, though less pronounced when patients were compared with their non-psychotic relatives. Cortical thickness reductions observed in unaffected relatives compared to age-similar CC relatives suggestive of schizophrenia-related genetic liability were marginal, surviving correction for the left parahippocampal gyrus and inferior occipital cortex only.

Conclusions—Observations of pronounced fronto/temporal cortical thinning in schizophrenia patients replicate prior findings. The lack of marked cortical thickness alterations in non-psychotic relatives of patients, suggests that disease processes are primary contributors toward cortical thickness reductions in the disorder. However, genetic factors may have a larger influence on abnormalities in the medial temporal lobe.

Keywords

Schizophrenia; cortical thickness; relatives; MRI

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Introduction

Neuroimaging studies have consistently demonstrated structural brain abnormalities in patients with schizophrenia. Gray matter (GM) volume reductions, often accompanied by cerebrospinal fluid (CSF) increases, are amongst the most frequently observed findings, although results are less consistent when evaluated at the regional level (Lawrie & Abukmeil, 1998; Shenton et al., 2001; Wright et al., 2000). Recently, the development of sophisticated surface-based imaging analysis methods has permitted the identification of more subtle and highly localized changes in morphological features (e.g. cortical thickness) that are not detectable using traditional volumetric methods. Several studies using these methods have demonstrated with relative consistency that schizophrenia patients exhibit widespread cortical thinning, most prominently within heteromodal prefrontal (medial and dorsolateral) and temporal association cortices (Kuperberg et al., 2003; Narr et al., 2005a, 2005b; Nesvåg et al., 2008).

Although the etiology of schizophrenia remains unclear, there is little doubt that this is a highly heritable disorder (Cardno et al., 1999). Despite the evidence showing morphological characteristics are also highly heritable (Wright et al., 2002; Thompson et al., 2001), whether structural abnormalities are related to the neurobiological vulnerabilities for developing schizophrenia remains less clear. Several structural imaging studies have reported prefrontal and temporal morphological changes in healthy relatives of schizophrenia compared to normal controls that appear to vary in accordance with the strength of biological relatedness to the affected individual (Boos et al., 2007; Lawrie et al., 2008). Specifically, studies on first-degree non-psychotic relatives of schizophrenia patients have reported significantly reduced gray matter volume, particularly in the medial frontal, cingulate and medial and superior temporal regions, and enlarged third and lateral ventricles compared to controls (Boos et al., 2005; Lawrie et al., 2004; Honea et al., 2008; Cannon et al., 1998; McIntosh et al., 2006; Job et al., 2003; Diwadkar et al., 2006; Staal et al., 2000). To date, only two studies have demonstrated the genetic effects of schizophrenia in regional cortical thickness variation by comparing healthy relatives of schizophrenia to controls (Goghari et al., 2007a, 2007b). Schizophrenia patients themselves were not included in these examinations and thus variances associated with disease processes specifically were not addressed.

Only one study to date has addressed regional cortical thinning with respect to the possible influences of both schizophrenia-related genetic and disease-related factors using a large sample of 115 schizophrenia patients, 192 unaffected siblings, and 196 normal controls (Goldman et al., 2009). This investigation used an automated analysis approach and found effects of schizophrenia in cortical thickness variations in the frontal and temporal regions, consistent with prior reports (Kuperberg et al., 2003; Narr et al., 2005a, 2005b; Nesvåg et al., 2008). Comparisons between patients and siblings of patients revealed a similar spatial pattern of results, although less prominent. In contrast, examination of cortical thickness changes between siblings and healthy controls did not survive correction for multiple comparisons. However, when using an alternative analysis strategy that averaged across gyral regions in a subsample of related individuals, results indicated a significant heritable component for cortical thickness reduction. Given the absence of reliable cortical thinning in siblings of schizophrenia patients, investigators concluded that cortical thinning is not a strong intermediate biological marker for schizophrenia-related genetic predisposition.

