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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.

Keywords: Schizophrenia; family risk; clinical risk; prodrome; cerebellum; MRI

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 has been 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, 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 sub-threshold 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 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.

Methods

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.

Subject selection process: the Oulu Brain and Mind Study

Written informed consent was obtained from all participants. Details of subject selection are shown in Figure 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 1972-2005. 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 operation 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 here). From those 175 invited to join the control group, 80 (31 males) were finally scanned (46%).

All the members of the groups were asked to participate in a clinical assessment during which examination with a psychiatric interview that used the SCID (Structured Clinical Interview with psychotic screen) (Spitzer et al., 1992) and the SIPS. This was performed to define those that either currently or previously met psychosis prodromal syndrome criteria: we term these individuals to be at clinical risk for psychosis. We also invited cohort members with a previous diagnosis of ADHD or previous diagnosis of psychosis, and applied the same diagnostic interview in case they had been misclassified and in fact met clinical risk criteria. This procedure also allowed us to test subjects for clinical risk of psychosis in the control group and in the family risk group, so finally we could determine which individuals were at family risk of illness but not clinical risk, and which were at clinical risk but not family risk, and which individuals were at both family and clinical risk for psychosis.

Final study groups

After the diagnostic interviews (SIPS and SCID) were applied to all the people

participating, the groups were reclassified into three risk groups and controls (Table1). These risk groups were:

Family Risk Group (FR)

60 subjects with a parental history of psychosis and who did not meet clinical risk criteria. From those subjects included in this group, 18 had a parent with schizophrenia, 41 had parents with other psychosis, and 1 subject had a parent with A type personality disorder.

Clinical Risk Group (CR)

This group was composed of 26 subjects who met prodromal syndrome criteria either currently or previously as defined by the SIPS and who did not meet family risk criteria. Fourteen patients from this group had been hospitalized receiving in patient treatment. 4 subjects had received outpatient treatment. Eight subjects had received no treatment at all. 1 member from this group had previously been misclassified as psychosis, and one came from a previous ADHD sample.

Family plus Clinical Risk Group (FRCR)

Composed of those subjects with a family history of psychosis according to the inclusion criteria of the invitation groups that subsequently and according to the SIPS were labeled as being at clinical risk of psychosis. This group was composed of 13 subjects. Two subjects had a parent with schizophrenia and 11 had a parent who had been diagnosed with other psychotic disorders. Five subjects from this group had been treated as outpatients and one had been hospitalized. Seven participants received no treatment.

Control Group

After applying the SIPS and SCID questionnaires and clinical interviews, 6 people

were excluded from the control group for clinical reasons (1 who met criteria for psychosis and 5 who met criteria for clinical risk of psychosis). One subject had to be excluded as well due to the very low quality of his scan. The group finally consisted of 73 people.

The total number of people in these groups was 172.

MRI data acquisition and preprocessing

All subjects (n=172) were scanned using GE Signa EchoSpeed HDx 1.5 Tesla MRI scanner in Oulu University Hospital. T1-weighted images were acquired with inversion recovery (IR) prepared ("BRAVO") 3D Fast Spoiled Gradient Echo (FSPGR) sequence using the following parameters: TR 12.4 ms, TE 5.2 ms, FA of 20 degrees, FOV 24 cm x 24 cm, 256x256 acquisition matrix, 1 mm slice thickness, half k-space coverage in the phase encoding direction (GE "fractional NEX" with 0.5 factor). After scanning, three images from the total were excluded. One because of severe movement; one for very bad quality, due to interference in the magnetic field during the scanning and the last one due to a large ventricle enlargement that made it impossible to preprocess.

Structural data was analyzed with FSL-VBM, a voxel-based morphometry style analysis (Ashburner and Friston 2000; Good et al., 2001) carried out with FSL tools. Structural images were brain-extracted using BET (Smith 2002.). Tissue-type segmentation was carried out using FAST4 (Zhang and Sejnowski, 2000). Resulting grey-matter partial volume images were then aligned to MNI152 standard space using the affine registration tool FLIRT followed by nonlinear registration using FNIRT which uses a b-spline representation of the registration warp field. The resulting images were averaged to create a study-specific template, to which the native grey

matter images were then non-linearly re-registered using FNIRT. The registered partial volume images were then modulated (to correct for local expansion or contraction) by dividing them by the Jacobian of the warp field. Finally the images were smoothed with a Gaussian kernel of full-width half-maximum of 1.175mm (sigma of 0.5). Note that because we use non-parametric statistics only minimal smoothing is required.

