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Archival Report

Cortical Surface Area Differentiates Familial High Risk Individuals Who Go on to Develop Schizophrenia

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ABSTRACT

BACKGROUND: Schizophrenia is associated with structural brain abnormalities that may be present before disease onset. It remains unclear whether these represent general vulnerability indicators or are associated with the clinical state itself.

METHODS: To investigate this, structural brain scans were acquired at two time points (mean scan interval 1.87 years) in a cohort of individuals at high familial risk of schizophrenia ($n = 142$) and control subjects ($n = 36$). Cortical reconstructions were generated using FreeSurfer. The high-risk cohort was subdivided into individuals that remained well during the study, individuals that had transient psychotic symptoms, and individuals that subsequently became ill. Baseline measures and longitudinal change in global estimates of thickness and surface area and lobar values were compared, focusing on overall differences between high-risk individuals and control subjects and then on group differences within the high-risk cohort.

RESULTS: Longitudinally, control subjects showed a significantly greater reduction in cortical surface area compared with the high-risk group. Within the high-risk group, differences in surface area at baseline predicted clinical course, with individuals that subsequently became ill having significantly larger surface area than individuals that remained well during the study. For thickness, longitudinal reductions were most prominent in the frontal, cingulate, and occipital lobes in all high-risk individuals compared with control subjects.

CONCLUSIONS: Our results suggest that larger surface areas at baseline may be associated with mechanisms that go above and beyond a general familial disposition. A relative preservation over time of surface area, coupled with a thinning of the cortex compared with control subjects, may serve as vulnerability markers of schizophrenia.

Keywords: Cortical thickness, High-risk, Longitudinal, Schizophrenia, Structural MRI, Surface area

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Schizophrenia is a complex, heterogeneous, and debilitating psychiatric disorder that has been associated with structural abnormalities spanning distributed brain regions (1–3). It has been suggested that while particular regions of the brain may be involved in the underlying pathology of schizophrenia, some abnormalities may also be present in a widespread form, thus producing global alterations to brain structure (4,5). There is some evidence that early diagnosis is associated with better outcomes for patients, which has prompted interest in identifying predictive markers of the disorder (6). Such predictive studies also offer the possibility of assessing whether neuroanatomical markers for schizophrenia precede illness onset and, critically, whether these changes reflect the illness itself as opposed to other factors, such as the medication and substance abuse that often accompanies the disorder (7,8).

The power of prospective studies is greatly enhanced by additionally considering familial risk. Schizophrenia is a highly heritable disorder (9) and evidence to date suggests that some structural abnormalities are present in nonpsychotic relatives of patients. These changes may therefore reflect general familial markers of schizophrenia, with subsequent transition to psychosis associated with further abnormalities (10–13). For these reasons, prospective familial high risk (HR) research allows researchers to more thoroughly disentangle the extent to which structural brain abnormalities form part of a general vulnerability to the disorder or are only present in individuals that subsequently go on to develop schizophrenia, thus more accurately characterized as markers associated with clinical risk.

Most studies that investigate familial HR cohorts have been cross-sectional; however, some have shown that dynamic changes occur before disorder onset in those at HR for familial or clinical reasons (14–17). This suggests that a vulnerability to schizophrenia entails both initial structural abnormalities coupled with aberrant development. Clearly, cross-sectional studies cannot distinguish whether incipient changes alone characterize susceptibility for psychosis or whether such vulnerability is also associated with additional abnormal developmental trajectories. Longitudinal analyses of those at familial HR for schizophrenia are a critical complement to cross-sectional observations.

To accurately specify markers of psychosis, the choice of adequate structural parameters is crucial. To date, the majority of structural analysis has focused on cortical gray matter volume, although findings are currently heterogeneous (18–20). The migration of neurons formed through mitosis during fetal development gives rise to the cortex (21–23). Cortical thickness is formed by the asymmetrical division of radial glia in the ventricular and subventricular zones (21,22), while surface area is determined by symmetrical division of progenitor cells in these cortical layers. These processes occur at distinct periods of development (22) and are thought to be mediated by different genes (24). For this reason, investigating thickness and area separately in individuals at familial HR of schizophrenia may help improve the sensitivity of structural imaging studies to different developmental disruptions (25). Cross-sectional studies have found divergent effects of these parameters, in that larger surface areas are often linked to thinner cortices (4,26), and longitudinal studies have shown a negative relationship between area and thickness over time, such that as area deceases, thickness increases (27–29).

