TITEL: Association between psychotic symptoms and cortical thickness reduction across the schizophrenia spectrum

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Abstract

The current study provides a complete MRI analysis of thickness throughout the cerebral cortical mantle in patients with schizophrenia (SZ) and rigorously screened and matched unaffected relatives and controls and an assessment of its relation to psychopathology and subjective cognitive function. We analyzed 3D-anatomical magnetic resonance imaging data sets, obtained at 3 Tesla, from three different subject groups: 25 SZ patients, 29 first-degree relatives and 37 healthy control subjects. We computed whole-brain cortical thickness using the Freesurfer software and assessed group differences. We also acquired clinical and psychometric data. The results showed markedly reduced cortical thickness in SZ patients compared with controls, most notably in the frontal and temporal lobes, in the superior parietal lobe and several limbic areas, with intermediate levels of cortical thickness in relatives. In both patients and relatives, we found an association between subjective cognitive dysfunction and reduced thickness of frontal cortex, and predisposition towards hallucinations and reduced thickness of the superior temporal gyrus. Our findings suggest that changes in specific cortical areas may predispose to specific symptoms, as exemplified by the association between temporal cortex thinning and hallucinations.

1. Introduction

Cortical thickness is defined as the local or average distance between the white matter surface and the pial surface of the cortex. It correlates with the number of neurons and the neuropil within an ontogenetic column, the cohort of cortical neurons that originate from a single neuronal progenitor (Rakic, 2008). Measurement of cortical thickness may thus allow probing alterations in brain growth and maturation (Magnotta et al., 1999; Salat et al., 2004; Sowell et al., 2001; Sowell et al., 2003), which are increasingly being discussed as potential pathogenetic mechanisms of schizophrenia (SZ) (Thompson et al., 2004). Cortical thickness mapping in SZ has indeed revealed thinning of the cortical sheet, particularly in parts of the frontal and temporal lobes (Goldman et al., 2009; Haukvik et al., 2009; Kuperberg et al., 2003; Lawyer et al., 2008; Venkatasubramanian et al., 2008), and some of these changes seem to progress during the transition from prodromal to clinical states (Wood et al., 2008). The putative genetic contribution to reduced cortical thickness in SZ can be studied by including patients' first-degree relatives, where genetic traits can potentially be observed without the confounding factors of medication or illness effects. However, only few studies have compared cortical thickness measures across SZ patients, relatives and controls (Calabrese et al., 2008; Yang et al., 2010; Goldman et al., 2009; Harms et al., 2010;), and of these only the latter two mapped the whole cortical mantle.

Yang et al. (2010) reported whole-brain significant differences between relatives and controls, and these were confined to left parahippocampal and inferior occipital gyrus. Some of the studies that examined only subregions of cortex reported thinner cortex in relatives compared to controls in the frontal lobe (Harms et al., 2010; Yang et al., 2010), specifically in the cingulate gyrus (Calabrese *et al.*, 2008; Goghari *et al.*, 2007b, 2007a) and in the temporal lobe (Calabrese *et al.*, 2008; Goghari *et al.*, 2007b, 2007a; Gogtay et al., 2007; Yang *et al.*, 2010), but these results were not corrected for comparisons across the whole brain and in some studies may have been affected by the inclusion of individuals with psychiatric

symptoms in the relatives groups (Calabrese *et al.*, 2008; Goghari *et al.*, 2007b, 2007a; Harms *et al.*, 2010; Yang *et al.*, 2010).

Inconsistencies across studies may be further explained by differences in magnet field strength and imperfect matching for gender and handedness. Both handedness and gender have been associated with structural changes in schizophrenia (e.g., Nopoulos et al., 1997, Gur et al., 1999; Gur et al., 2004). In the present whole-brain study of cortical thickness differences between schizophrenia patients, unaffected relatives and controls without family history of mental disorder, we therefore applied rigorous exclusion and matching criteria. Furthermore, we scanned at a field strength of 3 Tesla on the basis that the improved signal-to-noise ratio is particularly beneficial for the white/grey matter contrast that is crucial for accurate cortical segmentation (Kruggel et al., 2010). Many previous studies (Harms *et al.*, 2010; Goldman *et al.*, 2009; Yang *et al.*, 2010) assessed cortical thickness using 1.5 Tesla systems.