Since regional cortical thickness reduction appears to be a robust neurobiological marker for schizophrenia, prior results concerning the contributions of schizophrenia related genetic or disease-related factors warrant replication in an independent sample. We thus applied cortical pattern matching methods that take advantage of both manual landmarking and sophisticated cortical surface warping algorithms to map highly localized changes in cortical thickness in a

large sample of adult-onset schizophrenia patients, first-degree relatives of schizophrenia patients, community comparison (CC) probands, and CC relatives (total N = 226). Analyses were designed to assess (1) schizophrenia effects by comparing patients with unrelated CC probands, (2) disease-related effects by comparing patients with their relatives controlling for subject relatedness, defined here as first-degree biological relatives belonging to the same family, and (3) effects of schizophrenia-related genetic predisposition by comparing patient relatives with CC probands and relatives. Since the age spread for relatives included for study was relatively large, and shared environmental factors are expected to be different for parents and siblings, for comparison #3 we analyzed possible genetic liability effects by comparing patient siblings with CC probands and siblings and patient parents with CC parents again controlling for subject relatedness. Based on the findings discussed above, we predicted that patients would show cortical thinning, especially in prefrontal and temporal cortices, compared to CC probands. We hypothesized that when compared to their relatives, patients would show similar patterns of cortical thinning, though effects would be of smaller magnitude. Finally, we expected that patient relatives would show cortical thickness values intermediate between schizophrenia patients and CC participants that would be indicative of genetic liability.

Materials and Methods

Subjects

This study is a component of the larger UCLA Family Study, which involves schizophrenia and CC probands and first-degree relatives of both proband groups (Asarnow et al., 2000; Fogelson et al., 2007; Nuechterlein et al., 2002). Subjects included 48 adult-onset schizophrenia patients and 66 non-psychotic first-degree biological relatives of the patients (24 siblings and 42 parents), 27 CC probands and 77 non-psychotic first-degree relatives of CC probands (38 siblings and 39 parents) from 96 nuclear families (see Table 1). For schizophrenia probands, 30 patients had at least one relative in the relative group. Specifically, 16 schizophrenia patients had 1 relative, 11 patients had 2 relatives and 3 patients had 3 relatives included in the relative groups. For CC probands, 23 subjects had at least one relative included. Specifically, 5 CC probands had 1 relative, 7 CC probands had 2 relatives, 6 CC probands had 3 relatives, 4 CC probands had 4 relatives, and 1 CC probands had 5 relatives.

Individuals with schizophrenia were recruited through current and former patients of the UCLA Aftercare Research Program (Nuechterlein et al., 1992; Narr et al., 2009). The CC probands with demographic characteristics similar to those of the schizophrenia probands were recruited using lists provided by a survey research company and telephone contact. For the determination of Axis I diagnoses, the Structural Clinical Interview for DSM-IV – Patient version (SCID-I/P) (First et al., 1997) was administered to all patients and the DSM-IV – Non Patient (SCID-NP) was administered to CC probands and both CC and patient relatives. In addition, all participants received diagnostic interview with selected sections of the Structural Clinical Interview for DSM-IV Axis II disorders (First et al., 1996). 44 CC relatives and 27 patient relatives were shown to meet diagnostic criteria for Axis I or II diagnoses (e.g. mood disorders: n=26, n=18, respectively, anxiety disorder: n=11, n = 4, respectively, substance abuse: n=16, n=7, respectively, attention-deficit/hyperactivity disorder: n=6, n=2, respectively, conduct disorders n=3, n=1, respectively; and antisocial personality disorder: n=1, n=1, respectively). For patients, schizophrenia diagnosis was determined by DSM-IV criteria and by informant information as reviewed and confirmed by consensus (Fogelson et al., 2007; Nuechterlein et al., 2002; Narr et al., 2009). Clinical information derived from an integration of family history, direct interview, and/or medical records, were used to best estimate diagnoses for all participants. Reliability and consensus diagnosis procedures have been described in prior publications (Asarnow, 2001; Fogelson et al., 1991, Ventura et al., 1998). Clinical symptoms were assessed using the expanded 24-item Brief Psychiatric Rating Scale (BPRS; Ventura et

al., 2000) for which reliability procedures have also been described previously (Fogelson et al., 1991; 2007) and clustered into withdrawal (negative symptoms) factor and thinking disorder (positive symptoms) factor scores (Burger et al., 1997). In addition, information regarding current social economic status derived from the Total Socioeconomic Index (TSEI; Stevens & Cho, 1985) and the number of years of education completed was also collected from the subjects.

