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Heritability of cortical thickness changes over time in twin pairs discordant for schizophrenia

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ABSTRACT

Background: Cortical thickness and surface area changes have repeatedly been found in schizophrenia. Whether progressive loss in cortical thickness and surface area are mediated by genetic or disease related factors is unknown. Here we investigate to what extent genetic and/or environmental factors contribute to the association between change in cortical thickness and surface area and liability to develop schizophrenia.
Method: Longitudinal magnetic resonance imaging study over a 5-year interval. Monozygotic (MZ) and dizygotic (DZ) twin pairs discordant for schizophrenia were compared with healthy control twin pairs using repeated measures analysis of variance (RM-ANOVA) and structural equation modeling (SEM). Twins discordant for schizophrenia and healthy control twins were recruited from the twin cohort at the University Medical Centre Utrecht, The Netherlands. A total of 90 individuals from 46 same sex twin pairs were included: 9 MZ and 10 DZ discordant for schizophrenia and 14 MZ and 13 (11 complete and 2 incomplete) DZ healthy twin-pairs. Age varied between 19 and 57 years.
Results: Higher genetic liability for schizophrenia was associated with progressive global thinning of the cortex, particularly of the left superior temporal cortex. Higher environmental liability for schizophrenia was associated with global attenuated thinning of the cortex, and including of the left superior temporal cortex. Cortical surface area change was heritable, but not significantly associated with higher genetic or environmental liability for schizophrenia.
Conclusions: Excessive cortical thinning, particularly of the left superior temporal cortex, may represent a genetic risk marker for schizophrenia.

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1. Introduction

Schizophrenia is characterized by structural brain abnormalities that appear to progress with longer illness duration (Pantelis et al., 2005; DeLisi, 2008; Hulshoff Pol and Kahn, 2008; Van Haren et al., 2008; Kempton et al., 2010; Andreasen et al., 2011; Olabi et al., 2011; Haijma et al., 2013). One of the brain areas in which progressive structural brain abnormalities have been implicated in schizophrenia is the cerebral cortex. Excessive thinning of the cortex, particularly of the frontotemporal cortices, has been reported in childhood onset (Thompson et al., 2001; Greenstein et al., 2006), recent onset (Ziermans et al., 2012), first episode (Rais et al., 2010), as well as in more advanced stages of schizophrenia (Rimol et al., 2010; Van Haren et al., 2011). One would assume that these data suggest that the progressive cortical thinning in schizophrenia is related to the effects of the illness. However, schizophrenia is highly heritable (Sullivan et al., 2003), and brain volume and cortical thickness are also considerably influenced by genes (Peper et al., 2007; Blokland et al., 2012). Indeed, recent studies using genome-wide associations have identified genes implicated in schizophrenia (Schizophrenia Working group of Psychiatric Genomics Consortium, 2014), in brain volumes (Stein et al., 2012; Hibar et al., 2015) and in a thinner cortex in schizophrenia (Bakken et al., 2011). Moreover, progressive brain volume loss in schizophrenia, particularly of the frontal and temporal lobes, is at least partially heritable through genes implicated in the illness (Brans et al., 2008). Thus, it is reasonable to hypothesize that the cortical thickness changes observed in schizophrenia could be related to the genetic risk to develop the illness. Interestingly, while several imaging studies in twin and siblings of schizophrenia patients have been done (Moran et al., 2013), it has not been studied if genetic risk for schizophrenia is related to excessive thinning of the cortex. What is known is that, *cross-sectionally*, a thinner cortex in schizophrenia can in part be attributed to genes conferring risk to develop the disorder (Goldman et al., 2009; Hulshoff Pol et al., 2012). That *progressive* cortical thinning in schizophrenia may indeed be (partially) attributable to schizophrenia risk genes as well is suggested by a study where increased familial risk was related to excessive thinning of prefrontal and temporal cortices in childhood schizophrenia

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(Gogtay et al., 2007). However, since so far twins have not been studied, it remains unresolved whether the reported progressive cortical thinning is related to the effects of (increased) genetic burden or whether it is attributable to the environment.

In addition to changes in cortical thickness, reduced cortical surface area has also been found in schizophrenia (Hartberg et al., 2011; Palaniyappan et al., 2011; Rimol et al., 2012). Since brain volume is represented by combined aspects of cortical thickness and surface measures (Winkler et al., 2010), each of which are influenced by their own genetic factors (Panizzon et al., 2009; Winkler et al., 2010) it is therefore possible that genes for schizophrenia are differentially associated with changes over time in cortical thickness or surface area in schizophrenia. Localized surface area contraction has been reported to occur in patients (Palaniyappan et al., 2011) and may be related to the risk to develop schizophrenia (Prasad et al., 2010). However, these studies did not include twins, and therefore cannot resolve the issue of whether cortical surface area (contraction) is associated with the genetic liability to develop schizophrenia. The purpose of the current study was to establish the relative contributions of genetic and environmental (disease-related) factors to progressive changes in cortical thickness and surface area over time in schizophrenia. Specifically, we hypothesized that increased genetic risk for schizophrenia contributes to excessive thinning of the cortex.

