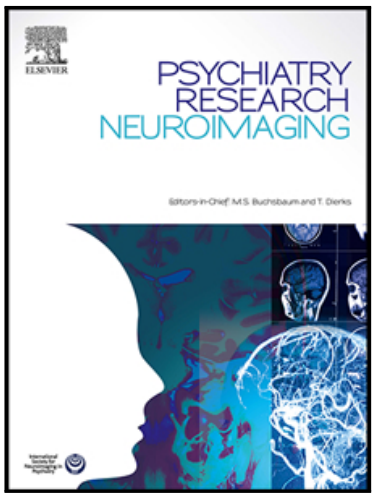

Cerebellar white matter in young adults with a familial risk for psychosis

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Highlights:

- No findings in cerebellar white matter in those with a familial risk for psychosis
- No findings in cerebellum for participants with a parent with schizophrenia
- Familial risk might not manifest as structural changes in cerebellar white matter

Cerebellar white matter in young adults with a familial risk for psychosis

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1. INTRODUCTION

The cerebellum has been traditionally associated with motor function, but it also has a role in regulation of a number of higher brain functions. It is connected to several neocortical areas through polysynaptic circuits via basal ganglia and thalamus. These pathways operate in functions such as cognition and social skills (Crippa et al., 2016). The role of the cerebellum in emotional regulation has been established through the study of emotional disturbances in children and adults with cerebellar lesions (Adamaszek et al., 2017). Cognitive defects resulting from cerebellar dysfunction have been termed ”dysmetria of thought”: the way that the cerebellum modulates and fine-tunes rate, force, rhythm, and accuracy of movement is analogous to the way it regulates speed, capacity, consistency and appropriateness of cognitive and emotional responses and coordinates and monitors errors in thought (Schmahmann et al., 2007). The dysmetria of thought hypothesis has been used to explain the cognitive, affective, and psychotic symptoms in schizophrenia and it has been supported by both structural and functional neuroimaging studies (Wolf et al., 2009). The cerebellum has both structural and functional connections to the prefrontal cortex, the limbic system and also to the brainstem nuclei, which produce serotonin, norepinephrine, and dopamine for the limbic system and the cerebrum (Konarski et al., 2005).

Schizophrenia patients have been reported to exhibit grey matter deficit in the vermis of the cerebellum (Cohen et al., 2012) and in the anterior cerebellum (Edwards et al., 2008). In addition, the proportional relationship of grey and white matter between regions of the vermis may be altered (Lawyer et al., 2009). Cerebellar white matter microstructure has been associated with cognitive, language and emotional function, for example reading skills (van Baarsen et al., 2016; Travis et al., 2015). Motor dysfunction related to cerebellar deficits has been documented in schizophrenia patients and those at risk for psychosis, which may indicate a more general dysfunction of the cerebellum in the emergence of psychotic disorders (Bernard and Mittal, 2014). Further, learning of a task known to activate cerebello-thalamo-cortical circuit has been shown to be poorer on youth with clinical high risk for schizophrenia, while learning rate was associated with symptom severity (Bernard et al., 2018). Both increased and decreased connectivity of the cerebellar default mode network to thalamus and several frontal regions have been reported in schizophrenia patients (Chen

et al., 2013; Wang et al., 2014). Deficits in white matter integrity early in schizophrenia suggest that these abnormalities may be related to the illness onset (Kyriakopoulos and Frangou, 2009). Understanding these neurofunctional correlates of vulnerability to psychosis is essential to research of schizophrenia (Fusar-Poli et al., 2007). Changes in the cerebellum are not specific to psychosis but have been found also in other psychiatric conditions such as mood disorders (Johnson et al., 2018; Minichino et al., 2014), fear and anxiety related disorders (Moreno-Rius, 2018; Schutter et al., 2017), attention-deficit and hyperactivity disorder (Curtin et al., 2018; Stoodley, 2016) and post-traumatic stress disorder (Baldaçara et al., 2012, Rabellino et al., 2018).

Diffusion-weighted imaging (DWI) is a modality magnetic resonance imaging (MRI) that measures diffusion of water in tissue. Fractional anisotropy (FA) and mean diffusivity (MD) are DWI-based measures. FA describes the anisotropy of the diffusion process. Anisotropy is caused by obstacles that inhibit the movement of water molecules to some directions more than to other directions. In white matter, macroscopic anisotropy is caused by bundles of neuronal axons running in parallel: Water molecules move faster in the direction of the axonal fibers compared to the perpendicular direction (Le Bihan and Johansen-Berg, 2012). MD describes the overall magnitude of the molecular displacement in the diffusion process. FA and MD are both used as measures of white matter integrity because they are sensitive to different changes in water diffusion: For example, alterations in FA can result from changes in axial diffusivity (AD) or radial diffusivity (RD). FA decrease and MD increase are usually interpreted as signs of compromised white matter integrity. AD represents diffusivity parallel to the axons and it can be affected by axonal degeneration. RD represents diffusivity perpendicular to axons and it is affected by axonal myelination (Alexander et al., 2007). FA increase and MD decrease with age have been consistently reported in childhood and adolescence, suggesting a relationship between variation in these measures and the development of adult white matter structure (Asato et al., 2010; Lebel and Deoni, 2018). DWI-studies have shown reduced FA of the frontal and temporal white matter in patients suffering from psychotic disorders (Tamnes and Agartz, 2016). The correspondence between MRI and immunohistochemistry indicates that these imaging approaches correctly reflect microstructural organisation of cerebellar tissue (Dell'Acqua et al. 2013).

