Jenni Koivukangas

BRAIN WHITE MATTER STRUCTURE, BODY MASS INDEX AND PHYSICAL ACTIVITY IN INDIVIDUALS AT RISK FOR PSYCHOSIS

THE NORTHERN FINLAND BIRTH COHORT 1986 STUDY
JENNI KOIVUKANGAS

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The Northern Finland Birth Cohort 1986 Study

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Abstract

Recognition of individuals at highest risk for psychosis is challenging and no definitive biomarkers are yet available. Physical illnesses associated with a sedentary lifestyle are common in patients with severe mental illness. Both, bodyweight and risk for psychosis are associated with brain white matter (WM) abnormalities. There are several dysregulated pathways which are common in psychiatric illnesses and weight-related processes, but it is not known how weight and vulnerability for psychosis interact in the brain. The present study examines brain WM microstructure and its association to body mass index (BMI) in young adults with a familial risk for psychosis (FR). In addition, the level of physical activity and cardiorespiratory fitness in individuals vulnerable to psychosis was examined.

Participants of the present study are members of the Northern Finland Birth Cohort 1986. Two separate clinical subsudies were conducted. The first having been done when the participants were at age 15–16. At that time, physical activity was defined by postal questionnaire (n=6,987) and cardiorespiratory fitness was measured by a submaximal cycle ergometer test (n=4,803). Risk for psychosis was viewed from three perspectives, with possible overlap between groups: having familial risk for psychosis, existing prodromal symptoms at age 15–16, and development of hospital treated psychosis between the ages of 16 and 20 years. The latter substudy was conducted when the participants were aged between 20 and 25 years. Diffusion tensor imaging was performed on 108 participants.

Our study showed that there was no difference in WM microstructure between FR and control groups suggesting that WM abnormalities are not a genetic feature for risk of psychosis in all populations. However, the association between BMI and WM microstructure differed significantly between the FR and control groups. We also demonstrated that the level of physical activity was lower before the onset of psychotic illness. Therefore, these results imply that it would be of great importance to consider weight and physical activity levels in subjects at risk for psychosis, in order to avoid the detrimental effects of a sedentary lifestyle on overall health.

Keywords: adolescent, birth cohort-study, body mass index (BMI), diffusion tensor imaging (DTI), exercise, physical fitness, risk for psychosis, white matter, young adult
Koivukangas, Jenni, Aivojen valkean aineen rakenne, painoindeksi ja liikunta psykoosiriskissä olevilla henkilöillä. Pohjois-Suomen 1986 syntymäkohorttitutkimus

Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Aurora tohtorihjelma; Oulun yliopistollinen sairaala


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Tiivistelmä

Korkeimmassa psykoosiriskissä olevien tunnistaminen on haastavaa, eikä kunnollisia biomarkerereita ole käytettävissä. Vähäiseen liikunta-aktiivisuuteen liitetty fysiset sairaudet ovat yleisiä vakavaa mielenterveyshäiriöä sairastavilla. Sekä kehonpaino että psykoosialttiutus on yhdistetty aivojen valkean aineen rakenteen poikkeavuuksiin. Useat kehon säätelymekanismien poikkeavuudet liittyvät sekä psykiatriisiin sairauksiin että painoon liittyviin prosesseihin, mutta ei ole olemassa tutkimustietoa siitä, miten paino ja psykoosialttiutus vaikuttavat yhdessä aivojen rakenteeseen. Tässä osajulkaisu viitoitetaan tutkitaan aivojen valkean aineen mikrorakennetta nuorilla aikuisilla, jotka ovat sukuriskissä sairastaa psykoosin, sekä painon vaikutusta valkean aineen rakenteeseen psykoosiriskissä. Lisäksi tutkitaan psykoosialttiiden nuorten liikunta-aktiivisuutta ja kuntoa.


Mikrorakennetustutkimus ei ollut selkeää, että aivojen valkean aineen mikrorakennetusta on eri tavoin, mutta se ei eroinneutautumuksesta ja eikä keskeistä, että painoindeksi valkean aineen rakenteen ja lihasten välillä olisi erilainen suurin merkitystä. Tutkimus osoitti myös, että liikunta-aktiivisuus on erottelnut jo ennen psykoosissairauksien puhkeamista, vaikka psykoosiriskissä olevien liikkeetutkimuksiin ja tiedon tulisi kiinnittää erityistä huomiota jo varhaisessa vaiheessa elinikäisten sairauksien ehkäisemiseksi.

Asiakirjat:
- diffuusiotensorikuvaus, kunto, liikunta, nuoret aikuiset, nuori, painoindeksi, psykoosialttiutus, syntymäkohorttitutkimus, valkea aine
To my family
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Jenni Koivukangas
Abbreviations

AD Axial diffusion
APA American psychiatric association
BD Bipolar disorder
BMI Body mass index
BS Basic symptoms criteria
CAARMS Comprehensive assessment of at risk mental state
CHR Clinical high risk
CNS Central nervous system
CNV Copy number variant
CRHC Care register for health care
DSM-III-R Diagnostic and statistical manual of mental disorders. 3rd edition, revised
DSM-IV Diagnostic and statistical manual of mental disorders. 4th edition
DWI Diffusion weighted imaging
DTI Diffusion tensor imaging
FA Fractional anisotropy
FOV Field of view
FR Familial risk for psychosis
FWE Family wise error
GWAS Genome wide association study
ICD International classification of diseases, injuries and causes of death
IFOF Inferior fronto-occipital fasciculus
ILF Inferior longitudinal fasciculus
IQ Intelligence quotient
MD Mean diffusivity
MNI Montreal neurological institute
MRI Magnetic resonance imaging
NFBC Northern Finland Birth Cohort
RD Radial diffusion
ROI Region of interest
SCH Schizophrenia
SIPS Structured interview for prodromal syndromes
SLF Superior longitudinal fasciculus
SPSS Statistical package for the social sciences
TBSS Tract based spatial statistics
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<tr>
<td>TE</td>
<td>Time of echo</td>
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<tr>
<td>TR</td>
<td>Time of repetition</td>
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<tr>
<td>UHR</td>
<td>Ultra high risk</td>
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<tr>
<td>VBA</td>
<td>Voxel-based analysis</td>
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<td>WHO</td>
<td>World health organization</td>
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<td>WM</td>
<td>White matter</td>
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List of original publications

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1 Introduction

Schizophrenia and other psychotic illnesses are often severe and enduring, and are among the leading causes of the worldwide burden of disease. The prevalence of schizophrenia varies considerably in different parts of the world. In the worldwide population, the estimated lifetime prevalence for schizophrenia is 0.4% and lifetime morbid risk, 0.7% (Saha et al. 2005). Northern Finland is an area where schizophrenia and other psychotic disorders have been found to be prevalent. In the two northernmost provinces in Finland, the lifetime prevalence of schizophrenia has been found to be 1.8% and for any psychotic disorders 4.6% (Perälä et al. 2008). These figures are amongst the highest reported worldwide.

For over two decades, efforts to identify and offer an intervention to individuals at increased risk for psychosis have been of great interest in the research field (Fusar-Poli et al. 2014). Increased risk for psychosis can be defined as having a familial or genetic risk (Gottesman 1991, Rasic et al. 2014, Cardno & Owen 2014) or a clinical risk (Yung & McGorry 1996, Fusar-Poli et al. 2014). Recognition of individuals at highest risk for psychosis is challenging and no definitive biomarkers are yet available. A major ambition of neuroimaging studies in individuals at risk for psychosis has been to identify early neuronal signs of the prodromal phase of psychosis.

Despite progress in the research field, aetiology of schizophrenia is still not fully understood (Owen et al. 2016). It has been suggested that schizophrenia is associated with impairments in structural and functional connectivity (Fornito et al. 2012). It has become evident that there is no single dysfunction within the brain networks, but rather, a contribution of various networks of the brain, which result in the development and progression of psychotic symptoms (Schmidt et al. 2015). The dysconnectivity model suggests that disturbed integration of neural communication plays a fundamental role in the pathology of schizophrenia (Friston and Frith 1995, Petterson-Yeo et al. 2011). As part of the model, white matter (WM) has been hypothesised to be integral in the development of schizophrenia. Patients with schizophrenia show WM abnormalities in several brain areas (Ellison–Wright & Bullmore 2009, Bora et al. 2011).

Individuals with schizophrenia have higher morbidity and mortality rates than the general population, partly due to natural causes, including cardiovascular diseases (Brown et al. 1997, Saha et al. 2007, Tiihonen et al. 2009, Lahti et al. 2012, Crump et al. 2013). They also have a higher risk for weight gain and for developing metabolic co-morbidities (Mitchell et al. 2013, Ventriglio et al. 2015).
Physical activity and fitness are predictors of cardiovascular disease mortality (Blair et al. 2001, Lee & Skerret 2001). It may, therefore, be important to consider the risk for cardiovascular illnesses.

Participants of the present study are members of the unique Northern Finland Birth Cohort 1986 (NFBC 1986). The aim was to examine the physical activity and cardiorespiratory fitness in adolescents at risk for psychosis. The aim was also to investigate the WM structure of young adults at risk for psychosis and to find out if BMI and genetic liability for psychosis interact in the brain. The present study of WM adds complement knowledge of the grey matter findings in the same NFBC 1986 participants (Jukuri et al. 2013, 2015a, 2015b, Roman-Urrestarazu et al. 2014, Pulkkinen et al. 2015).
2 Risk for psychosis

Psychotic illnesses are serious mental disorders characterised by episodes with symptoms that indicate an impaired sense of reality. Psychotic symptoms include, e.g. hallucinations, delusions, disorganised speech, and disorganised behaviour (ICD-10, World Health Organization, WHO 1992, DSM-IV, American psychiatric Association, APA 1994). The most common and severe psychotic illness is schizophrenia. The illness usually starts in late adolescence or early adulthood (Delisi 1992, Häfner et al. 1994, van Os & Kapur 2009, Owen et al. 2016). Other functional non-affective psychotic disorders include e.g. schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, and unspecified nonorganic psychosis. Psychotic affective disorders include manic, bipolar, and depressive episodes with psychotic symptoms (WHO 1992, APA 1994).

Currently there are two main approaches adopted in research on risk for psychosis. One is a familial risk approach studying those having a family member with a psychotic illness (Gottesman 1991, Cardno & Owen 2014, Rasic et al. 2014). And the other is a clinical risk approach studying those at risk due to the presence of clinical symptoms in help-seeking individuals (Yung & McGorry 1996, Fusar-Poli et al. 2013, Fusar-Poli et al. 2014).

2.1 Familial risk

Familial risk factors may be both genetic and environmental. There is strong evidence from family, twin, and adoptive studies that schizophrenia is attributable to genetic factors (Gottesman 1991, Cardno & Gottesman 2000, Tienari et al. 2003). Heritability estimates have been around 80% (Cardno et al. 1999, Sullivan et al. 2003, Cardno & Owen 2014). A family history of psychosis is probably the most evident risk factor and the risk of schizophrenia is correlated with the percentage of shared genes (Gottesman 1991). Figure 1 presents the morbidity risk of the relatives of schizophrenia patients. For example, first-degree relatives of the patients share 50% of their genes, and the parents, siblings and children of the patients have a risk of 6%, 9% and 13%, respectively. Whereas monozygotic twins sharing 100% of the genes, have a 48% risk for the illness (Gottesman 1991).
In a large population-based cohort study, based on information from Danish registers, the relative risk ratio for schizophrenia was shown to be 6.6, 7.5, 9.0 and 37.5 in father, sibling, mother or both mother and father, respectively (Mortensen et al. 2010). In a large Danish register study, individuals having one parent with schizophrenia had a 7.0% risk for developing schizophrenia, calculated as a cumulative incidence, by age 52. When both parents were affected, the risk was 27.3%. For bipolar disorder, respective figures were 4.4% and 24.9% (Gottesman et al. 2010).

The concordance rates of schizophrenia in monozygotic (MZ) twins is 41–65% and 0–28% in dizygotic twins (Cardno & Gottesman 2000). The rates are lower than the percentage of shared genes would suggest, indicating a role of non-genetic and random genetic factors in the risk of developing illness, such as environmental factors, epigenetic mechanisms, and developmental events like copy number variants (CNV) (Singh et al. 2009, Cardno & Owen 2014, Castellani et al. 2014).

Adoption studies offer an opportunity to investigate the effect of environment. The Finnish adoption study suggested that children with a high genetic risk for schizophrenia showed that the risk of developing a schizophrenia spectrum disorder was higher among those living in a disturbed family environment, when compared with adoptees at low genetic risk (Tienari et al. 2004).
Several candidate susceptibility genes for schizophrenia have been identified and the general opinion is that schizophrenia is viewed as an illness with a polygenic background. A large genome-wide association study (GWAS) by the Schizophrenia Working Group of the Psychiatric Genomics Consortium identified 108 schizophrenia-associated independent genetic loci probably contributing to the risk for developing schizophrenia. Associations were enriched among genes expressed in the brain that were involved in glutamatergic neurotransmission and synaptic plasticity. Associations were also enriched among genes expressed in tissues that play important roles in immunity, supporting the hypothesised link between the immune system and schizophrenia (Schizophrenia Working Group 2014).

Bipolar disorder (BD) and depression with psychotic symptoms have also been shown to have a genetic liability. Heritability estimates have been around 58–93% for BD (Kieseppä et al. 2004, Song et al. 2015), and 39% for psychotic depression (Domschke 2013). Genetic overlap between psychotic disorders has been shown in several studies (Lichtenstein et al. 2009, Cross-Disorder Group of the Psychiatric Genomics Consortium 2013, Domschke et al. 2013, Cardno & Owen 2014, Song et al. 2015). Lichtenstein et al. (2009) showed in their population-based study that both the risk for schizophrenia and bipolar disorder were increased if a parent had either of these disorders, indicating partial genetic overlapping. A recent meta-analysis of family high-risk studies showed that when a parent had schizophrenia, the risk for schizophrenia was 7-fold and the risk for any mental illness (including schizophrenia, bipolar disorder, major depressive disorder) was 2-fold in the offspring. When a parent had BD, risk for BD in the offspring was 4-fold and 2-fold for any mental illness (Rasic et al. 2014).