2. Methods

2.1. Subjects

Participants were recruited from the twin-pair cohort at the University Medical Centre Utrecht (Brans et al., 2008). A total of 109 twins completed the baseline study. In the baseline sample discordant twins were matched to control twins for zygosity, age, gender, birth order, handedness, socioeconomic status of their parents, and follow-up duration. A total of nine MZ and ten DZ twin-pairs discordant for schizophrenia and 14 MZ and 11 DZ healthy comparison twin-pairs plus two singletons DZ healthy controls (i.e. from incomplete pairs) completed the longitudinal MRI study (total N = 90 subjects) after an interval of approximately five years (T5) (mean = 4.86 years; SD = 0.57) (Table 1). All twins participated after written informed consent was obtained.

2.2. Brain imaging

T1 and T2-weighted magnetic resonance brain scans were acquired on a Philips NT scanner (Philips Medical Systems, Best, The Netherlands) operating at 1.5 T in all participants (for details see Supplementary data). Processing was done on the neuroimaging computer network from the Department of Psychiatry, University Medical Center Utrecht, The Netherlands. All images were coded to ensure blindness of participant identification and diagnoses. Scans were manually put into Talairach frame (no scaling) for segmentation purposes and corrected for inhomogeneities in the magnetic field (Sled et al., 1998). Intensity histogram analysis on the T1 image yielded thresholds for separating brain tissue from the cerebrospinal fluid and, within the brain, gray matter (GM) from white matter (WM); GM and WM segments were created by applying these thresholds to the images (Schnack et al., 2001).

For cortical measurements, we used the CLASP (Constrained Laplacian Anatomic Segmentation using Proximity) algorithm designed at the McConnell Brain Imaging Centre of the Montréal Neurological Institute (MacDonald et al., 2000; Kabani et al., 2001; Kim et al., 2005). For a detailed description of the image processing methods see (Schnack et al., 2015, Supplementary data).

The analysis involved two stages. First, the ROIs were used in the statistical analyses to allow for acceptable statistical power for the twin analyses. For each person, the mean change in cortical thickness and in surface area per ROI was calculated. Secondly, a vertex-wise analysis for cortical thickness change was carried out to display the results in high-resolution maps. Thus, all statistical analyses were done on the AALs. We did not have sufficient statistical power to find significant vertex-wise based effects. We presented the figure based on vertex-wise analysis to provide the most local information available.

2.3. Statistical analyses

Cortical thickness and surface area change data over the 5-year interval were calculated (Table 2). Moreover, cortical thickness and surface area change data per year were computed and subsequently prepared using regression analysis to control for the effects of age, sex, and handedness. Unstandardized residuals were saved for further statistical analysis. For statistical analysis of the data, the approach was two-fold, including multiple repeated-measures univariate analyses of variance (RM-ANOVA) and structural equation modeling (SEM) (see also Brans et al., 2008; Hulshoff Pol et al., 2012). RM-ANOVA made the findings comparable with earlier studies and provided the correction for multiple comparison selection of ROIs. SEM provided estimates of genetic and environmental influences.

2.3.1. RM-ANOVA

Unstandardized residuals for change in total and ROI cortical thickness/surface area were entered one by one as dependent variables.

Table 1
Demographic characteristics of monozygotic and dizygotic patients with schizophrenia, their co-twins and healthy control twin pairs.

Characteristic	Monozygotic twins				Dizygotic twins			
	Pat	Co-twins	HC 1	HC 2	Pat	Co-twins	HC 1	HC 2
No	9	9	14	14	10	10	12	12
Age, mean (SD), year	40.2 (12.2)	40.2 (12.2)	35.5 (11.8)	35.5 (11.8)	37.1 (11.9)	37.2 (11.9)	34.0 (9.9)	36.3 (10.6)
Sex, M/F, no	4/5	4/5	9/5	9/5	6/4	6/4	7/5	8/4
Follow-up duration, mean (SD), year	4.88 (1.02)	4.83 (0.98)	4.80 (0.22)	4.78 (0.21)	4.98 (0.59)	4.92 (0.69)	4.91 (0.43)	4.83 (0.41)
Handedness, right/left/both, no	8/1/0	8/0/1	11/1/2	10/3/1	9/1/0	9/1/0	10/2/0	10/1/1
Parental education mean (SD), year[a]	12.44 (2.65)	12.44 (2.65)	10.93 (2.43)	10.93 (2.43)	11.90 (2.51)	11.90 (2.511)	10.92 (2.61)	10.92 (2.57)
Education, mean (SD), year[a]	11.56 (3.05)	12.00 (2.83)	12.36 (2.41)	12.93 (3.10)	10.40 (2.27)	13.20 (3.01)	12.83 (2.53)	12.75 (2.56)
Medication nr typical/atypical/both	4/3/2				3/3/3[b]			
Cumulative haloperidol eq., mean (SD)	10,427 (6477)				8606 (6931)[b]			
Age at illness onset, mean (SD), year	22.78 (5.54)				22.50 (6.10)			
Duration of illness, mean (SD), year	17.41 (11.82)				14.63 (8.73)			
PANSS total score at t0 mean (SD)	67.67 (29.49)[c]				55.30 (16.44)			
PANSS total score at f-u mean (SD)	50.78 (14.99)				50.00 (18.51)			

Pat = patient; HC = healthy control; t0 = baseline; f-u = follow up. For details see Supplementary data.
[a] Significant difference between groups.
[b] Data was missing for one individual.
[c] Data was missing for three individuals.