Current understanding views psychosis and schizophrenia as disruptions in the connectivity of the brain. This “disconnectivity hypothesis” suggests that psychosis is a result of abnormalities in

white matter tracts. Alterations in connectivity have been shown in imaging studies in all stages of schizophrenia (Canu et al., 2015; Coyle et al., 2016).

White matter changes in psychosis patients have been observed repeatedly (Domen et al., 2013; Michielse et al., 2017; Ordonez et al., 2016). Further, white matter integrity has been shown to decrease with time in psychotic patients with childhood trauma compared to their siblings (Domen et al., 2018). It has been also reported that the siblings of young adults with schizophrenia showed higher mean FA in some regions compared to both their siblings with schizophrenia and controls, even though the schizophrenic siblings themselves did not differ in white matter FA from healthy controls (Boos et al., 2013). The study also found negative correlation with symptom severity and FA in the arcuate fasciculus in schizophrenia. In another study psychosis patients and their healthy siblings have been observed to share white matter integrity disruptions in the left prefrontal cortex and the hippocampus (Hao et al., 2009). However, Harms et al. found no significant differences between schizophrenia patients and their non-psychotic siblings in FA when compared to controls (Harms et al., 2015).

The aim of this study was to compare the estimates of white matter microstructure of the cerebellar peduncles between those with a familial risk for psychosis (FR) and a control group (CO). The study setting is similar to our previous study on white matter integrity of the cerebrum (Koivukangas et al. 2015). In this study, familial risk for psychosis was defined as having one or both parents with a psychotic disorder. Participants were members of the Northern Finland Birth Cohort 1986 (NFBC 1986).

Our hypotheses were based on previous studies on microstructural changes in the cerebrum in those suffering from psychosis, which report FA decreases in schizophrenia (Kelly et al., 2018; Keymer-Gausset et al., 2018; Squarcina et al., 2017; Tønnesen et al., 2018). MD increases have also been reported in schizophrenia patients (Kelly et al., 2018; Squarcina et al., 2017). Our hypotheses were as follows:

1. Cerebellar FA is lower in participants with familial risk for psychosis than in the control group.
2. Cerebellar MD is higher in participants with familial risk for psychosis than in the control group.

2. METHODS

2.1. The Northern Finland 1986 Birth Cohort

Participants were members of the Northern Finland Birth Cohort 1986 (NFBC 1986). NFBC 1986 consists of children with an expected date of birth between the 1st July 1985 and the 30th June 1986, born in the two northernmost provinces of Finland: Oulu and Lapland. The population-based birth cohort consists of 9479 children, of whom 9432 were live-born, and includes 99% of all births in the given area and time (Järvelin et al., 1993). Data collection was started before the birth of the participants and is still ongoing. Data has been supplemented with questionnaires collected when participants were 7, 8 and 15-16 years old, and with hospital register data. The Ethical Committee of the Northern Ostrobothnia Hospital District in Finland has approved the study. All participants of the present study have given written informed consent.

2.2. Participant selection and invitation

The Oulu Brain and Mind Study, as a part of NFBC 1986, aims to study the emergence and causes of psychosis by following young people. Details of participant selection and the field study conducted between 2007 and 2010, when the participants were 20-25 years old, have been described in (Veijola et al. 2013).

The FR study group consisted of individuals whose parent had been treated in hospital due to a psychotic disorder according to the Finnish Hospital Discharge Register (FHDR) between 1972 and 2005 (ICD-8 and ICD-9: codes 295–299 and ICD-10: codes F20-33, excluding non-psychotic mood disorders). We excluded participants who had a history of psychotic episodes according to FHDR (Figure 1). Of the cohort members, 272 were found to have a parent with a psychotic disorder. Of these one had died, five were living abroad, and for four individuals no address was available, leaving 262 FR potential participants to be invited to the study. Finally, 78 individuals (34 males) participated in the present study.

From the remainder members of the NFBC 1986, a random sample of 193 individuals was selected as a control group. Of these, one had died and one had no address available. Of the invited 191 individuals, 80 (31 males) participated.