Exclusion criteria applied to all participants included neurological disorders (e.g. temporal lobe epilepsy), mental retardation, and a history of drug abuse or alcoholism in the six months prior to the assessment. An additional exclusion criterion for the schizophrenia patients was substance abuse that immediately preceded and may have triggered the psychotic episode or interfered with a definite diagnosis of schizophrenia. A diagnosis of schizophrenia spectrum disorder (i.e. schizophrenia, schizoaffective disorder, or schizotypal, paranoid, avoidant, schizoid personality disorders) was an exclusion criterion for CC probands. Relatives of probands with psychotic disorders were also excluded. Patients were currently receiving standard antipsychotic medication treatments (risperidone: $n = 20$, olanzapine: $n = 7$, ziprasidone: $n = 3$, aripiprazole: $n = 8$, haloperidol: $n = 2$, clozapine: $n = 7$, quetiapine: $n = 5$, fluphenazine: $n = 2$). The UCLA Institutional Review Board (IRB) approved all research procedures and informed written consent was obtained from all subjects.

Image Acquisition and Preprocessing

High-resolution T1-weighted structural magnetic resonance imaging (MRI) scans were collected on a Siemens 1.5 Tesla Sonata system using a 3D MPRAGE sequence (TR = 1900 ms; TE = 4.28 ms; TI = 1100; flip angle: 15° ; field of view = 256×256 ; matrix = $256 \times 256 \times 160$; voxel size = $1 \times 1 \times 1$ mm³). A series of previously detailed preparatory steps (Narr et al., 2009; Yang et al., 2009; Narayan et al., 2007) were applied to the MR data including the removal of extra-cortical tissue, the correction for inhomogeneities, head tilt and orientation, and place the data into the ICBM-305 common stereotaxic space. Next, a fully-automated partial volume classifier was applied to classify voxels into GM, white matter (WM) and CSF. Total intracranial volumes (excluding the pons and cerebellum) and volumes of each brain tissue compartment were estimated. Finally, a surface-rendering algorithm was used to create a three-dimensional model of the cortical surface for each individual.

Cortical Pattern Matching

Thirty-one sulcal landmarks were delineated manually in each hemispheric surface following previously validated protocols (Narr et al., 2005a, 2005b, 2009; Yang et al., 2009; Narayan et al., 2007; Sowell et al., 2004) for which intra- and inter-rater reliability has been established (Narr et al., 2005a, 2005b). Cortical pattern matching methods were then applied to spatially relate homologous regions of the cortex between subjects that allows for measurement and comparison of cortical thickness at homologous locations in each individual (Narr et al., 2005a, 2005b, Sowell et al., 2004). Next, the previously obtained tissue classified brain volumes were used to calculate the GM thickness at all spatially aligned hemispheric surface points within subjects and then compared between groups to provide spatially detailed maps indexing very local differences across the brain.

Statistical Analysis

Since the Kolmogorov-Smirnov Z test showed that all estimated volumes were normally distributed across the samples (all $p > .66$), all four of the analyses described earlier were conducted using the general linear model implemented in R (www.r-project.org). Analyses were conducted including age and sex as covariates and were run both with and without additionally controlling for intracranial volume (using the cubed root). However, since including this covariate made little measurable difference to regional cortical thickness