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Table 2
The magnitude of change in cortical thickness and surface area over 5 years.

Characteristic	Monozygotic twins				Dizygotic twins			
	Pat	Co-twins	HC 1	HC 2	Pat	Co-twins	HC 1	HC 2
Cortical thickness change mean (SD) in mm								
Global cortex	−0.02 (0.11)	−0.09 (0.04)	−0.01 (0.08)	−0.01 (0.09)	−0.08 (0.15)	−0.06 (0.07)	0.00 (0.08)	−0.01 (0.06)
Left hemisphere	−0.02 (0.11)	−0.08 (0.05)	0.00 (0.07)	−0.01 (0.10)	−0.07 (0.12)	−0.07 (0.09)	0.00 (0.09)	−0.03 (0.07)
Right hemisphere	−0.02 (0.11)	−0.08 (0.05)	0.00 (0.07)	−0.01 (0.10)	−0.07 (0.12)	−0.07 (0.09)	0.00 (0.09)	−0.03 (0.07)
Left superior temporal cortex	−0.01 (0.13)	−0.10 (0.09)	0.03 (0.09)	−0.02 (0.12)	−0.12 (0.10)	−0.15 (0.14)	0.02 (0.11)	−0.01 (0.11)
Cortical surface area change mean (SD) in cm^2								
Global surface area	−5.77 (27.71)	−7.12 (20.80)	−10.42 (21.17)	−10.79 (34.15)	−19.81 (33.05)	−9.08 (24.10)	−17.19 (22.96)	−17.73 (24.40)
Left surface area	−0.36 (16.92)	−3.71 (9.57)	−3.71 (11.79)	−5.76 (17.63)	−10.18 (20.60)	−3.50 (13.97)	−8.76 (12.05)	−7.14 (16.14)
Right surface area	−5.41 (13.62)	−3.41 (15.15)	−6.71 (10.80)	−5.04 (17.31)	−9.63 (13.90)	−5.58 (11.32)	−8.43 (12.72)	−10.59 (11.19)
Left superior temporal area	−0.26 (3.84)	−0.59 (1.70)	1.13 (3.62)	0.08 (1.95)	0.22 (2.10)	−1.17 (2.96)	0.68 (1.65)	−1.06 (2.64)

Twin (twin 1 = patient with schizophrenia or healthy control, twin 2 = co-twin of patient or healthy control) was entered as within-subjects factor. Between-subjects factors were Group (discordant twin pair, healthy twin pair) and Zygosity (MZ, DZ). To correct for multiple comparisons for Group main effects taking the dependencies between the ROIs into account, we first computed the effective number of independent variables based on spectral decomposition of the correlation matrix (Nyholt, 2004; Li and Ji, 2005). The threshold for significance was set by dividing the alpha level by the effective number of independent variables, which resulted in a critical p-value of $0.05/43 = 1.19 * 10^{-3}$ for cortical thickness.

Post-hoc bivariate correlations were done on unstandardized residuals to examine the potential influence of cumulative haloperidol equivalents.

2.3.2. Genetic model fitting

Structural equation modeling was performed to further investigate the relative contributions of genetic and environmental factors to all change measures and their associations with the risk for schizophrenia (for baseline cortical thickness analyses in this twin cohort see Hulshoff Pol et al., 2012). By applying bivariate genetic models, genetic and/or environmental related factors were estimated to explain the phenotypic correlations (r_{ph}) between schizophrenia liability (constrained at $h^2 = 81\%$, $c^2 = 11\%$ and $e^2 = 8\%$ (Sullivan et al., 2003)) and cortical thickness/surface area changes (Fig. 1, Supplementary data). Cross-twin cross-trait correlations provide information regarding the extent to which the same genetic and unique environmental effects influence the risk to develop schizophrenia and cortical thickness/surface area changes. Genetic model fitting was based on the same twin model as described in more detail in Hulshoff Pol et al. (2012).

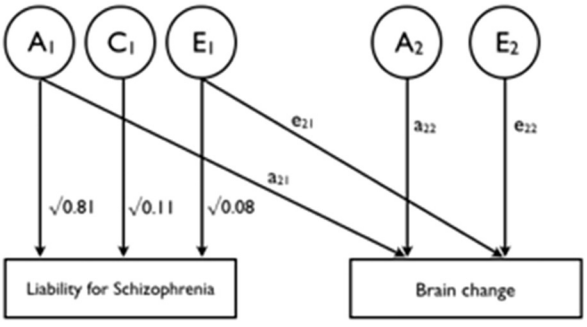

Fig. 1. Bivariate genetic modeling. Genetic model-fitting was carried out in each trait (i.e., change in cortical thickness/surface area, or change in predefined ROIs that differed significantly between discordant and control pairs) (for details on the procedure see Supplementary data).

