Longitudinal Gray Matter Change in Young People Who Are at Enhanced Risk of Schizophrenia Due to Intellectual Impairment

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Background: Existing studies of brain structural changes before the onset of schizophrenia have considered individuals with either familial risk factors or prodromal symptomatology. We aimed to determine whether findings from these studies are also applicable to those at enhanced risk of developing schizophrenia for another reason—intellectual impairment.

Methods: Participants with intellectual impairment (mean IQ: 78.2) received magnetic resonance imaging of the brain at baseline (mean age: 16 years old) and again 6 years later. The Positive and Negative Syndrome Scale was used to assess psychotic symptoms. Participants were dichotomized using their Positive and Negative Syndrome Scale scores at follow-up and gray matter changes were compared between the groups using tensor based morphometry and semiautomated region of interest analysis.

Results: Forty-six individuals had scans of sufficient quality to be included in the study. The tensor based morphometry analyses revealed that those with psychotic symptoms at follow-up showed significantly greater gray matter reductions over 6 years in the medial temporal lobes bilaterally. Region of interest analyses revealed that those individuals with psychotic symptoms at follow-up showed a reduced right hippocampal volume at age 16 and reduced bilateral hippocampal volumes at follow-up.

Conclusions: This unique study of individuals vulnerable to schizophrenia due to intellectual impairment highlights aberrant development in the medial temporal lobe associated with the occurrence of psychotic symptoms. These developmental changes are also evident in populations at enhanced risk of schizophrenia for familial and symptomatic reasons, suggesting they are central to the development of the disorder regardless of the nature of the vulnerability state.

Key Words: Hippocampus, learning disability, longitudinal change, psychotic symptoms, schizophrenia high risk, tensor based morphometry

It has been established that the volume of brain tissue in people with schizophrenia is less than that in control subjects (1–4). In early imaging work on schizophrenia, it was assumed that brain tissue loss was part of a degenerative process that developed after the illness became manifest (5). However, over time, it has become clear that reduced volume of brain tissue is evident when the illness first declares itself (6) and indeed can be detected before the onset of schizophrenia in certain populations at particular risk of the disorder (7–11).

To examine the structural brain differences that occur before the onset of frank psychotic symptoms, one would ideally study the general population with serial magnetic resonance imaging (MRI) scans throughout adolescence with a view to comparing those who do and do not develop schizophrenia. However, the relative infrequency of the condition (life time risk 8/1000) makes this study design impracticable. To overcome this difficulty, studies have been carried out examining groups considered to be at enhanced risk of developing schizophrenia, including studies of people with prodromal symptomatology (i.e., people at ultra high risk [UHR]) (8,12,13) and studies of people at high familial risk, such as the Edinburgh High Risk Study (EHRS) (14–16).

It is clear from both these approaches that loss of brain tissue does indeed precede illness in these high-risk groups and that this is particularly evident in the temporal and frontal lobes (7,8,17,18). Ultra high risk studies have shown left temporal lobe volume loss to occur at a greater rate before the onset of illness in those who later develop schizophrenia compared with those who do not (8). In the EHRS, a smaller medial temporal lobe was found in individuals at risk of schizophrenia using a region of interest (ROI) approach, and a voxel-based analysis indicated focal reductions in the left parahippocampal gyrus (7,14,19). In addition, over a 10-year follow-up of EHRS participants, the temporal lobes of those who displayed psychotic symptoms and those who went on to develop schizophrenia were found to be significantly smaller than those who did not develop schizophrenia, and this difference progressively increased over time, until the onset of illness (7,17). However, these studies focus on a restricted group of individuals with schizophrenia; not all individuals with schizophrenia have a family history of the disorder, such as in the EHRS, or show prodromal symptoms, as in the UHR studies. It is therefore not clear whether the findings of temporal and frontal lobe loss generalize outside these groups to other people with schizophrenia. We therefore aimed to determine whether these findings could be extended to individuals vulnerable to schizophrenia for another reason—intellectual impairment.

Individuals with low IQ are known to have increased rates of functional psychiatric disorder compared with the general population, with the largest increase in risk being in psychotic disorders, particularly schizophrenia (20,21); although estimates vary, it is widely accepted that low IQ conveys a threefold to fivefold increase in liability to schizophrenia (21–24). This population may therefore represent a suitable group in which to

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extend findings from familial and clinical high-risk studies of schizophrenia.

We have previously reported findings that are consistent with this idea from the baseline investigation and 18-month follow-up of a cohort of adolescents receiving special education assistance (25). At baseline, we found that mild psychotic symptoms correlated positively with gray matter density (26), and in cross-sectional analyses, schizotypal traits were associated with increased right prefrontal cortical folding (27), findings that are in keeping with those of the EHRS study (28). In addition, at the end of the first follow-up period (mean age 17.1 years), we identified gray matter losses in the left medial temporal lobe in those who had schizotypal traits at baseline (29).