We also explored the functional significance of any changes in cortical thickness through correlation with clinical and subclinical symptoms. Several studies have shown associations between structural abnormalities and symptom severity in SZ patients (Gaser et al., 2004; Levitan et al., 1999; Oertel et al., 2010; Sumich et al., 2005; Venkatasubramanian *et al.*, 2008; Venkatasubramanian et al., 2011), and specifically between cortical thinning in SZ and impairments of verbal learning, working memory and executive control (Ehrlich et al., 2011; Hartberg et al., 2010). Although few studies of the cortical thickness studies in relatives assessed correlations with cognitive performance (Harms *et al.*, 2010) and acute symptoms (Goldman *et al.*, 2009; Yang *et al.*, 2010), associations with subclinical symptoms such as propensity to develop hallucinations, which is increased in relatives compared to the general population (Kendler et al., 1995), have not been addressed. Subclinical symptoms are of particular interest, though, because cortical thickness is being explored as a structural trait marker of SZ and thus potential associations with psychological traits might be more likely

than those with acute symptoms. We therefore tested, for the first time, whether cortical thickness changes would correlate not only with clinical symptoms in SZ patients but also with subclinical traits in relatives.

Methods and Materials

Participants

We included 31 SZ patients (mean age: M = 38.00 [SD: 11.24]) diagnosed with paranoid schizophrenia according to DSM-IV criteria (APA, 2000). All patients were in-patients of the Department of Psychiatry, Psychosomatic Medicine and Psychotherapy of Frankfurt University. All patients were treated with atypical antipsychotics, and four patients additionally with typical antipsychotic medication at the time of testing. To ensure that the results of our study were not modulated by a specific medication effect from typical antipsychotics (Dazzan et al., 2005), we repeated the analysis for group differences on the structural measures without the four patients with typical antipsychotics. Mean duration of illness was 12.48 years [SD = 7.33]

----------Insert table 1 about here----------

29 first-degree relatives (mean age: M = 40.34 [SD = 15.84]) and 37 healthy controls (mean age: M = 39.36 [SD = 9.97]) also participated in the study (see Table 1 for further details). Contact to the relatives was established through participating patients, from a support group for relatives of SZ patients, through newspaper articles, flyers and advertisements in the hospital. The first-degree relatives were requested to bring a letter from the psychiatrist treating the patient of the affected family to confirm the diagnosis. The relative group included parents (n = 16) and siblings (n = 13) of other SZ patients than those included in the study.

The control group was matched with the groups of patients and relatives for handedness (all right handed; The Edinburgh Inventory; (Oldfield, 1971), age, sex and parental education. Statistical tests (ANOVA, Scheffé post-hoc contrast analyses) for differences between the groups regarding age and years of education revealed no significant

differences ($p > .05$). Chi-square test showed that gender distribution was equal across groups ($p > .05$). Exclusion criteria for control and relative participants were any psychiatric disorder according to DSM-IV, left-handedness, current drug-abuse, any neurological pathology and inability to provide informed consent. None of the controls had any positive family history of schizophrenia.

The anatomical MRI scans were reviewed by a neuroradiologist who did not find underlying pathology. Participants were provided with a description of the study and gave written informed consent before participation. Experimental procedures were approved by the ethical board of the medical department of the Johann Wolfgang Goethe-University, Frankfurt/Main, Germany. For further use in a separate study, additional functional and diffusion tensor imaging were performed (see (Oertel *et al.*, 2010; Rotarska-Jagiela, 2009).

Assessment of psychopathology

The Structured Clinical Interview for DSM-IV (German version, (Wittchen et al., 1996) was carried out in schizophrenia patients, in controls and first-degree relatives. Relatives of individuals with SZ or control participants who met criteria for psychiatric or neurological disorders were excluded from the study. SZ patients had no other concurrent psychiatric diagnoses in addition to schizophrenia. The final sample ($n = 29$) included only first-degree relatives without any psychiatric, neurological or personality disorders. Current psychopathology of the SZ patients was assessed using the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987) (view table 1 for further details).

All patients had a history of auditory hallucinations as assessed by the PANSS interview and a semi- structured interview based on the criteria proposed by Aggernaes (Aggernaes, 1972) to assess the contents, phenomenology, severity and occurrence of hallucinations in more detail. The last period of auditory hallucinations ranged from 13 days to 8 months before the scanning. None of the patients reported any hallucinations while they

were scanned.

All participants were screened for predisposition towards hallucinations with the Revised Hallucination Scale (RHS; (Morrison et al., 2002). Subjective cognitive dysfunction was assessed using the Eppendorf Schizophrenia Inventory (ESI; (Mass et al., 2000). The ESI assesses psychosis-related symptoms and subjective cognitive dysfunction in schizophrenia and integrates over four weeks. Participants have to rate 40 items based on 4 subscales (attention and speed impairment, ideas of reference, auditory uncertainty and deviant perception on a 4-point-Likert scale). The ESI is considered to be a sufficiently reliable and valid instrument (Cronbach's alpha: .60-.90; Mass et al., 2000).