findings, results are reported with correction only. Further, to ensure that nonrandom assignment of subjects to groups did not influence results (Miller and Chapman, 2001), post-hoc analyses were performed without including these variables in the statistical model. Results from these analyses (without including sex and age in the model) are provided as Supplementary Material. For all statistical tests including related individuals, subject relatedness was included as a random factor using a mixed model. Uncorrected probability values from each comparison were mapped onto the group averaged cortical surface where color encodes directional and regionally significant differences between the respective groups. Since comparisons were made at thousands of spatially correlated cortical locations, permutation tests performed using the reduced model were conducted to ensure that the overall pattern of effects in the uncorrected statistical maps could not have been observed by chance alone (Anderson & Legendre, 1999; Anderson & Braak, 2003). Specifically, the number of surface points across the hemisphere or within the region of interest that were significant at a threshold of $p < .05$ for each statistical comparison was compared to the number of significant surface points across the hemisphere or within the region of interest that occurred by chance when subjects were randomly assigned to groups across 10,000 new randomized analyses. Permutation testing was performed for each hemisphere and within 20 gyral regions obtained using the Laboratory of NeuroImaging Probabilistic Brain Atlas (LPBA40) (Shattuck et al., 2008) (<http://www.loni.ucla.edu/Atlases/LPBA40>) to test our *a priori* hypothesis that significant schizophrenia disease-related effects would be pronounced in prefrontal and temporal regions and that genetic liability effects would be present in the same regions though of lesser magnitude. For descriptive purposes, permutation results for all cortical regions are reported in Table 2.

The same statistical models described above were used to describe group differences in total brain volume, brain tissue volume and mean cortical thickness across the hemispheres. Furthermore, within the schizophrenia patient group, post-hoc analyses were performed to assess whether positive symptoms, negative symptoms, or illness duration showed significant relationships with regional cortical thinning.

Results

Demographic and Clinical Assessments

Table 1 shows demographic and clinical details of subjects. Groups differed significantly in age ($F(5, 212) = 82.70, p < .001$) and gender ($\chi^2(5, 212) = 19.33, p = .002$), but not handedness ($\chi^2(5, 212) = 1.36, p = .93$), current socioeconomic status ($F(5, 212) = 1.88, p = .10$) or years of education completed ($F(5, 212) = 1.57, p = .17$). Specifically, schizophrenia patients and siblings were on average slightly older than CC probands and their siblings (all $p < .047$). Both parent groups are of course on average older than proband and sibling groups (all $p < .001$). Schizophrenia patient group had more males than females compared to their parents ($p < .001$) and CC siblings and parents ($p = .016, p = .006$, respectively). In addition, there were more females than males in patient parents and CC parents compared to CC probands ($p = .003, p = .032$, respectively).

Total Brain Volume, Brain Tissue Volume and Mean Cortical Thickness

When compared to CC probands, schizophrenia probands showed significantly reduced total GM volume ($F(1, 70) = 8.15, p = .006$), increased total WM volume ($F(1, 70) = 4.32, p = .041$) and reduced left and right mean cortical thickness ($F(1, 70) = 8.46, p = .005$; $F(1, 70) = 9.46, p = .003$; respectively), but did not differ in total brain ($p = .44$) or CSF volume ($p = .48$). When compared to patient relatives, schizophrenia probands showed reduced left and right mean cortical thickness ($F(1, 61) = 4.6, p = .035$; $F(1, 61) = 7.6, p = .007$; respectively), but did not differ in total brain ($p = .83$), GM ($p = .31$), WM ($p = .49$), and CSF volume ($p = .53$).

Patient siblings showed no significant difference in total brain ($p = .92$), GM ($p = .22$), WM ($p = .48$), CSF volume ($p = .39$), or left or right mean cortical thickness ($p = .13$; $p = .22$; respectively) when compared to CC probands and CC siblings. Similarly, patient parents and of CC probands did not differ in total brain ($p = .23$), GM ($p = .44$), WM ($p = .8$), CSF volume ($p = .09$), or left or right mean cortical thickness ($p = .83$; $p = .65$; respectively).

Cortical Pattern Matching Analysis

Schizophrenia Effects—Schizophrenia probands showed significant cortical thinning compared to CC probands in bilateral prefrontal, temporal cortices and additional cortical regions after covarying for gender, age, and the cubed root of whole brain volume (Figure 1, top row). Specifically, patients exhibited cortical thinning in the dorsolateral prefrontal, inferior frontal, medial frontal (encompassing cingulate cortices), superior temporal, and middle temporal cortices (encompassing the parahippocampal gyri) as well as in medial occipital cortices. No significant regional increases in cortical thickness were observed in schizophrenia patients. Permutation testing confirmed results in these and other cortical regions (Table 2). Beta maps corresponding to the probability maps (computed using identical statistical models) showing regional thickness differences between diagnostic groups in mm are provided in Figure 2. When sex and age were not included in the statistical models findings remained similar for all group comparisons with the exception of the contrast between patients and their relatives (see Figure S1 & S2). For this comparison the spatial distribution of disease-related effects were observed in more dorsal prefrontal regions as opposed to temporal regions. Since variations in cortical gray matter are shown to differ regionally in association with age across the lifespan (Sowell et al., 2003), the age disparity between groups likely account for differences in results and underscore the importance of removing age-related variance from the data.