The Oulu Brain and Mind Study protocol allowed for about two thirds of the participants to be scanned with DWI, resulting in 53 FR participants and 55 control participants. This was due to time limit. The Structured Interview for Prodromal Syndromes (SIPS; McGlashan et al., 2001) was used to measure psychotic-like symptoms. The SIPS allows definition of three separate prodromal syndromes for psychosis: brief intermittent psychotic syndrome, attenuated positive prodromal syndrome, and genetic risk and deterioration syndrome. We assessed if the participant had current prodromal syndrome. Structured Interview for DSM-IV disorders, SCID-I (First et al., 1997) was used to determine psychiatric episodes.

According to the SIPS and SCID-I interviewers, one participant in the FR and one in the control group had a history of psychotic episodes. Both of these were excluded from the study. One participant from the control group was excluded for having had earlier head trauma with 30 min or more of unconsciousness. Six participants from the FR and three from the control group were excluded because of poor scan quality. The final FR group included 46 and control group 50 participants.

Five participants from the FR group and no controls had a current prodromal syndrome according to the SIPS. According to SCID interview both in the FR and control group three participants had current mood disorder episode and none had any substance use disorders. Two participants from the FR group and three from the control group had current anxiety disorder. No participants in the FR and one in the control group used psychotropic medication. The medication used was SSRI-medication (Table 1). One participant had a missing urine drug test and one tested positive for opioids in the control group. All urine drug tests were negative in the FR group. According to FHDR, among the FR participants, 13 had a parent with schizophrenia and 34 with another psychotic disorder. Of these other psychotic disorders, two had schizoaffective disorder, two schizophreniform disorder, four delusional disorder, six psychotic depressive disorder, eight psychotic bipolar disorder and 12 some other psychotic disorder. None had both parents with psychosis.

Participants were asked which hand they preferred to use when writing (Table 1). Educational level was in two categories (matriculation or no matriculation) as reported by the participant. IQ of the participants was estimated using Matrix Reasoning and Vocabulary tests of the WAISIII (Wechsler Adult Intelligence Scale III Edition, Finnish version) (Wechsler, 1997). Level of the participants' functioning was evaluated in the SIPS interview using Global Assessment of Functioning, GAF (American Psychiatric Association, 1994). Alcohol use of the participants was based on their answers to a question that asked if they drink too much alcohol with three possible answers: not true, somewhat or sometimes true, very true or often true.

2.3. Image acquisition

All participants were scanned using GE Signa 1.5 Tesla 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°, field of view (FOV) 24 cm × 24 cm, acquisition matrix 256 × 256, 1 mm slice thickness, half k-space coverage in the phase encoding direction (GE "fractional NEX" with 0.5 factor). T1-weighted images of three participants were excluded: one because of severe movement, one because of low image quality due to interference in the magnetic field during the scanning and one due to failed image registration (ventricular enlargement). Diffusion-weighted imaging data were acquired with single-shot echo-planar imaging. The parameters for the DWI were as follows: FOV 24 cm^2, matrix size 128 × 128, slice thickness 3.0 mm. The data were reconstructed into a 256 × 256 matrix, with a resulting voxel size of 1.875 × 1.875 × 3 mm. The diffusion gradients were acquired along 40 nonparallel gradient directions (b = 1000 s/mm^2). Datasets included one image without diffusion weighting (b=0).

2.4. Image Processing

The DWI data was inspected manually for slice-wise errors and other significant artifacts. Preprocessing of DWI data was carried out in ExploreDTI v4.8.6 (Leemans et al., 2009) in MATLAB R2016a (The MathWorks, Inc., Natick, Massachusetts, United States). First, b0 images were stripped of non-brain tissue using FSL Brain Extraction Tool (BET (Smith, 2002)). Brain-only

b0 images were then used as reference for correcting head motion and eddy current artefacts, after which b-vectors were rotated according to the new orientations (Leemans and Jones, 2009). Diffusion tensors were estimated using the REKINDLE algorithm (Tax et al., 2015) and FA and MD maps were calculated. Finally, echo-planar imaging artefacts were corrected by registering FA images nonlinearly to undistorted high resolution T1-weighted images in the anterior-posterior phase-encoding direction (Irfanoglu et al., 2012; Leemans and Jones, 2009).

Whole brain global tractograms were estimated for each individual in the native T1w space by using constrained spherical deconvolution and recursive calibration of the response function, as implemented in ExploreDTI (Jeurissen et al., 2011; Tax et al., 2014). In order to reconstruct the WM tracts of interest, binary ROIs ('AND' and 'NOT' gates) were drawn on the MNI152 1-mm brain template as explained in Figure 2. The ROIs were then projected to each individual's native T1w space using the inverse of the above native T1-weighted-to-MNI152-template nonlinear registration (ANTs, (Avants et al., 2011)). Streamlines presenting tract bundles of interest were extracted from global tractograms using 'AND' and 'NOT' gate ROIs in each individual's native T1w space. The tracts included altogether six cerebellar peduncle segments: the inferior, middle and superior cerebellar peduncles (ICP, MCP and SCP, respectively) on the left and right hemisphere. The resulting streamlines were visually inspected for inappropriate connections and aberrant tracings using TrackVis software (http://trackvis.org (Wang et al., 2007)). Finally, cerebellar tract mean values were extracted for FA, MD, AD and RD in each individual.