Controls and relatives also completed the German version of the Schizotypy Personality Questionnaire (SPQ; (Klein, 1997; Raine, 1991). The SPQ is a 74 item self-report measure that was designed to measure schizotypal traits in non-clinical populations. Items address unusual perceptual and cognitive experiences and subjects are required to indicate whether an item is appropriate to their own situation by marking True or False. True-scores are summed to obtain a total score with a higher total score implying the presence of more schizotypal experiences. (Klein, 1997) suggested a two-factor model of the SPQ, where the original factors were reconfigured into a cognitive-perceptual factor and an interpersonal factor. We computed ANOVAs with RHS and ESI as dependent variable and group as fixed factor with three levels (controls, relatives, SZ patients) (Table 1). The psychometric data from the participants of this study contributed to the larger sample documented in (Oertel et al., 2009).

Data acquisition and image processing

For anatomical measurement, we acquired a high-resolution T1-weighted MDEFT sequence (Deichmann et al., 2004) (176 slices, 1x1x1 mm^3, matrix size 256*256, Slice thickness 1mm, Flip angle: 16°) covering the whole brain on a Siemens Magnetom Allegra 3 Tesla MRI

system (Siemens Medical Systems, Erlangen, Germany) at the Frankfurt University Brain Imaging Center, Germany. Analysis of structural MRI data was performed using the software tools of MATLAB® (The Mathworks Inc., Natick, MA, USA), Freesurfer® (Freesurfer Troubles shooting Reconstruction work flow), and QDec®.

Methods and Materials

Cortical thickness was estimated at each vertex across the brain surface using a semi-automated approach implemented in the Freesurfer software (http://surfer.nmr.mgh.harvard.edu/) (Dale et al., 1999; Fischl et al., 2001; Fischl et al., 1999; Salat *et al.*, 2004; Segonne et al., 2004; Segonne et al., 2005). Thickness measurements were obtained by reconstructing representations of the gray matter (GM) / white matter (WM) boundary and the cortical surface and then calculating the distance between those surfaces at each point across the cortical mantle (Dale *et al.*, 1999). The analysis includes several segmentation steps to create white matter (WM), grey matter (GM) and pial borders for each individual brain. The segmentation included a Talairach transformation, manual stripping of the optical nerve and the dura mater, and an automated strip of the skull and subcortical structures (Segonne *et al.*, 2004). For quality control, all 97 segmentations were inspected, manually corrected and re-inspected as described by (Fischl *et al.*, 2001) and (Goldman *et al.*, 2009) by three independent raters (V.O., C.K., B.R.). For inter-rater reliability, raters, blinded to group membership, independently performed the correction steps. Inter-rater reliability computed by using 5 randomly selected brains and corrected by each of the 3 raters reached .93 to .96 for all brains. In addition, intra-rater reliability for five other, randomly selected brains was good (rater 1: .95, rater 2: .95, rater 3: .96).

We then applied a validated surface reconstruction algorithm (Dale *et al.*, 1999; Han and al., 2006; Rosas, 2002) to the volume data. Briefly, WM segmentations were first produced (Dale *et al.*, 1999), using information from the subcortical segmentations to also fill

in areas that commonly produce topological defects (such as basal ganglia and lateral ventricle). Cutting planes were used to isolate each cerebral hemisphere, and final binary WM masks were produced. Tessellation was then performed to produce a triangle-based mesh of the WM surface, and a smoothing algorithm was used to alleviate the voxel-based nature of the initial curvature (Dale *et al.*, 1999). Topological defects in the surfaces were then corrected using an automated topology fixer (Segonne *et al.*, 2005). Preprocessing involved a registration to a reference brain, which is an average template of all anatomies of our study. This average brain was used as a template for the visualization of the results.

The surfaces produced are in Talairach space, allowing direct, anatomically accurate measurements of thickness but also necessitating an algorithm for surface-based inter-subject registration. To achieve this, surfaces were spherically inflated (Fischl *et al.*, 1999), and spherical surfaces for each subject were registered to a common space spherical deformation guided by automatically defined cortical features derived from a population atlas (Fischl *et al.*, 1999). Final surface data were then parcellated into cortical regions using an automated algorithm, which used a manually labelled training data set, as well as knowledge of curvature and the spatial relationship between regions (Desikan et al., 2006; Fischl *et al.*, 2001). The atlas (Desikan *et al.*, 2006) included 33 gyral regions of interest. At the end of this process, each subject's reconstruction was again visually inspected for gross topological inaccuracies. Cortical thickness was calculated for each vertex in the triangulated surfaces by finding the point on the white matter surface that was closest to a given point of the pial surface (and vice versa) (Fischl and Dale, 2000; Han and al., 2006).