2.2 Clinical risk

Prodromal symptoms are early symptoms that may precede the illness onset, in this case psychosis. In psychosis research, the prodrome is defined retrospectively. The prodromal phase usually takes place during young adulthood and the duration of the prodromal phase varies from months to several years (Fusar-Poli et al. 2014). The peak risk for schizophrenia onset is during young adulthood (Delisi et al. 1992, Häfner et al. 1994).

Prodromal symptoms of psychosis include symptoms such as depressive mood; anxiety; reduced energy, motivation and anergia; social withdrawal; suspiciousness; reduced attention and concentration; sleeping disturbances and irritability (Yung &
McGorry, 1996). As the concept is retrospective, symptoms will not always lead to the onset of illness.

A clinical-high risk CHR is defined prospectively to identify individuals at putative prodrome for psychosis. The individual qualifies as being at clinical-high risk (CHR) if the ultra-high risk (UHR) or basic symptoms (BS) criteria are fulfilled (Gross & Huber 1985, Fusar-Poli et al. 2014). BS criteria is defined as having neurocognitive disturbances indicative of a high risk for psychosis and was originally based on the Bonn Scale for the Assessment of Basic Symptom (Klosterkötter et al. 2001).

There are several instruments for detecting individuals at UHR. The two main interview instruments are the Structured Interview of Prodromal Syndromes (SIPS; Miller et al. 2003, McGlashan et al. 2001) and the Comprehensive Assessment of at Risk Mental State (CAARMS) (Yung et al. 2005). An individual must fulfil the criteria for one, or a combination of the three separate prodromal syndromes, in order to meet UHR status (McGlashan et al. 2001, Yung et al. 2005, Fusar-Poli et al. 2013, Fusar-Poli et al. 2014):

1. Brief limited intermittent psychotic syndrome (BLIPS).
2. Presence of attenuated positive prodromal syndrome and/or (APS)
3. Genetic risk combined with a decline in functioning (GRD).

Recently published meta-analysis showed evidence that the GRD subgroup is infrequent and not associated with psychosis (Fusar-Poli et al. 2016). According to recently published meta-analysis, 10% of the CHR individuals (defined as meeting any of the UHR or BS criteria) fall ill within six months, 15% within a year and 19% within two years (Schultze-Lutter et al. 2015).

Several first-step self-report questionnaires have been developed to detect individuals at high risk. The PROD-screen is a Finnish questionnaire for screening prodromal symptoms of psychosis (Heinimaa et al. 2003). The PROD-screen scale has 21 items, of which there are 12 symptom items specific to psychosis risk. These items include questions of whether the subject had experience of, for example, feeling that something strange or inexplicable is taking place in him/herself or the environment, feeling that one is being followed or influenced in some special way, experience of thoughts running wild or difficulty in controlling the speed of thoughts, amongst other symptoms. The items are based on symptoms included in previously used scales and structured interviews, i.e. the Interview for the Retrospective Assessment of the Onset of Schizophrenia (Häfner et al. 1992), the
Bonn Scale for the Assessment of Basic Symptoms (Gross & Huber, 1985) and the SIPS (McGlashan et al. 2001).

Kline et al. (2014) conducted a systematic review including studies in which self-report questionnaires were used as a first-step screening tool with the aim of identifying individuals at CHR for psychosis. They identified 34 studies in which, in addition to PROD-screen, 12 self-report measures were used, in 14 countries. The questionnaires were the Prodromal Questionnaire, Prodromal Questionnaire — Brief, Prodromal Questionnaire-16, Prime Screen — Revised, Youth Psychosis At-Risk Questionnaire Brief Version, Eppendorf Schizophrenia Inventory, Early Recognition Inventory (ERIraos) Checklist, BASC Atypicality Scale, Composite Psychosis Risk Questionnaire, Early Detection Primary Care Checklist, General Health Questionnaire and Community Assessment of Psychic Experiences. They concluded that, in help-seeking populations, these screening tools have been found to be useful, with positive predictive values of 39–53%. Contrarily, in the general population, the specificity of the questionnaires was found to be poor.

Two of the best-known multisite longitudinal studies to focus on individuals at clinical risk for psychosis are the NAPLS and NAPLS-2 (Northern American Prodrome Longitudinal Study) and the EPOS (The European Prediction of Psychosis Study). Both of these studies used SIPS interviews as the main instrument for detecting subjects at high risk for psychosis. In NAPLS, a total of 888 subjects prodromal for schizophrenia were included into the study (Addington et al. 2007). One objective of NAPLS-2 is to investigate clinical and biological factors that may contribute to the development of psychosis (Addington et al. 2012). EPOS is a multicentre, prospective, longitudinal, naturalistic study focusing on early detection of persons at UHR for psychosis, particularly schizophrenia. The study covers a catchment area with approximately 7.5 million inhabitants (Klosterkötter et al. 2005).
3 Physical activity, fitness and psychosis risk

The risk for death from natural causes is greater in people with schizophrenia, when compared to the general population; cardiovascular diseases are amongst the leading causes of natural death. (Brown et al. 1997, Saha et al. 2007, Tiihonen et al. 2009, Lahti et al. 2012, Crump et al. 2013). Genetic overlap between psychiatric illnesses and cardiometabolic diseases has been established (Mothi et al. 2015, Malan-Muller et al. 2016). An unhealthy lifestyle, adverse effects of antipsychotic medication and disparities in health care access contribute to higher morbidity and mortality rates in patients (De Hert et al. 2006, De Hert et al. 2011). Physical inactivity and fitness are predictors of cardiovascular disease mortality (Blair et al. 2001, Lee & Skerret 2001).

The physical health of individuals with risk for psychosis is generally impaired. Individuals vulnerable to psychosis are shown to have a relatively large proportion of self-reported physical symptoms as well as diagnosed physical illnesses (Korkeila et al. 2007, Korkeila et al. 2013). A lower level of physical activity and higher rates of both smoking and alcohol abuse are reported in individuals with UHR, when compared to controls (Carney et al. 2016). Some publications are available that address the issue of exercise level and fitness in individuals with UHR for psychosis (Deighton & Addington 2015, Mittal et al. 2013, Carney et al. 2016, Hodgekins et al. 2015).

Deighton & Addington (2015) investigated young adults recruited from the NAPLS 2 (Addington et al. 2012). Participants self-reported physical activity levels, the duration and type of activities and barriers preventing participants from exercising. UHR participants reported lower perceived fitness, lower intensity of the activity level and more barriers to exercise than the controls. The barriers were related to self-esteem and self-perception. Control participants reported more positive reasons endorsing exercising (i.e. “Exercising makes me feel better”, “Exercise makes me feel more self-confident”, “I will feel better about myself”). Hodgekins et al. (2015) examined how much time adolescents and young adults with UHR spent in structured activities (e.g., work, education, housework and childcare, sport and leisure activities). They reported that UHR subjects spent less hours participating in structured activities than controls, but time spent among sports did not differ from the controls. Mittal et al. (2013) examined the relationship between physical activity levels measured with actigraphy, brain structure (hippocampus and parahippocampal gyrus) and symptoms in adolescents and young adults having UHR for a psychosis. They reported lower physical activity
levels and higher sedentary activity in the UHR group, when compared to controls. Lower physical activity levels were correlated with a smaller parahippocampal volume bilaterally, in the UHR group. Fitness was only examined in one study where controls reported better perceived fitness levels than subjects with a clinical risk for psychosis (Deighton & Addington 2015).

No correlations between symptoms (positive symptoms, negative symptoms, role functioning, social functioning, depression, anxiety) and physical exercise levels were found (Deighton & Addington 2015). Mittal et al. (2013) reported a negative correlation between physical activity and poorer occupational function. The results suggested an association between less activity and higher negative symptoms, although there was no statistical significance. No association between physical activity and positive symptoms were detected.

Taken together, these previous studies indicate that adolescents and young adults with UHR undertake lower levels of physical activity and spend more time among sedentary activities, than controls (Deighton & Addington 2015, Mittal et al. 2013). One study found no difference between the UHR and the control group in exercise level, as indicated by the time spent participating in sports (Hodgekins et al. 2015). No correlation between clinical symptoms and physical activity levels were observed (Deighton & Addington 2015, Mittal et al. 2013).
4 Brain white matter microstructure and familial risk for psychosis

4.1 Anatomy of white matter

The WM of the central nervous system (CNS) is integral for the smooth flow of neural impulses across the brain functional networks. Almost half of the brain volume is occupied by WM. Most of this space is taken up by axons, which are the nerve fibres extending from the neuronal cell body. Axons transmit information from one CNS region to another. Most of the axons are surrounded by lipid-rich myelin sheaths, which gives the characteristic white colour to tissue. Four different regions can be identified from a neuron: soma, dendrites, axon, and the axon terminals (Johansen-Berg & Behrens 2014, Paus et al. 2010, Paus et al. 2014).

Axons are bundled into WM tracts. Water is the major component in WM and is located in intracellular as well as in the extracellular spaces. In WM, the extracellular space is small due to tightly packed axons. In addition to neurons, the brain contains different types of glial cells; oligodendrocytes, astrocytes, microglia, and ependymal cells. Oligodendrocytes are the cells that produce myelin. Astrocytes have a maintenance task in the CNS and microglia are phagocytic immune cells of the CNS (Johansen-Berg & Behrens 2014).

4.2 Diffusion tensor imaging

Diffusion tensor imaging (DTI) is a non-invasive magnetic resonance imaging (MRI) technique, which yields information about the microstructure of tissues in vivo. To determine the diffusion tensor, diffusion weighted images need to first be collected. Diffusion weighted imaging (DWI) is a technique in which the pulsed magnetic field gradients are applied in different orientations to sensitise MRI signal intensity for the amount of water diffusion and, thus, gain information about the strength of diffusion by mean diffusivity (MD) (Le Bihan et al. 2001, Le Bihan & Johansen-Berg 2012).

In living organisms, diffusion often also has a directionality. This feature carries important information about the microarchitecture of tissues. Diffusion tensor imaging (DTI) offers a method for examining this directionality of the molecular motion of water in tissues (Basser et al. 1994, Le Bihan et al. 2001). Molecules exhibit a preference for diffusing from an area of higher concentration to a lower
concentration. When water diffuses in all directions, with equal amounts, the diffusion is isotropic. In organised structures diffusion is anisotropic due to structures such as cell membranes and myelin sheaths (Beaulieu 2002, Le Bihan 2003).

Fig. 2. Water diffusion carries information about whether the environment is random (a) or ordered (b) (Modified from Mori & Tournier 2014).

The diffusion tensor is a mathematical model of three dimensional diffusion in one voxel. Altogether, a minimum of seven images per voxel are needed; six with diffusion weighted gradients in certain directions and one reference image without a gradient. The diffusion can be modelled as a sphere or ellipsoid (Figure 2). To define an ellipsoid, six parameters are needed. First, the principal diffusivities called “eigenvalues” (L₁-L₃), which are three lengths perpendicular to each other and second, three “eigenvectors” V₁-V₃ to determine an orientation, are defined. These parameters can be determined using tensor calculus (Basser & Pierpaoli 1996, Mori & Tournier 2014).

When the aim is to explore the anatomy, the DTI data may be quantified morphometrically. In that case, tractography may be performed to visualise anatomical structures. When the aim is to investigate the contrast of intensity between groups, photometrical methods are used. In this case tensor information is processed to scalar maps, which can be visualised in a grayscale as conventional
MRI images. The most commonly used images are fractional anisotropy (FA) and MD maps. In addition, radial (RD) and axial (AD) diffusivity may be calculated from the data. FA is a measure having scalar values between 0 and 1, where 0 represents unrestricted isotropic diffusion and 1 indicates diffusion along the axis (Le Bihan et al. 2001, Beaulieu 2002).

There are two main approaches for analysing group differences depending on if the study is explorative or hypothesis driven. One approach is that of region of interest analysis (ROI), which is a method where an investigator is focusing on one or more regions with a priori hypothesis. The other approach is an explorative whole brain analysis (Mori & Tournier 2014). There are several software packages available to conduct automated analyses.

4.3 White matter microstructure in individuals at familial risk for psychosis

Friston and Firth (1995) reported aberrant prefronto-temporal functional connectivity in patients with schizophrenia. Later WM was hypothesised to play a central role in the development of schizophrenia. Patients with schizophrenia have shown WM abnormalities in several brain areas (Ellison–Wright & Bullmore 2009, Bora et al. 2011).

In recently published review by Arat et al. (2015), DTI findings in first degree relatives of schizophrenia and bipolar disorder patients are reviewed. The majority of the studies examining WM microstructure, in subjects at familial risk for psychosis (FR), have been conducted on individuals with a familial risk for schizophrenia and schizophrenia related disorders, and the minority on individuals a with familial risk for affective psychosis. No studies with longitudinal settings are available.

4.3.1 White matter microstructure in individuals at familial risk for schizophrenia and related disorders

FA is the most consistently reported measure of DTI. Altogether sixteen studies have compared WM fractional anisotropy (FA) using DTI between controls and relatives of those with schizophrenia and schizophrenia related disorders (FR) (Table 1).

In addition to relatives of schizophrenia patients, six studies included relatives of patients with schizophrenia spectrum disorders, three studies included relatives
of patients with schizophreniform disorder (Boos et al. 2013, Domen et al. 2013, de Leeuw et al. 2015) and six, relatives of patients with schizoaffective disorder (Hoptman et al. 2008, Boos et al. 2013, Domen et al. 2013, Goghari et al. 2014, de Leeuw et al. 2015, Prasad et al. 2015). Domen et al. (2013) examined relatives of patients with schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, and psychotic disorder not otherwise specified. One study included two risk groups, one with schizophrenia and the other with psychotic BD, the groups were analysed separately (Skudlarski et al. 2013).

