White matter alterations in first episode psychosis: A one-year follow-up comparison of schizophrenia and other psychotic disorders

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Valkean aineen muutokset ensipsykoosissa: Skitsofreniapotilaiden pitkittäisvertailu muihin psykoosipotilaisiin vuoden aikana

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Contents

ITÄ-SUOMEN YLIOPISTO

Tiedekunta Filosofinen tiedekunta	**Osasto** Psykologian osasto

Tekijät
Ilja Solovjew

Työn nimi
Valkean aineen muutokset ensipsykoosissa: Skitsofreniapotilaiden pitkittäisvertailu muihin psykoosipotilaisiin vuoden aikana

Pääaine	**Työn laji**		**Päivämäärä**	**Sivumäärä**
Psykologia	Pro gradu -tutkielma	**X**	**9.1.2020**	**44**
	Sivuainetutkielma			
	Kandidaatin tutkielma			
	Aineopintojen tutkielma			

Tiivistelmä

Aikaisempi diffuusiotensorikuvantamistutkimus on osoittanut skitsofrenian liittyvän vahvasti valkeassa aineessa tapahtuvaan fraktionaalisen anisotropian (FA) laskuun, verrattuna terveisiin verrokeihin. FA:n muutoksia skitsofreniassa verrattuna muihin ensipsykoosipotilaisiin ei ole vielä kattavasti tutkittu. Myös skitsofrenian FA-muutosten potentiaalinen progressiivisuus on laajan väittelyn alla. Tutkimuksessa vertailtiin skitsofreniapotilaiden sekä muiden psykoosia sairastavien potilaiden FA:n etenemistä kahdella poikittaismittauksella sairauden puhjettua ja vuoden jälkeen. Kaikki potilaat sairastivat lähtötilanteessa ensipsykoosia. Antipsykoottisen lääkityksen mahdollista vaikutusta FA-muutoksiin tutkittiin korrelaatioanalyysillä. Ensimmäisessä mittauksessa potilasryhmien välillä ei löytynyt merkitseviä FA-eroja. Vuoden jälkeen skitsofreniaryhmän FA oli merkitsevästi alhaisempi, mm. alueilla: anteriorinen corona radiata, aivokurkiasen frontaaliosa ja capsule interna. Merkitsevästi eronneet alueet eivät korreloineet lääkitysmuuttujien kanssa. Tulokset tukevat hypoteesia, jonka mukaan skitsofreniaan vakavampana psykoosisairautena voi liittyä muihin psykooseihin verrattuna erilainen, mahdollisesti progressiivisesti huononeva, sairaudenkulku.

Avainsanat
Skitsofrenia, ensipsykoosi, diffuusiotensorikuvantaminen, seuranta, valkea aine, progressio

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Abstract

Comprehensive evidence from diffusion tensor imaging (DTI) studies has shown schizophrenia to associate with white matter (WM) fractional anisotropy (FA) decreases, when compared against healthy controls. Whether the WM FA changes in schizophrenia follow a different trajectory when compared with other patients with first episode psychosis (FEP) has not been well studied. The potential progression of WM abnormalities in schizophrenia after illness onset also remains as a subject of heavy debate. We compared schizophrenia patients against patients with other psychotic disorders, in 1-year follow-up cross-sectional setting. The potential effect of antipsychotic medication on FA was studied with correlational analysis. The between group FA was not significant at baseline, but at 1-year follow-up schizophrenia patients showed significantly lower FA. The FA -values from regions that differed between groups did not correlate with antipsychotic medication. The results also indicated a decreasing trend in schizophrenia patients FA in multiple regions such as right anterior corona radiata, genu of corpus callosum and anterior limb of internal capsule. Our results imply that schizophrenia, as a diagnosis of more severe degree may follow a different, potentially progressing, course in comparison to other psychotic disorders.

Keywords
Schizophrenia, DTI, FA, white matter, follow-up, FES, FEP, progression

1. Schizophrenia as a disorder

Schizophrenia is a severe mental disorder that causes serious impairment in one's perception of reality. The symptoms of schizophrenia vary significantly between individuals, but commonly include delusions, distorted thinking, hallucinations, abnormal social behavior, disturbances of emotion and loss of motivation (American Psychiatric Association [APA], 2013), although cognitive deficits are also often mentioned as an essential feature of the illness (National institute of mental health, 2018). Schizophrenia is estimated to affect 23 million people globally (Millier & al. 2014). In comparison to the general population, people who have schizophrenia are 2-3 times more likely to die early (World Health Organization, 2018). The direct total health care expenditures of schizophrenia treatment in Western countries have been estimated to vary from 1,6 % to 2,6 % (Chong et al, 2016). In 2013 schizophrenia was ranked as one of the top 25 foremost causes of disability in the world (Vos et al. 2015). As schizophrenia is a considerable burden to the patient, family and society, identifying the causes of the disease is crucial. However, the history of scientific research on schizophrenia demonstrates that understanding the etiology of the disorder has proven to be remarkably challenging, concerning the biological markers and the diagnostic conceptualization. Although progress has been made, schizophrenia remains elusive to the scientific community.