Statistical analysis

Node-by-node contrasts of cortical thickness were performed for healthy controls versus SZ patients, controls versus unaffected relatives, and SZ patients versus unaffected relatives. For

this, an average normal control surface was generated, and thickness data from each subject were mapped to this average surface and smoothed using a standard gaussian filter. Finally, each contrast was entered into an ANCOVA, including diagnosis, intracranial volume (ICV; (Prvulovic et al., 2002) sex and age as covariates. Results were thresholded at a surface-wide $p < 0.05$. We corrected for multiple comparison with permutation testing with Monte Carlo simulation and cluster analysis, as implemented in Freesurfer 4.50. In this procedure, the analysis is repeated 10,000 times with arbitrary group labels in order to generate a distribution under the null hypothesis of no difference between groups. This distribution then yields the minimum cluster size for the threshold-based comparison. The basic assumption of this approach is that random fluctuations of signal (in this case cortical thickness differences) are unlikely to cluster in space (Nichols and Holmes, 2002), and its implementation in Freesurfer is a standard procedure for the comparison of cortical thickness data between patients and controls (Pereira et al., 2011).

In addition, we computed the chlorpromazine equivalence doses for the patients' antipsychotic medication (Woods, 2003). Individual doses ranged from 200 to 1600 mg/d (mean: 613 [399]). We computed the correlation between the chlorpromazine equivalents and the cortical thickness indices to investigate a possible medication effect (Pearson bivariate correlation, 2-tailed). We also computed bivariate correlation analysis (Spearman rank correlation, 2-tailed) between the predisposition towards hallucinations (RHS, (Morrison *et al.*, 2002), the subjective cognitive dysfunction (ESI; Maß et al., 2000), the schizotypy (SPQ; (Klein, 1997) and the individual psychopathology (PANSS, (Kay *et al.*, 1987) with the cortical thickness indices.

3. Results

3.1 Statistical comparison between the subject groups

The group differences in psychometric data are documented in Table 1. For the cortical thickness, we found significant group differences in frontal, temporal and limbic areas (Table 2, Fig. 1). Patients showed significant cortical thinning in comparison with relatives and controls bilaterally in the inferior frontal gyrus, in the left superior temporal gyrus (BA 41) and the right lingual gyrus. Here, the contrasts between relatives and controls were not significant.

Both patients and relatives showed significantly lower cortical thickness in comparison with controls bilaterally in the middle frontal gyrus, in the left precentral gyrus, in the right superior temporal gyrus (BA 41), the left inferior parietal lobule, the right insula, the left anterior cingulate and bilaterally in the hippocampus and parahippocampal gyrus. Thickness values in these areas did not differ between relatives and patients.

Several other areas showed a continuum of cortical thickness across subject groups (CON> REL > PAT). This pattern of significant differences between all groups was observed in the right inferior frontal gyrus, the right precentral gyrus, the middle temporal gyrus bilaterally and the superior parietal lobule bilaterally. Conversely, we did not observe higher cortical thickness values in patients or relatives compared to controls in any area, even when lowering the threshold to $p = 0.1$.

In general, our results of the current study are in line with the estimates for cortical thickness (Fischl and Dale, 2000), with the lowest value for patients in the right inferior frontal gyrus (1.89 mm) and the highest value for controls in the left superior temporal gyrus (3.98 mm). We computed power calculations on the cortical thickness findings (Cohen, 1992) for any contrast (controls vs. patients / controls vs. relatives / relatives vs. patients). These calculations revealed effect sizes between $r = 0.45$ and $r = 0.61$ for all involved areas.

----------Insert table 2 and figure 1 about here----------

3.2 Correlation between cortical thickness and symptom severity

Because of previous reports links between cortical thickness in the temporal lobe with hallucinations (Kuperberg et al., 2003), we computed the correlation between RHS and PANSS and left superior temporal cortex thinning. No significant correlation was found between any of the PANSS scores and cortical thickness in any of the assessed areas ($p > 0.05$). However, we did find a significant correlation between the predisposition towards hallucinations (RHS) and left superior temporal cortex thinning in patients (rho = 0.43, $p = 0.03$) and relatives (rho = 0.38, $p = 0.04$), but not in controls (rho = 0.21, $p > 0.05$).

Following Hartberg et al (2010) and Ehrlich et al. (2011), who reported relationships between cortical thinning in frontal regions and cognitive functioning in patients with schizophrenia, we computed bivariate correlation analysis with ESI (subjective cognitive dysfunction) and cortical thickness measures for the frontal areas (bilateral inferior and middle frontal gyrus). The results showed that the inferior frontal gyrus cortical thickness bilaterally was significantly correlated with the subjective cognitive dysfunction in SZ patients (rho = 0.48, $p < 0.01$) and relatives (rho = 0.40, $p < 0.01$), but again not in controls (rho = 0.24, $p > 0.05$). All other computed correlations were non-significant ($p > 0.05$).