3. Results

3.1. Demographics

A significant difference in subject's level of education was found between control twins, patients and co-twins ($F_{(2,87)} = 3.21$, $p = 0.045$). Pairwise comparisons showed that controls had a significantly higher level of education relative to patients ($p < 0.05$) while level of education between controls and co-twins of patients did not differ significantly. Discordant twins differed significantly from the healthy twins on parental education ($t_{(88)} = -2.37$, $p < 0.05$), with parents of discordant twins having a higher level of education level as compared with parents of control twins (Table 1).

3.2. Change in global and ROI-based cortical thickness and surface area over the five-year interval

3.2.1. Repeated measures analysis of variance

Over time, the patients and their co-twins combined showed an overall progressive decrease in cortical thickness as compared with the healthy control twins expressed as a significant main effect of Group ($F_{1,40} = 7.46$; $p = .01$) (Fig. 2, Table 2). No significant main or interaction effects were found for change in surface area (Fig. 2, Table 2). ROI analyses for cortical thickness change revealed significantly more pronounced cortical thinning over time in the discordant twin pairs as compared with the healthy control twin pairs (i.e., main effect of Group) in the left superior temporal cortex ($F_{1,40} = 13.65$; $p = .001$) (Table 3). Running the analyses without correcting for age, sex, and handedness did not alter the findings. This finding remained significant after Bonferroni correction for multiple comparisons ($p < 1.19 * 10^{-3}$). None of the ROI analyses for local surface area change survived correction for multiple comparisons.

Post-hoc paired t-test analyses between the probands and their co-twins to test whether there were any significant differences between the slopes of change in global cortical thickness and global surface area were not significant (smallest $p = 0.104$ for cortical thickness change in MZ discordant pairs).

3.2.2. Genetic modeling

Genetic liability for schizophrenia was significantly associated with more pronounced cortical thinning over time ($r_{ph\text{-}a} = -.20$), particularly for the left superior temporal cortex ($r_{ph\text{-}a} = -.25$) (Fig. 3, Table 4). No significant associations between genetic liability for schizophrenia and cortical surface area change were found (Table 4). Environmental factors implicated in schizophrenia were significantly associated with less prominent cortical thinning over time ($r_{ph\text{-}e} = .10$), including the less prominent left superior temporal thinning ($r_{ph\text{-}e} = .13$). Environmental factors implicated in schizophrenia were not significantly associated with cortical surface area change. The phenotypic correlations,