The aim of the present study was to assess cross-sectional and longitudinal change in both global and lobar cortical thickness and surface area in the Edinburgh High Risk Study (EHRS), a large group of young people recruited from multiply affected families with schizophrenia. We were interested in whether any alterations were evident at baseline or occurred over time and whether these alterations were global or whether more localized lobar deficits were present when comparing all those at HR with healthy control subjects. As a secondary aim, we also wished to assess whether these alterations could be more accurately specified as markers of clinical risk and thus only present in those at HR that developed schizophrenia after the two scans (HR[ill]) compared with high-risk individuals that remained well (HR[well]) and those that presented only isolated psychotic symptoms (HR[symp]).

Based on existing evidence that surface area and thickness reflect distinct developmental processes, we hypothesized that cortical thickness and surface area would be differentially affected in those at HR compared with control subjects, both at baseline and longitudinally. We also predicted that within the HR cohort, those that subsequently became ill would show the greatest alterations, as it has been suggested that the brain alterations found in schizophrenia may be present before disorder onset to a greater extent in those at HR that go on to transition to the disorder compared with those that do not.

METHODS AND MATERIALS

Participants

The recruitment and clinical assessment process for the EHRS have been described in detail elsewhere (30). All participants volunteered to be a part of the EHRS and had the right to withdraw at any time. Informed consent was obtained from all participants, as approved by the Psychiatry and Clinical Psychology subcommittee of the Multi-Centre Research Ethics Committee for Scotland. All applications for continuation and amendment to this study have been filed appropriately with the Scotland Research Ethics Committee.

In summary, HR individuals aged 16 to 25 years with no personal history of psychiatric disorder were contacted throughout Scotland based on the criteria that they had at least two first-degree and/or second-degree relatives with a diagnosis of schizophrenia. Healthy control subjects (HC) without personal or family history of major psychiatric disorder were recruited from the same social and geographical networks as the HR subjects to minimize potential confounding environmental influences. More male than female subjects developed schizophrenia, but the groups were otherwise similar in age, paternal social class, and education, with the vast majority of HC and HR individuals being either in full-time employment or education at baseline scanning. Structural magnetic resonance imaging (MRI) scans of the brain were conducted for HR and HC participants at baseline and repeated after a mean scan interval of 1.87 years.

During the course of the study, 21 HR individuals developed schizophrenia, 19 of whom had full clinical assessments and 17 who had at least one structural MRI scan. Those in the HR[ill] group were formally diagnosed after an average of 929 days (SD = 138) and were not offered rescanning once this diagnosis had been made (13). Once a diagnosis of schizophrenia had been made, these individuals were not formally followed up, nor were those participants that dropped out for other reasons. However, several of these individuals were managed by senior clinicians in the research team, and the diagnoses of those that developed schizophrenia have not changed, nor were any other psychotic diagnoses recorded. For those individuals that remained in the study, the clinical observation lasted up to 10 years.

The presence and absence of symptoms for all four groups was established by subsequent Present State Examination (PSE), which was the main clinical assessment used for the present study (31). Individuals that developed schizophrenia were given a formal diagnosis based on ICD-10. In contrast, individuals in the symptomatic group were never ill enough to be given this diagnosis, as they either had only one key symptom or their symptoms were too transient or mild to satisfy diagnostic criteria. None of those scanned were on any form of antipsychotic medication at baseline or at follow-up scanning. For the present analysis, 178 baseline scans were included. At follow-up, 82 scans were included for the analysis. The present numbers are the same as all other studies of this sample, apart from the five scans at baseline and the two scans at follow-up that had to be excluded due to gross segmentation errors produced by the FreeSurfer algorithm (http://freesurfer.net).

Imaging Parameters

Concurrently with baseline and follow-up clinical assessments, participants underwent structural MRI. The present analysis focuses on those individuals with either one or two scans. The scans were taken between 1994 and 1999 and on the same scanner, a 42 SPE Siemens Magnetom (Siemens, Erlangen, Germany) operating at 1.0 T. The scanning sequence was the same for both scans and the scanner was not upgraded between the two scans. The sequence was a three-dimensional magnetization prepared rapid acquisition gradient-echo sequence consisting of a 180° inversion pulse followed by a fast low-angle shot collection (flip angle 12°, repetition time 10

msec, echo time 4 msec, inversion time 200 msec, relaxation delay time 500 msec, field of view 250 mm × 250 mm), giving 128 contiguous slices with a thickness of 1.88 mm. The sequence was selected to obtain optimal gray/white matter contrast.