The most commonly reported exclusion criteria were drug or alcohol abuse, or neurological illness, while in control groups it was history of psychotic illness of a first-degree relative. The number of participants varied between the studies, from 31 (Knöchel et al. 2012b) to 232 (Boos et al. 2013) and the number of FR participants, between 16 (Knöchel et al. 2012b) and 123 (Boos et al. 2013). The mean age of the participants varied broadly, in FR subjects between 18.1 (Moran et al. 2015) and 54.4 (Phillips et al. 2011) and in controls between 20.3 (Harms et al. 2015) and 55.7 (Phillips et al. 2011). Two studies investigated young adults, defined as a mean age in both groups of 19–24 years (Hoptman et al. 2008, Harms et al. 2015).

In FR groups, the amount of male participants varied between 10% (Prasad et al. 2015) and 57% (de Leeuw et al. 2015) and in the control groups between 21% (Prasad et al. 2015) and 60% (de Leeuw et al. 2015). Four studies reported how the control and FR groups were matched. Knöchel et al. (2012a, 2012b) matched groups for handedness, age, gender and parental education while Clark et al. (2011) matched for age and gender. Moran et al. (2015) matched for age, gender, race and handedness. De Leeuw et al. 2015 mentioned that groups were matched.

In most of the studies, FR for psychosis was defined as having a first-degree relative with schizophrenia or schizophrenia related disorder. In one study, the inclusion criterion was having two or more affected first- or second-degree relatives (Muñoz Maniega et al. 2008). Hoptman et al. (2008) recruited subjects who had at least one first-degree relative and/or multiple second-degree relatives with schizophrenia or schizoaffective disorder. In most studies the FR subjects were siblings of the patients. In five studies, parents of the patients were also included (Camchong et al. 2009, Phillips et al. 2011, Knöchel et al. 2012b, Goghari et al. 2014, Prasad et al. 2015). In one study, siblings, parents and offspring of patients were included (Goghari et al. 2014). Skudlarski et al. (2013) did not specify the familial relationships.
In 14 studies, the diagnosis of the patients was defined using the DSM-IV (APA 1994) or DSM-IV-TR (Revised version of the DSM-IV, APA 2000) as a diagnostic instrument. De Leeuw et al. 2015 used the DSM-IV or the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al. 1992) as the diagnostic instrument. Moran et al. (2015) examined parents of subjects with childhood onset schizophrenia and used the DSM-III-R (revised version of the DSM III, APA 1987). None of the authors reported the use of ICD classification. For one study, no information about the diagnostic system used was available (Camchong et al. 2009).


Other parameters, in addition to FA, were also investigated. Three studies measured the MD (Clark et al. 2011, Knöchel et al. 2012b, Goghari et al. 2014). Goghari et al. (2014) and Skudlarski et al. 2013 studied FA, MD, RD, and AD. Prasad et al. (2015) measured RD in addition to FA.

A 1.5T magnetic field MRI scanner was used in seven studies and a 3T scanner in nine of the sixteen studies. The number of diffusion-weighted volume gradient directions varied between 6 to 73. In one study, two MRI scanners and, thus, two different sequences, were used (Skudlarski et al. 2013). The same scanner, but two different imaging sequences, were used in two studies. In a study by Domen et al. (2013), the sequence changed, due to a scanner update during the study. In a study by Camchong et al. (2009), TR, TE and FOV were changed during the study with no explanation for the reason.
Table 1. Studies of risk for schizophrenia and related disorders and white matter microstructure.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Sample</th>
<th>Male/Female</th>
<th>Mean age, years (SD)</th>
<th>Analysis method</th>
<th>WM changes in familial risk participants compared to controls</th>
<th>Field strength</th>
<th>Number of diffusion weighted gradients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoptman et al. 2008</td>
<td>22 Relatives</td>
<td>7/15</td>
<td>20.1 (4.1)</td>
<td>WB</td>
<td>FA ↓ left inferior frontal gyrus, cingulate and angular gyri bilaterally</td>
<td>1.5 T</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>37 Controls</td>
<td>17/20</td>
<td>23.1 (4.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muñoz Maniega et al. 2008</td>
<td>22 Relatives</td>
<td>13/9</td>
<td>30 (3)</td>
<td>ROI</td>
<td>ROI no differences</td>
<td>1.5 T</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>51 Controls</td>
<td>27/24</td>
<td>35 (11)</td>
<td>Automated ROI</td>
<td>Automated ROI FA ↓ anterior limb of internal capsule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Camchong et al. 2009</td>
<td>22 Relatives</td>
<td>8/14</td>
<td>48.5 (8.2)</td>
<td>WB</td>
<td>WB no differences</td>
<td>3 T</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>30 Controls</td>
<td>18/12</td>
<td>43.8 (11.4)</td>
<td>TBSS, ROI</td>
<td>ROI FA ↓ corpus callosum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hao et al. 2009</td>
<td>34 Relatives</td>
<td>20/14</td>
<td>25.8 (7.1)</td>
<td>WB</td>
<td>FA ↓ left prefrontal cortex, hippocampus</td>
<td>1.5 T</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>32 Controls</td>
<td>19/13</td>
<td>26.6 (6.0)</td>
<td></td>
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<tr>
<td>Clark et al. 2011</td>
<td>20 Relatives</td>
<td>13/7</td>
<td>41.1 (13.0)</td>
<td>ROI</td>
<td>FA ↓ left inferior longitudinal fasciculus</td>
<td>1.5 T</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>32 Controls</td>
<td>17/15</td>
<td>34.8 (14.0)</td>
<td></td>
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</tr>
<tr>
<td>Phillips et al. 2011</td>
<td>49 Relatives</td>
<td>13/20</td>
<td>54.4 (8.3)</td>
<td>lobar ROIs</td>
<td>No differences</td>
<td>1.5 T</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>33 SCH Parents</td>
<td>10/6</td>
<td>30.06 (11.5)</td>
<td></td>
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<tr>
<td></td>
<td>16 SCH Siblings</td>
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</tr>
<tr>
<td></td>
<td>54 Relatives of controls</td>
<td>26 Parents</td>
<td>12/14</td>
<td>55.7 (8.5)</td>
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<tr>
<td></td>
<td></td>
<td>28 Siblings</td>
<td></td>
<td>27.0 (9.8)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>26 SCH</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>21 Controls</td>
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<tr>
<td>Author, Year</td>
<td>Sample</td>
<td>Male/Female</td>
<td>Mean age, years (SD)</td>
<td>Analysis method</td>
<td>WM changes in familial risk participants compared to controls</td>
<td>Field strength</td>
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<tr>
<td>Knöchel et al. 2012a</td>
<td>18 Relatives</td>
<td>9/9</td>
<td>39.4 (10.8)</td>
<td>TBSS-WB</td>
<td>WB no differences</td>
<td>3 T</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22 Controls</td>
<td>12/10</td>
<td>41.9 (10.5)</td>
<td>TBSS-ROI</td>
<td>ROI FA ↓ association fibres, arcuate fasciculus, cingulum; FA ↑ arcuate fasciculus</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Knöchel et al. 2012b</td>
<td>16 Relatives</td>
<td>41.9 (8.6)</td>
<td>ROI</td>
<td>FA ↓ corpus callosum</td>
<td>3 T</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 Controls</td>
<td>39.3 (11.0)</td>
<td>MD ↑ corpus callosum</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Boos et al. 2013</td>
<td>123 Relatives</td>
<td>56/67</td>
<td>26.7 (6.4)</td>
<td>TBSS-ROI</td>
<td>FA ↑ arcuate fasciculus bilaterally</td>
<td>1.5 T</td>
<td></td>
</tr>
<tr>
<td></td>
<td>109 Controls</td>
<td>54/55</td>
<td>27.3 (8.2)</td>
<td>TBSS-WB</td>
<td>No differences</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>126 SCH</td>
<td>49/44</td>
<td>29.4 (8.8)</td>
<td></td>
<td></td>
<td>3 T</td>
<td></td>
</tr>
<tr>
<td></td>
<td>80 Controls</td>
<td>29/51</td>
<td>30.8 (10.8)</td>
<td></td>
<td></td>
<td>72, 73</td>
<td></td>
</tr>
<tr>
<td></td>
<td>85 SCH</td>
<td>40/79</td>
<td>42.5 (1.5)</td>
<td>TBSS-WB</td>
<td>WB Mean FA was lower in the relatives than in the controls</td>
<td>3 T</td>
<td></td>
</tr>
<tr>
<td></td>
<td>104 Controls</td>
<td>43/61</td>
<td>38.9 (1.3)</td>
<td>TBSS-ROI</td>
<td>ROI FA ↓ anterior corona radiata, posterior corona radiata</td>
<td>32, 30</td>
<td></td>
</tr>
<tr>
<td>Skudlarski et al. 2013</td>
<td>119 Relatives</td>
<td>10/14</td>
<td>40.2 (15.0)</td>
<td>ROI</td>
<td>ROI no differences</td>
<td>3 T</td>
<td></td>
</tr>
<tr>
<td></td>
<td>125 SCH</td>
<td>13/14</td>
<td>40.7 (11.1)</td>
<td>Along-tract measure</td>
<td>Along-tract analysis FA ↑ right fimbria of the fornix</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Goghtari et al. 2014</td>
<td>24 Relatives</td>
<td>17/13</td>
<td>31.4 (1.2)</td>
<td>Tractography</td>
<td>FA ↓ striatum</td>
<td>3 T</td>
<td></td>
</tr>
<tr>
<td></td>
<td>27 Controls</td>
<td>35/23</td>
<td>28.8 (1.0)</td>
<td>ROI</td>
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<td>Author, Year</td>
<td>Sample</td>
<td>Male/Female</td>
<td>Mean age, years (SD)</td>
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<td>WM changes in familial risk participants compared to controls</td>
<td>Field strength</td>
<td>Number of diffusion weighted gradients</td>
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<tr>
<td>Harms et al. 2015</td>
<td>29 Relatives</td>
<td>14/15</td>
<td>24.2 (3.6)</td>
<td>ROI</td>
<td>No differences</td>
<td>3 T</td>
<td>30</td>
</tr>
<tr>
<td>17 Controls</td>
<td>9/8</td>
<td>20.3 (4.9)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>25 SCH</td>
<td></td>
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<tr>
<td>Moran et al. 2015</td>
<td>39 Relatives</td>
<td>22/17</td>
<td>18.1 (7.4)</td>
<td>ROI</td>
<td>FA ↓ cuneus bilaterally</td>
<td>1.5 T</td>
<td>6</td>
</tr>
<tr>
<td>50 Controls</td>
<td>31/19</td>
<td>19.3 (6.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>39 SCH</td>
<td></td>
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</tr>
<tr>
<td>Prasad et al. 2015</td>
<td>21 Relatives</td>
<td>2/19</td>
<td>23.0 (4.1)</td>
<td>TBSS-WB</td>
<td>TBSS-WB no differences</td>
<td>3 T</td>
<td>30</td>
</tr>
<tr>
<td>29 Controls</td>
<td>9/20</td>
<td>27.1 (6.8)</td>
<td>ROI</td>
<td>ROI FA ↓ forceps minor; RD ↓ superior longitudinal fasciculus</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>39 SCH</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

SCH = schizophrenia and schizophrenia related disorders, SD = standard deviation, TBSS = tract based spatial statistic, WB = whole brain, ROI = region of interest T = tesla
↓ = decreased, ↑ = increased
Setting and results of the studies

In the following section, the study designs of the 16 studies are presented. Results are reported only between the FR and control groups.

The first DTI study measuring FA in individuals at FR for psychosis was conducted by Hoptman et al. (2008). Patients with schizophrenia, individuals with a high risk for schizophrenia and controls were included in the study. High risk was defined as having at least one first-degree relative and/or multiple second degree relatives with schizophrenia or schizoaffective disorder, and being still at the peak age of risk for falling ill (between ages of 12 and 30). Families were recruited by placing advertisements in newspapers and newsletters distributed by the National Alliance for the Mentally Ill. Also, families who previously participated in other genetic studies on schizophrenia were contacted (Delisi et al. 2002). Controls were enrolled from the community by advertisement. An explorative, whole brain analysis was conducted. High risk individuals showed decreased FA in the left inferior frontal gyrus, the posterior cingulate bilaterally and in the angular gyri bilaterally, compared to controls. They also showed increased FA in the left subgenual anterior cingulate, bilateral pontine tegmental WM, and right middle frontal gyri.

Muñoz Maniega et al. (2008) evaluated WM structure in schizophrenia, FR, and control groups. FR was defined as having two or more affected first- or second-degree relatives with schizophrenia. All the participants were identified in the same geographical regions. Priori hypothesised WM tracts, namely the arcuate and uncinate fasciculus, anterior limb of internal capsule and cingulum cingulate gyri, were examined. In voxel-based analysis (VBA), no differences between the FR and the control groups was found, but with automated ROI analysis, decreased FA in the anterior limb of internal capsules was detected in the FR group.

In a study by Camchong et al. (2009), relatives of schizophrenia patients were compared to controls. Both groups were recruited from a broader family study conducted by the Minneapolis VA Medical Center. Of the participants, three had a parent with schizophrenia and for the remaining nineteen, the affected family member was a sibling. They used ROI analysis and focused on anterior brain regions; the cingulum bundle and the genu of corpus callosum. Also an exploratory whole brain voxel-wise analysis was conducted. No differences between groups in the whole brain analysis were found; however, ROI analysis showed decreased FA in two clusters in the right genu of the corpus callosum, in the FR subjects.
Hao et al. (2009) recruited schizophrenia patients from inpatient and outpatient units at the Department of Psychiatry, the Second Xiangya Hospital of Central South University, China. One sibling for each patient was also recruited. Controls were enrolled from the community sample. A whole brain VBA method was used. FR participants showed decreased FA in left prefrontal cortex and hippocampus, when compared to controls.