Grooved Pegboard Test:

As an assay of motor and cerebellar function, we collected data on the grooved pegboard test (Trites, 1989.) which is known to be abnormal in schizophrenia. It is a test of dexterity where subject must place 25 pegs to the board as quickly as possible with the dominant hand and non-dominant hand. The pegs are grooved, so placing the pegs resembles to putting a key to a lock. We used the outcome variable time to fill the pegboard with the dominant hand.

Statistical analysis

Modulated grey matter images were analyzed using CamBA permutation statistics (<http://www.bmu.psychiatry.cam.ac.uk/software>). Analyses of covariance (ANCOVA) using the General Linear Model framework were used to investigate focal GM volume differences between the controls and risk groups. We used gender, total intracranial volume (TIC) and handedness as covariates in all group comparisons. Results, corrected for multiple comparisons, were considered significant at the threshold of less than one error cluster per image, resulting in a p-threshold of less than 0.00029. We first performed analyses comparing single risk factor groups to controls using ANCOVA models: clinical risk (CR) versus controls, family risk (FR)

versus controls, and the additive risk factor group of family plus clinical risk to controls (FRCR vs. controls). We hypothesized that both CR and FR groups would demonstrate differences from controls, and that the FRCR group would have the most pronounced abnormalities. In order to test this hypothesis we planned to use the results of the pairwise comparisons as a mask in which to perform tests to examine linear trends and order effects.

Results.

Voxelwise group comparisons of grey matter volume

We found no significant differences when comparing the single risk groups (clinical risk or family risk) to controls. In the comparison between FRCR and controls we found that subjects in the additive risk group had lower grey matter density than controls bilaterally in the cerebellar hemispheres (anterior and posterior lobes) and vermis (Figure 2). This cluster had a size of 1689 voxels, peak voxel at -4.00, -72.00, -18.00 MNI space coordinates. In the anterior lobe the main regions with lower grey matter volume were the vermis and hemispheres involving mostly the right culmen and lingula in the vermis. In the posterior lobe the main region with grey matter deficit was the superior part of the posterior lobe especially around the declive and folium and the lateral hemispheric areas around the primary fissure. We used the cerebellar cluster as a mask to extract the mean grey matter volume for each individual for this area. We then compared the grey matter volumes we extracted across groups in order to examine trend effects.

Cerebellar mask grey matter volumes comparison between groups

After masking and extracting mean grey matter volumes for this cerebellum cluster in all four groups, we compared cerebellar grey matter volume between the FR groups and the CR group and controls, and tested whether the FR group has a cluster grey matter volume intermediate between controls and the FRCR group (Figure 3). The FRCR group has less grey matter volume than FR alone in the cluster mask ($T=5.4$, $df=84$, $p<0.001$, one-tailed), and the FR group has less grey matter volume than the controls ($T=1.9$, $df=131$, $p=0.03$, one-tailed). This demonstrates that the FR group has an intermediate volume in this cluster between controls and the additive risk group, confirmed by a linear contrast across these three groups ($p<0.001$, $F(1,143)=24.7$). When we excluded one outlier (see Figure 3) with a low volume from the FR group from the analysis the linear trend across groups remained significant ($p<0.001$, $F(1,142)=29.1$) and the FR remained lower than the controls, but now with marginal (“trend-level”) statistical significance ($T=1.6$, $df=130$, $p=0.0059$, one-tailed). The CR group did not show lower grey matter volume in the cluster region than the controls ($T=1.1$, $df=97$, $p=0.15$ one-tailed).

Correlation of the Grooved Pegboard Test scores with cerebellum grey matter volume.

To examine the functional consequences of brain structural abnormality within the FRCR group, we regressed the degree of cerebellar structural deficits with the results for the dominant hand of the Grooved Pegboard Test, as this test has been shown to be sensitive to cerebellar lesions (Baser & Ruff 1987). Greater grey matter deficits predicted motor impairment after controlling for gender and total intracranial volume ($p=0.023$, $Beta=0.006$, $T=2.7$; Figure 4).

Discussion

In an epidemiologically principled study, we demonstrated that individuals who have both family risk and clinical risk for psychosis have cerebellar structural deficits that predict performance on a test of motor function, the grooved pegboard test. A cerebellar deficit was also present in cohort members at family risk of psychosis but without clinical manifestations of psychosis.