2. Historical perspectives

Descriptions of symptoms resembling schizophrenia have been found in texts as old as the ancient Egyptian era (Okasha & Okasha, 2000). As a distinct mental disorder schizophrenia was first defined in the 19th century by the German psychiatrist Emil Kraepelin. Kraepelin's most considerable influence on Western psychiatry was his classification of psychotic disorders, known as the Kraepelinian dichotomy. It consisted of two diagnostic categories, manic depression and dementia praecox, of which the latter was used by Kraepelin to describe schizophrenia in 1899 (as cited in Hoff, 2015). The term schizophrenia was coined later by Swiss clinician Eugen Bleuler in 1911 (Stotz-Ingenlath, 2000). The concept originates from the Greek words "schizein" and "phren", roughly translating to "the splitting of the mind" (Fusar-Poli & Politi, 2008). This idea was central in his conceptualization of the disorder, as Bleuler's view of the psychological problems of schizophrenia patients was that the associations between fundamental mental domains had been loosened or disintegrated (Peralta & Cuesta, 2011).

Whereas Kraepelin viewed schizophrenia as a progressing degenerative disease that causes cognitive deterioration and is not curable, like the neurodegenerative dementia discovered by Alois Alzheimer (as cited in Falkai et al. 2015), Bleuler did not agree with this assumption but rather emphasized the possibility of different outcomes and recovery. Although Bleuler's and Kraepelin's views were contrasting, they agreed schizophrenia to have a neural basis (Heckers, 2011), after having both observed behavioral and neurological deviances in the childhood histories of their patients (Gupta & Kulhara, 2010). Similar observation shared by many other researchers after them (e.g. Bender, 1947; Watt, 1978; Weinberger, 1987), led to the neurodevelopmental hypothesis of schizophrenia, as many potential signs, such as social disengagement, emotional instability and passive behavior, could be seen in preschizophrenic children.

With the development of neuroimaging technology, a new door to schizophrenia research was opened. The possibility of non-invasive study of the brain in vivo has led to the current consensus, that schizophrenia is indeed a brain related disorder (APA, 2013). Brain imaging as well as genetic, histological and behavioral studies have increased our knowledge of schizophrenia tremendously. However, the accumulating evidence has been pointing to several incongruous directions in the effort to understand the etiology of schizophrenia (Gupta et al. 2010; Lewis & Levitt, 2002; Rapoport, Giedd & Gogtay, 2012; Zipursky, Reilly & Murray, 2012). The Kraepelinian view of schizophrenia as a progressing disease and the neurodevelopmental hypothesis, are still the two main competing theories on the etiology of the disorder. Both have been fueled by positive and negative findings, and there has also been a proposition of combining the two frameworks (de Haan & Bakker, 2004; Gupta & Kulhara, 2010). Neurodevelopmental hypothesis in its present form proposes that schizophrenia is resulting from abnormal neural developmental processes, that are associated to various insults and possibly beginning as early as first or second trimester. Later, usually triggered by psychological and biological stress, the activation of the pathologic neural circuits leads to the outbreak of schizophrenia symptoms most often in the adolescence or young adulthood (Fatemi & Folsom, 2009).

Evidence of abnormal brain development in schizophrenia studies comes from various sources and is related to prenatal, perinatal and childhood related insults and factors such as prenatal infection (Brown & Derkits, 2010), obstetrical complications and delayed development in motor behavior (Clarke et al. 2011), premorbid cognitive deficits in childhood (Reichenberg et al. 2010), delayed motor development (Filatova et al. 2017), risk genes related to the brain development (Gejman,

Sanders & Duan, 2010), disruption of cortical synaptic pruning processes (Boksa, 2012) and various sorts of slight physical anomalies (Weinberg, Jenkins, Marazita & Maher, 2007). According to a popular developmental model, the “two-hit” hypothesis, these pre- or perinatal events produce a so-called vulnerability to the “second hit” — that is induced by an environmental or epigenetic event in the adolescence stage, then leading to the outbreak of psychosis (Maynard, Sikich, Lieberman & LaMantia, 2001). Such a model, though, has been proposed as too simplifying, as the outbreak of schizophrenia is likely preceded by more complicated risk factor processes (Davis et al. 2016).