Clark et al. (2011) recruited subjects from the UCLA Family Study. Patients were enrolled from public and private psychiatric hospitals and clinics in the Los Angeles area. Controls were from demographically similar backgrounds as patients. Groups with schizophrenia, first-degree relatives of schizophrenia, and controls were included. Three groups were compared using analysis of variance. Subjects at risk for psychosis showed intermediate values, compared to those with schizophrenia and the controls. In post hoc analyses, age as a covariate decreased FA in the left ILF was reported in FR participants when compared to controls. No differences in MD were found.

Phillips et al. (2011) modelled the degree of relatedness and investigated if there is a correlation between the genetic risk and the superficial WM (SWM) FA. Families were enrolled through the same UCLA family study as in the study by Clark et al. (2011). They recruited patients with schizophrenia, parents and siblings of patients, controls, and parents and siblings of controls. In addition to other comparisons, they compared siblings of patients to controls and control siblings. They detected decreased FA, which varied in accordance with relatedness, in both hemispheres and in the bilateral temporal and occipital lobes. The effects did not survive correction procedures in two-group comparisons.

Knöchel et al., (2012a) enrolled schizophrenia patients from inpatients of the Department of Psychiatry, Psychosomatic Medicine and Psychotherapy of the University of Frankfurt. Siblings were contacted through participating patients, from a support group for relatives and through local media advertisements. The whole brain analysis showed no differences between siblings and controls. ROI analysis showed that relatives had intermediate FA values between patients and controls, which were significant in association fibres, the arcuate fasciculus the and cingulum bundle. In a study by Knöchel et al. (2012b) the volume and integrity measured by the FA and MD of the corpus callosum, were compared between groups. Decreased FA and increased MD were found in the corpus callosum of relatives, when compared to controls.

In a study by Boos et al. (2013) the participants were members of a longitudinal study in the Netherlands (Genetic Risk and Outcome of Psychosis; GROUP). They
recruited families with a patient with schizophrenia and their non-psychotic siblings. Controls were selected through a system of random mailings to addresses in the catchment areas. A mean FA was compared between schizophrenia, the FR for schizophrenia and controls along multiple tracts; genu, splenium, left and right uncinate fasciculus, cingulum, inferior fronto-occipital fasciculus, fornix, arcuate fasciculus, and inferior longitudinal fasciculus. In the FR group the FA was found to be increased in the arcuate fasciculus bilaterally, when compared to controls and patients.

In a study by Domen et al. (2013), the participants were members of the ongoing longitudinal GROUP study from the Netherlands and Belgium. They studied patients with psychotic disorders (schizophrenia, schizoaffective disorder, schizoaffective disorder, brief psychotic disorder, and psychotic disorder not otherwise specified), siblings of patients and healthy controls. The siblings were contacted through the patients. Controls were recruited in the same geographical area via mailings and advertisements in local newspapers. The voxel-based whole-brain TBSS (Tract-based Spatial Statistics) approach was used to study a relatively large sample. Mean FA values were found to be generally lower in siblings than in controls, but differences were not extensive or statistically significant.

In a study by Skudlarski et al. (2013) data was collected from the participants at two sites of the Bipolar-Schizophrenia Network on Intermediate Phenotypes study (B-SNIP). Participants were enrolled through word of mouth, advertisements and community support groups. Patients with schizophrenia and bipolar disorder, their relatives, relatives with cluster A or B personality traits and controls were examined. Both, whole brain (global mean FA) and ROI TBSS-analyses were performed. The whole-brain average for FA was lower in the FR group when compared to controls. FA was lower in anterior and posterior corona radiata in FR group than in controls.

Goghari et al. (2014) enrolled patients with schizophrenia and schizoaffective disorder through outpatient clinics and community support programs. Research staff completed a pedigree with the patients and all first degree relatives of the patients that were recruited. Controls were recruited through flyers and advertisements around the community. The area of fornix was examined using two methods. Firstly, a whole-tract ROI analysis was conducted and the means of the tracts calculated. Secondly, a novel method was used: along-tract analysis, which enables finding the local defects. In ROI analysis, no difference in any measures was found between subjects with the FR group and the controls. In the long-tract
analysis, the FR group showed significantly increased FA in the right fimbria of the fornix, when compared to controls.

De Leeuw et al. (2015), examined schizophrenia patients, unaffected siblings, and healthy controls. The patients were enrolled from the Department of Psychiatry at the University Medical Center Utrecht and participating in an ongoing longitudinal study. They conducted tractography and compared the mean FA between groups. There were no differences in the mean FA between groups, when investigating the whole striatum. They also conducted a subregion analysis of the striatum, which showed decreased FA in the FR group, when compared to the controls.

The subjects, in the study by Harms et al. (2015), participated in studies of brain structure and function at Washington University School of Medicine in St. Louis. Ten ROIs were examined; anterior limb of internal capsule, cingulate portion of cingulum, hippocampal portion of the cingulum, column and body portion of the fornix, crus/stria terminalis portion of the fornix, inferior frontal-occipital fasciculus, uncinate fasciculus, genu of the corpus callosum and splenium of the corpus callosum. They reported reduced FA in the FR group, in a portion of the fornix, when compared to controls, but this did not survive correction for multiple comparisons.

Moran et al. (2015) examined patients with Childhood onset schizophrenia (COS) and their siblings. The study included families, and some of the participants in the family risk group were related. The families were recruited as part of the ongoing NIMH COS and Normal Brain Development studies. Controls were recruited from the community. Eleven ROIs were examined; cuneus, superior frontal gyrus, precuneus, cingulate gyrus, middle frontal gyrus bilaterally and right cerebellum. For each ROI the mean FA was calculated for further analyses. Their study showed decreased FA bilaterally in the cuneus in siblings of COS patients, when compared to controls.

Prasad et al. (2015) recruited adolescents and young adults with schizophrenia or schizoaffective disorder and healthy controls at the University of Pittsburgh, and subjects who had at least one first-degree relative, with schizophrenia or schizoaffective disorder. FR subjects were not related to patients participating in the study. No differences between the FR and the controls were found in the whole brain TBSS analyses. In further ROI analyses, the FR group showed decreased FA in the forceps minor and decreased RD in the superior longitudinal fasciculus (SLF), compared to the control group.
4.3.2 White matter microstructure in individuals at familial risk for affective psychotic disorders

No studies examining WM FA in relatives of patients with psychotic depression exist in the literature. Altogether, ten studies examined the WM structure in the subject at FR for bipolar disorder (BD) (Frazier et al. 2007, Chaddock et al. 2009, Versace et al. 2010, Sprooten et al. 2011, Mahon et al. 2013, Linke et al. 2013, Emsell et al. 2014, Skudlarski et al. 2013, Sprooten et al. 2013, Roybal et al. 2015). Five of these studies reported that the relative had a history of psychotic symptoms (Chaddock et al. 2009, Linke et al. 2013, Skudlarski et al. 2013, Sprooten et al. 2013, Emsell et al. 2014). Four of the studies did not report if the patients had a history of psychotic symptoms or not (Frazier et al. 2007, Versace et al. 2010, Mahon et al. 2013, Roybal et al. 2015). Sprooten et al. 2011 reported that lifetime psychotic symptoms were absent in their sample. In the following section, only the five studies, in which the family members with psychosis were reported having affecting disorder with psychotic symptoms, are reviewed.

The number of BD relatives and control participants varied from 39 (Chaddock et al. 2009, Emsell et al. 2014) to 187 (Skudlarski et al. 2013) and the number of FR subjects, between 21 (Chaddock et al. 2009, Emsell et al. 2014) and 83 (Skudlarski et al. 2013). The mean age of the FR participants varied between 28 (Linke et al. 2013) and 42.5 (Chaddock et al. 2009, Emsell et al. 2014).

Two of the five studies found no difference between the FR and the control groups (Chaddock et al. 2009, Emsell et al. 2014). In these two studies, the same sample was investigated. Both studies investigated the association between genetic liability and DTI measures, however, different analysis methods were used. Chaddock et al. (2009) conducted whole brain voxel-based analyses, while Emsell et al. (2014) conducted tractography and regression analyses for several ROIs.

In three studies, WM alterations in the FR for BD subjects were reported, compared to controls. Linke et al. 2013 conducted the ROI analysis and reported decreased FA and increased RD in the right anterior limb of the internal capsule and decreased FA in the right uncinate fasciculus, in the FR group, when compared to controls. Skudlarski et al. 2013 included relatives of those with BD or manic schizoaffective disorder. They reported decreased FA in the right posterior corona radiata in relatives, when compared to controls. Sprooten et al. (2013) reported that BD relatives had decreased FA in the corpus callosum, posterior thalamic radiations, posterior corona radiata and left SLF.
4.3.3 Summary of the findings

The results of the studies of FR for schizophrenia and related disorders are described in Table 1. All but three of sixteen studies reported alterations in WM structure in individuals with an FR for schizophrenia or related disorders. Decreased FA was found in 11 studies and increased FA in four studies. Decreased FA was found in diverse WM regions. The most consistent areas were the frontal and temporal brain regions and the corpus callosum, although the corpus callosum was the most commonly examined ROI. In addition to decreased connectivity, increased FA was found in the left subgenual anterior cingulate, the bilateral pontine tegmental WM, the right middle/superior frontal gyri, the arcuate fasciculus and the right fimbria of fornix. The number of studies examining individuals with FR for BD was small and the results were conflicting. Two studies did not find FA differences between groups (Chaddock et al. 2009, Emsell et al. 2014), while three showed diverse findings (Linke et al. 2013, Skudlarski et al. 2013, Sprooten et al. 2013).

The existing literature on WM abnormalities in people with FR for psychosis is heterogenic, settings varies, and the results are inconsistent.
5 White matter structure and BMI in mental illnesses

In non-psychotic populations, adiposity is associated with WM abnormalities e.g. in the corpus callosum (Mueller et al. 2011, Stanek et al. 2011, Karlsson et al. 2013, Xu et al. 2013). In individuals at risk for psychosis WM abnormalities are detected in many diverse WM regions (Arat et al. 2015, Peters & Karlsodt 2015). There are several biological pathways, which are disrupted in both weight-related processes and psychiatric disorders (Lopresti and Drummond, 2013). External factors, such as the systemic inflammation associated with obesity, may disturb immunological processes of the brain (Hotamisligil 2006, Cazettes et al. 2011). Abnormal inflammatory activation plays a role in disturbed WM development in schizophrenia (Chew et al. 2013, Bakshsi et al. 2015, Najjar and Pearlman 2015). Little is known about how weight and genetic liability for psychosis interact in the brain.

There is scarce if any literature exploring the association between weight and WM microstructure in subjects at risk for psychosis. However, there are some studies exploring this association in mental illnesses. Tang et al. (2011), examined whether BMI (≥ 25) or hypertension has an effect on WM structure in schizophrenia. They included 100 schizophrenia patients and 53 non-psychiatric controls, aged over 29 years. The ROI approach was used and the selected tracts were the corpus callosum, forceps minor, forceps major and inferior longitudinal fasciculus. No association between BMI and FA measures were found, nor any interaction effects between a high BMI and a schizophrenia diagnosis. However, an interaction effect for a schizophrenia diagnosis and hypertension was detected in the left inferior longitudinal fasciculus.

Kuswanto et al. (2014) conducted a study with 26 remitted first episode mania patients and 28 controls. They compared the FA of the frontal, temporal, parietal, and occipital brain regions of normal weight participants to overweight or obese subjects. WM reductions in overweight mania patients in the right parietal and occipital regions were detected, when compared to normal weight patients. When compared to overweight controls, FA reductions were found in the parietal, temporal, and occipital brain regions, in overweight mania patients. The obese control participants showed an increased FA in the occipital and temporal brain regions, when compared to normal weight controls.
6 Aims and Hypotheses

The purpose of this work was to explore brain WM structure and the association between BMI and WM microstructure in individuals at FR for psychosis. In addition, the level of physical activity and cardiorespiratory fitness in adolescents at risk for psychosis were examined. The aims and hypotheses of the original Publications were:

I The aim of the study was to examine whether there is a difference in WM microstructure between young adults with and without a parent with a history of psychosis.

Our hypothesis was that there would be abnormal WM integrity in individuals at FR for psychosis.

II The aim of the study was to examine the relationships between BMI and the WM microstructure in young adults with a FR for psychosis and in control subjects.

We hypothesised that the FA would be lower in individuals with a higher BMI, in both groups. Our second hypothesis was that the effect of BMI on WM would be more robust in subjects with an FR for psychosis.

III The aim was to investigate whether there is a difference in physical activity level and cardiorespiratory fitness between adolescents at risk for psychosis and control subjects.

Our hypothesis was that adolescents vulnerable for psychosis would show a lower level of physical activity and they would have poorer cardiorespiratory fitness, when compared to age mates.
7 Materials and methods

7.1 The Northern Finland Birth Cohort 1986

The Northern Finland Birth Cohort 1986 (NFBC 1986) is comprised of 9,432 individuals live born, in Northern Finland, in the provinces of Oulu and Lapland with an expected date of birth falling between 1 July 1985 and 30 June 1986 (Järvelin et al. 1993). There have been follow-ups during gestation, at birth, 1 y, 7 y, 8 y, 15–16 y and 20–25 y (http://www.oulu.fi/nfbc/). In this dissertation, data collections at ages of 15–16 y (Study III) and 20–25 y (Studies I–II) were used. Data has been collected from the Care Register for Health Care (CRHC, previously known as the Finnish Hospital Discharge Register) and the Registers of the National Social Insurance Institute (SII) and combined with study data.

7.2 The Oulu Brain and Mind Study (I–II)

The original Publications I and II are based on a psychiatric substudy "The Oulu Brain and Mind Study", which was conducted between 2007 and 2010, when the participants were aged between 20 and 25 years. The study aimed to detect young adult members of the NFBC 1986 who would be at risk for developing a psychosis or had been diagnosed having ADHD in adolescence (Veijola et al. 2013).