Moreover, correlation analysis between the total score of the schizotypy questionnaire (SPQ) was not correlated with any of the cortical thickness scores in any of the groups. Only the cognitive-perceptual factor was significantly associated with inferior frontal gyrus cortical thickness bilaterally in the relatives group (rho = 0.47, $p < 0.01$). Finally, parahippocampal / hippocampal volume was significantly associated with duration of illness in our patient group (rho = 0.55, $p < 0.01$).

4. Discussion

We demonstrate marked cortex thinning in SZ patients and relatives, most notably in frontal

and temporal lobes, in the superior parietal lobe and several limbic areas. We show, for the first time, a significant association between clinical and cognitive traits of SZ and cortical thinning in frontal and temporal regions in unaffected relatives.

Cortical thinning in SZ patients: frontal lobe, temporal lobe and limbic areas

Our findings cortical thinning in SZ patients replicates previous reports for frontal (Kuperberg *et al.*, 2003; Narr et al., 2005; White et al., 2003) and temporal (e.g., (Kubota et al., 2011; Kuperberg *et al.*, 2003) regions of SZ patients. Only one study (using a non–surface-based method) has found no reduction in frontal regions of SZ patients, but they investigated first-episode patients who would have been less affected by any progressive volume loss (Wiegand, 2004). Our findings are also in line with volumetric studies, which have indicated volume reduction in SZ mainly in prefrontal areas (Henn and Braus, 1999; Honea et al., 2005; Wright, 2000) and the superior temporal gyrus (Kuperberg *et al.*, 2003; Narr *et al.*, 2005; Oertel *et al.*, 2010; White *et al.*, 2003), and middle temporal gyrus (Goldman *et al.*, 2009; Henn and Braus, 1999; Honea *et al.*, 2005; Wright, 2000) and medial temporal lobe (Henn and Braus, 1999; Honea *et al.*, 2005; Wright, 2000). However, although prefrontal and temporal regions are generally the most strongly implicated in schizophrenia, cortical volume loss was not confined to these regions, which is again consistent with previous literature (Goldman *et al.*, 2009; Henn and Braus, 1999; Honea *et al.*, 2005; Wright, 2000). This supports the idea that the predominant functional impairment of prefrontal and temporal structures in schizophrenia may not be exclusively due to localized structural-functional effects, but also mediated through the extensive interconnections that these regions maintain with the rest of the brain (Goldman *et al.*, 2009; Harrison and Weinberger, 2005; Meyer-Lindenberg, 2009; Weinberger and Lipska, 1995).

Our SZ sample also showed significant thickness reductions in parahippocampal gyrus/hippocampus in comparison with controls. Previous results in the parahippocampal

gyrus were equivocal, with some studies reporting reduced thickness (Kuperberg *et al.*, 2003; Murakami et al., 2010) but others failing to find parahippocampal gyrus thinning in first-episode schizophrenia (Narr *et al.*, 2005), in the first 5 years of childhood-onset schizophrenia (Thompson, 2004) and in chronic SZ patients (Goldman *et al.*, 2009). The inconsistencies in the literature may be the result of inter-individual variability and different morphometric methods, and the present approach of cortical thickness mapping at 3 Tesla may be have been more sensitive than some of the previous studies.

The cortical thickness reductions observed in imaging studies are plausible considering the findings of post-mortem studies, which have indicated an overall decrease in brain size (Bruton et al., 1990), volume reduction of the cerebral hemispheres (Pakkenberg, 1993), and several regional alterations, e.g., reduced size of temporal lobe structures (Vogeley et al., 1998). In addition to reduced size and number of neurons, their positioning across layers was also altered in various brain regions in post-mortem brains from SZ patients (Harrison, 1999). (Harrison, 1999) suggested that these alterations may indicate a reduced number of synaptic contacts in the affected areas. Another possibility is that neuronal apoptosis might contribute to gray matter alterations in schizophrenia (Glantz et al., 2006). Post-mortem studies of schizophrenia indicate that apoptotic regulatory proteins and DNA fragmentation patterns are altered in several cortical regions (Benes et al., 2003) and (Jarskog et al., 2004).

However, the underlying pathology of cortical thinning in SZ is not yet well understood (DeLisi et al., 2006; Harrison, 1999; Keshavan et al., 2008). Higher cell density (Pakkenberg, 1993; Selemon et al., 1995), smaller neuropil (Selemon et al., 1998) and reduced neuron size (Rajkowska et al., 1998) in the cortical gray matter have been suggested as potential explanation, but these findings were not consistently confirmed (Arnold et al., 1995; Cullen et al., 2006; Harrison, 1999). Cortical thickness does not need to be synonymous to volume (Goldman *et al.*, 2009), especially if altered gyrification patterns are taken into

account (Tepest et al., 2008). Furthermore, findings of (Murakami *et al.*, 2010) – as well as the present study - indicate that the duration of illness might be one additional factor contributing to volumetric and cortical thickness findings, which may explain some of the inconsistencies in the previous literature highlighted above. Another potential confound, as pointed out by (Goldman *et al.*, 2009), is that structural changes measured with MRI may not correspond to cellular changes but rather to changes in tissue fluid levels and vascularization.