Neurodevelopmental theories however fail to adequately address the progression of brain abnormalities observed in many studies. One of the earliest findings to support the neurodegeneration hypothesis has been the progressive enlargement of brain ventricles, a set of interconnected cavities that produce cerebrospinal fluid, occurring over time after illness onset (DeLisi, 2008; Kemali, Maj, Galderisi, Milici & Salvati, 1989; Kempton, Stahl, Williams & DeLisi, 2010). Frequently reported observation, albeit inconsistently in terms of specific brain regions, in longitudinal studies has also been a decrease in brain volume, in both gray and white matter (WM) (DeLisi, 2008; Olabi, Ellison-Wright, McIntosh, Wood, Bullmore & Lawrie, 2011). Recently, more attention has been drawn to the WM abnormalities with the advent of diffusion tensor imaging (DTI). Evidence of WM related progression produced by DTI studies will be discussed in more detail below.

Nevertheless, the neurodegenerative theory of schizophrenia is also associated with some shortcomings. Albeit schizophrenia can have a very debilitating course, many patients show clinical improvement. According to many follow-up studies, 21–57% of schizophrenia patients show a good long-term outcome after treatment (Jobe & Harrow, 2005). Although some longitudinal studies have reported decline in the cognitive functioning of schizophrenia patients after the onset of illness (Fujino et al. 2017; Seidman, Buka Goldstein & Tsuang, 2006), many other studies have found this course to remain stable or improve (Lewandowski, Cohen & Ongur, 2011; Szöke, Trandafir, Dupont, Méary, Schürhoff & Leboyer, 2008). It is also well established that schizophrenia patients exhibit a lower premorbid IQ in comparison to healthy subjects (Woodberry, Giuliano & Seidman, 2008), which indicates a deficit of developmental origin. Another point of criticism arises from post mortem studies, which have been unable to find sufficiently significant gliosis — a reactive change of glial cells, which is held as a central feature of

neurodegenerative diseases (Gupta et al. 2010; Schnieder & Dwork, 2011; Roberts, Colter, Lofthouse, Johnstone & Crow, 1987).

Some researchers have proposed the "neurodevelopmental versus neurodegenerative" -dichotomy to be rather arbitrary (Gupta et al. 2010; Andreasen, 2010; Nour & Howes, 2015). Described as a neurodegenerative disorder, schizophrenia does not seem to fit the category of classic neurodegenerative disorders such as Alzheimer's disease, because of its early developmental features. Also, the view of schizophrenia as the end state of abnormal developmental trajectory does not take the potential progression of brain abnormalities into account. Instead, Andreasen (2010) proposes that in light of the current evidence schizophrenia is best understood as a developmental disorder that involves continuing changes after the illness onset, possibly affecting the whole lifetime trajectory. In Andreasen's view, *neuroprogression* might be a more accurate term to describe schizophrenia than *neurodegeneration*.

3. Dysconnection hypothesis

The history of schizophrenia research is indeed largely characterized by inconsistencies. In 1972 neurologist Fredrick Plum famously stated schizophrenia to be the "graveyard of neuropathology" (as cited in Coyle, Balu, Puhl & Konopaske, 2016). However, Bleuler's view of the "loosening of associations" or "disintegration of the psyche" as a consequence of abnormal neural functioning, is underlying the dysconnection hypothesis (Friston, Brown, Siemerkus & Stephan, 2016; Friston & Frith, 1995; Weinberger, 1993; Stephan, Friston & Frith, 2009), perhaps the most central theory of the neuropathology of psychosis today. According to the dysconnection hypothesis, the symptoms of schizophrenia are generated by the abnormal neuromodulatory functioning of synapses. This impaired synaptic efficacy can be detected in many levels, including dendritic and myelination related changes. The key assumption is that instead of being caused by regionally specific neuronal deficits, the problem lies in the abnormal connectivity of the different parts of brain (Friston et al. 2016). Although today schizophrenia is without a doubt considered to be a disorder where the wiring of the brain is aberrant, the cause of this dysconnectivity is yet unknown. The evidence for dysconnectivity hypothesis comes from a broad range of methodologies, but this paper will be focusing mainly on WM related abnormalities in schizophrenia.

4. Diffusion tensor imaging

Diffusion tensor imaging (DTI) is an advanced MRI technique employed to study microstructural changes of tissue properties and connectivity extensively in the WM of the brain. DTI was introduced to the brain imaging repertoire in 1994 by Peter Basser (Basser, Mattiello & LeBihan, 1994a; Basser, Mattiello & LeBihan, 1994b), and since then has become increasingly popular in studying various diseases. Schizophrenia has been one of the first disorders DTI has been applied to (Xiang & al. 2018).