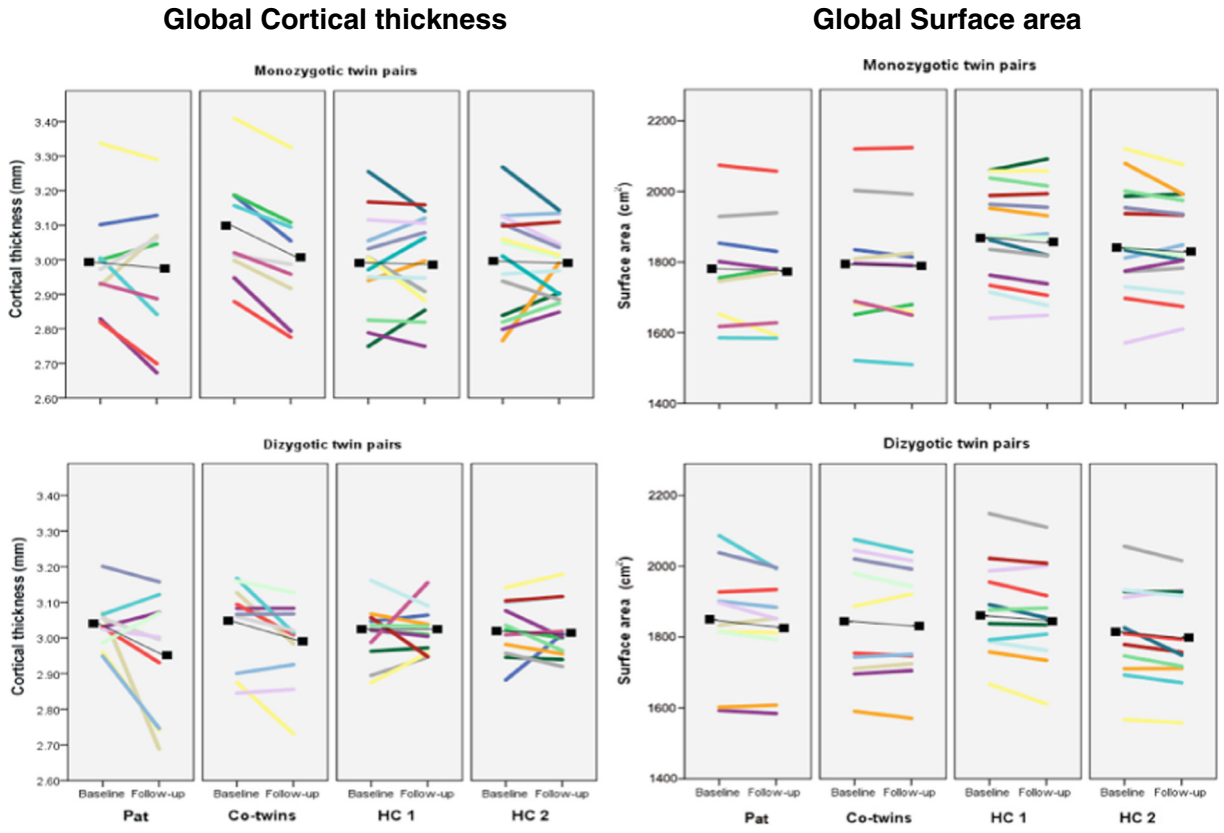

Fig. 2. Individual changes in cortical thickness and surface area over time. Brain changes in MZ and DZ twin pairs discordant for schizophrenia and control twin-pairs over the 5-year interval are represented through color-coding. The average for each group is represented in black squares. Raw data are shown. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

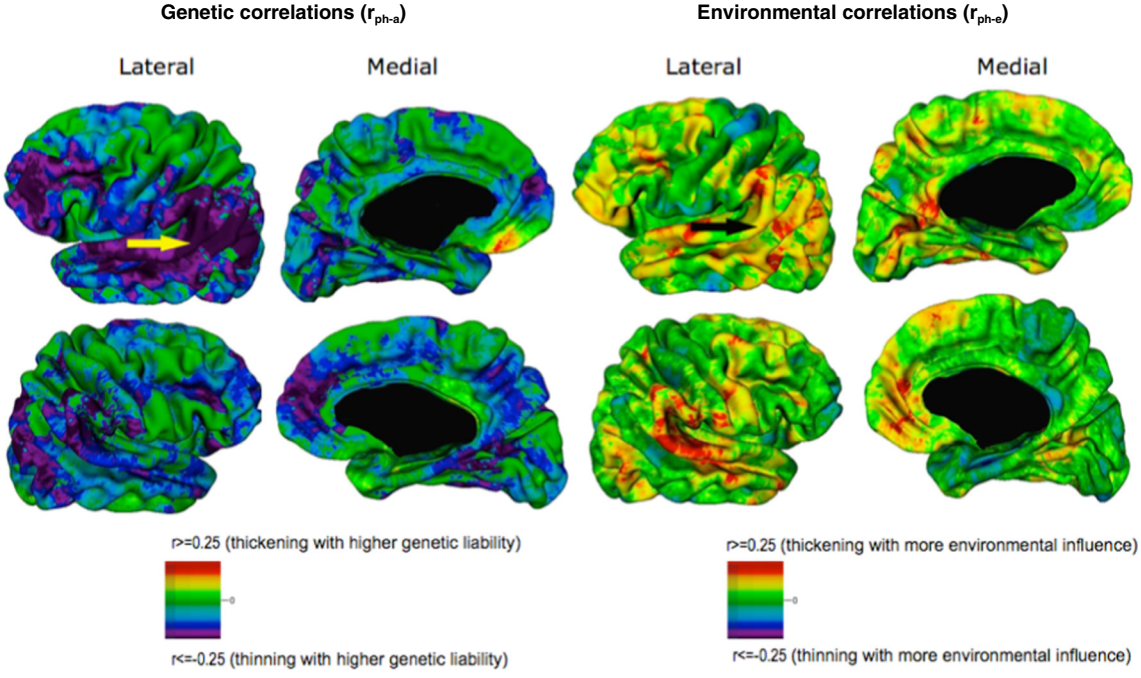

Fig. 3. Genetic and environmental liability for schizophrenia and cortical thickness change over time. Higher genetic (r_{ph-a}) and environmental (r_{ph-e}) correlations between liability for schizophrenia and cortical thinning over the 5-year interval are represented by negative correlations (up to blue/purple), and cortical thickening by positive correlations (up to orange/red) presented for each vertex. Arrow shows the left superior temporal cortex as based on the ROI analysis ($p < 1.19 * 10^{-3}$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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Table 3
Significance of change in cortical thickness and surface in twin pairs discordant for schizophrenia as compared to control twins over 5 years.[a]

