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Brain structure in different psychosis risk groups in the Northern Finland 1986 Birth Cohort

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ABSTRACT

We tested the hypothesis that family risk for psychosis (FR) and clinical risk for psychosis (CR) are associated with structural brain abnormalities, with increased deficits in those at both family risk and clinical risk for psychosis (FRCR). The study setting was the Oulu Brain and Mind Study, with subjects drawn from the Northern Finland 1986 Birth Cohort (n = 9479) using register and questionnaire based screening, and interviews using the Structured Interview for Prodromal Symptoms. After this procedure, 172 subjects were included in the study, classified as controls (n = 73) and three risk groups: FR excluding CR (FR, n = 60), CR without FR (CR, n = 26), and individuals at both FR and CR (FRCR, n = 13). T1-weighted brain scans were acquired and processed in a voxel-based analysis using permutation-based statistics. In the comparison between FRCR versus controls, we found lower grey matter volume (GMV) in a cluster (1689 voxels at −4.00, −72.00, −18.00 mm) covering both cerebellar hemispheres and the vermis. This cluster was subsequently used as a mask to extract mean GMV in all four groups: FR had a volume intermediate between controls and FRCR. Within FRCR there was an association between cerebellar cluster brain volume and motor function. These findings are consistent with an evolving pattern of cerebellar deficits in psychosis risk with the most pronounced deficits in those at highest risk of psychosis.

1. Introduction

Schizophrenia is associated with brain structural abnormalities (Hulshoff Pol et al., 2002; Meda et al., 2008; Tanskanen et al., 2010). At least some of the abnormalities are present at the time of initial diagnosis, leading to the hypothesis that these abnormalities develop in a prodromal or premorbid phase of illness (Steen et al., 2006; Ellison-Wright et al., 2008). One approach to address this hypothesis is to study people at risk of psychotic illness (Yung et al., 2004). This has the advantage of reducing potential confounds due to medication effects (Harrison and Lewis, 2003) or illness duration, and may have a clinical impact in improving early interventions available for this group of patients.

Two main approaches have been taken to define transition risk to psychosis. The first has been studying those at genetic risk due to a family history of illness (Lawrie et al., 1999). The second has been studying those at risk due to the presence of clinical features (most notably subthreshold psychotic symptoms) in help-seeking individuals recruited from specialist clinics (Yung et al., 2004). It remains unclear whether these two risk groups are associated with the same brain structural abnormalities as each other, or whether clinical and familial risk factors have their own unique brain structural signatures. It is also unknown whether or not these risk factors interact: if so, people with both risk factors would have the most pronounced brain deficits.

We aimed to evaluate brain structure in psychosis risk profiles through a cross sectional comparison between young clinical risk, family risk and individuals with both family risk and clinical risk using voxel based morphometry. We conducted our study in the Oulu Brain and Mind Study (Veijola et al., 2013), part of the Northern Finland 1986 Birth Cohort (NFBC86), which sets our study in an epidemiologically

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principled framework. This provides an additional and complementary perspective on psychosis risk studies, which are more usually selected from clinic samples.

We defined the population at clinical risk of psychosis in a two-stage approach: first we used a population based methodology that allowed us to screen our study subjects for non-specific psychotic like symptoms and then a clinical interview that allowed us to detect those at higher risk of transition to psychosis. We used registry data to identify those at familial risk of psychosis and we combined information from registries and clinical interviews to define those individuals who were at both family and clinical risk for psychosis. We gathered structural MRI data on these individuals in order to test whether brain structure varies in different risk groups and whether there is a trend in brain structural abnormality such that those at both family and clinical risk have more severe abnormalities than those at family risk alone.

2. Methods

2.1. The Northern Finland 1986 Birth Cohort

The population from whom the participants were selected was composed of children with an expected date of birth between July 1st, 1985 and June 30th, 1986, in the two northernmost provinces of Finland (Oulu and Lapland). This population based birth cohort included 99% of all births in the area at that time and consisted of 9479 children, of whom 9432 were live-born (Jarvelin et al., 1997) (http://kelo.oulu.fi/NFBC). The ethical committee of Oulu University Hospital approved the study.

2.2. Subject selection process: the Oulu Brain and Mind Study

Written informed consent was obtained from all participants. Details of subject selection are shown in Fig. 1 and are described by Veijola and colleagues (Mukkala et al., 2011; Veijola et al., 2013). To find a family risk group in the 1986 cohort, subjects were also asked to participate if they had a parent with a diagnosis of any functional psychotic disorder or A-type personality disorder in the nationwide Finnish hospital discharge register between 1972 and 2005. From those invited at family risk (272), 77 (33 males) agreed to participate and were finally scanned (28%).