DTI utilizes MRI sequences to map the diffusion of mainly water molecules in the nervous system. The diffusion of molecules refers to the Brownian motion (thermally induced random motion of molecules). This movement does not occur freely in the tissue but depends on the microenvironmental architecture where the diffusion occurs. For example, in the cerebrospinal fluid, where cell membranes do not restrict the diffusion, molecules are able to move more freely. This type of diffusion, where the mobility of molecules is equally free in all directions, is called isotropic diffusion, and is represented by a 3-dimensional sphere. In the WM tissue, diffusion occurs more freely along the direction of the tubular structures consisting of axonal fibers. This type of directional diffusion is strongly associated to the fiber structure of the WM (Beaulieu, 2002). This directionally oriented diffusion is called anisotropic diffusion, and it is modelled as a "cigar-shaped" 3-dimensional ellipsoid if one direction is dominating, and with a flat "pancake-shaped" ellipsoid if one direction is not contributing as much as others (LeBihan & Johansen-Berg, 2012; O'Donnell & Westin, 2011). These shapes, called diffusion tensors, are modelled in each voxel (a 3D equivalent of a pixel) as a 3 x 3 matrix with 6 defining values. In addition to axonal structure, other factors such as macromolecules, cell membranes and the myelination of axons contribute to further restrict the free diffusion of molecules (Song, Sun, Ramsbottom, Chang, Russell & Cross, 2002).

Diffusion is measured with MRI by using magnetic field gradients that create an image sensitive to the direction of diffusion. By adding extra gradient pulses, first gradient causes protons in molecules to attain phase shifts, that are then cancelled for stationary molecules by a second, rephasing gradient. For freely diffusing molecules, this causes a random phase shift, due to which signal from them is lost. These voxels appear dark on the diffusion-weighted images. In voxels in which the diffusion is restricted, the signal intensity is higher, and the voxels appear lighter on

diffusion-weighted images. The diffusion weighted sequence is repeated multiple times for different directions, so that the 3D tensor can be estimated. For calculating a diffusion tensor, minimum of 7 such measurements is required (O'Donnell & Westin, 2010).

There are several different scalars to represent diffusivity, but the most often used diffusion scalar is fractional anisotropy (FA) (LeBihan & Johansen-Berg, 2012). FA is calculated from the tensor eigenvalues, and it is generally considered to reflect microstructural integrity of the WM tissue. Although it is quite sensitive to changes of WM and many pathological conditions, defining the type of change often requires the use of other DTI measures as well (Alexander, Lee, Lazar & Field, 2007; Alexander et al. 2011). The value of FA can range from 0 that indicates maximal isotropy to 1 that indicates maximal anisotropy. FA results from multiple factors, including fiber orientation, axonal density and myelin sheath integrity (Bealieu, 2002; Tournier, Mori & Leemans, 2011). FA reductions are generally considered as a marker of myelin related aberrations or axonal disturbances but can also be associated to other factors, such as axon formation (Klauser & al. 2017; Mori & Leemans, 2011). Another commonly used DTI measure, recommended to be included in analyses, is mean diffusivity (MD). MD is calculated as an average of the tensor eigenvalues, and it gives an inverse measure of the membrane density (Alexander & al. 2011). MD has shown to be a sensitive marker to necrosis, cellularity and edema and it is often reported to show increases in schizophrenia patients (Clark et al. 2011).

5. Schizophrenia and white matter

As previously mentioned, research has demonstrated schizophrenia to be strongly associated with a variety of brain abnormalities. The dysconnectivity hypothesis has raised the WM-related abnormalities to a crucial role in schizophrenia research. Myelination is an important developmental process in the mammalian brain that begins prenatally and progresses into early adulthood. By forming lipid-rich multilamellar sheat structures around axons, which the WM is mainly composed of, myelin enables faster neuronal signal transmission with lower energy expenditure (Lindahl, Kjellsen, Tigert & Miskimins, 2008). Oligodendrocytes — glial cells that produce myelin sheaths for axons — as well as oligodendrocyte-related genes seem to be associated to the pathology of schizophrenia (Takahashi, Sakurai, Davis & Buxbaum, 2010). There have been observations of oligodendrocyte density reductions in both gray and white matter of prefrontal cortex in schizophrenia patients (Hof et al. 2003; Uranova, Vostrikov, Vikhreva, Zimina,