One potential limitation of studies investigating brain morphology in SZ patients is the confounding effect of present or past antipsychotic medication. Studies in monkeys treated long-term with antipsychotic drugs have demonstrated that cortical volume is reduced by these agents (Dorph-Petersen et al., 2005). (Tost et al., 2010) reported an induction of reversible striatal volume changes and structural-functional decoupling in motor circuits within hours through acute D2 receptor blockade. However, cortical volume reduction in previous patient studies mainly resulted from typical antipsychotics (Dazzan *et al.*, 2005), whereas our patients were all treated with atypical antipsychotics. To control for this factor, we performed an additional analysis of the cortical thickness without the four patients with additional typical antipsychotics, which showed similar results to the main analysis. We further controlled for medication effects by correlation analysis with chlorpromazine equivalents in our patient group.

Cortical thinning in unaffected first-degree relatives

Our unaffected first-degree relatives showed cortical thickness reductions in frontal, precentral, temporal, parietal and limbic (insula, anterior cingulate, hippocampal gyrus / hippocampus) areas. Temporal, parietal and cingulate cortical thinning in unaffected relatives of SZ patients has been shown previously (Calabrese *et al.*, 2008; Goghari *et al.*, 2007b, 2007a; Goldman *et al.*, 2009; Yang *et al.*, 2010). However, the literature is contradictory with respect to altered frontal and especially prefrontal lobe structure (Goldman *et al.*, 2009;

Callicott et al., 2003; Goghari *et al.*, 2007b, 2007a).

Reasons for such contradictory findings may be difference in sample selection, small sample sizes, heterogeneous study groups and sensitivity of the imaging procedure. We recruited relatives of patients from other patients than those included in this study, which is an accepted procedure (Repovs et al., 2011). Although in some respects it may be even better to recruit relatives of the study patients (Venkatasubramanian *et al.*, 2011), this poses additional difficulties with respect to participant matching and would induce a bias in the patient group (by confining it to those who have siblings). Assuming that for all their genetic heterogeneity, patients with schizophrenia have consistent abnormalities in the brain (e.g. cortical thinning), it makes sense to probe the same effects in a relative group who also carry schizophrenia risk genes (although not necessarily the same) but are not affected by secondary effects of the illness. The theoretical rationale behind this is that the various risk genes will converge on biological pathways, for example those regulating brain development (Owen et al., 2010).

Some previous studies did not compare patients and relatives directly, but only relatives and controls (Goghari *et al.*, 2007b, 2007a; Gogtay *et al.*, 2007; Mattai et al., 2011). We would suggest that it is important to compare across all three groups (controls, unaffected relatives and patients) to confirm that observed changes in relatives are actually trait markers of the disorder rather than, for example, indicators of resilience. There is some indication that cortical abnormalities in relatives of schizophrenia patients are most prominent during brain development (Gogtay *et al.*, 2007). (Gogtay, 2008) reported that younger healthy siblings of SZ patients showed significant GM deficits, but that these changes disappeared by age 20. This dynamic pattern, which has recently been replicated (Mattai et al., 2011) may indeed indicate preserved plasticity and resilience in the non-psychotic siblings (Gogtay, 2008).

Association with symptom severity and cognitive function

We tested whether altered cortical thickness may predispose patients to specific symptoms,

probing for subclinical psychotic symptoms in all participants. We provide evidence for a significant correlation between predisposition towards hallucinations (RHS) and left superior temporal cortex thinning in both patients and relatives Our results revealed no significant association between state markers of symptom severity, as measured with the PANSS, and cortical thinning. (Goldman *et al.*, 2009) report only an association between left superior temporal cortex thinning and the general psychopathology subscale of the PANSS in patients, and did not address associations in the relatives group or use scales assessing trait markers of prepsychotic symptomatology as used in the present study (RHS, ESI, SPQ).

Our finding of an association between the subjective cognitive dysfunction (ESI) and perceptual-cognitive factor (SPQ) (only relatives) and thinning of frontal areas in patients and relatives expand on the findings by (Hartberg *et al.*, 2010) and (Ehrlich et al., 2010), who reported a significant positive relationship between volume loss in frontal, temporal and occipital regions and tests for verbal IQ, verbal learning and executive functions in SZ patients.