	Cortical thickness		Cortical surface area	
	Left	Right	Left	Right
Precentral	0.010249[b]	0.026368	0.942499	0.995169
Frontal sup	0.038697	0.126870	0.982524	0.445866
Frontal sup orb	0.818421	**0.003741**	0.642806	0.222512
Frontal mid	**0.009376**	0.072374	0.551523	0.537141
Frontal mid orb	0.073125	0.033060	0.909901	0.898585
Frontal inf oper	0.644209	0.525835	0.718599	0.083343
Frontal inf tri	0.035190	0.010733	0.912676	0.025700
Frontal inf orb	0.409583	0.080897	0.158019	0.055978
Rolandic oper	0.151280	0.716579	0.439152	0.294437
Supp motor area	0.103592	0.033533	0.042208	0.091544
Olfactory	0.932923	0.110995	0.923555	0.125332
Frontal sup medial	0.132453	0.122875	0.826345	0.308363
Frontal med orb	0.104486	0.135693	0.350882	0.031087
Rectus	0.140537	0.384736	0.322253	0.727415
Insula	0.250414	0.081456	0.609285	0.869846
Cingulum ant	0.504273	0.074245	0.129863	0.320411
Cingulum mid	0.107406	0.187738	0.597358	0.874015
Cingulum post	0.955063	0.266593	0.172021	0.891100
Parahippocampal	0.040993	0.117375	0.230725	0.412775
Calcarine	0.033129	0.048649	0.356536	0.869775
Cuneus	0.105223	0.015475	0.138634	0.266145
Lingual	0.264601	0.019933	0.787503	0.970749
Occipital sup	0.150874	0.042722	0.770015	0.291022
Occipital mid	0.013200	0.130124	0.063864	0.915497
Occipital inf	0.041410	0.949248	0.476861	0.677175
Fusiform	0.394580	0.026238	0.721216	0.988369
Postcentral	0.172857	0.100494	0.043559	0.722437
Parietal sup	0.072922	0.025557	0.889057	0.168979
Parietal inf	**0.007556**	0.624898	0.664239	0.815019
Supramarginal	0.013739	0.021044	0.563197	0.755908
Angular	**0.007662**	0.011050	0.931890	0.747822
Precuneus	0.427969	0.035213	0.243157	0.240087
Paracentral lobule	0.465771	0.256483	0.217278	0.315631
Heschl	0.323772	0.370240	0.268885	0.231281
Temporal sup	**0.001265**	0.155920	0.291989	0.821858
Temporal pole sup	0.194097	0.315568	0.856608	0.585248
Temporal mid	0.054768	0.057299	0.847948	0.405175
Temporal pole mid	0.139055	0.326217	0.026372	0.541585
Temporal inf	0.059345	0.053748	0.204845	0.605110

In bold values of $p < 0.01$; underlined values significant after correction for multiple comparisons.

[a] ROI represents the 78 regions of interest as based on the AAL regions.

[b] p-Values represent the differences between discordant twin pairs (patients and their cotwins) and healthy pairs (healthy twin 1, healthy twin 2) as based on the RM-ANOVA.

representing the sum of the influences of genetic and environmental risk factors for schizophrenia on cortical thinning/surface contraction ($r_{ph} = r_{ph\text{-}a} + r_{ph\text{-}e}$), were largely negative but did not reach significance (Fig. 4, Table 4).

Irrespective of disease, heritability significantly influenced cortical thickness change over time (25%), left superior temporal cortical thickness change (50%), and cortical surface area change (52%) (Table 4).

3.2.3. Correcting for parental education and antipsychotic medication

These findings remained essentially the same after correcting for parental education.

Cumulative antipsychotic medication dose (in haloperidol equivalents) was not significantly associated with change in cortical thickness or surface area or with change in the left superior temporal cortex in patients.

4. Discussion

To our knowledge, this is the first longitudinal study measuring change in cortical thickness and surface area over time in twin pairs discordant for schizophrenia. We find increased genetic liability for schizophrenia to be associated with excessive cortical thinning, particularly of the left superior temporal cortex. In addition, unique environmental influences associated with the illness may attenuate cortical thinning in patients. Moreover, while individual variation in cortical surface area contraction over time was found to be highly heritable irrespective of disease, we did not find significant associations with increased genetic or environmental liabilities for schizophrenia. Thus, excessive cortical thinning of the cortex, particularly of the left superior temporal cortex, may be a genetic marker for schizophrenia.

We find increased genetic risk for the disease to be significantly implicated in the progressive cortical thinning in schizophrenia. Thus, the excessive cortical thinning found in several studies in schizophrenia (Thompson et al., 2001; Greenstein et al., 2006; Van Haren et al., 2011; Cobia et al., 2012; Ziermans et al., 2012) can be attributed, at least in part, to genes implicated in the disease. This implies that disease-related factors cannot fully explain the progressive cortical thinning in patients. Our results are in line with and extend previous findings of excessive cortical thinning as a familiar risk marker for schizophrenia (Gogtay et al., 2007; Prasad et al., 2010; Rimol et al., 2012). Here we add that excessive cortical thinning in schizophrenia is not only familial, it is of genetic origin.

In contrast, we find that total cortical surface contraction is not significantly associated with increased genetic or environmental liability for schizophrenia. This extends previous results (Bakken et al., 2011) but differs from a report that cortical surface contraction may be familial in schizophrenia (Prasad et al., 2010). However, this study had examined adolescent offspring of affected patients, who carry a different genetic risk than do twins (Gottesman, 1991), and clearly their environments differ as well. Therefore their results are difficult to compare with ours. This may suggest that the cortical surface contraction in offspring of patients reflects a non-genetic, familial, aspect of being a child of a parent with schizophrenia. Alternatively, it may represent that cortical surface change may be a genetic marker for schizophrenia in adolescence but no longer in adulthood. Indeed, the rate of change in area surface is dependent of age throughout life (Schnack et al., 2015; Giedd et al., 2015). Based on our findings we conclude that cortical surface area change is not significantly associated with the genetic risk for schizophrenia, at least in adulthood.