In order to define a group of individuals at clinical risk for psychosis, a stepped approach was used, in which we first defined an invitation group utilizing screening questionnaires for prodromal symptoms of psychosis in the general population. Then we invited those deemed at highest risk to a clinical assessment using the Structured Interview for Prodromal Syndromes (McGlashan et al., 2001) to identify individuals who met operational criteria for being at clinical risk for psychosis. The initial screening was performed in a procedure at age 15–16; cohort members were invited to complete a set of questionnaires, including the PROD-screen (Heinimaa et al., 2003). We used the 21 item version calculating the final score based on 12 items, specifically probing for psychotic-like experiences (Yung et al., 2006). We recorded whether symptoms had been experienced ('no/yes') in the past 6 months. We also used the Youth Self-Report, YSR (Achenbach, 1991). From those invited, 74% (n = 6795) participated in the screening (n = 6298; 3043 boys). The cut off point was defined as subjects who had more than 2 symptoms in the Thought Disorder subscale (8 item) of the YSR and more than 2 specific symptoms (12 items) in the PROD-screen and who had had either no friends, had repeated a class in school or who had been treated in a psychiatric hospital due to non-psychotic disorder after the age of 12 until 2005. Furthermore, we invited also individuals who had been treated in hospital in 2003–2005 for substance abuse (ICD-10 diagnoses: F10–19); mood, neurotic (F30–49) and personality disorders (F60–69), and disorders of psychological and developmental origin (F80–89). We term these individuals symptomatic risk. From those who were invited in the symptomatic risk group (n = 137), 58 (24 males) were finally assessed with a detailed psychiatric assessment (42%), in order to determine who met clinical risk criteria according to operational criteria (see below).

A control group was randomly selected representing about 1% of other cohort members having excluded any people who had first-degree relatives with a history of psychosis, symptomatic risk (based on invitation group), diagnosed psychosis, or ADHD (as the control group also served as controls for a study of ADHD, not presented

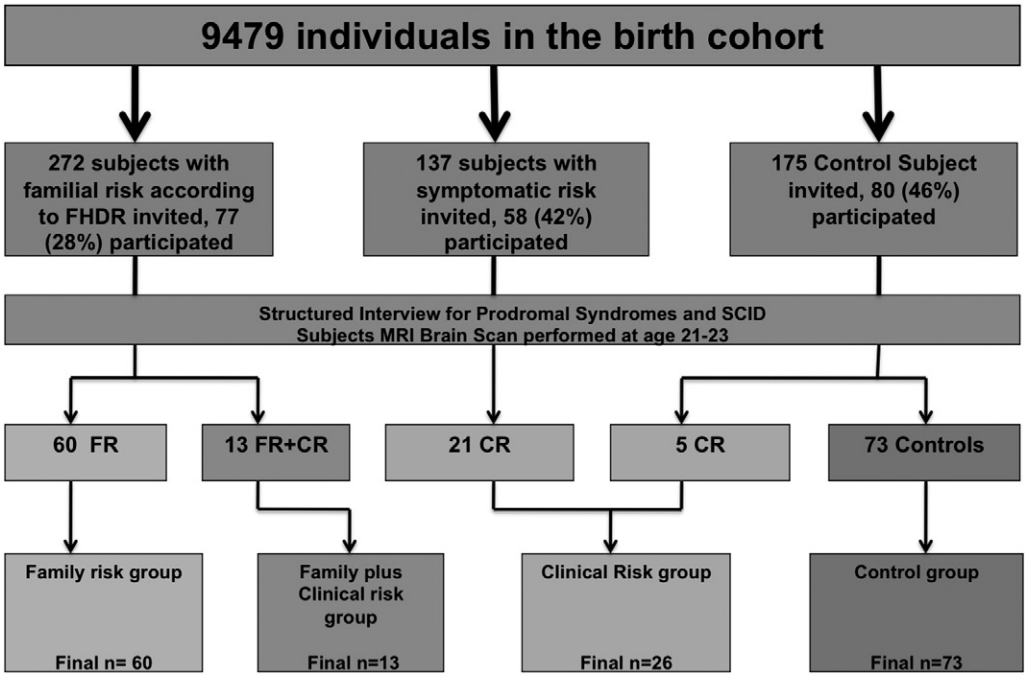

Fig. 1. Participant recruitment and constitution of groups. FHDR Finnish Hospital Discharge Registry. SCID Structured Clinical Interview for DSM-IV. FR Family Risk. CR Clinical Risk. 2 subjects were recruited to the clinical risk group through other sources (see text for details). After the SIPS interview, individuals deemed to be psychotic patients were subsequently excluded from the study. Participants with poor scan quality were also excluded.