Disease-Related Effects—Comparisons between schizophrenia probands and non-psychotic first-degree relatives of patients (Figure 1, second row) performed to assess schizophrenia-disease specific effects were similar, although somewhat less pronounced, to the results described above for comparisons between patients and CC probands. Cortical thinning was most prominent in the medial prefrontal, superior frontal, inferior frontal, and superior temporal regions in patients compared to their biological relatives. Corresponding beta maps are provided in Figure 2. Permutation testing confirmed the findings in the superior temporal and orbitofrontal cortex (see Table 2).

Genetic-Liability Effects—Comparisons performed to address potential schizophrenia-related genetic liability effects showed significant regional cortical thinning in non-psychotic patient siblings compared to CC probands and siblings in the right medial frontal, right dorsolateral prefrontal, and medial temporal cortices (Figure 1, third row). However, significant genetic liability effects were not observed at any cortical location when comparing patient parents with CC parents (Figure 1, last row). Beta maps corresponding to the probability maps are provided in Figure 2. Permutation analysis confirmed the findings in the left parahippocampal gyrus and inferior occipital gyrus ($p = .02$ and $.04$ respectively; Table 2) in patient siblings compared to CC probands and siblings. However, permutation analysis was not able to provide confirmatory evidence for cortical thinning within any other hypothesized regions for either of the two comparisons performed (all corrected p -value $> .06$; see Table 2).

Illness Duration and Symptom Scores—Post-hoc analyses performed to assess relationships between illness duration and positive and negative symptom scores and cortical thickness variations in schizophrenia patients did not survive permutation analyses in any cortical region (corrected p -value: all $> .3$) (statistical maps not shown).

Discussion

The current investigation sought to clarify whether regional variations in cortical thickness may be attributable to disease-related or schizophrenia-related genetic (and/or potentially shared environmental) factors in the disorder. To address this issue, cortical pattern matching analysis methods were applied to examine localized thickness changes in schizophrenia patients, CC probands, and their siblings and parents. Results demonstrated marked thickness reductions in schizophrenia when compared to unrelated CC subjects, most notably in the frontal and temporal lobes, which are largely consistent with prior studies (Kuperberg et al., 2003; Narr et al., 2005a, 2005b; Nesvåg et al., 2008; Goldman et al., 2009). Comparisons between nonpsychotic relatives compared to CC subjects performed to assess potential schizophrenia genetic liability effects revealed only slight reductions of cortical thickness in patient siblings that survived correction procedures for the left parahippocampal gyrus and inferior occipital gyrus only and showed no significant regional reductions of cortical thickness in patient parents. Neither risk group showed any regional increases in cortical thickness with respect to controls. These findings are consistent with the prior report of Goldman et al (2009). Thus, our overall findings support the argument that cortical thickness reductions in schizophrenia are primarily driven by factors attributable to disease processes and less influenced by genetic factors associated with the disorder. Our results also provide some evidence to indicate that schizophrenia-related genetic factors might exert more focal influences in the medial temporal lobe, particularly in the left hemisphere.