FIGURE 2

2.5. Tractography

Streamline tracing of the six cerebellar peduncle segments was successfully performed in 93 participants (97% out of all participants) for the left ICP, 95 participants (99%) for the right ICP, 94 participants (98%) for the left MCP, 95 participants (99%) for the right MCP, 64 participants (67%) for the left SCP and 59 participants (61%) for the right SCP. Tracing was successfully performed for all six segments in 16 participants (35%) in the FR group and 19 participants (38%) in the control group, for five segments in 23 participants (50%) in the FR group and 27 participants (54%) in the control group, for four segments in five participants (11%) in the FR group and four participants (8%) in the control group, for three segments in one participant (2%) in the FR group

and none in the control group, and for one segment in one participant (2%) in the FR group and none in the control group. Tract reconstruction of an example subject is shown in Figure 3.
FIGURE 3

2.6. Statistical Analysis

Differences in FA, MD, AD and RD between the FR and CO groups were examined using Welch's two-sample *t*-test and Cohen's *d*. We used independent-samples t-test (*t*) for continuous variables and Pearson's chi-squared test (χ^2) and Fisher's exact test for categorical variables. R software package version 3.5.1 was used for statistical analysis (R Core Team, 2016). We used false discovery rate (Benjamini–Hochberg procedure) to account for multiple comparisons in each microstructural measure. A *p*-value of <0.01 was considered significant. We also adjusted the results using the following covariates: sex, age and handedness.

2.7. Attrition Analysis

Out of 272 (17%) invited potential FR participants, 46 participants with FR participated in the study. The corresponding figures in the control group were 50 out of 193 (26%) potential control participants.

Of the non-participant FR group members 56.6% and of the participants 34.8% were male. Of the non-participant CO group members 52.4% and of the participants 34.0% were male.

According to FHDR, 30% of the non-participating FR individuals and 28% of the participants had a parent with schizophrenia (Pearson Chi-Square Test p=0.727). In the FR group 8.0% of the non-participants and 6.4% of the participants had been treated in hospital between the years 2001 and 2005 due to a psychiatric disorder. In controls 2.8% (n=4) of the non-participating and none of the participating individuals had been treated in hospital due to a non-psychotic psychiatric disorder (Fisher's Exact Test p=0.575).

3. RESULTS

3.1. Demographic and clinical characteristics

The demographic characteristics and clinical data of the groups are presented in Table 1. Of the 96 participants, 33 (34.4%) were males. The mean age of the whole sample was 22.7 (SD 0.8) years. The groups were not significantly different with respect to demographic and clinical variables.

TABLE 1

3.2. Differences in FA, MD, AD and RD

Familial risk and control groups showed no significant differences in FA ($t \leq 1.81$, $p \geq 0.07$), MD ($t \leq 2.08$, $p \geq 0.04$), AD ($t \leq 1.66$, $p \geq 0.10$) or RD ($t \leq 2.24$, $p \geq 0.03$) in any of the cerebellar peduncle segments before or after adjusting for covariates. In the right MCP unadjusted model there was a trend for increased FA (t=1.76, p=0.08), decreased MD (t=-2.00, p=0.05), decreased AD (t=-1.58, p=0.12) and decreased RD (t=-2.15, p=0.04) as compared to the control group. The mean values of combined left and right tracts are shown in Figure 4 a, b, c and d. Findings in individual peduncle segments are shown in Supplement Table s1 a, b, c and d and Supplement Figure s1 a, b, c and d.

FIGURE 4a

FIGURE 4b

FIGURE 4c

FIGURE 4d

4. DISCUSSION

Contrary to our expectations, we found no link between cerebellar white matter microstructure and familial risk for psychosis. Our findings suggest that familial risk for psychosis is not linked to structural changes of cerebellar white matter.

Our results are in discrepancy with some other studies on the subject. Decreases in white matter integrity have been established in psychosis patients in sibling studies (Domen et al., 2013; Michielse et al., 2017; Ordonez et al., 2016). Collin et al. (2011) found that, not only do schizophrenia patients show impaired functional connectivity between the cerebellum and some cerebral regions, but that some of these abnormalities are present in siblings of the patients, as compared to a healthy control group, indicating a possible familial component to psychosis risk. Functional and anatomical connectivity abnormalities in the cerebellum of schizophrenia patients have been reported repeatedly (Kanaan et al., 2009; Kyriakopoulos and Frangou, 2009; Liu et al., 2011). It is possible that white matter abnormalities are better seen in those who have already developed schizophrenia, but there are also studies suggesting a link between lowered connectivity and increasing number of psychotic-like experiences in healthy individuals (Oestreich et al., 2018). Also, abnormal functional and structural cerebellar network development has been reported in individuals with high-risk for psychosis, specifically association between cerebello-thalamo-cortical network development and connectivity and positive symptom course (Bernard et al., 2017). Abnormalities in functional connectivity have also been reported in temporal areas in adolescents and young adults at clinical high risk for psychosis (Colibazzi et al., 2017). Another study has indicated that individuals with attenuated positive psychotic symptoms may have white matter microstructure alterations independent of clinical high risk for psychosis status (Cooper et al., 2018). Discrepancy with other studies can possibly be explained by the fact that tractography results seem to vary depending on the method used (Christidi et al., 2016).