7.2.1 Study population

The flowchart of the study samples in the original Publications I and II are presented in Figure 3. Two groups were formed for invitation: FR and the control group. The FR group was formed as following; Cohort members with a parent with psychotic episodes or A-type personality disorder (ICD-8, and ICD-9 codes 295–299 and ICD-10 codes F20–33, except for non-psychotic mood disorders) between 1972 and 2005, according to the CRHC, were identified. NFBC 1986 members with a history of psychotic episodes, according to the CRHC (until the end of 2008) or the right to antipsychotic reimbursement from the SII (until the end of 2005) were excluded. After exclusions, 272 cohort members formed the basic invitation group of the FR subjects. Of them, one had died, five were living abroad and no address information was available for four of them, and therefore, the invitation letter was sent to 262 cohort members.
Those with no history of psychosis, no FR for psychosis as described above, no symptomatic risk for psychosis, or no known ADHD were considered as potential controls. Symptomatic risk for psychosis was defined as having attenuated psychosis-like experiences, based on the examination performed at the age of 15–16 years, together with some degree of functional impairment in the educational, social or health domain. These criteria were defined as follows: more than two of the eight symptoms on the thought disorder subscale in the Youth Self Report (YSR) questionnaire (Achenbach 1991), and more than two of the twelve specific symptoms in the PROD-screen questionnaire screening prodromal symptoms (Heinimaa et al. 2003), and who had had no friends, had repeated class in school or had been treated in hospital due to a non-psychotic psychiatric disorder during 2001–2005. In addition, those participants who had been treated in psychiatric hospital due to non-psychotic disorder for over 1 week during 2003–2005 were considered as being at high clinical risk for psychosis.

Of the cohort members 193 (2.2%) individuals were randomly selected as the basic invitation group of control subjects. Of them one had died and no address was available for another, and therefore, 191 cohort members were invited to the field study.
7.2.2 Participants

The flowchart of the individuals participating in the Oulu Brain and Mind Study and the exclusion of participants in the original Publications I and II are presented in Figure 3. Clinical variables used in Studies I and II are described in Table 2. The study procedure included psychiatric interviews, a cognitive test battery, a urine test to assess drug use and MRI scanning. The study protocol allowed two-thirds to be scanned with DTI. The participants also answered questionnaires during the study. In psychiatric interviews, the SIPS (McGlashan et al. 2001) was used to determine possible lifetime psychotic episodes, previous prodromal syndromes and current prodromal symptoms and the Structured Interview for DSM-IV disorders, SCID-I (First et al. 2002) to assess current axis-I disorders.
Study I

The exclusion criteria for both groups were: 1) history of head trauma with loss of consciousness for 30 minutes or more; 2) severe neurological illness; 3) history of psychosis and 4) low quality scan. The final groups consisted of 47 FR and 51 control participants. Of the FR group, 13 had a parent with schizophrenia and 34 with another psychotic disorder (schizoaffective disorder, \( n = 2 \); schizophreniform disorder, \( n = 2 \); delusional disorder, \( n = 4 \); psychotic depressive disorder, \( n = 6 \); psychotic bipolar disorder, \( n = 8 \); other psychotic disorder, \( n = 12 \)).

According to the CRHC, in our final sample none of the participants had both parents with a psychosis or a parent who solely had a diagnosis of an A-type personality disorder. Seven participants in the FR group and two in the control group had a current prodromal syndrome, according to the SIPS interview.

Study II

Participants were excluded for any of the following: 1) missing BMI data; 2) history of psychosis; 3) history of head trauma with loss of consciousness for 30 minutes or more; 4) severe neurological illness; 5) diabetes or arterial hypertension with medication and 6) low quality scan. The final groups consisted of 42 FR and 46 control participants (Figure 3). According to the SIPS interview, seven participants in the FR group and two control subjects had a current prodromal syndrome. According to the SCID interview, one participant had current bulimia nervosa and no one fulfilled the criteria for current anorexia. Of the FR participants, 12 had a parent with schizophrenia and 30, a parent with another psychotic disorder (schizoaffective disorder, \( n = 2 \); schizophreniform disorder, \( n = 2 \); delusional disorder, \( n = 2 \); psychotic depressive disorder, \( n = 6 \); psychotic bipolar disorder, \( n = 8 \); other psychotic disorder, \( n = 10 \)). None of the participants had two parents with psychosis or a parent who only had a diagnosis of an A-type personality disorder.
Table 2. Demographic and clinical variables used in the original Publications I and II.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data source</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental psychosis</td>
<td>Care Register for Health Care</td>
<td>All cohort members who had one or more parents who had experienced a psychotic episode or had A-type personality and was treated in hospital (ICD-8, and ICD-9 codes 295–299 and ICD-10 codes F20–33, except for non-psychotic mood disorders) between 1972–2005 according to the Care Register for Health Care, were invited to participate.</td>
</tr>
<tr>
<td>Handedness</td>
<td>Questionnaire during the clinical study</td>
<td>Handedness was defined by asking which hand the subjects preferred to use when writing.</td>
</tr>
<tr>
<td>Education</td>
<td>Questionnaire during the clinical study</td>
<td>Educational level was based on a question about basic education and categorised into three classes in the original Publication I: less than nine school years, comprehensive school, and matriculation, and into two classes in the original Publication II: elementary school and matriculation</td>
</tr>
<tr>
<td>White matter microstructure</td>
<td>DTI imaging during the clinical study</td>
<td>GE Signa 1.5 T</td>
</tr>
<tr>
<td>Body mass index (BMI) (II)</td>
<td>Questionnaire during the clinical study</td>
<td>Weight and height were self-reported and BMI calculated using the formula BMI = mass (kg)/(height (m))^2</td>
</tr>
<tr>
<td>Intelligence quotient (IQ)</td>
<td>Cognitive test battery during the clinical study</td>
<td>IQ was estimated by two subtests from the Wechsler intelligence Scale III, Finnish version. Vocabulary from the Wechsler Adult Intelligence Scale was used to assess word knowledge and ability to express word meanings, and matrix reasoning was applied in assessment of analogy-related reasoning, perception of details, and spatial perception (Wechsler Adult Intelligence Scale III Edition; Wechsler 1997; Finnish Version; Mukkala et al. 2011).</td>
</tr>
<tr>
<td>Global Assessment of Functioning (GAF)</td>
<td>Psychiatric interview during the clinical study</td>
<td>The interviewer rated occupational, social and psychological functioning on a numeric scale from 0 to 100 (APA, 1994)</td>
</tr>
<tr>
<td>Cigarette smoking (II)</td>
<td>Questionnaire during the clinical study</td>
<td>Was defined by asking: “Do you currently smoke cigarettes?” and categorised into three classes: Not at all, Occasionally - 1 day/week and 2 days or more/week or Often</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Variable</th>
<th>Data source</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol use</td>
<td>Questionnaire during the clinical study</td>
<td>Participants were asked if they drank too much alcohol with the following response alternatives: Not true, Somewhat or sometimes true, Very true or Often true</td>
</tr>
</tbody>
</table>
7.2.3 Imaging Methods

All MRI scans were obtained using a GE Signa 1.5 Tesla system at the Oulu University Hospital. Diffusion-weighted imaging data were acquired with single-shot echo planar imaging. DTI images were acquired with TR (time of repetition) 8700 ms, optimized TE (echo time) by the scanner (approximately 90-100 ms), NEX (number of excitations) = 1, and FOV (field of view) 24 x 24 cm². Matrix size was 128 x 128 and slice thickness 3.0 mm, with resulting voxel size of 1.875 x 1.875 x 3.0 mm³. The diffusion gradients were applied along 40 nonparallel directions (b = 1000 s/mm²) and one without diffusion weighting (b = 0).

7.2.4 DTI data processing and analysis

Diffusion-weighted images were checked for errors in all 40 gradient directions and bad gradients were removed. FSL 5.01 software package (Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library; see www.fmrib.ox.ac.uk/fsl) script “eddy correct” was used to linearly register the diffusion-weighted images into individual structural images to account for image distortions. Results of the brain extraction (BET (Smith 2002)) of the structural modality were used as masks to remove the skull from the diffusion-weighted images. Voxel-wise diffusion tensor calculus was then performed with a FDT (FMRIB’s Diffusion Toolbox), which produced values for FA along with MD, RD, and AD.

Images were run through TBSS (Smith et al. 2006) pipeline that created skeletonised presentations of each individual’s WM tracts. In short, the pipeline involves non-linear registering of each FA map into FMRIB58 FA standard-space (FNIRT (FMRIB technical reports TR07JA1 & TR07JA2 from www.fmrib.ox.ac.uk/analysis/techrep), creating a group mean image and skeletonising it by finding the maximum FA value in the tract perpendicular direction. The resulting skeleton was thresholded at 0.3 and each individual’s FA maps were projected onto this skeleton by searching for the maximum local FA value. The steps were repeated for the other diffusion modalities.

In the original Publication 1, we tested the differences in the FA, MD, RD and AD maps between participants with FR for psychosis and the controls. In addition, a subgroup of participants with FR for schizophrenia were compared to a gender-matched, randomly selected group of controls. To compare the groups, a non-parametric randomise tool (FSL) with threshold-free cluster enhancement
correction option (corrected for multiple comparison [FWE, family wise error correction]) and 5,000 permutations was used. A p-value < 0.05 was considered statistically significant in all of the analyses. Additional analysis of the corpus callosum, cingulum, fornix, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus and uncinate fasciculus was conducted. The ROIs were formed by masking the original FA skeleton (thresholded at 0.3), with one structure at a time, according to two atlases included in FSL, namely the JHU ICBM-DTI81 White-Matter Labels and JHU White-Matter Tractography Atlas.

In the original Publication II, the effect of the BMI was tested voxel-wise using a non-parametric randomise tool (FSL) with threshold-free cluster enhancement correction option (FWE correction) and 5,000 permutations. First, the group and BMI interaction was tested for all DTI modalities (FA, MD, RD and AD maps) separately. Then, both groups (controls, FR) were tested separately for covariance with a continuous BMI variable in those modalities that showed statistically significant interaction. In both analyses, the effects of gender and education were removed by adding these variables as regressors of no interest. Three atlases were used to identify the most probable anatomical localisation of statistically significant results: (i) ICBM-DTI-81 white-matter labels 1 mm, (ii) probabilistic JHU white-matter tractography 1 mm and (iii) probabilistic Harvard-Oxford subcortical structural 1 mm (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). A probability threshold of 15% was applied to (ii). Any overlapping regions with the other two atlases were removed from (iii), which, thus, only accounted for unspecific left/right subcortical WM voxels. Overlapping regions, however, remained in (i) and (ii), accounting for 27.6% of their total volume. A p-value < 0.05 was considered statistically significant in all of the analyses.

### 7.2.5 Statistical analyses of demographic and clinical variables

The demographic and clinical variables were compared between study groups using chi-square tests for categorical variables, and independent-samples t-tests for continuous variables using IBM SPSS statistics, Version 20 (1989, 2011 SPSS Inc., an IBM Company).
7.2.6 Attrition

In the original Publication I, 47 subjects with FR, out of 272 (17%) invited FR subjects, participated in the study. The figures in the control group were 51 out of 193 (26%) control subjects, respectively. Thirty percent of the non-participating FR subjects and 28% of the participants had a parent with schizophrenia, according to the CRHC (Pearson Chi-Square Test $p = 0.73$). In the FR group, 8.0% of the non-participants and 6.4% of the participants had been treated in a hospital between the years 2001 and 2005 due to a psychiatric disorder. Of the controls, 2.8% ($n = 4$) of the non-participating and none of the participating subjects had been treated in a hospital due to a non-psychotic psychiatric disorder (Fisher's Exact Test $p = 0.58$).

In the original Publication II, 42 subjects with FR, out of 272 (15%) invited FR subjects, participated in the study. The figures in the control group were 46 out of 193 (24%) control subjects. Thirty percent of the non-participating FR subjects and 29% of the participants had a parent with schizophrenia, according to the CRHC (Pearson Chi-Square Test $p = 0.85$). In the FR group, 14% of the non-participants and 7% of the participants had been treated in a hospital due to a non-psychotic psychiatric disorder, between the years 2001 and 2005. Of the controls, 2.9% of the non-participating and none of the participating subjects had been treated in a hospital due to a non-psychotic psychiatric disorder (Fisher’s Exact Test $p = 0.46$).

7.3 Physical activity and fitness study (III)

The follow-up was carried out between 2001 and 2002, when the subjects were aged between 15 and 16 years. Adolescents and their parents received a postal questionnaire. On average, six months after the postal questionnaire, the adolescents were invited to participate in a clinical examination.

7.3.1 Study population

The flow-chart and the number of the participants is presented in Figure 4. Those 9,215 adolescents who were living and whose addresses were known received a postal questionnaire that included questions about their physical activity (Hurtig et al. 2005). Of the subjects, 80% ($n = 7,344$) answered the mailed questionnaire. Their parents also received a questionnaire that included questions on family income, the mother’s and father’s education, family structure, and the parents’
physical activity. Of the parents, 76% (n = 6,985) returned the questionnaire. Adolescents who had filled in the question concerning physical activity (Tammelin et al. 2007a) and who had given a written consent to use their data were included (n = 6,987; boys n = 3,367, girls n = 3,620) in the present study. Of the adolescents 74% (n = 6,798) participated in the clinical study.

Fig. 4. Flow chart of the NFBC 1986 physical activity and fitness study.

7.3.2 Risk for psychosis

Vulnerability for psychosis was assessed in three ways with possible overlap between groups: having a parental risk for psychosis, existing prodromal symptoms at age 15–16, and development of hospital treated psychosis between ages 16 and 20 years.