These findings signal the importance of cerebellar structural abnormalities in hereditary risk for psychosis. Cerebellar deficits have long been implicated in the origins and evolution of schizophrenia (Andreasen, 1999), and a recent meta-analysis of voxel based morphometry studies of medication naïve psychosis patients identified the cerebellum as one of only two brain regions (the other was the insular cortex) with grey matter volume deficits in antipsychotic naïve patients (Fusar-Poli 2011c). The model developed by Andreasen and colleagues (Andreasen et al., 1998) implicates deficits in the cerebellum producing a so-called "cognitive dysmetria," which entails difficulty in prioritizing, processing, coordinating, and responding to information, and our own previous findings from a related cohort, the Northern Finland 1966 Birth Cohort, provided evidence for abnormal cerebellar neurodevelopment in schizophrenia (Ridler et al., 2006)

Of particular interest is our finding that there is a trend in structural cerebellar deficits such that family risk subjects have deficits compared to controls, but not as severe deficits as do those who have additive family risk and clinical risk. One potential explanation is that cerebellar deficits are a manifestation of genetic liability, such that those with the highest genetic loading for psychosis have both the most pronounced cerebellar deficits and other manifestations of disorder, such as clinical symptoms.

Alternatively, there may be an evolving pattern of deficits: as an individual at family risk for psychosis starts to develop clinical manifestations of illness, cerebellar brain abnormalities may concurrently progressively worsen. Longitudinal follow-up with repeat brain imaging of the individuals in this cohort (or similar cohorts) may help to decide between these interpretations.

Our study utilises a unique methodology for risk group definition, which presents what we believe is an approach complementary to the majority of brain structural risk for psychosis studies, which tend to be either clinic based or family risk based, as opposed to examining both risk factors within the same population base. The framework we used to study subjects at high risk of psychosis was first to examine the role of single risk factors (clinical or family risk) on brain structure, then analyzing the additive effect of both risk factors (family plus clinical risk).

We tried to separate the effects of prodromal symptoms from familial structural deficits. When we excluded clinical risk individuals from our family risk group, the comparison between the family risk group and controls showed no significant brain differences on voxelwise analysis. This may be surprising given that twin studies consistently show heritable structural deficits in schizophrenia and there have been several studies of patients at family risk of psychosis that show brain structural abnormalities in various brain regions, including the medial and lateral temporal lobe, the dorsolateral prefrontal cortex, medial prefrontal cortex, parietal cortex, cingulate cortex, precuneus, (Bhojraj et al 2010; Bhojraj et al 2011; Kubicki et al., 2013; Smieskova et al., 2013). However, a closer reading of the literature reveals that the studies that have found brain structural differences in family risk individuals versus controls have usually employed region of interest analyses, which have increased power compared to whole brain analyses as they avoid the necessity to make corrections for multiple comparisons. Our family risk whole brain analysis family risk

null result is concordant with findings of other family risk group studies such as the Edinburgh High-Risk Study (Lawrie et al., 2001), where no differences were found on whole brain, voxel-wise analysis, and where differences were only found on region of interest based analyses. This matter has also been discussed in a review by Lawrie and colleagues (2008), which showed that no previous study found differences in whole-brain, voxelwise analysis between a psychosis-offspring group and controls.

It is also important to consider our negative results for the clinical risk group versus controls comparison. Several previous groups, have found differences on whole-brain voxelwise analysis comparing those at clinical risk for psychosis versus controls (Pantelis et al., 2003; Borgwardt et al., 2007; Meisenzahl et al., 2008; Fusar-Poli et al 2011). Although not all the studies have found deficits (Nakamura et al 2013), a meta-analysis of over 700 clinical risk subjects confirmed the presence of grey matter deficits in the right superior temporal gyrus, left precuneus, left medial frontal gyrus, right middle frontal gyrus, bilateral parahippocampal/hippocampal regions and bilateral anterior cingulate (Fusar-Poli et al 2011). It is therefore surprising that our CR group did not differ from controls in brain structure. One major difference between our CR group and previous studies' CR group is that our group was not defined by help-seeking behaviour. It may be that brain structural deficits previously noted in persons at risk for psychosis attending prodromal clinics are partly associated with specific symptomatology but also partly associated with a general impairment of function, which is fairly intact in our CR group who had an average Global Assessment of Function (GAF) level of 69. Furthermore, the broad cognitive profile of our risk samples recruited from the general population is also fairly intact (Mukkala et al 2011), again suggesting that the participants in our risk samples are, compared to some previous risk studies, fairly healthy. Embedding our study within a population-based cohort allows us to make robust conclusions about psychosis risk in the general population. This has the advantage of avoiding the referral selection

effects that most clinical high-risk studies rely on, and it helps to ensure that our controls are truly representative of the population as opposed to being high-functioning, supra-normal controls. However, it also may limit the power of our study to detect subtle effects.