Excessive cortical thinning was found throughout the cortex, but was predominantly associated with increased genetic liability for schizophrenia in the superior temporal cortex of the left hemisphere. In addition, the left inferior parietal and left angular cortices as well as the left frontal middle and right superior orbitofrontal cortices seemed to be thinning excessively in patients and their co-twins. Although, in contrast to the left superior temporal cortex, these areas did not survive correction for multiple comparisons, excessive thinning of prefrontal and parietal cortices may represent additional areas of interest associated with the genetic risk for schizophrenia. These regions represent core areas of the working memory circuitry (Karlsgodt et al., 2011). Also, the frontal cortex has dense connections with the superior temporal cortex for processing of auditory information (Plakke and Romanski, 2014). Interestingly, Kraepelin already mentioned the left superior temporal cortex involvement in schizophrenia, based on clinical observations (Kraepelin, 1893). Moreover, early brain imaging studies reported the left posterior superior temporal gyrus to be significantly decreased in volume and associated with the severity of thought disorder in schizophrenia (see e.g. Shenton et al., 1992). Here we show that individual variation in progressive thinning of the left superior temporal cortex can be explained – at least partly – by genes implicated in schizophrenia. This finding is particularly interesting in light of the superior temporal gyrus being specialized in processing of voices (Belin et al., 2000) a specialization that develops in infancy (Grossman et al., 2010).

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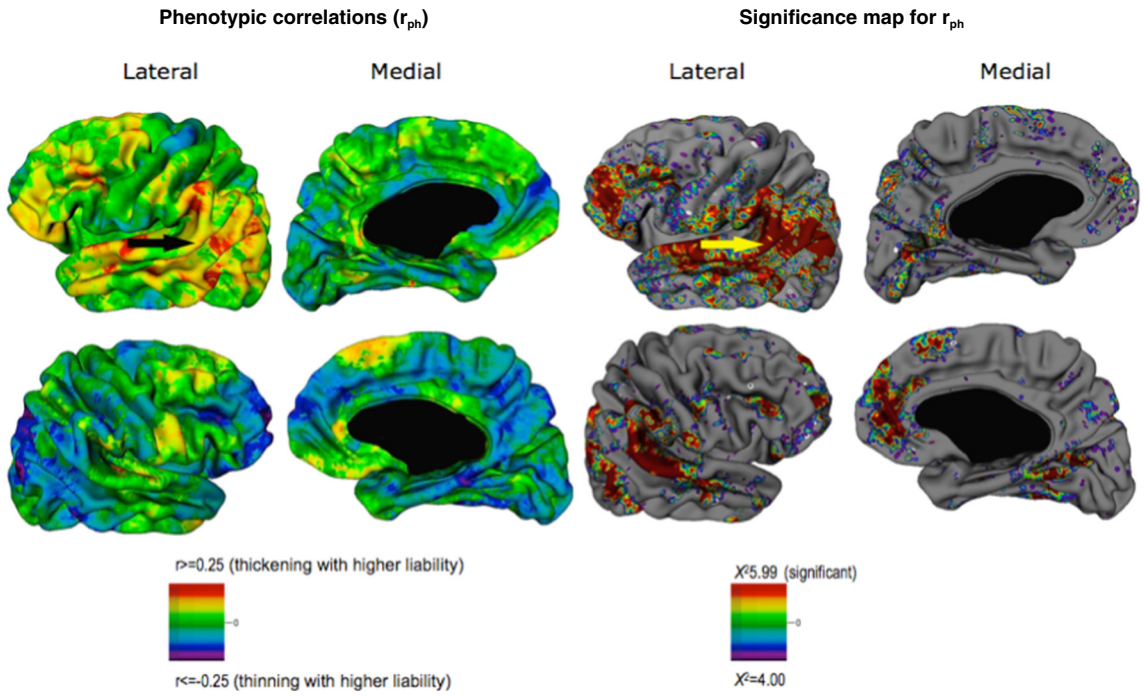

Fig. 4. Change in cortical thickness over time and liability for schizophrenia. Cortical thickness change over the 5-year interval is shown as phenotypic correlations (r_{ph}) with liability for schizophrenia and their significance (X^2 map) presented for each vertex. Cortical thinning associated with higher disease liability in blue/purple (negative correlations), and cortical thickening/less pronounced cortical thinning in yellow/red (positive correlations). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Unique environmental influences implicated in schizophrenia also contributed to the cortical thickness change over time in schizophrenia although this effect was considerably smaller than the genetic one. Interestingly, increased environmental risk for schizophrenia was associated with *less* prominent cortical thinning. There are several potential explanations for this finding. Possibly, after having already lost a considerable amount of cortical tissue in this chronic phase of the disease, cortical thinning in patients may have reached a so-called floor effect, resulting in less prominent progressive loss when compared with their co-twins. Environmental influences such as early-life urbanicity have indeed been associated with gray matter tissue loss possibly leading to an increased risk for schizophrenia (Haddad et al., 2015). However, these circumstances would usually be shared among twins. Alternatively, antipsychotic medication may have attenuated cortical thinning. Indeed, in patients, atypical antipsychotic medication has been shown to be associated with less prominent progressive brain tissue loss (Lieberman et al., 2005; DeLisi et al., 2006; Van Haren et al., 2011); but see Ho et al. (2011). We found no significant association between cumulative haloperidol equivalents and cortical thickness change in the current study. However, we have to emphasize that the number of patients (n = 19) left us statistically underpowered to address this question appropriately.