7.3.3 Physical activity and fitness

Physical activity was self-reported in the postal questionnaire (Tammelin et al. 2007a). During the examination cardiorespiratory fitness was measured by a submaximal cycle ergometer test (Tammelin et al. 2007b). More detailed information about variables used in the study are presented in Table 3.
### Table 3. Demographic and clinical variables used in original Publication III.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data source</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk for psychosis</td>
<td></td>
<td>The possible psychiatric diagnoses of the parent were obtained from the 1972 to 2000 Care Register for Health Care, which covers all general and mental hospitals in Finland, without gaps, since 1972.</td>
</tr>
<tr>
<td>Parental psychosis</td>
<td>Care Register for Health Care</td>
<td>The possible psychiatric diagnoses of the parent were obtained from the 1972 to 2000 Care Register for Health Care, which covers all general and mental hospitals in Finland, without gaps, since 1972.</td>
</tr>
<tr>
<td>Prodromal symptoms</td>
<td>PROD-screen questionnaire</td>
<td>Participants filled in the questionnaire during the clinical study, in 2001–2002. The PROD-screen scale has 21 items; we used only 12 symptom items, specific for psychosis risk. These items include questions of whether the subject had experience of, for example, feeling that something strange or inexplicable is taking place in him/herself or the environment, feeling that one is being followed or influenced in some special way, experience of thoughts running wild or difficulty in controlling the speed of thoughts, amongst other symptoms. We counted symptoms (no/yes) during the last six months (Heinimaa et al. 2003).</td>
</tr>
<tr>
<td>Later psychotic illness onset</td>
<td>Care Register for Health Care and Finnish Social Insurance Institute's register</td>
<td>After the follow-up visit we collected the psychiatric hospitalisation data for any non-organic psychosis (ICD-10 codes F20–F33 except non-psychotic mood disorders, between 1 Jan 2002 and 31 Dec 2005, from the Care Register for Health Care. As all psychotic disorders may not have been treated in hospital, we also collected data from the Finnish Social Insurance Institute’s register for antipsychotic reimbursement.</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Postal questionnaire to the adolescents</td>
<td>Physical activity was evaluated by asking: “Outside school hours, how many hours a week do you spend on brisk physical activity?” Physical activity causing at least some sweating and shortness of breath was defined as brisk in the questionnaire. The response alternatives were 1) Not at all, 2) About half an hour a week, 3) About an hour a week, 4) 2–3h a week, 5) About 4–6h a week, and 6) 7h a week or more. Categories were combined as follows; 1 and 2, 3 and 4, 5 and 6, forming three classes, which are inactive, somewhat active and active, respectively (Tammelin et al. 2007a).</td>
</tr>
<tr>
<td>Cardiorespiratory fitness</td>
<td>Clinical cycle ergometer test</td>
<td>Cardiorespiratory fitness was measured by a submaximal cycle ergometer test and expressed as peak oxygen uptake (VO2peak) in ml·kg·1·min-1. Gender-specific tertiles were used to classify peak oxygen uptake into three categories (Tammelin et al. 2007b).</td>
</tr>
<tr>
<td>Family’s socio-economic status (SES)</td>
<td>Postal questionnaire to the parents</td>
<td>Both the mother’s and father’s socio-economic status was recorded and the highest alternative was used to form a 2-class variable describing the family’s SES.</td>
</tr>
</tbody>
</table>
Family structure was divided into two classes: intact and non-intact, where the latter included divorced and reconstructed families, single parents and widows.

Both mothers' and fathers' activities were assessed by asking "How often does the mother/father exercise in her/his leisure time? Brisk physical activity (at least slightly out of breath and sweating" with the following response categories: 1) 1 Once a month or less, 2) 2–3 times a month, 3) Once a week, 4) 2–3 times a week, and 5) 4–6 times a week or more often. In this study, category 1 was defined as being inactive, 2 and 3 as somewhat active, and 4 and 5 as active.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data source</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family structure</td>
<td>Postal questionnaire to the parents</td>
<td>Family structure was divided into two classes: intact and non-intact, where the latter included divorced and reconstructed families, single parents and widows.</td>
</tr>
<tr>
<td>Parents' physical activity</td>
<td>Postal questionnaire to the parents</td>
<td>Both mothers' and fathers' activities were assessed by asking &quot;How often does the mother/father exercise in her/his leisure time? Brisk physical activity (at least slightly out of breath and sweating&quot; with the following response categories: 1) 1 Once a month or less, 2) 2–3 times a month, 3) Once a week, 4) 2–3 times a week, and 5) 4–6 times a week or more often. In this study, category 1 was defined as being inactive, 2 and 3 as somewhat active, and 4 and 5 as active.</td>
</tr>
</tbody>
</table>
7.3.4 Statistical methods

Chi-square tests and logistic regression analyses were used to explore the associations between physical activity, fitness and risk for psychosis. For logistic regression, variables describing adolescents' and parents' physical activity levels were dichotomised into inactive vs. others. Similarly, cardiorespiratory fitness was dichotomised into the lowest tertile vs. the other two tertiles. First, unadjusted associations were explored. Second, the models were then adjusted for parental SES and family structure. The physical activity models also included the adolescent's gender, whereas cardiorespiratory fitness assessments were already done gender-specifically. Finally, parents' leisure-time physical activity was adjusted for the models. The associations are reported in odds ratios (OR) with 95% confidence intervals (CI). Statistical analyses were conducted with the SAS version 9.1. (SAS Institute Inc., Cary, NC, USA).

7.3.5 Attrition

Of the 9,215 living subjects with a known address at the age of 16 years, 6,987 (76%) answered the question concerning their physical activity and gave written consent to use their data. The rate of non-participants for boys was 29% and for girls 19% (p < 0.0001). There were more non-respondents among those adolescents who had a parent with a history of psychosis (33% vs. 24%, p = 0.004), but the proportion of non-respondents was approximately the same among those who developed psychosis after the field study and those who did not (21% vs. 24%, p = 0.68).

In addition, 4,803 (52%) subjects took part in the clinical study and performed a cycle ergometer test. The rate of non-participants for boys was 50% and for girls 46% (p = 0.0004). Subjects who had a parent with a history of psychosis were more prone not to participate (54% vs. 48%, p = 0.09), as were those who later developed psychosis, compared to those who did not (69% vs. 48%, p = 0.006).
8 Ethical considerations

The overall study plan of the NFBC 1986 was approved by the Ethical Committee of the Northern Ostrobothnia Hospital District. The follow-up study conducted between 2001–2002 was approved by the Ethical Committee of the Faculty of Medicine, University of Oulu, Finland in 2001. The research plan for the NFBC 1986 psychiatric follow-up study in 2007–2010 was approved in 2006 by the Ethical Committee of the Northern Ostrobotnian Hospital District. Data protection has been approved by the Finnish Privacy Protection Agency. The Finnish Ministry of Social Affairs and Health has permitted the use of the register data and patient records. All participants and their parents gave written informed consent and they have an option to refuse to allow use of their data.
9 Results

9.1 White matter structure in individuals at familial risk for psychosis (I)

9.1.1 Characteristics of the sample

Of the cohort members, 98 were finally included in the study. The FR group consisted of 47 participants, of whom 17 (36%) were male. Of the 51 participants in the control group, 17 (33%) were male. The mean age of the whole sample was 22.3 (SD 0.8) years. Groups were similar with respect to gender, age, handedness and educational level. We found no significant difference between the groups in intelligence, GAF or alcohol use (Tables 1 and 2 in original Publication I).

9.1.2 White matter structure

In the TBSS analyses, no significant differences between participants with an FR for psychosis and the control group were found in the FA, MD, RD or AD. The mean FA values were 0.664 (SD 0.0194) for participants with an FR for psychosis and 0.663 (SD 0.0188) for controls. Analysis of the FA skeleton of 0.3 or the more strongly limited skeleton of 0.5 threshold resulted in no difference between the groups. In the ROI analysis with 12 separate ROIs, no significant differences between the FR and the control group were found. There were no differences in these measures when comparing a subgroup of participants with the FR for schizophrenia (n = 13) to a gender-matched control group (n = 13).

9.2 Association between white matter structure and BMI in individuals at familial risk for psychosis (II)

9.2.1 Characteristics of the sample

Altogether 88 participants were included to the study. The FR group consisted of 42 participants of whom 13 (31%) were male. The control group consisted of 46 participants of whom 16 (35%) were male. The mean age of the whole sample was 22.2 (SD 0.7) years. Groups were similar with respect to age, gender, handedness and educational level. There were no significant differences between the groups in
BMI, estimated IQ, GAF, cigarette smoking or alcohol use. The mean BMI of the whole sample was 23.3 (SD 4.52; range 17.30–47.83). Of the participants in the FR group, 5% were underweight (BMI < 18.5), 76% normal weight (18.5–24.9), 14% overweight (≥ 25) and 5% obese (≥ 30). The numbers in the control group were 2%, 72%, 15%, and 11%, respectively (Tables 1 and 2 in original Publication II).

### 9.2.2 White matter microstructure and BMI

**Interaction effects**

Statistically significant BMI and group interaction effects on FA, RD and MD were detected in widespread WM areas (Figure 5). The number of significant voxels for each interaction analysis are presented in Table 6 (Appendix). There was no interaction effect on AD.
Fig. 5. Group and BMI interaction in diffusion measures (FA, RD and MD). Results’ significance (only p < 0.05 are shown) increases from dark to light blue colour in sagittal, frontal and horizontal views. TBSS group mean tract (red) and MNI152 template brain are shown in the background. The right side column shows 3D views of significant voxels with the MNI152 brain template (Figure S1 in the original Publication II).

To test the direction of interaction, post hoc analyses were conducted in both groups separately.

**Familial risk group**

In the FR group, a negative association between the BMI and FA was found in the right parietal and periventricular area (Figure 6). There was also a positive trend similar to the association between the BMI and MD, but this finding was not statistically significant (for statistically most significant voxel p = 0.07). There was no association between the BMI and AD.
Fig. 6. Correlation of diffusion measures (FA/RD) and BMI in familial risk group + for positive and - for negative correlation. Results’ significance (only p < 0.05 are shown) increases from dark to light blue voxels in sagittal, frontal and horizontal views. The TBSS group mean tract (red) and MNI152 template brain are shown in the background. The right column shows 3D views of the significant voxels, with superior longitudinal fasciculus (red-yellow) as a landmark on the MNI152 brain (Figure 2 in original Publication II).

The largest cluster contained 239 voxels (MNI atlas coordinates for the statistically most significant voxel were 57, 79 and 88 for x, y and z, respectively) and was located periventricularly. The most probable tracts located in this area were the inferior longitudinal fasciculus (ILF) and inferior fronto-occipital fasciculus (IFOF). The affected area also contained voxels from the posterior corona radiata, the retrolenticular part of the internal capsule and posterior thalamic radiation (including optic radiation). Another cluster containing 211 voxels (69, 79, 113) was located parietally and contained voxels of the SLF and corticospinal tract. The third largest cluster contained 153 voxels (71, 72, 106), and the most probable anatomic WM structures in this area were the IFOF and the cingulum (Table 4). RD increased extensively with increasing BMI in both hemispheres. The number of voxels, by three different WM atlases, are presented in Table 7 (Appendix).
Table 4. Significant clusters of correlation between BMI and white matter fractional anisotropy among participants with familial risk for psychosis (Table 3 in original Publication II).

<table>
<thead>
<tr>
<th>Size (voxels)</th>
<th>p</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Side</th>
<th>Most probable white matter structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>239</td>
<td>0.033</td>
<td>57</td>
<td>79</td>
<td>88</td>
<td>Right</td>
<td>IFOF, ILF, Posterior corona radiata</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Posterior thalamic radiation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Retro lenticular part of internal capsule</td>
</tr>
<tr>
<td>211</td>
<td>0.034</td>
<td>69</td>
<td>79</td>
<td>113</td>
<td>Right</td>
<td>SLF, Corticospinal tract</td>
</tr>
<tr>
<td>153</td>
<td>0.042</td>
<td>71</td>
<td>72</td>
<td>106</td>
<td>Right</td>
<td>Cingulum, IFOF</td>
</tr>
<tr>
<td>45</td>
<td>0.048</td>
<td>67</td>
<td>93</td>
<td>120</td>
<td>Right</td>
<td>SLF, Corticospinal tract</td>
</tr>
<tr>
<td>7</td>
<td>0.049</td>
<td>68</td>
<td>97</td>
<td>113</td>
<td>Right</td>
<td>Superior corona radiata, Corticospinal tract</td>
</tr>
<tr>
<td>2</td>
<td>0.0496</td>
<td>58</td>
<td>92</td>
<td>83</td>
<td>Right</td>
<td>IFOF, Retro lenticular part of internal capsule</td>
</tr>
</tbody>
</table>

For statistically most significant voxel, MNI atlas coordinates

IFOF = inferior fronto-occipital fasciculus, ILF = inferior longitudinal fasciculus, SLF = superior longitudinal fasciculus

Control group

In the control group the opposite pattern was seen: the FA increased extensively, alterations being more robust on the left side of the brain. In addition, RD decreased as the BMI increased (Figure 7). The number of voxels, by three different WM atlases, are presented in Table 8 (Appendix). BMI had no effect on the AD or MD.
9.3 Physical activity and cardiorespiratory fitness in individuals at risk for psychosis (III)

9.3.1 Physical activity

Parental risk for psychosis was discovered among 51 boys and 71 girls, whereas 3,316 boys and 3,549 girls did not have this risk. Of the subjects 24% (n = 1,492) reported 3–5 symptoms by a PROD-screen questionnaire, and 7% (n = 401) more than five specific symptoms. Girls reported more prodromal symptoms of psychosis than boys (p < 0.0001). Thirty-three individuals (14 boys, 19 girls) developed psychosis after the field study. Of the subjects who fell ill, 9% (three out of 33) had had a psychotic parent; and of the 25 subjects who developed psychosis and had filled in the PROD-screen questionnaire 15 (60%) had at least 3 prodromal symptoms.