As hypothesized, significant schizophrenia effects for cortical thickness were most striking for frontal and temporal lobe regions. Specifically, patients with schizophrenia showed significant cortical thinning in the medial and lateral surface of the prefrontal and temporal cortices as well as the anterior cingulate cortex compared to their nonpsychotic relatives and CC subjects. Several previous studies have demonstrated cortical thinning in almost identical regions in first-episode and chronic patients with schizophrenia (Kuperberg et al., 2003; Narr et al., 2005a, 2005b; Nesvåg et al., 2008; Goldman et al., 2009), findings that are in line with postmortem findings of dendritic arborization, glial cell loss and alterations in the neuronal cell size and density in these regions in schizophrenia (Harrison, 1999; Selemon & Goldman-Rakic, 1999; Stark et al., 2004). Cortical thinning observed in schizophrenia may therefore reflect disruptions in the architectural integrity contributing towards symptom profiles as well as disturbances in executive function (working memory, abstraction, top-down attentional control), declarative memory processing, and performance monitoring (Wright et al., 2000; Weinberger, 1998; Pearlson, 1997). In addition, cortical thinning was also observed within occipital cortex and inferior parietal regions on the medial aspects of the hemispheres, consistent with some prior reports (Narr et al., 2005a), supporting the view that the neuropathology underlying schizophrenia involves temporal and prefrontal cortices as well as other cortical regions that share extensive interconnectivities.

In line with the majority of prior findings, patients with schizophrenia did not show significant differences in whole brain volumes compared to controls (Steen et al., 2006) where intracranial volumes (including extra-cortical CSF) were larger on average in patients compared to controls as consistent with some of our prior observations in independent samples (Narr et al., 2005a, 2005b, 2006). Though significant differences in CSF volumes are more frequently reported in schizophrenia (e.g., Shenton et al., 2001), intracranial CSF increases observed in patients were below the threshold of significance in the current sample. However, it is important to note that total CSF volumes, which included both extra-cortical and ventricular CSF, were examined in this study and thus results may not be directly comparable to the majority findings in the literature, which largely focus on ventricular CSF. It is also worth noting that brain CSF volumes vary considerably amongst individuals and in association with age, and may be influenced by clinical outcome or medication treatment as has been previously suggested

(Cahn et al., 2002 and Lieberman et al., 2005), all factors that may contribute to the sub-threshold schizophrenia CSF findings reported here. Despite the lack of group difference in CSF volume, schizophrenia patients were found to show significantly reduced total gray matter volumes and marginally increased total white matter volumes compared to CC probands that are in line with several previous reports (e.g. Lim et al., 1996; Zipursky et al., 1992; Highley et al., 2003; Taylor et al., 2005; Cahn et al., 2006; Mitelman et al., 2007).

Regarding the effects of diagnostic measures, no significant relationships were observed between illness duration and cortical thickness changes in schizophrenia. Findings suggest that cortical thinning may remain relatively stable over the course of illness and are consistent with observations that cortical thinning is present both near disease onset and in chronic schizophrenia (Kuperberg et al., 2003; Narr et al., 2005a, 2005b; Nesvåg et al., 2008; Goldman et al., 2009). Significant relationships between regional cortical thickness patterns and positive/negative symptom scores in patients were also absent, suggesting that cortical thinning represents a trait marker of disease processes in schizophrenia. However, the majority of patients was receiving standard antipsychotic medication treatment and was largely asymptomatic at the time of scan. Therefore, we were not able to fully address the influence of symptom ratings on cortical thickness variations in the current sample.