Conclusion

The main finding of the present study was widespread cortical thinning in unaffected relatives of patients with schizophrenia compared to healthy matched controls. These were largely intermediate to the differences found between patients and controls, suggesting the possibility that they constitute an endophenotype of the disorder (Gottesman and Shields, 1973; Gottesman and Gould, 2003; Shields and Gottesman, 1972; Van Os and Jones, 2001). Interestingly, thinning in frontal areas correlated with cognitive complaints and that in temporal areas with the propensity to develop hallucinations. Our findings are relevant for neurodevelopmental models of schizophrenia and indicate new quantitative trait loci for

association studies that explore the genes that confer vulnerability to abnormal brain development in SZ.

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Table 1: Sociodemographic and clinical variables across all groups (SZ patients, relatives, controls). Abbreviations: PAT = SZ patients, REL = first-degree relatives, CON = healthy controls.

	PAT	**REL**	**CON**	**F test (One-way ANOVA)**
N	31	29	37	97
Gender	15 female, 16 male	15 female, 14 male	20 female, 17 male	
Years of education**	14.26 (2.57)	15.05 (4.12)	16.05 (2.63)	
Parental Education (years, SD)	Mother: 12.84 (2.36) Father: 12.93 (2.70)	Mother: 12.69 (2.24) Father: 13.72 (3.01)	Mother: 12.92 (2.79) Father: 13.40 (3.00)	
Age (years, SD)	38.00 (11.24)	40.38 (15.84)	39.36 (9.97)	
Handedness	All right-handed	All right-handed	All-right handed	
RHS (mean) Significance	33.31 (4.87) PAT / REL: p = 0.03	27.50 (5.66) REL / CON: n.s.	23.67 (3.02) PAT / CON: p < 0.01	F (2, 95) = 8.99, p< 0.01
ESI (mean, SD)	22.31 (6.17) PAT / REL: p < 0.01	10.87 (8.08) REL / CON: n.s.	5.64 (0.70) PAT / CON: p < 0.01	F (2, 95) = 19.80, p<0.01
SPQ (mean, SD)		13.02 (6.13)	4.57 (1.54) REL / CON < 0.01	F (1, 65) = 43.18, p <0 .01
SPQ cognitive-perceptual factor (mean, SD)		7.34 (4.03)	2.45 (1.14) REL / CON < 0.01	F (1, 65) = 45.65, p < 0.01
SPQ interpers. factor (mean, SD)		4.23 (2.32)	4.98 (2.43) REL / CON n.s.	F(1, 65) =19.15 p <0 .01
Diagnosis	Paranoid SZ (DSM-IV criteria 295.30 [APA, 1994])			
History of hallucinations	All (n = 25) history of hallucinations → n = 12: this episode, 6 of them in the week of the measurement → n = 13: earlier episode			
Age of onset	24.43 (6.63)			

Years of illness	13.71 (6.87)
Medication	27 atypical 4 atypical and typical,
PANSS	Positive 15.69 (3.20), Negative 15.13 (1.78), General 32.06 (4.07), Sum 62.75 (5.30), Hallucination: 3.08 (1.40)

P = significant on a > 0.05-threshold.

Table 2: The table contains all regions which showed significant differences in cortical thickness (in mm) across groups (group contrast; left column). The middle rows shows in all significant areas mean values (in mm) of cortical thickness across groups. The table shows also post-hoc single contrast analysis between all groups (right column). All areas, which show a significant continuum of controls, relatives and patients are highlighted in bold face. Abbreviations: BA = Brodmann area, l. = left, r. = right, inf. = inferior, sup. = superior.

Region (BA)	**PAT** Mean mm (SD)	**REL** Mean mm (SD)	**CON** Mean mm (SD)	**Significance F, p**
L. inf. frontal gyrus (45/46/47)	2.11 (0.24)	2.56 (0.22)	2.51 (0.22)	CON/PAT: F(95) = 6.19, p = 0.02 REL/ PAT: F(95) = 6.95, p = 0.01 CON/ REL: n.s.
R. inf. frontal gyrus (45)	2.03 (0.12)	2.34 (0.18)	2.35 (0.29)	CON/PAT: F(95) = 5.53, p = 0.03 REL/PAT: F(95)=7.65, p = 0.01 CON/REL: n.s.
R. inf. frontal gyrus (9)	**1.89 (0.14)**	**2.01 (0.14)**	**2.88 (0.21)**	**CON/PAT: F(95) = 8.71, p < 0.01** **REL/PAT: F(95)=17.56, p < 0.01** **CON/REL: F(95)=12.70, p< 0.01**
L. mid. frontal gyrus (6,10)	2.10 (0.15)	2.08 (0.22)	2.79 (0.18)	CON/PAT: F (95) = 8.07, p <0.01 REL/PAT: n.s. CON/REL: F(95) = 6.79, p= 0.02
R. middle frontal gyrus (6,10)	2.44 (0.29)	2.35 (0.24)	2.98 (0.31)	CON/PAT: F(95)= 4.65, p = 0.04 F(95) = 7.71, p = 0.01 REL/PAT: n.s. CON/REL: F(95) = 5.57, p= 0.03
L. precentral gyrus (4)	2.36 (0.14)	2.35 (0.25)	2.78 (0.22)	CON/PAT: F(95) = 6.31, p = 0.02 REL/PAT: n.s. CON/REL: F(95)= 4.43, p = 0.04
R. precentral gyrus (6)	**2.65 (0.26)**	**3.01 (0.22)**	**3.33 (0.34)**	**CON/PAT: F(95)=8.07, p < 0.01** **REL/PAT: F(95) = 6.55, p = 0.02** **CON/REL: F(95) = 8.12, p= 0.01**
L. inf. temporal gyrus (20)	**2.03 (0.14)**	**2.87 (0.18)**	**3.21 (0.45)**	**CON/PAT: F(95) = 6.98, p =0.01** **REL/PAT:F(95) = 11.31, p < 0.01** **CON/REL: F (95)= 5.43, p= 0.02**