In our earlier study with the same study sample Koivukangas et al. (2015) found no evidence of a link between familial risk for psychosis and white matter microstructure in the cerebrum. This finding is in line with the results of the present study. Additionally, Jukuri et al. (2015) found that alterations in functional connectivity in the grey matter of the anterior lobe of the right cerebellum

may be associated with increased vulnerability to psychosis. Findings of our earlier and present study suggest that cerebellar structural anomalies associated with psychosis risk are mainly found in grey matter.

The use of a birth cohort research setting should be considered as the main strength of this study. NFBC 1986 is a general population cohort: the individuals had the same ethnic background and were of the same age. The age range of the participants was from 21 to 24 years, which is within the average range of onset for schizophrenia (Owen et al., 2016).

Our control group was similar to the study group regarding sex, age, intelligence, general functioning, alcohol problems, handedness and education distribution. This is a strength of the study. Another strength was that we did not exclude participants based on prodromal syndromes, opioid usage and use of psychotropic drugs, either in the control or the study group. This way control group might represents a sample from the general population.

The use of a whole brain CSD tractography approach allows estimating diverse fiber populations and crossing fibers (Farquharson et al., 2013, Kristo et al., 2013). Whole brain tractography also reduces user bias of selection of seed ROI locations. Tractography methods allow avoiding registering ROIs on the tracts, thus reducing registration errors and partial volume effects because streamlines, by definition, only traverse regions of sufficiently stable diffusion parameters. It must be noted, however, that CSD tractography, while offering technical benefits, is suboptimal for the single-shell low b-value data used.

Limitations of this study include the sample size, which may limit making statistical inferences. We did not perform a priori power calculation as our our goal was to simply include all the suitable individuals from the Oulu Brain and Mind Study. It is possible that our lack of results is due to the study being underpowered. Possibly a larger sample size would be required to reliably detect the small differences in the microstructural measures between the groups. The fact that the groups consist of only of those who were willing to participate is a possible confounding factor. The lack of participants with two parents with psychosis means that we were unable to compare the possible difference between those participants with only one and those with both parents with psychosis. This comparison could have been useful in studying whether there is an increased familial risk when both parents are psychotic. Our FR group is very heterogenic as it includes children of parents with schizophrenia, delusional disorder, psychotic depressive disorder and

psychotic bipolar disorder. These various psychotic disorders may have differences in gene expression and brain alterations. In addition, our control group was not completely mentally healthy but included in total five cases with mood or anxiety disorder. This might be considered also a strength of the study as discussed above.

We had only subjective questionnaire data on alcohol use. This may be an inaccurate measure of actual use of alcohol. It is possible that our findings are affected by continuing white matter development in the early 20's especially in males (Asato et al., 2010; Lebel and Deoni, 2018). This is however contradicted by the similar age and sex distribution of control (mean age 22.6 years, 17 males out of 46 participants) and FR (mean age 22.8 years, 16 males out of 50 participants) groups. Another major limitation is the relatively low magnetic field strength of 1.5 T and the resulting voxel size of 2×2×3mm that may limit the detection of differences in the fine cerebellar microstructure. This might also be the reason behind the relatively low number of succesful tracings in the superior peduncles: for left 67% and for right 61% even though for other peduncles the number of succesful tracings ranged from 97% to 99% (see Section 2.5). Even though the images were adjusted for head motion, we cannot totally rule out motion artifacts. We cannot exclude the possible effect of anisotropic voxels in our findings. However, we found no preference towards the inferior-superior axis in visual inspection. Additionally, the partial volume effect adds noise to the data and is a possible source of error.

Only 17% of the invited FR individuals and 26% of the control individuals participated. As our attrition analysis shows, there were no significant differences between the participant and non-participant groups regarding key characteristics. However, there is still a possibility that the non-participant group could have had more substantial psychosis risk related alterations in their white matter structure. Parents of the participants were not interviewed for prodromal symptoms, making it possible that some of the participants' psychotic parents went undetected if they had had no hospital treatment for their psychotic disorders. We also had no data on parents treated as outpatients. However, FHDR is able to capture majority of those with lifetime diagnosis of psychotic disorder (Perälä et al. 2007).