Of the subjects, 20% were physically inactive, 43% somewhat active, and 37% were active. Boys were physically more active and they had better cardiorespiratory fitness than the girls. The mean peak oxygen consumption was 48.8 (SD 8.9)
ml·kg−1·min−1 in boys and 34.2 (SD 5.7) ml·kg−1·min−1 in girls. For the whole sample, the mean peak oxygen consumption was 41.4 (SD 10.4) ml·kg−1·min−1.

There were no statistically significant differences in the level of physical activity between the subjects with and without a familial risk for psychosis (p = 0.21) (Figure 8). Those who reported several prodromal symptoms were physically more inactive than subjects with few or no prodromal symptoms (p < 0.001). The more symptoms the subjects had, the less physically active they were. Subjects who actually developed psychosis had a lower level of physical activity than those who did not develop a psychosis (p = 0.003).

The results of physically inactive subjects and those with low fitness are presented in Table 5 using logistic regression. Those individuals who developed psychosis were more likely to be physically inactive (OR 3.3; 95% CI 1.4-7.9 adjusted for gender, parental socio-economic status, family structure and parents' physical activity). The results of all analyses were essentially similar when boys and girls were analysed separately (data not shown).
Table 5. Physical inactivity and low cardiorespiratory fitness at age 16 by different variables describing risk for psychosis (Table 2 in original Publication III)

<table>
<thead>
<tr>
<th>Variables describing risk for psychosis</th>
<th>Physical inactivity&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Low cardiorespiratory fitness&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted OR (95% CI)</td>
<td>Adjusted&lt;sup&gt;3&lt;/sup&gt; OR (95% CI)</td>
</tr>
<tr>
<td>Familial risk for psychosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>1.34 (0.88–2.02)</td>
<td>1.29 (0.79–2.11)</td>
</tr>
<tr>
<td>Prodromal risk for psychosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>3–5</td>
<td>1.21 (1.05–1.40)</td>
<td>1.11 (0.94–1.30)</td>
</tr>
<tr>
<td>6–12</td>
<td>1.49 (1.18–1.90)</td>
<td>1.30 (0.99–1.70)</td>
</tr>
<tr>
<td>Onset of first-episode psychosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>2.55 (1.27–5.14)</td>
<td>2.83 (1.20–6.66)</td>
</tr>
</tbody>
</table>

<sup>1</sup> Less than one hour of moderate to vigorous intensity of physical activity per week

<sup>2</sup> Lowest tertile of cardiorespiratory fitness

<sup>3</sup> Adjusted for SES and family structure, and in physical inactivity models also for gender

<sup>4</sup> Additionally adjusted for father’s and mother's leisure-time physical activity

Statistically significant results at p < 0.05 level indicated in bold
9.3.2 Cardiorespiratory fitness

There was no statistically significant difference in the level of cardiorespiratory fitness in any of the psychosis risk groups compared to the controls, when cardiorespiratory fitness was classified into tertile groups (Table 5).
10 Discussion

10.1 Main findings

The main findings of the study were:

1. In Publication I, we studied young adults at FR for psychosis. We compared 47 participants with FR for psychosis and 51 controls. There were no differences in WM microstructure between FR and the control groups. Our study suggests that WM abnormalities are not genetically determined features of psychosis in all populations.

2. In Publication II, we studied the association between BMI and WM microstructure in 42 FR participants and 46 controls. Interaction between the BMI and FR for psychosis on WM microstructure was detected. In the FR group, decrease in FA and increase in RD were associated with an increase in BMI in several brain areas. In controls, the opposite pattern was seen. RD was globally associated with BMI in both groups, while there was no effect on axial diffusion, suggesting myelin pathology with intact axons.

3. In Publication III, we examined adolescents with vulnerability to psychosis. Risk for psychosis was viewed from three perspectives with possible overlap between groups: having a familial risk for psychosis, existing prodromal symptoms of psychosis measured by the PROD-screen questionnaire at age 15–16, and development of hospital treated psychosis between ages 16 and 20 years. Adolescents who developed psychosis, or had several prodromal symptoms, were more likely to be physically inactive.

10.2 White matter structure in individuals at risk for psychosis (I)

In contrast to majority of earlier findings, our study suggested that WM abnormalities are not genetically determined features of psychosis and that structural dysconnectivity may not be a primary sign of psychosis. The majority of the earlier studies report diverse disturbed WM microstructure in subjects with a family member with psychosis, when compared to healthy controls (Arat et al. 2015, Peters & Karlsgodt 2015). The recently published Utrecht twin cohort study by Bohlken et al. 2015 showed that lower global FA was correlated with schizophrenia disease liability. Genetic liability for schizophrenia was associated with a reduction in connectivity in the frontal and subcortical regions.
Comparisons of literature are challenging because of variable scanning methods, data processing, analytical methods, and study populations. For example, five earlier studies did not find statistically significant results between groups in some analyses, but findings were significant when using other methods (Muñoz Maniega et al. 2008, Camchong et al. 2009, Knöchel et al. 2012a, Goghari et al. 2014, Prasad et al. 2015).

We examined young adults at the age of high risk for developing psychosis. Also Hoptman et al. (2008) and Harms et al. (2015) examined young adults. Hoptman et al. (2008) reported both increased and decreased FA values. In their study, participants had multiple first- or second degree relatives with psychosis. Harms et al. (2015) reported no differences in FA between FR and control groups in any of the investigated tracts. The age of subjects is an important factor when examining brain structure. The association between age related and illness related changes is complex in schizophrenia. The development of grey and white matter in schizophrenia differs from the development of healthy controls (Douaud et al. 2009, 2014, Nour & Howes 2015, Peters & Karlsgodt 2015). Non-psychotic siblings of patients with childhood-onset schizophrenia show slower WM development growth rates in the parietal lobes (Gogtay et al. 2012) and grey matter deficits (Gogtay et al. 2007) during childhood, when compared to controls; however, these changes seem to normalise with age. In a systematic review by Chiapponi et al. (2013), age-related structural WM trajectories in patients with schizophrenia were reviewed. They concluded that results are variable and different brain areas change with different trajectories; in some regions changes appear at the time of illness onset, while in other brain areas, they are present in earlier stages of life. Some changes stabilise after the acute phase and some impairments continue to worsen.

Our study population was drawn from the general population-based birth cohort sample. All the participants were born in northern Finland, which is known to be a geographic area with high prevalence of schizophrenia. One possible explanation for the high prevalence is a clustering of genes that predispose psychotic disorders (Perälä et al. 2008). Differences in the genetic background of the study population may partly explain the disparity of the findings, when compared to earlier studies.

In our study, all the subjects had only one parent with a psychotic illness and only offspring of the patients were included. Individuals having one parent with psychosis have a lower risk of developing psychosis compared to subjects with both parents affected (Gottesman et al. 2010, Mortensen et al. 2010). In most of the earlier studies, the genetic liability for psychosis has been defined as having a
first-degree relative with psychosis. In one study, subjects with two or more
affected first- or second-degree relatives were recruited (Muñoz Maniega et al.
2008). Hoptman et al. (2008) recruited subjects who had at least one first-degree
relative and/or multiple second-degree relatives with schizophrenia or
schizoaffective disorder. In most studies, the FR subjects were siblings of the
patients. In addition, nine studies included parents and/or offspring of the patients
2015).

Our finding, that there is no difference in WM microstructure between the FR
and the controls, is consistent with five previous studies investigating individuals
2013, Emsell et al. 2014, Harms et al. 2015). In the present study, the FR group
was heterogenic with respect to diagnosis of parental psychosis. Also, Domen et al.
(2013) studied siblings of patients with a heterogenic group of psychotic disorders
(schizophrenia, schizoaffective disorder, schizophreniform disorder, brief
psychotic disorder, and psychotic disorder not otherwise specified). They used the
TBSS method and explored a relatively large sample. Finding generic biomarkers
for genetic liability for psychosis may be challenging in respect to heterogenic
diagnosis of probands, as psychoses are a heterogeneous group with respect to
aetiology, although there is overlap in symptomology and genetics (Lichtenstein et
al. 2009, Cross-Disorder Group of the Psychiatric Genomics Consortium 2013,
Domschke et al. 2013, Cardno & Owen 2014). To create a more homogenous group,
we conducted an additional analysis for the FR for schizophrenia.

In an analysis of the resting state functional MRI in this same cohort, the FR
participants showed lower activity in the central executive network and default
mode network, and increased activity in the anterior lobe of the right cerebellum
(Jukuri et al. 2013, 2015a, 2015b). Additionally, in the facial recognition test, we
found that the FR subjects had increased activity in the left premotor cortex and
reduced deactivation of the prefrontal cortex structures, during happy facial
expression (Pulkkinen et al. 2015). The neurocognitive profile of the FR
participants was not significantly different from that of the control subjects
(Mukkala et al. 2011). Combining these findings with our present finding of no
disruptions in the WM tract integrity, it may be concluded that familial risk does
not work through connectivity in white matter, but through connectivity in certain
grey matter networks.
10.3 White matter and BMI in individuals at risk for psychosis (II)

In the present study, approximately a quarter of the participants were overweight or obese, and few participants slightly underweight. Individuals in their early 20s showed a difference in WM microstructure, in relation to BMI, between FR and control groups indicated by FA, MD and RD. In the FR group, a negative association between BMI and FA in parietal and periventricular regions in the right hemisphere was detected. In the control group, the association was positive and widespread, being more robust in the left hemisphere. RD was associated globally with BMI in both groups, whilst no difference in axial diffusion was observed.

Literature exploring the association between weight and WM microstructure in mental disorders is scarce and appears to be non-existent for individuals with an FR for psychosis. No association was found between an elevated BMI and an FA in patients with schizophrenia, or in controls with no psychosis when using a ROI analysis (Tang et al. 2011). However, one limitation of the ROI is that the analysis is hypothesis driven and, therefore, some potentially interesting tracts may have been excluded from the analyses. Furthermore, the study population demographics were different, as Tang et al. (2011) excluded subjects younger than 29 years of age. In line with our findings, another study exploring overweight/obese individuals with a first episode of mania showed decreased FA in the right parietal and occipital lobes, when compared to normal weight, first episode mania subjects, and in the right parietal, temporal, and occipital regions when overweight patients were compared to overweight controls (Kuswanto et al. 2014).

In the present study, a higher BMI was associated with decreased FA and increased RD in the FR group. In animal models, this kind of pattern, with no change in axial diffusion, has been shown to be linked to dysmyelination (Song et al. 2002) or demyelination (Song et al. 2005). It has been suggested that some oligodendrocyte-myelin-related genes and myelin-related pathways may be associated with increased risk for schizophrenia (Mighdoll et al. 2015).

In a review by Lopresti and Drummond (2013), they list some dysregulated pathways, which are common in psychiatric illnesses and weight-related processes, such as oxidative stress, hypothalamus-pituitary-adrenal axis disturbances, neurotransmitter imbalances, mitochondrial disturbances, neuroprogression and dysregulated inflammatory pathways. The dysregulation of inflammatory pathways is interesting, as a recently published study showed that schizophrenia is linked to a chromosome region that contains genes, which play an important role in acquired immunity (Schizophrenia Working Group, 2014). Another recently published study
suggested excessive complement activity in the development of schizophrenia (Sekar et al. 2016). These findings indicate immunological dysfunction and possibly abnormal inflammatory responses, which may also explain the WM deficits. This is due to the possible role of abnormal inflammatory activation in disturbed WM development in schizophrenia (Chew et al. 2013, Bakshsi et al. 2015, Najjar & Pearlman 2015). External factors, such as the systemic inflammation associated with obesity, may disturb immunological processes of the brain (Hotamisligil 2006, Cazettes et al. 2011).

In the control group, a higher BMI was associated with an increased FA through a decrease in RD. Increased FA and decreased RD may indicate e.g. improved myelination, increased axon coherence or reduced axonal diameter (Beaulieu, 2002; Jones et al. 2013). Previous studies, conducted with otherwise healthy obese subjects, have shown conflicting results. The majority of the studies have shown that adiposity and FA are negatively associated, e.g. in the corpus callosum (Mueller et al. 2011, Stanek et al. 2011, Verstynen et al. 2012, Karlsson et al. 2013, Xu et al. 2013). Conversely, a positive association has been found by Verstynen et al. (2012), Kuswanto et al. (2014) and Ou et al. (2015), and one relatively large study found no association between BMI and WM microstructure in children and adolescents (Alosco et al. 2014).

The results of Ou et al. (2015) are similar to the present study; FA was increased, likely from decreased RD on association and projection fibres in the left hemisphere detected using TBSS. They examined children aged between 8 and 10 years, in a small sample (n = 24). However, as we examined adults, the study population is not necessarily comparable with ours. Kuswanto et al. (2014) reported increased FA in overweight subjects when compared to normal weight ones. The study population was Asian, and, thus, overweight was defined as a BMI falling between 23 and 25. The proportion of obese participants with a BMI over 25 was rather modest. In the present study, the number of obese participants was also small.

Verstynen et al. (2013) reported that systemic inflammation and glucose regulation were negatively associated with FA throughout the brain. They also reported that vascular factors such as elevated blood pressure, dyslipidaemia and insulin regulation systems are associated with increased FA. We did not adjust our analyses for these factors. In the present study, the participants were relatively young and the development of vascular diseases usually does not happen until a much later age (Jousilahti et al. 1999). Stanek et al. (2011) detected that increasing age was associated with lower FA and they also found an age and BMI interaction
effect on FA in the corpus callosum. They concluded that the longer duration of obesity or being obese at critical periods of brain development would have greater adverse consequences on the brain.

Our findings in the control group are in contrast with some of the published studies on this topic (Mueller et al. 2011, Stanek et al. 2011, Karlsson et al. 2013, Xu et al. 2013). The small number of overweight/obese participants, in the present study, and the difference in age of the study populations, may have contributed to the discrepancy of the findings.