FreeSurfer Acquisition

Cortical reconstructions were generated using FreeSurfer, version 5.3.0 (http://surfer.nmr.mgh.harvard.edu/fswiki/ recon-all/). This processing includes motion correction and averaging (32) of T1-weighted images, removal of nonbrain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, intensity normalization (33), tessellation of the gray matter/white matter boundary, automated topology correction (34,35), and surface deformation to optimally place the gray/white and gray/cerebrospinal fluid borders (36). This method uses both intensity and continuity information from the entire three-dimensional magnetic resonance volume in segmentation and deformation procedures to produce representations of cortical thickness and surface area (32). The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. Procedures for the measurement of cortical thickness have been validated against histological analysis (37) and manual measurements (38).

All scans were manually checked for inaccuracies by a trained rater (C.B.) blinded to diagnostic status. At this stage, editing procedures outlined on the FreeSurferWiki (http://freesurfer.net/fswiki/Edits) were then performed on all scans to remove nonbrain from brain, and white matter edits were performed to increase the accuracy of the pial surface. After these steps, five of the baseline scans and two of the follow-up scans were excluded due to defective surface generation that was not fixed by manual intervention procedures. Average global and lobar cortical thickness and surface area per hemisphere were then extracted from individual images and compared across groups.

Statistical Analysis

All statistics were computed with R version 3.0.2 (http://www.r-project.org) using linear mixed models with package nlme (version 3.1-109). Analyses were initially carried out for group differences in mean thickness and area. These analyses were then repeated for the frontal, temporal, cingulate, insular, parietal, and occipital lobes. Lobar comparisons were corrected

for multiple comparisons using false discovery rate (39). Only those group effects that remained significant after this correction are reported in this article. Comparisons were first conducted between HC and all those at HR. These analyses were then repeated between high-risk participants based on their clinical outcome: HR[well], HR[symp], and HR[ill]. In the mixed linear models conducted, hemisphere was entered as a factor with two levels (left/right). Thus, the combined results of both left and right thickness and surface area are presented throughout this article. For the baseline analysis, group differences were modeled including the fixed effects of age, sex, Wechsler Adult Intelligence Scale IQ, and random effects of individual. For longitudinal comparisons, covariates were entered as in the cross-sectional analyses, including also the group by time interaction and scan interval. A quadratic term for age was entered and removed if it did not improve the model's fit. Although distinct surface area and thickness have been shown to be mechanically related with each other in that as the cortex expands, it folds and fissures, resulting in greater degrees of gyrification, which, in turn, has been shown to be associated with thinner cortices (27,28,40). For this reason, we controlled for total surface area in our analysis of thickness. PSE factors, as used in McIntosh et al. (17), including increasing severity of hallucinations, delusional construction, and disorder of possession of thought, were obtained and correlated with structural brain parameters in the HR cohort. Logistic regressions were also performed to assess the correlation between area and thickness and how this differed across groups both at baseline and longitudinally. Post hoc significance testing was conducted with package lsmeans (version 2.00-1).

RESULTS

Relevant demographics and statistics are presented in Table 1. No significant correlations were found between the clinical PSE factors and thickness and area estimates.

Global Analyses—Baseline Analyses between Groups in Mean Surface Area and Cortical Thickness

All High-Risk Participants versus Healthy Control Subjects. When the high-risk groups were considered together and compared with HC, there were no significant differences in thickness or area (Table S1 in Supplement 1).