The age of onset of schizophrenia tends to be younger in those with intellectual impairment (30), but nonetheless, we expected that there would still be some progression of psychotic symptoms in our cohort beyond the end of the initial 18-month follow-up period. We therefore re-contacted the participants after a further 5 years to re-assess their mental state and conduct an additional MRI scan. We employed a combination of tensor based morphometry (TBM) and semiautomated ROI tracing to examine whether the development of psychotic symptoms was associated with reductions in volume in the frontal and temporal areas of the brain over the 6 years of the study, particularly in the medial temporal lobe. In essence, we sought to establish that there are commonalities between the different states that confer vulnerability to schizophrenia by showing similar findings in the current population as have previously been reported in clinical and familial high-risk studies.

Methods and Materials

Recruitment of Participants

Full details of the recruitment process are given in Supplement 1. From schools and colleges around Scotland, pupils receiving special educational assistance with an estimated IQ of between 50 and 80 were identified. IQ is rarely measured in the Scottish special education system therefore the final sample contained individuals who were functioning outside this range (Table 1). Indeed, the mean IQ of our sample is actually 78, i.e., around the upper end of that which we originally sought. After exclusions, 394 pupil participants remained. This group was then screened using the Structured Interview for Schizotypy (31) and the Childhood Behavior Checklist (32) and sampled on the basis of their scores on these measures to ensure an even distribution across the ranges. One hundred sixty-eight adolescents were therefore recruited for the phase 1 MRI assessment in 2003/2004 (mean age 15.7 years), and 123 were recruited for the phase 2 assessment in 2005/2006 (mean age 17.1 years). At the conclusion of that initial study, the participants were asked for their consent to be re-contacted for follow-up assessment in some years time and 120 gave consent. These are the individuals who were approached for the present third phase of the study, and details of the tracing and assessments conducted are illustrated in Figure 1.

Table1. Characteristics of Subjects in the TBM and Volumetric Analyses Giving Gender, Age, Employment Status, PANSS, and IQ Scores

	Symptom Free	Psychotic Symptoms
n (Male:Female)	29 (20:9)	17 (13:4)
Employed : Unemployed	16:13	4:13
Age at Baseline (SD)	15.8 (1.9)	16.1 (2.5)
Age at Follow-up (SD)	21.7 (2.1)	22.2 (2.6)
IQ (SD)	80.5 (15.9)	74.4 (17.2)
PANSS Positive Phase 3 (SD)	7.6 (1.0)	11.1 (3.3)
PANSS Negative Phase 3 (SD)	10.4 (1.9)	14.5 (6.2)
PANSS General Phase 3 (SD)	18.6 (3.1)	23.7 (8.1)

PANSS, Positive and Negative Syndrome Scale; TBM, tensor based morphometry.

Clinical Assessments

As before, the Clinical Interview Scale (CIS) (33,34) was used, having been shown to be acceptable and reliable in a population such as those assessed here. We also conducted the Positive and Negative Syndrome Scale (PANSS) (35), largely on the basis of the CIS interview, but with some additional questions where required.

On the basis of their PANSS scores, the participants were divided into two a priori groups, i.e., those with significant psychotic symptoms and those without. Given the difficulties in assessing psychotic symptoms in a population such as this, we decided that for both positive and negative symptoms, a score of 3 or above in any domain at follow-up would assign participants to the psychotic symptoms group. A score of 3 was chosen, as this is the first score on the PANSS at which symptoms are considered to be beyond the upper extreme of normal limits (35). Otherwise, the participants were assigned to the symptom free group. Assessment of the concrete thinking and lack of spontaneity and flow of conversation items on the negative items of the PANSS scale was very difficult in this population and most participants scored above a 1 on these items by virtue of their intellectual impairment. We therefore took the view that a score of 3 would be the baseline for these items and that a subject would only be assigned to the psychotic symptoms group if they scored 4 or more on these negative symptoms. However, no participants were included in the psychotic symptoms group solely on the basis of their scores on concrete thinking or lack of spontaneity and flow of conversation.

Individuals were excluded if they were previously known to have, or recognized during assessment as having, a clinically diagnosed syndrome associated with intellectual disability. Furthermore, all but six participants provided blood samples, which were used to exclude diagnoses of Down syndrome, fragile X syndrome, and Velocardiofacial syndrome.

Image Acquisition and Processing

A detailed description of the image acquisition and processing is given in Supplement 1. The images were processed in SPM5 (http://www.fil.ion.ucl.ac.uk; Wellcome Department of Imaging Neuroscience, University College London, United Kingdom) (36). The TBM protocol was implemented by following a staged procedure (29,37–39). This procedure is susceptible to participant movement and we were limited to using scans from 46 participants. Measurements of hippocampal volumes were conducted using a semiautomated tracing technique that follows ROI extractions derived from a recent survey of hippocampal protocols (40).

TBM Analyses

Comparisons were made between those with psychotic symptoms at phase 3 and those without such symptoms. Age, interscan time interval, sex, and full-scale IQ were included in the model as covariates. The SPM5 t-contrast was thresholded at $t = 3.00$ (uncorrected) and we report cluster results corrected for multiple comparisons at $p < .05$. In our earlier study of comorbid intellectual disability and schizophrenia (30,41), we reported