5. Conclusions

Contrary to our hypothesis, no significant differences in FA or MD of the cerebellar peduncles were found between the FR and control groups. Our findings suggest that the familial risk for psychosis may not manifest as structural changes in cerebellar white matter. It is possible that the structural changes are found mainly in grey matter. Our results did not support, but neither disconfirm, the disconnectivity model, which proposes that irregularities in neural connections have an essential role in the development of psychosis.

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Contributors

Juho Pudas, Lassi Björnholm, Juha Nikkinen and Juha Veijola contributed to the study design. Juha Veijola and Juha Nikkinen participated in collection of the data. Lassi Björnholm and Juha Nikkinen analysed the DWI data. Juho Pudas conducted statistical analyses. Juho Pudas, Juha Veijola and Lassi Björnholm drafted the first version of the manuscript. All authors have taken part in drafting the manuscript and approved the final version.

Conflict of interest

The authors declare no conflicts of interest.

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Figure legends

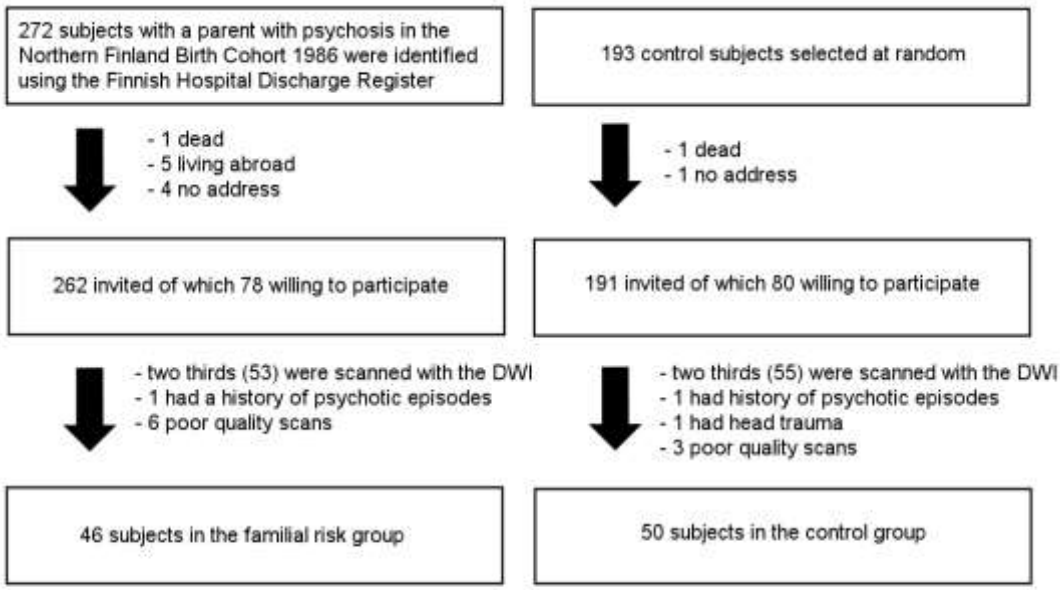

Fig. 1. Flowchart of the study groups with the explanations for exclusion.

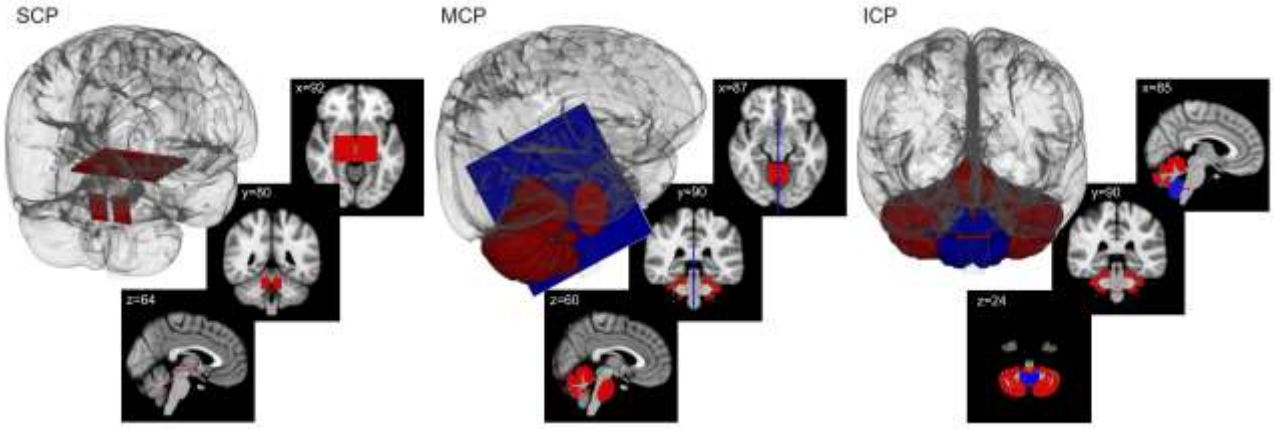

Fig. 2. The locations of tractography ROIs for extracting cerebellar peduncles overlaid on MNI152 1-mm brain template. For extracting SCP, two vertical 'AND' gates were drawn on the right and left dentate nuclei (red) and two horizontal 'AND' gates below thalamus (red, left panel), as located in Oxford Thalamic Connectivity Atlas (Behrens et al., 2003). For the left SCP, the left cerebellar