Differences between HR[ill], HR[symp], and HR[well]. No significant group differences emerged for thickness when the

Table 1. Mean Age and WAIS IQ and Associated Standard Errors and Statistics for HR[symp], HR[well], HR[ill], and Healthy Control Subjects, Along with Numbers and Sex Distributions of Each Group and Scan Intervals

		Healthy Control Subjects	HR[well]	HR[symp]	HR[ill]	Statistic
WAIS-IQ	Range	79–140	77–139	77–128	75–129	
	Mean (SE)	105 (2.17)	99 (1.58)	96 (1.67)	100 (3.07)	$F_{3,169} = 3.48, p < .05$
Age	Range	16–26	16–27	16–26	16–23	
	Mean (SE)	21 (.28)	22 (.25)	21 (.29)	20 (.40)	$F_{3,175} = 1.6$, ns
Numbers at Baseline Scan	Male:Female	17:19	36:32	24:33	11:6	
Numbers at Follow-up Scan	Male:Female	11:7	18:12	11:15	5:3	
Mean Scan Interval		2.21 (.031)	1.90 (.108)	1.65 (.05)	1.64 (.19)	

HR[ill], high-risk subjects that developed schizophrenia after the two scans; HR[symp], high-risk individuals that presented only isolated psychotic symptoms; HR[well], high-risk individuals that remained well; WAIS-IQ, Wechsler Adult Intelligence Scale-IQ.
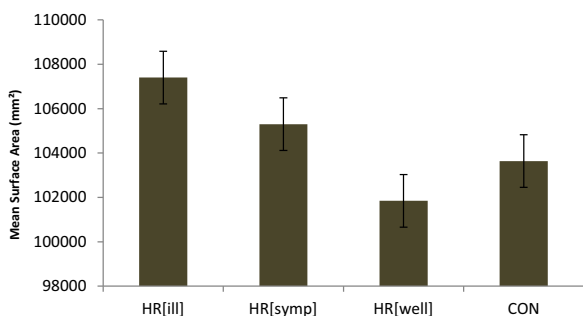
Figure 1. Baseline mean values surface area (mm²) and associated standard errors of the mean displayed as error bars in the high-risk subgroupings and healthy control subjects (CON). HR[ill], high-risk subjects that developed schizophrenia after the two scans; HR[symp], high-risk individuals that presented only isolated psychotic symptoms; HR[well], high-risk individuals that remained well.

HR cohort was considered based on clinical outcome (Table S1 in Supplement 1). However, a HR subgroup analysis of area showed a significant main effect ($F = 4.83$, $df = 132$, $p < .001$). Post hoc tests showed this was because HR[ill] had a significantly larger surface area than HR[well] ($t = -2.61$, $df = 132$, $p < .05$). A trend emerged for significantly larger areas in HR[symp] compared with HR[well] ($t = -2.33$, $df = 132$, $p < .06$). There were no significant differences between HR[symp] and HR[ill], $p =$ ns. Graphs of baseline means and surface area are presented in Figure 1.

Global Analyses—Longitudinal Comparisons between Groups in Mean Surface Area and Cortical Thickness

All High-Risk Participants versus Healthy Control Subjects. For longitudinal comparisons in area, a significant time by group interaction emerged ($F = 4.4$, $df = 324$, $p < .01$). When all the HR participants were considered together and compared with HC, those at HR had significantly smaller reductions in surface area over time relative to HC ($t = 3.32$, $df = 328$, $p = .001$) as illustrated in Figure 2. A significant group by time interaction also emerged for thickness ($F = 7.97$, $df = 332$, $p < .001$). This was due to HC increasing significantly more in thickness than those at HR ($t = 3.36$, $df = 486$, $p < .001$), who in contrast underwent a relative thinning illustrated in Figure 3. The mean cortical thickness and surface area estimates at baseline and follow-up, adjusted for age, sex, and IQ, are shown in Table 2.

Differences between HR[ill], HR[symp], and HR[well]. When the HR subgroups (HR[well], HR[symp], and HR[ill]) were analyzed based on subsequent clinical outcome, there was no significant time by group interaction for thickness or for surface area (Table S1 in Supplement 1).

Lobar Analyses—Baseline Analyses between Groups in Mean Surface Area and Cortical Thickness per Lobe

All High-Risk Participants versus Healthy Control Subjects. For the baseline lobar comparisons comparing all HR participants together with HC, there were no significant group effects on any of the six lobes in either area or thickness (Table S2 in Supplement 1).

Differences between HR[ill], HR[symp], and HR[well]. When the HR groups were analyzed based on subsequent clinical outcome, there were no significant differences in lobar thickness or area (Table S2 in Supplement 1).