Whilst the only area in which we found differences between risk groups and controls was in the cerebellum, previous evidence indicates that there is more to the pathology of psychosis than cerebellar dysfunction; for example meta-analysis suggests widespread cortical and hippocampal deficits in schizophrenia (Ellison-Wright et al 2008). As our study was a straightforward voxel based morphometry study we did not examine gyrification patterns, or laterality effects such as torque (Crow et al 2013); our failure to document cortical deficits or laterality effects in our risk groups cannot be used as evidence that such abnormalities are not present, as absence of evidence is not evidence of absence.

In summary, our results highlight the importance of cerebellum abnormalities in hereditary risk for psychosis. These abnormalities may be developmental in nature (as we detect them in those without symptoms) but may also be progressive, as they are more pronounced in those individuals who have both a presumed psychosis genotype (family history) and phenotypic expression (a history of subthreshold psychotic symptoms).

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Figure Legends:

Figure 1. Participant recruitment and constitution of groups. FHDR Finnish Hospital Discharge Registry. 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.

Figure 2. Regions marked in blue indicate where people with both family and clinical risk for psychosis have lower grey matter volume than controls.

Figure 3. Cerebellum cluster volume in cubic cm by psychosis risk group.

Figure 4. Scatter plot of the regression analysis performed on the cerebellum cluster grey matter volume, against the dominant hand performance of the pegboard task in the family and clinical risk group (regression analysis: $p=0.023$, $\text{Beta}=0.006$, $T=2.7$).

Table 1. Demographic Description of the Psychosis Risk Groups for the Structural MRI

		General population controls (n= 73)	Family Risk (n = 60)	Clinical Risk (n = 26)	Family and Clinical Risk (n = 13)	Total (n = 172)
Age		21.96 (0.68)	22.09 (0.7)	22.08 (0.69)	21.79 (0.7)	21.98 (0.69)
Sex		43 F: 30 M	27 F: 33 M	17 F: 9 M	12 F: 1 M	99 F: 73 M
Handedness		69 R: 4 L	52 R: 8 L	26 R: 0 L	12 R: 1 L	159 R: 13 L
IQ	Mean (std dev)	109.52 (20.9)	108.67 (21.6)	115.38 (25.2)	111.15 (22.8)	111.18 (22.6)
	No information	1	0	0	0	1
Educational Level	<9 School years	0	1	0	0	1
	High School enrolment	23	29	15	2	69
	High School Graduation	49	30	11	11	101
GAF current	Mean (std dev)	80.47 (SD 16.15)	83.63 (SD 7)	68.58 (SD 15.3)	72.38 (SD 12.38)	76.24 (10.9)
SOPS Score for Positive Symptoms	Mean (std dev)	1.09 (1.5)	1.13 (1.5)	9.19 (3.72)	7.15 (3.87)	
Family Members Diagnosis of the Family Risk Group (FHDR 1972-2005)	Schizophrenia Spectrum	0	23	0	3	26
	Schizoaffective	0	10	0	0	10
	Bipolar Psychosis	0	5	0	5	10
	Psychotic Depression	0	12	0	1	13
	Delusional disorder	0	5	0	2	7
	Other Psychoses	0	5	0	2	7
Psychosis diagnosis of either father or mother Family Risk Group	Mother, psychosis 1972-2005	0	41	0	6	47
	Father, psychosis 1972-2005	0	19	0	7	26
	No data	0	0	0	0	0
I drink too much alcohol or get drunk ***	Not true	72	22	49	6	149
	Somewhat or sometimes true	1	17	11	4	33
	Very true or often true	0	1	0	3	4
I use drugs, for nonmedical purposes: ***	Not true	72	59	22	12	165
	Somewhat or sometimes true	1	1	3	1	6
	Very true or often true	0	0	1	0	1
Alcohol use disorder * until 2008		0	1	1	0	2
Cannabis use disorder * until 2008		0	0	2	0	2
Other substance use disorder *		0	0	3	0	3
Drug use detected by urine sample **	Amphetamine and other stimulants	0	0	0	0	0
	Benzodiazepine	0	1	0	0	1
	Buprenorphine	0	0	0	0	0

	Cannabis	1	0	3	0	4
	Cocaine	0	0	0	0	0
	Opioids	1	0	0	0	1
	All drugs	2	1	3	0	6
History of Psychiatric Treatment****	No treatment	60	8	42	7	117
	Inpatient	1	14	6	1	22
	Outpatient	11	4	12	5	32

*Finnish Hospital Discharge register (FHDR) until 2008

**Drug use was measured at the time of the scan with a urine sample

***Adult Self Report (ASR) items (Achenbach scale)

**** History of psychiatric treatment was assessed with self-report in the clinical examination and with register data on in-patient admissions

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