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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.

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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