Lobar Analyses—Longitudinal Comparisons between Groups in Mean Surface Area and Cortical Thickness per Lobe

All High-Risk Participants versus Healthy Control Subjects. When all HR individuals were compared together against HC and after false discovery rate correction, a significant group by time interaction emerged for frontal thickness, ($F = 17.84$, $df = 1,331$, $p = <.0001$), occipital thickness ($F = 12.01$, $df = 1,331$, $p = <.0001$), and cingulate thickness ($F = 7.84$, $df = 1,331$, $p = <.001$). Subsequent post hoc testing showed that for the frontal lobe and cingulate, those at HR exhibited significantly more thinning over time than HC ($t = -4.29$, $df = 356$, $p < .001$; $t = -2.2$, $df = 397$, $p = <.05$, respectively). In contrast in the occipital lobe, HC increased significantly more in thickness compared with those at HR ($t = -2.7$, $df = 356$, $p = <.001$) (Figure 4). There were no similar group by time changes in lobar surface area (Table S3 in Supplement 1). Table 3 presents a summary of all significant findings of the present study.

Differences between HR[ill], HR[symp], and HR[well]. When the HR groups were analyzed based on subsequent clinical outcome, no significant differences emerged for any of the six lobes in cortical thickness (Table S4 in Supplement 1) or surface area (Table S3 in Supplement 1).

Global Logistic Regression Analyses

The results of these analyses are presented in Supplement 1.

Table 2. Cortical Thickness (mm) and Surface Area (mm²) Estimates at Study Baseline and Follow-up for HR[symp], HR[well], HR[ill], and Healthy Control Subjects, Adjusted for Age, Sex, and IQ

	Baseline Estimates		Follow-up Estimates	
	Cortical Thickness	Surface Area	Cortical Thickness	Surface Area
Healthy Control Subjects	2.31 (.015)	103,638 (1476)	2.33 (.03)	101,606 (1522)
HR[well]	2.28 (.01)	101,845 (1059)	2.26 (.01)	100,519 (1102)
HR[symp]	2.28 (.02)	105,301 (1133)	2.27 (.01)	103,872 (1163)
HR[ill]	2.27 (.02)	107,402 (2072)	2.24 (.02)	106,466 (2089)

HR[ill], high-risk subjects that developed schizophrenia after the two scans; HR[symp], high-risk individuals that presented only isolated psychotic symptoms; HR[well], high-risk individuals that remained well.

Table 3. Table Showing All Significant Findings of the Present Study

		HR Versus HC	HR[ill] Versus HR[well]
Baseline	Global surface area		$F = 4.83$, $df = 132$, $p < .001$
Longitudinal	Global thickness	$F = 7.97$, $df = 332$, $p < .001$	
	Global surface area	$F = 4.4$, $df = 324$, $p < .01$	
	Frontal thickness	$F = 17.84$, $df = 1331$, $p = <.0001$	
	Cingulate thickness	$F = 7.84$, $df = 1331$, $p = <.001$	
	Occipital thickness	$F = 12.01$, $df = 1331$, $p = <.0001$	

HC, healthy control subjects; HR, high-risk subjects; HR[ill], high-risk subjects that developed schizophrenia after the two scans; HR[well], high-risk individuals that remained well.

DISCUSSION

We examined whether baseline abnormalities in surface area and cortical thickness were present in a familial HR cohort compared with HC, as well as between the HR subgroupings based on subsequent clinical outcome, and whether these alterations were present cross-sectionally and/or longitudinally.

We found that at baseline, HR[ill] had a significantly larger cortical surface area compared with HR[well]. Intriguingly, this effect did not seem to have a more regional locus, as we found no evidence for group differences in baseline lobar surface area but only a significantly larger mean surface area. Thus, our results suggest a more global alteration in surface area may serve as a putative marker for subsequent transition to psychosis. Longitudinally, we found that all HR participants had a relatively preserved developmental trajectory of area compared with HC, who in contrast underwent a significantly greater decrease in area. These longitudinal abnormalities may thus be accurately specified as a general vulnerability marker of psychosis. These results are consistent with the literature suggesting that HR individuals share certain alterations, with further brain abnormalities differentiating those that transition to psychosis (12–15).

No cortical thickness differences between the groups were evident at baseline in either our global or lobar analyses; however, longitudinal analysis indicated that HC showed a significantly greater increase in global cortical thickness compared with all HR individuals, who in contrast showed a relative thinning. Furthermore, significant regional thickness abnormalities were found in the frontal, cingulate, and occipital lobes, in that those at HR showed significant thinning over time, while HC underwent a relative thickening over time. These abnormalities were not linked to subsequent clinical outcome, suggesting that these alterations may also be specified as markers of a general vulnerability to psychosis. Areas of the frontal, occipital, and cingulate lobes have previously been shown to be abnormal in HR research (41–43), as well as established schizophrenia (44,45), suggesting that these regions may form part of localized brain networks disrupted in psychosis.