The findings for genetic liability effects are consistent with Goldman et al. (2009) in that only subtle changes in cortical thickness were observed in nonpsychotic patient siblings compared with CC probands and their siblings, with the exception of the left parahippocampal gyrus and left occipital gyrus. Nonpsychotic patient parents showed cortical thickness variations largely indistinguishable from those of CC parents. It is possible that increased variance associated with aging may lead to decreased statistical power for group contrasts in spite of correction for age. Observations of localized thinning in parahippocampal cortices in patient siblings, particularly in the left hemisphere, converge with independent observations suggesting that schizophrenia-related genetic factors may contribute to abnormalities in the medial temporal lobe and/or that genetic risk factors may render individuals more susceptible to harmful environmental effects in these regions particularly. For example, structural abnormalities of medial temporal lobe regions including the hippocampus and overlying cortex, are widely reported in schizophrenia (Wright et al., 2000; Nelson et al., 1998) and have been observed in patient relatives (e.g. Seidman et al., 2002; Narr et al., 2002). This is consistent with evidence suggesting that both patients and their asymptomatic relatives exhibited disturbances in declarative memory processing (e.g. Saykin et al., 1991; Goldberg et al., 1995), which is mediated by the medial temporal lobe (Eichenbaum & Cohen, 2001). Moreover, because medial temporal cortex is highly sensitive to environmental insults (Schmidt-Kastner & Freund, 1991; Fujioka et al., 1997; Katz et al., 1982), genetic-liability findings of parahippocampal abnormalities in patient siblings may point to a gene-environment interaction account of the neurodevelopmental pathogenesis of schizophrenia. Our failure to observe significant parahippocampal findings in patient parents in relation to CC parents may be attributable to increased age-related variance in both groups, or suggest age by gene interactions. Our failure to observe significant parahippocampal findings in patient parents in relation to CC parents may be attributable to increased age-related variance in both groups, or suggest age by gene interactions. Beyond the fronto-temporal regions that were hypothesized to show both schizophrenia and genetic liability effects, significant thickness reductions were also observed in left occipital gyrus in patient siblings, again in line with prior reports (Goldman et al., 2009). These findings may relate to observations of visual processing deficits in both patients and their unaffected siblings where early visual processing relies on the lateral occipital cortex and connected regions (Kérl et al., 2005; Green et al., 2006). Although some regional thinning was observed in the cingulate cortex in patient siblings, consistent with findings reported by Goghari et al (2007a), this group difference did not survive correction for multiple comparisons. Therefore, although it remains plausible that regional variations in cortical

thickness may be attributable to schizophrenia-related genetic factors, the more global patterns of cortical thinning observed in schizophrenia patients may not represent a strong neurobiological marker of increased genetic risk for schizophrenia.

Although this study has major strengths including the use of a comparatively large sample and well-validated imaging analysis methods, some factors may have served to impact or limit the interpretation of results. First, to avoid a “supernormal” comparison group (Kendler, 1990) in this family genetic study, less stringent exclusion criteria for Axis I and II diagnoses were followed (see Methods). Second, results may be influenced in part by the age differences within and between groups due to the inclusion of both younger and older relatives (Lenroot et al., 2009), however, the separate analyses of siblings and parents and the inclusion of age as a covariance served to limit this source of variance. Last, it is possible that exposure to antipsychotic medications may contribute to variations in cortical thickness observed in patients (Thompson et al., 2009). However, several prior studies have demonstrated cortical thinning in first-episode schizophrenia patients with little or no prior medication exposure (Narr et al., 2005a, 2005b; Nesvåg et al., 2008) suggesting that cortical thinning is a trait marker of schizophrenia though different medication treatments may both intensify or protect against the trajectory of brain tissue loss associated with ongoing disease processes (Lieberman et al., 2005; Thompson et al. 2005).

In conclusion, results of this study add confirmatory evidence for relatively widespread cortical thinning, particularly in prefrontal and temporal cortices, in patients with schizophrenia. However, influence of schizophrenia-related genetic predisposition was confirmed only for the left parahippocampal and inferior occipital gyrus in siblings. Thus, most cortical thinning appears to be attributable to disease-related rather than genetic liability effects of this disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Uncorrected statistical maps showing significant regional differences in cortical thickness between groups. The color bar encodes the p value associated with comparisons using the general linear model performed at each cortical surface point while controlling for gender, age, whole brain volume and subject relatedness (if appropriate).

Figure 2.

Beta maps that correspond to the probability maps (Figure 1) show cortical thickness changes between groups defined by biological risk for schizophrenia in mm. Negative beta values index regional reductions of cortical thickness in schizophrenia patients or in their nonpsychotic relatives when compared to CC subjects.

Demographic, clinical, and MRI measures for schizophrenia patients, non-psychotic relatives of patients, CC probands, and non-psychotic relatives of CC probands.