10.4 Physical activity and fitness in individuals at risk for psychosis (III)

Our study looked at the physical activity level and cardiorespiratory fitness in individuals at risk for psychosis. We found that participants who later developed psychosis, were physically more inactive than their peers who did not develop psychosis. Those who reported several prodromal symptoms were physically less active than those who reported few or no symptoms. Poor fitness was not associated with vulnerability for psychosis. Our results of lower physical activity in the psychosis risk group corresponds to those of Deighton & Addington (2015) and Mittal et al (2013). Whereas our findings, indicating an association between prodromal symptoms and level of physical activity, were not replicated in these studies (Deighton & Addington 2015, Mittal et al. 2013).

UHR subjects reported lower perceived fitness than controls (Deighton & Addington 2015). In the present study, there was no association between fitness and vulnerability for psychosis. The strength of our study was that we were able to measure fitness objectively and, thus, the measures are probably more reliable than self-reported data.

In our study, those who reported several prodromal symptoms were physically less active than those who reported few or no symptoms. The nature of prodromal symptoms of psychosis such as anergia, reduced motivation and social withdrawal may decrease motivation and limit social interactions and could, thus, have an effect on taking part in physical activities. In our study, the number of prodromal symptoms was inversely associated with physical activity, supporting this idea. Our finding differs from results by Deighton & Addington (2015) and Mittal et al. (2013). In both of these studies SIPS was used to detect prodromal symptoms, while we used the PROD-screen questionnaire. In the present study, the number of the
participants was high, which is a strength of the study, and decreases the possibility of false negative error.

There are several possible factors that have an influence on decreased physical activity levels in individuals vulnerable to psychosis. Motor skills in childhood predict participation in physical activities in adolescence (Barnett et al. 2009). Neuromotor abnormalities and developmental delays have been shown in individuals who later develop psychotic illnesses. In the British 1946 Birth Cohort, pre-schizophrenic children were found to have delayed motor development (Jones et al. 1994). In the Northern Finland 1966 Birth Cohort, ages at which the children learned to stand, walk and become potty-trained were related to the subsequent risk for schizophrenia and other psychoses; earlier achievement of developmental milestones reduced the risk, whereas later achievement of these milestones increased it (Isohanni et al. 2001). In a birth cohort from New Zealand, children who later developed schizophreniform disorder had persistently poor motor function over repeated measurements in childhood (Cannon et al. 2002).

In the general population, social factors and behavioural attributes are related to physical activity (Leslie et al. 1999). In a study of 185 subjects with severe mental illness, an association was found between a lack of social contacts and physical inactivity (Daumit et al. 2005). The nature of prodromal symptoms of psychosis, such as anergia, reduced motivation and social withdrawal, may decrease motivation and limit social interactions and could, thus, have an effect on taking part in physical activities. Finally, individuals with UHR for psychosis report more barriers to exercise than controls. The barriers are related to self-esteem and self-perception. They also report less positive reasons to exercise (Deighton & Addington 2015).

10.5 Strengths and limitations of the study

10.5.1 Strengths of the study

Our study has several strengths. The main strength of this study is the unique general population-based sample. The participants had similar demographic backgrounds and they were all young adults in their early twenties, the age at high risk for developing psychosis (Delisi 1992, Häfner et al. 1994). In our sample, the FR group was homogenous with respect to familial relationship to family member with psychosis, as all the participants were the offspring of the patients. In terms of
the psychosis data, the CRHC is found to be reliable (Perälä et al. 2007) as well as the Finnish Insurance Institute registers (Isohanni et al. 1997).

In Study III we were able to detect those individuals vulnerable to psychosis, who actually will develop psychosis. The participation rate to the postal inquiry and the fitness test was high. As far as we know, our study was the first examining the level of physical activity, and the association between BMI and WM microstructure in individuals at risk for psychosis, and, hence, these topics were novel.

Many studies have used a hypothesis-driven region-of-interest (ROI) approach. An important limitation of ROI studies is that they usually focus on one specific structure or only a few. We used the TBSS method to examine the WM in the whole brain level. For the analyses, we used TBSS, a method which does not need smoothing, and thus increases the sensitivity and interpretability of the results when compared to VBA (Smith et al. 2006).

10.5.2 Limitations of the study

There are also some limitations. The groups were heterogenic when considering gender. In all three studies, females were more prone to participate. There are gender differences in WM microstructure (Kanaan et al. 2014). In the TBSS analyses, we used gender as a covariate of no interest and also took gender into account in the physical activity and cardiorespiratory fitness analyses.

The FR group was heterogenic when considering the diagnosis of a parent. Although in Study I, we conducted a separate analysis for an FR for schizophrenia, only. Parental diagnoses were only register-based and parents did not take part in any clinical examinations or interviews.

In Study III, the number of participants who later developed psychosis was small. The participation rate was low in Studies I and II, increasing the possibility of selection bias and limiting the generalisability of the study results. This applies especially to the subgroup of subjects who had a parent with schizophrenia, which is why the further analyses with the subgroups may not be conclusive (Study I). However, attrition analyses showed that there was no difference in participants and non-participants when considering hospitalisation due to the psychiatric disorder or the parental diagnosis (schizophrenia vs other psychosis).

In Study I, the negative result in our group comparison may reflect a relative lack of power, because of data variance and a limited study sample, the effect of group difference is easily lost after correction for multiple comparisons. To confirm
the results, we further analysed the data with a higher FA skeleton threshold. This was done to limit the data studied to the tracts with minimum inter-subject variability and the least partial-volume-effect. The method also alleviates the problem of multiple comparisons by reducing the studied volume, thus amplifying the group differences found at these locations. Finally, a ROI analysis of the 12 tract volumes was conducted in order to reveal the effect of these interesting tracts on the group comparison, in the presence of a limited voxel number. The imaging protocol was not optimal for detecting small differences between groups. The slices were relatively thick (3.0 mm) and at the time, an MRI with 1.5 T magnetic field was used instead of a more accurate 3.0 T field. This may have caused a type II error, in the results.

FA is known to be sensitive to WM changes at the micro level, but it is not specific to the pathology of WM. One needs to be cautious when interpreting the results. There might be several reasons behind the changes in different parameters, for example, in nonisotropic voxels, FA may be influenced by crossing fibres, resulting in FA values that are too low (Oouchi et al. 2007).

The results are partly based on self-reported data (weight, height, physical activity level, prodromal symptoms) and are more prone to measurement errors than objective measurements. Social desirability bias can lead to over-reporting of physical activity (Sallis and Saelens, 2000) and overestimation of height and underestimation of weight (Connor Gorber et al. 2007). This might be problematic when groups are categorised. We used BMI as a continuous variable. In Study II, BMI was varied greatly, between 17.30 and 47.83, however, the results were essentially the same when extreme outliers were excluded. The PROD-screen questionnaire is not ideal for screening subjects with a high risk of developing psychosis, in general population (Study III). The questionnaire has been developed to be used, in clinical settings, to evaluate how prone an individual is to psychosis (Heinimaa et al. 2003, Kline et al. 2014).
11 Conclusion

11.1 Main conclusions

In this study, individuals vulnerable for psychosis in a unique birth-cohort setting, were examined. Participants were in their early adulthood, at the age of high risk for developing schizophrenia. Contrary to our hypothesis and earlier studies, we did not find differences in WM structure between individuals with an FR of psychosis and the controls. Our results suggest that WM abnormalities may not be a genetic feature of risk for psychosis, in all populations. However, our study suggested that the association between BMI and WM is different between the FR and the control groups. It is possible that there are genetic factors associated with metabolism and, which are responsible for psychosis, that may mediate this effect and, therefore, result in a difference between individuals with an FR for psychosis and those with no FR. It also became evident that adolescents who later develop psychosis are physically less active than their age mates and that those who reported several prodromal symptoms were physically less active than those who reported few or no symptoms. Low levels of physical activity in people with serious mental illness are not necessarily the consequence of the illness itself, but may reflect the general lifestyle of subjects at risk for psychosis.

11.2 Clinical and future implications of the study

Recognition of individuals at highest risk for psychosis and early intervention could prevent or delay the onset of the illness. Recognition of these people is challenging and no definitive biomarkers are yet available. A major ambition of neuroimaging studies, in individuals at risk for psychosis, has been to identify early neuronal signs of psychosis risk. Our study suggests that WM integrity is not the first sign of vulnerability to psychosis in all populations, and cannot be used as a biomarker to identify young people at highest risk of developing psychosis. Together with the grey matter findings from the same NFBC 1986 participants (Jukuri et al. 2013, 2015a, 2015b, Roman-Urrestarazu et al. 2014, Pulkkinen et al. 2015), this suggest that instead of abnormal WM integrity, abnormal grey matter networks might provide the early signs of psychosis risk. There are many studies on WM microstructure in FR for psychosis, most of them cross-sectional, which is why longitudinal studies are needed. In longitudinal
studies, the timing of WM abnormalities could be better understood. Also future studies with large samples and standardised methods, would be important. The variety of methods may explain the disparity in DTI findings.

To the best of our knowledge, this was the first study to explore the association between BMI and WM microstructure in individuals at risk for psychosis. The alterations in FA through radial diffusivity suggest a myelin pathology. The association between BMI and WM was different between the FR and the control groups. This is important as people with psychosis tend to gain weight, which is a risk factor for several somatic illnesses. Literature in this area is relatively non-existent and, therefore, these results warrant further investigation in order to explain the observed differences in the relationship between weight, WM microstructure and FR for psychosis. Future studies with bigger sample sizes are needed to repeat and expand upon these findings. It would be interesting to study how other metabolic factors, such as blood glucose levels, and exercise and genetic liability for psychosis interact in the brain. It would also be important to study WM microstructure in obese people at risk of developing psychosis.

The finding that individuals who later develop psychosis, had lower physical activity levels before the illness onset is important, as the point of view of prevention of somatic illnesses is associated with a sedentary lifestyle. In addition to the positive effects of physical activities on somatic health, regular exercise also often maintains good mental health. A recently published meta-analysis shows that exercise in patients with schizophrenia spectrum disorders has beneficial effects on clinical symptoms, global functioning, depressive symptoms, and quality of life (Dauwan et al. 2016). Physical training has also shown to improve WM integrity, both in schizophrenia patients and healthy controls (Svatkova et al. 2015). Early intervention to encourage people to participate in physical activities in the early stages of illness would be important to prevent detrimental health effects of a sedentary lifestyle. In addition, physical activity may also play an important role as a low-risk and cost-effective therapy for mental health problems.

According to previous findings from the Northern Finland 1986 Birth cohort (NFBC 1986), physical inactivity in adolescents was associated with several emotional and behavioural problems (Kantomaa et al. 2008). In the future, longitudinal studies are needed. In longitudinal studies, the possible causal relationship could be better understood, i.e., does prodromal symptoms cause reduced physical activity or vice versa.
References


## Appendix

Table 6. Number of significant voxels by white matter atlas; interaction between body mass index and familial risk for psychosis on fractional anisotropy, radial diffusivity and mean diffusivity.

<table>
<thead>
<tr>
<th>Tract</th>
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<th>RD (Number of voxels)</th>
<th>MD (Number of voxels)</th>
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<td></td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fontine crossing tract</td>
<td></td>
<td></td>
<td></td>
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<td>703</td>
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<td></td>
</tr>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
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Table 7. Number of significant voxels by white matter atlas; negative association between body mass index and fractional anisotropy and positive association between body mass index and radial diffusivity in familial risk group.

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<tr>
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<td></td>
</tr>
<tr>
<td>Pontine crossing tract</td>
<td></td>
<td></td>
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<td>Splenium of corpus callosum</td>
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98
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JHU white-matter tractography 1 mm

| Forceps major                               | 718                    |
| Forceps minor                               | 603                    |

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Probabilistic Harvard-Oxford subcortical structural 1 mm

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Table 8. Number of significant voxels by white matter atlas; positive association between body mass index and fractional anisotropy and negative association between body mass index and radial diffusivity in control group.

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<td>(Number of voxels)</td>
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<tr>
<td>ICBM-DTI-81 white-matter labels 1 mm</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Pontine crossing tract</td>
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<tr>
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<tr>
<td>Corticospinal tract</td>
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<td>Medial lemniscus</td>
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<td>Retrolenticular part of internal capsule</td>
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<td>Cingulum (hippocampus)</td>
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<td>Fornix (caudatus/stria terminalis)</td>
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<td>Superior longitudinal fasciculus</td>
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<td>Tract</td>
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<tr>
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<td>Forceps major</td>
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Original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals I–III:


The original papers have been reprinted with the permission from Elsevier (I, III).

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1361. Hannila, Ilkka (2016) T2 relaxation of articular cartilage: normal variation, repeatability and detection of patellar cartilage lesions

1362. Pihlaja, Juha (2016) Treatment outcome of zirconia single crowns and fixed dental prostheses


1365. Aro, Jani (2016) Novel load-inducible factors in cardiac hypertrophy

1366. Myllymäki, Mikko (2016) Hypoxia-inducible factor prolyl 4-hydroxylase-2 in Tibetan high-altitude adaptation, extramedullary erythropoiesis and skeletal muscle ischemia


1368. Krökki, Olga (2016) Multiple sclerosis in Northern Finland: epidemiological characteristics and comorbidities

1369. Mosorin, Matti-Aleksi (2016) Prognostic impact of preoperative and postoperative critical conditions on the outcome of coronary artery bypass surgery


1372. Hekkala, Anne (2016) Ketoacidosis at diagnosis of type 1 diabetes in children under 15 years of age


1375. Lehtonen, Ville (2016) Dental and otologic problems in cleft lip and palate patients from Northern Finland: Cleft associated problems

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BRAIN WHITE MATTER STRUCTURE, BODY MASS INDEX AND PHYSICAL ACTIVITY IN INDIVIDUALS AT RISK FOR PSYCHOSIS

THE NORTHERN FINLAND BIRTH COHORT 1986 STUDY