Irrespective of disease cortical thickness change over time (h^2 = 25%) and surface area change (h^2 = 52%), are heritable. Thus, not only cortical thickness (Thompson et al., 2001; Goldman et al., 2009; Rimol et al., 2010), and surface area (Panizzon et al., 2009; Winkler et al., 2010; Eyler et al., 2011), are influenced by genes, but also the extent to which those change over time. These findings are in line with previous heritability studies on cortical thickness change and surface area change in adults (Brans et al., 2010; Brouwer et al., 2014; a partly overlapping healthy cohort) and thickness change in children (Van Soelen et al., 2012). Identifying genes and environmental factors that contribute to changes in cortical thickness and surface will aid in finding mechanisms for aberrant brain plasticity. Our findings suggest that, while both cortical thickness and surface area changes are clearly influenced

Table 4
Genetic and environmental influences on change in cortical thickness and surface area in schizophrenia.

	h^2 (%)	r_g	r_e	r_{ph}	$r_{ph\text{-}a}$	$r_{ph\text{-}e}$
Cortical thickness change						
Global cortex	**25 (1 to 52)**	**−0.45 (−1.00 to −0.06)**	0.42 (−0.07 to 0.79)	−0.10 (−0.28 to 0.07)	**−0.20 (−0.37 to −0.02)**	**0.10 (0.03 to 0.17)**
Left hemisphere	**22 (1 to 49)**	**−0.44 (−1.00 to −0.03)**	0.38 (−0.11 to 0.76)	−0.09 (−0.27 to 0.08)	**−0.19 (−0.36 to −0.01)**	**0.10 (0.02 to 0.16)**
Right hemisphere	**27 (1 to 55)**	**−0.40 (−1.00 to −0.02)**	0.31 (−0.21 to 0.74)	−0.12 (−0.29 to 0.06)	**−0.19 (−0.36 to −0.01)**	**0.07 (0.01 to 0.14)**
Left superior temporal	**50 (25 to 68)**	**−0.39 (−0.73 to −0.11)**	**0.65 (0.19 to 0.90)**	−0.12 (−0.30 to 0.06)	**−0.25 (−0.41 to −0.07)**	**0.13 (0.08 to 0.17)**
Cortical surface area change						
Global surface area	**52 (25 to 70)**	0.07 (−0.23 to 0.37)	−0.05 (−0.53 to 0.46)	0.03 (−0.15 to 0.22)	0.04 (−0.15 to 0.23)	−0.01 (−0.11 to 0.09)
Left surface area	24 (0 to 49)	0.05 (−1.00 to 1.00)	0.16 (−0.36 to 0.62)	0.07 (−0.11 to 0.24)	0.02 (−0.16 to 0.20)	0.04 (−0.09 to 0.16)
Right surface area	**62 (37 to 77)**	0.01 (−0.26 to 0.29)	−0.23 (−0.69 to 0.32)	−0.04 (−0.22 to 0.15)	0.01 (−0.18 to 0.20)	−0.04 (−0.13 to 0.06)
Left superior temporal	0 (0 to 34)	0 (0 to 0.11)	0.09 (−0.33 to 0.68)	0.03 (−0.21 to 0.15)	0 (−0.27 to 0.11)	0.03 (−0.09 to 0.19)

h^2 = heritability in percentages; r_g = genetic correlation representing the extent of the overlap between genes influencing schizophrenia risk and the mean cortical thickness/surface area change; r_e = environmental correlation; r_{ph} = observed phenotypic correlation; $r_{ph\text{-}a}/r_{ph\text{-}e}$: genetic and environmental parts of the observed correlation, defined as the genetic/environmental correlations multiplied by the square roots of heritability/environmental variances of cortical thickness change and liability for schizophrenia. In bold = significant estimates; in parentheses = 95% confidence interval (CI).

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by genes, increased genetic liability for schizophrenia is primarily associated with excessive cortical thinning.

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Conflict of interest

None.

Contributors

Anna Hedman wrote the first draft of the manuscript. All authors interpreted the results, and contributed to and have approved the final manuscript. Hilleke Hulshoff Pol, Rene Kahn, Neeltje van Haren, and Rachel Brans designed the study and wrote the protocol. Rachel Brans acquired the data. Anna Hedman managed the literature searches. Anna Hedman, Caroline van Baal, Rachel Brouwer and Hugo Schnack performed the imaging analyses and undertook the statistical analyses.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2015.06.021.

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