A recent meta-analysis found a moderate effect size for increased whole-brain volume and gray matter volume in HR individuals compared with both HC and first-episode patients (20). It is possible that these changes were driven by an increase in surface area, as previous studies have suggested that volume is more driven by area than thickness (27). As these alterations are present in HR[ill] before disorder onset, our findings suggest a neurodevelopmental disruption to genes/processes involved in surface area expansion. Furthermore, as larger surface areas are associated with more gyrified cortices (27), it is likely that these changes to surface area may also be reflected in the morphology of the cortex, which future studies may wish to investigate. Our results of unaltered thickness between HR and HC at baseline suggest that processes involved in the proliferation and number of cells within cortical columns are unaltered at baseline but may interact with developmental processes, such as synaptic pruning, to produce longitudinal alterations with both global and localized consequences in those at HR of developing schizophrenia for familial reasons (21–23).

Our longitudinal findings suggest that different trajectories and patterns of change in thickness and area may differentiate HR from HC. In HC, area decreased over time, while thickness
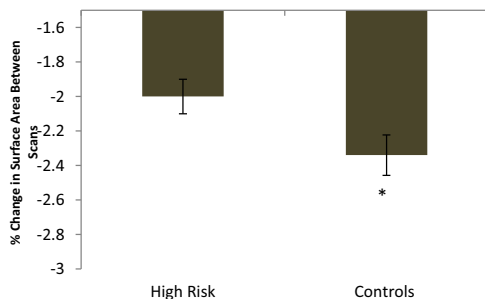
Figure 2. Baseline scan values of surface area were normalized to 100%, and the percentage value of the follow-up scan in relation to this was obtained. Y axis represents the % difference between the two scans in surface area between control subjects and all high-risk subjects. *Indicates significant difference in surface area change over time.
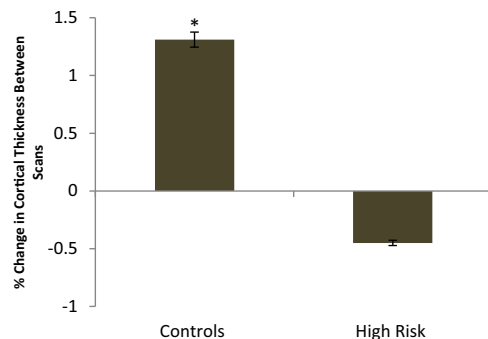
Figure 3. Baseline scan values of cortical thickness were normalized to 100%, and the percentage value of the follow-up scan in relation to this was obtained. Y axis represents the % difference between the two scans in cortical thickness between control subjects and all high-risk subjects. *Indicates significant difference in cortical thickness change over time.
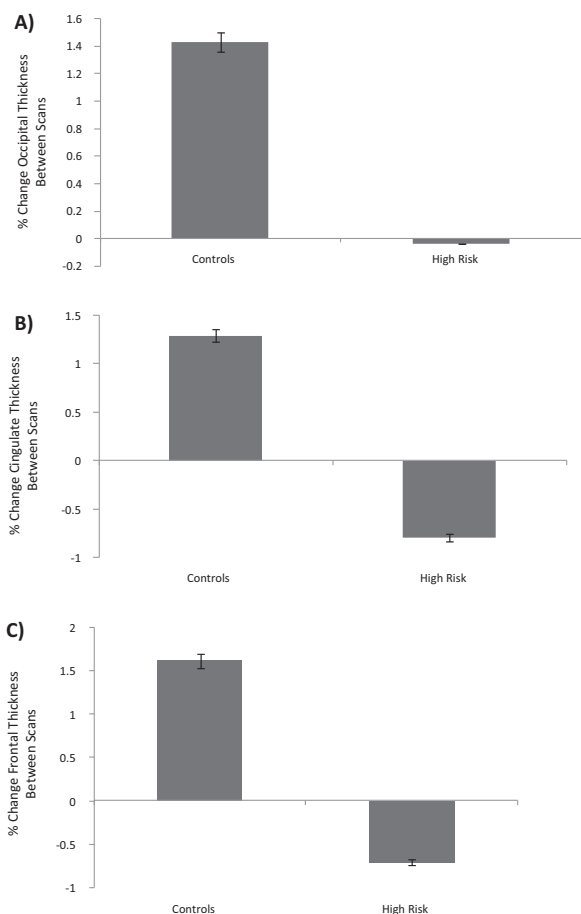
Figure 4. Baseline scan values of cortical thickness were normalized to 100%, and the percentage value of the follow-up scan in relation to this was obtained. Y axis represents the % difference between the two scans in cortical thickness of control subjects and all high-risk subjects for **(A)** occipital, **(B)** cingulate, and **(C)** frontal lobar thickness.