R. middle temporal gyrus (21)	**1.97 (0.21)**	**2.78 (0.22)**	**3.02 (0.11)**	**CON/PAT: F(95)=14.51, p < 0.01** **CON/ REL: F(95)= 4.01, p= 0.04** **REL / PAT: F(95) =6.33, p< 0.01**
L. sup. temporal gyrus (41)	2.82 (0.59)	3.55 (0.43)	3.98 (0.13)	CON/PAT: F(95)= 16.46, p< 0.01 CON/REL: F(95) = n.s. REL/PAT: F(95)= 15.07, p < 0.01
R. sup. temporal gyrus (41)	2.46 (0.15)	2.69 (0.25)	2.97 (0.17)	CON/ PAT: F(95)= 4.43, p = 0.04 CON/REL: F(95) = 4.91, p= 0.04 REL/PAT : n.s.
L. inf. parietal lobule (40)	2.14 (0.18)	2.34 (0.14)	2.82 (0.59)	CON/PAT: F(95) = 6.89, p = 0.02 CON/REL:F(95)= 14.19, p< 0.01 REL/PAT: n.s.
L. sup. parietal lobule (7)	**1.99 (0.19)**	**2.05 (0.16)**	**2.34 (0.15)**	**CON/PAT: F(95) = 8.57, p = 0.01** **CON/REL: F(95)= 5.31, p = 0.03** **REL/PAT: F(95) = 9.85, p < 0.01**
R. sup. parietal lobule (7)	**2.03 (0.23)**	**2.97 (0.17)**	**3.55 (0.43)**	**CON/PAT: F(95)= 28.06, p< 0.01** **CON/REL: F(95) = 4.01, p= 0.04** **REL/PAT: F (95) = 6.65, p = 0.02**
L. lingual gyrus (19)	2.35 (0.14)	2.56 (0.23)	2.96 (0.32)	CON/PAT: F(95) = 8.70, p < 0.01 CON/REL: F(95) = 9.32, p< 0.01 REL/PAT: 7.31, p = 0.01
R. lingual gyrus (19)	2.30 (0.22)	2.94 (0.13)	3.13 (0.21)	CON/PAT: F(95)=19.30, p< 0.01 CON/REL: n.s. REL/PAT: F(95): 8.88, p < 0.01
R. insula	2.17 (0.18)	2.34 (0.10)	2.86 (0.21)	CON/PAT: F(95)=14.19, p< 0.01 CON/REL: F (95)= 5.81, p= 0.03 REL/PAT: n.s.
L. para-hippocampal gyrus, Hippocampus (36)	2.36 (0.21)	2.66 (0.13)	2.95 (0.16)	CON/PAT: F(95) = 9.98, p < 0.01 CON/REL: F(95)= 8.07, p = 0.01 REL / PAT: n.s.
Right parahippocampal gyrus / hippocampus (36)	1.97 (0.19)	2.01 (0.13)	2.43 (0.14)	CON/PAT: F(95) = 7.12, p = 0.01 CON/REL: F(95) =5.28, p = 0.04 REL / PAT: n.s.
L. anterior cingulate, (24)	2.15 (0.12)	2.35 (0.14)	2.82 (0.29)	CON/PAT: F(95) = 9.53, p < 0.01 CON/REL: F(95) = 8.18, p< 0.01 REL/PAT: n.s.

Figure legend:

Figure 1: Statistical comparisons between all groups. The upper three rows show group comparisons between controls and patients, controls and relatives and relatives and patients in the left hemisphere, the lower three rows show group comparisons between controls and patients, controls and relatives and relatives and patients in the right hemisphere. The color bars denote t values (red: higher activation in the first compared to the second group of each contrast).