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

Anna M. Hedman, Neeltje E.M. van Haren, G. Caroline M. van Baal, Rachel M. Brouwer, Rachel G.H. Brans, Hugo G. Schnack, René S. Kahn, Hilleke E. Hulshoff Pol *

Brain Center Rudolf Magnus, Department of Psychiatry, University Medical Centre Utrecht, A01.126, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands

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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.

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

* Corresponding author. Tel.: +31 88 755 9019; fax: +31 88 755 5443.
E-mail address: H.E.Hulshoff@umcutrecht.nl (H.E. Hulshoff Pol).

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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.