gate was used in conjunction with the right thalamic gate, and *vice versa* for the right SCP. Middle cerebellar peduncle: two 'AND' gates were placed in the pons at the left and right side of the mid-sagittal plane (red)and separated with a large 'NOT' gate in the middle (blue). Parts 1-8 and 10 from "Cerebellar Atlas in MNI152 space after normalization with FNIRT" (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases), thresholded at 50%, were combined and used as a cerebellar 'AND' gate (red, middle panel). Inferior cerebellar peduncle was located by placing two 'AND' gates at the restiform body at *z*=24 (red) and using the same cerebellar 'AND' gate as above. Part 9 in "Cerebellar Atlas in MNI152 space after normalization with FNIRT" thresholded at 50%, was used as a 'NOT' gate (blue) to prevent tracts from crossing the cerebello-medullary fissure at tonsils. The scheme for extracting tract bundles was adapted from an article of cerebellar white matter architecture (van Baarsen et al., 2016). To allow robust detection of tracts after transformation of ROIs from MNI152 1-mm space to native space, the ROIs included two adjacent planes.

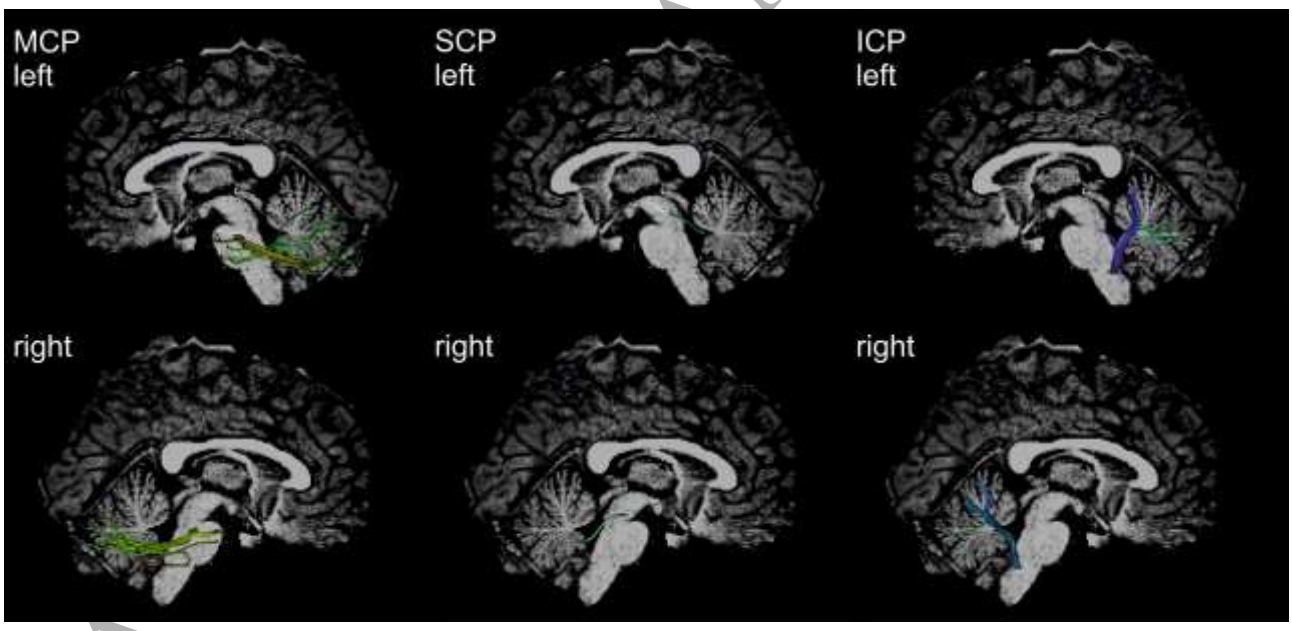

Fig. 3. Cerebellar tractography of an example participant for each peduncle. Colour scheme for tract directions: blue for cranial-caudal, red for left-right and green for anterior-posterior.