Table 1

	Schizophrenia Patients (N = 48)			Patient Relatives (N = 42)			CC Probands (N = 27)			Relatives of CC Probands (N = 39)		
	Mean	SD		Mean	SD		Mean	SD		Mean	SD	
<i>Demographic Measures</i>												
Age (Years) *	31.8	9.0		31.8	13.3		26.4	7.1		26.9	9.4	8.0
Handedness (Left/ Right)	4/44			2/22			2/25			1/37		3/36
Gender (Male/Female) *	35 / 13			13 / 11			19 / 8			18 / 20		17 / 22
Current socioeconomic status	Mean	SD		Mean	SD		Mean	SD		Mean	SD	
	29.8	12.7		38.5	20.1		39.0	17.4		42.8	17.5	21.1
Years of education completed	13.8	1.8		14.7	2.5		15.2	2.7		15.3	2.3	2.8
<i>Diagnostic Measures</i>	Mean	SD	Range									
Age of onset (Years)	22.2	4.4	14 - 35									
Duration of illness (Years)	8.7	7.4	0 - 26									
BPRS total score ^a	38.2	9.6	18 - 63									
Withdrawal factor score	1.6	.8	.4 - 4.4									
Thinking disorder factor score	1.7	.7	.8 - 3.8									
<i>MRI Measures</i>	Mean	SD		Mean	SD		Mean	SD		Mean	SD	
Total brain volume (cm ³) *	1427.3	135.9		1408.7	153.6		1398.4	114.5		1418.0	164.7	152.8
Total gray matter volume (cm ³) * ^b	667.1	42.4		677.0	42.0		707.3	38.1		709.0	41.3	45.0
Total white matter volume (cm ³) * ^b	537.5	35.0		532.8	39.7		517.0	24.1		511.5	34.9	34.1
Total cerebrospinal fluid (cm ³) ^b	188.5	42.5		183.3	51.3		168.8	30.2		172.6	37.4	44.0
Mean cortical thickness (mm) ^b												
Left *	4.51	.30		4.58	.22		4.74	.25		4.70	.20	.26
Right *	4.49	.26		4.58	.23		4.72	.21		4.68	.19	.25

* An assigned indicates significant group difference in this variable.

^a Scores were available for 46 schizophrenia patients;

^b Volumes were corrected for total brain volumes.

Table 2

Permutation derived probability values for LPBA40 regions of interest for each group comparison

		Schizophrenia Probands vs CC Probands	Schizophrenia Probands vs Patient Relatives	Patient Siblings vs CC Probands and Siblings	Patient Parents vs CC Parents
Hemisphere	Left	.007	.181	.239	.986
	Right	.003	.092	.169	.967
Superior frontal	Left	.010	.062	.261	.737
	Right	.008	.077	.082	1
Middle frontal	Left	.012	.151	.258	1
	Right	.015	.242	.064	1
Inferior frontal	Left	.041	.314	.353	.581
	Right	.008	.107	.688	1
Middle orbitofrontal	Left	.012	.151	.258	1
	Right	.015	.242	.064	1
Lateral orbitofrontal	Left	.065	.056	.430	.546
	Right	.011	.016	1	1
Gyrus rectus	Left	.004	.110	.239	.407
	Right	.232	.013	.704	.638
Superior temporal	Left	.060	.150	.336	1
	Right	.002	.045	.458	1
Middle temporal	Left	.034	.160	.413	.595
	Right	.015	.163	.592	1
Inferior temporal	Left	.044	.332	.176	1
	Right	.165	.442	.207	1
Parahippocampal	Left	.012	.547	.020	1
	Right	.045	1	.081	1
Superior parietal	Left	.579	1	.351	.318
	Right	.395	.313	.643	1
Middle occipital	Left	.088	1	.137	.481
	Right	.132	.360	.326	1
Inferior occipital	Left	.040	.361	.042	1

		Schizophrenia Probands vs CC Probands	Schizophrenia Probands vs Patient Relatives	Patient Siblings vs CC Probands and Siblings	Patient Parents vs CC Parents
Supramarginal	Right	.072	.146	.229	1
	Left	.231	1	.318	.372
Precentral	Right	.072	.261	.465	.220
	Left	.155	.597	.480	1
Postcentral	Right	.002	.133	.120	1
	Left	.470	1	.366	1
Cingulate	Right	.017	.413	.416	.301
	Left	.013	.070	.201	.701
Lingual	Right	.006	.128	.055	.934
	Left	.041	.581	.488	.660
Fusiform	Right	.005	.074	.380	1
	Left	.035	.359	.311	1
Angular	Right	.364	.261	.091	1
	Left	.440	1	1	.329
	Right	.360	.368	1	1