increased. However, for those at HR, surface area was relatively preserved over time, while thickness decreased. The interaction of these changes could also differentiate HR from HC, as indicated by our supplementary data. Previous studies have found that larger surface areas are linked to thinner cortices, while reduced surface area is linked to increased thickness (27,28). This inverse relationship may reflect the differential effect of genes that control the developmentally distinct periods of symmetric and asymmetric division. It may also reflect the mechanical effects of gyrification that occurs in more developed brains and is known to be driven by area expansion, as increased gyrification indices have been associated with both larger surface areas as well as decreased thickness (4). As this inverse relationship seems altered in those at HR compared with control subjects in that they showed a relatively preserved area coupled with increased thinning, it may be that genes involved in regulating the pattern of change in these two parameters may be disrupted in those at HR and may reflect a general vulnerability marker to schizophrenia.

Identifying markers of schizophrenia that are present in those at HR that develop schizophrenia compared with those at HR that do not could enhance the power of early detection of psychosis. This methodology allows researchers to delineate which structural changes are more likely to be specific markers of the disorder, facilitating the predictive value of brain imaging in clinical settings. As many individuals deemed at HR for psychosis due to familial or clinical reasons never go on to develop psychosis, this approach may also help researchers examine whether aspects of brain structure confer resilience to the disorder in those at HR that remain well. It is possible that a relatively smaller surface area in HR[well] compared with HR[ill] serves as a resilience factor against schizophrenia and warrants further investigation. It is interesting to note that the abnormalities in surface area found in the present study are on a global scale, while the cortical thinning was also evident in localized regions of the cortex. To our knowledge, this is the first longitudinal study of global surface area in individuals at familial HR of developing psychosis. Localized cortical thinning may serve as a general vulnerability indicator in HR individuals, while global surface area abnormalities are associated to a larger degree with subsequent psychosis and illness. However, it also remains possible that a larger sample size or longer follow-up period would have enabled us to detect more regionally localized alterations to surface area as well as lobar differences between HR[ill], HR [symp], and HR[well].

There are some limitations to the present study. The relatively small size of HR[ill] may have limited our ability to elucidate further structural changes occurring selectively in this subgroup. Furthermore, we were unable to control for potentially important environmental factors, such as social functioning and socioeconomic status, which could have impacted on the results found. One potential limitation of the present study is that more male subjects than female subjects became ill in the HR[ill] group. This may, however, reflect sex differences in the incidence of schizophrenia (46), and moreover, since we controlled for sex in all analyses performed, it is unlikely to have confounded our main findings. Nonetheless, this study remains the largest longitudinal study of individuals at familial HR of psychosis. Given that the scans were acquired before disorder onset, our results have allowed us to quite robustly distinguish general and more specific markers of the disorder in antipsychotic-naive HR individuals. Future work is required to determine whether these abnormal developmental trajectories are further augmented with progression of the disease.

Conclusions

Our findings suggest that abnormal cortical development occurs over time in a familial HR cohort, specifically in the frontal, occipital, and cingulate cortices compared with HC, and may be tied to a general familial risk of the disorder. We found that baseline measures of surface area distinguished HR[ill] from HR[well] and that this was not specifically localized to any lobe, potentially reflecting a disrupted developmental process with global consequences. This alteration may be associated with mechanisms related to the transition to psychosis, as opposed to a general familial disposition to the disorder. Progressive changes in both area and thickness

were not related to subsequent clinical outcomes of the HR cohort but rather seemed to reflect differential developmental trajectories present in all HR individuals and may therefore serve as a marker of a general vulnerability to develop schizophrenia.

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