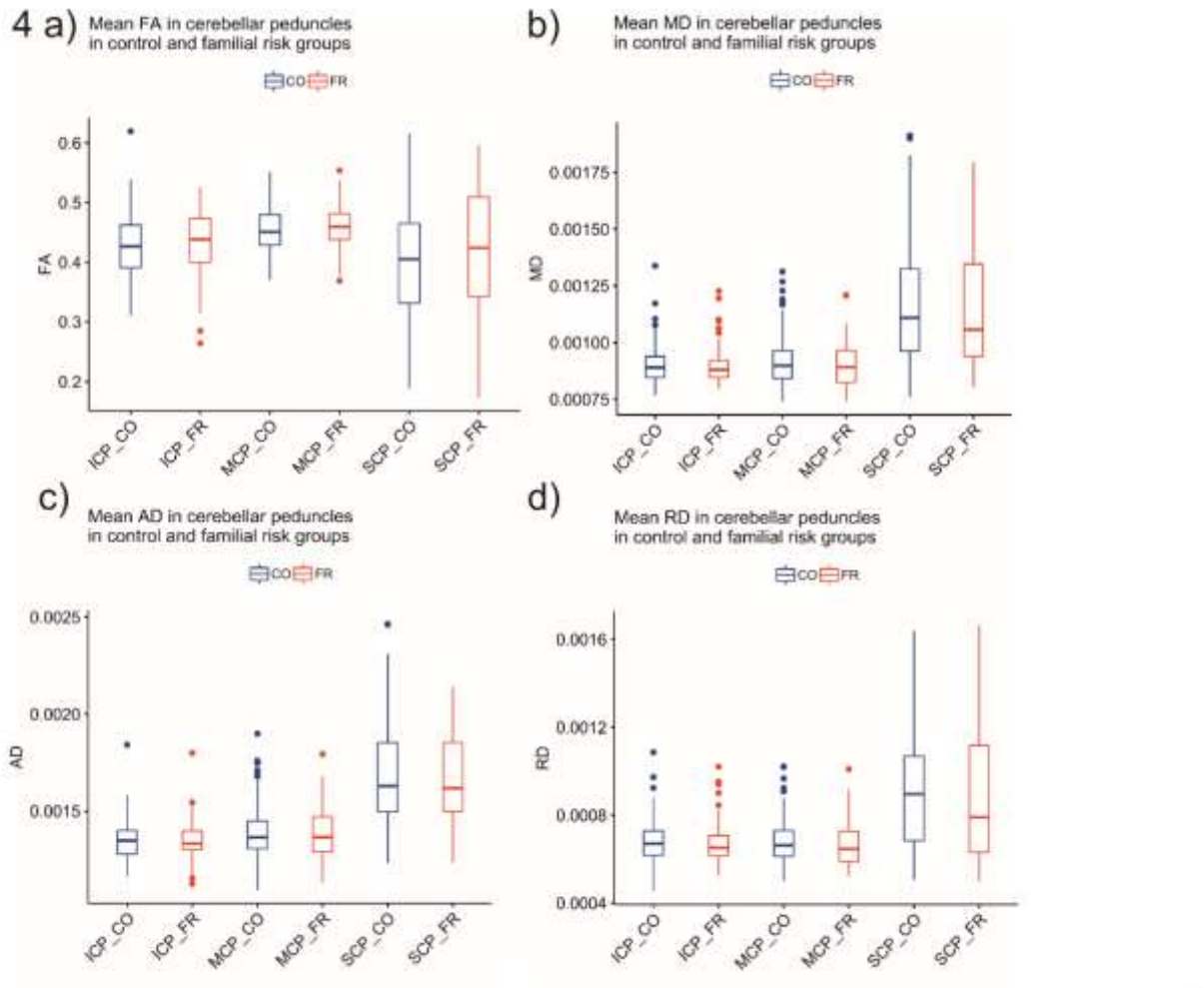

Fig. 4. Microstructural measures of cerebellar peduncles for control and familial risk groups. Left and right sided tracts were averaged together in a) FA, b) MD, c) AD and d) RD. ICP, inferior cerebellar peduncle; MCP, middle cerebellar peduncle; SCP, superior cerebellar peduncle.

Table 1

Demographic and clinical data in the familial risk for psychosis (FR) and control groups.

Variable	FR group (*n* =46)	Control group (*n* =50)	Statistical test	P-value
Age, years (*M*)	22.7	22.6	t=0.43	0.666
Gender, male (*n*)	16	17	χ^2=0.01	0.936
Handedness, right (*n*)	43	49	χ^2=1.15	0.283
Education level			χ^2=1.34	0.248
No matriculation (*n*)	19	14		
Matriculation (>11 school years) (*n*)	27	36		
Estimated IQ (*M*)	110.8	109.2	t=0.35	0.727
GAF (M)	82.0	82.7	t=-0.45	0.652
Alcohol use: I drink too much alcohol *			χ^2=0.03	0.872
Not true (*n*)	30	36		
Somewhat true or very true (*n*)	13	13		
Current substance use disorders	0	0	-	-
Current mood disorder (*n*)	3	3	-	1.000
Current anxiety disorders (*n*)	2	3	-	1.000
Current prodromal syndrome (*n*)	5	0	-	0.022
Current psychotropic medication (SSRI) (*n*)	0	1	-	1.000

Estimated IQ = intelligence quotient estimated by two subtests from the Weschsler intelligence scale III, Finnish version. GAF = Global Assessment of Functioning. *M* = mean. * Missing data on two participants