Kolomeets & Orlovskaya, 2007). Also, many oligodendrocyte- and myelin-related genes show altered expression in schizophrenia patients (Dracheva, Davis, Chin, Woo, Schmeidler & Haroutunian, 2006; Tkachev et al. 2003). The effects of oligodendrocyte alteration and demyelination have also been studied with animals: By feeding rats and mice cuprizone (a demyelination-inducing chemical agent) during particular developmental phases, consequences of demyelination associating to specific brain region can be examined (Herring & Konradi, 2011). Of significance to schizophrenia, these studies report that demyelination associating to prefrontal cortex causes schizophrenia-like symptoms, such as disturbance of attentional set switching (Birrell & Brown, 2000), spatial memory deficits (Xu, Yang, Clough, Browning, Zhang & Li, 2009) and other behavioral symptoms like social withdrawal (Hibbits, Pannu, Wu & Armstrong, 2009; Makinodan & al. 2009).

As currently maybe the most popular method to study WM alterations in humans, DTI has been widely employed to map out the possible patterns of the pathology in schizophrenia in recent years. Numerous DTI studies have compared first episode psychosis (FEP) schizophrenia patients or chronic patients with healthy controls. FEP studies have the advantage of patients not being yet predisposed to great amounts of antipsychotic medication, that might potentially contribute to WM abnormalities (Szeszko et al. 2014). Although wide spread FA decreases in schizophrenia patients compared with healthy individuals are frequently reported, results have often been heterogeneous in terms of significant regions; Specific areas showing FA alterations vary considerably between separate studies, and many studies have reported no significant differences between schizophrenia patients and healthy controls (Kubicki & al. 2005; Kyriakopoulos, Bargiotas, Barker & Frangou, 2008; Pettersson-Yeo, Allen, Benetti, McGuire & Mechelli, 2010; Wheeler & Voineskos, 2014). However, a recent meta-analysis of the ENIGMA Schizophrenia DTI Working Group (Kelly & al. 2017), so far the largest of its kind, consisting of 1936 schizophrenia patients and 2359 healthy controls identified 20 regions where schizophrenia patients had significantly decreased FA, compared with healthy controls. Albeit the effects were shown globally through the whole WM, some regions showed more pronounced decrease than others. The greatest effects were shown in the frontal part of corona radiata and corpus callosum, especially its body and genu. WM fibers connecting through corpus callosum allow for the communication between the two cerebral hemispheres. Corpus callosum, the largest WM structure, has been demonstrated to associate with verbal fluency and language lateralization (Hines, Chiu, McAdams, Bentler &

Lipcamon, 1992) and intelligence (Chiang & al. 2009). Corona radiata, consisting of fibers that radiate from the internal capsule to different parts of the cortex, are known to act as an essential structure for information processing, associating with intellectual performance (Chiang & al. 2009), delusions (Nakaaki & al, 2013), certain parts of attention (Stave, De Bellis, Hooper, Woolley, Chang & Chen, 2017) and motor function (Takenobu, Moriwaki, Nagatsuka, Naritomi & Fukuyama, 2013).

5.1 Progression of the white matter abnormalities

Longitudinal studies have established a connection between regionally and temporally specific gray matter loss and disease progression in schizophrenia (Vita, De Peri, Deste & Sacchetti, 2012). Furthermore, gray matter loss has also been indicated to associate with the neurodevelopmental features of the disorder, as for example in the 12-year longitudinal study by Ho, Andreasen, Dawson and Wassink (2007) they reported ongoing gray matter tissue loss in schizophrenia patients carrying a known neurodevelopmental gene, in comparison to schizophrenia patients with a different genotype grouping. In contrast, studies of WM progression have produced somewhat more inconclusive results. In their 1-year follow-up study, Ota, Obu, Sato, Mizukami & Asada (2009) reported decrease of FA in schizophrenia patients in anterior cingulate cortex, genu of corpus callosum and bilateral posterior superior temporal lobe, in comparison to healthy controls. Sun, Chen, Lee, Bezerianos, Collinson & Sim (2016) compared structural brain networks of schizophrenia patients and healthy controls in longitudinal study using DTI. In their 5-year study they reported progressive global disruption in schizophrenia patients brain networks that correlated with clinical symptoms. Accelerated WM volume decrease, particularly pronounced in the frontal lobe, has also been reported by volumetric longitudinal studies (Ho, Andreasen, Arndt, Magnotta, Flaum, 2003; Mitelman et al. 2009; Ota et al. 2009). In a volumetric study by Andreasen, Nopoulos, Magnotta, Pierson, Ziebell & Ho (2011) FEP patients with schizophrenia were followed up to 15 years and during the time decreases in multiple gray and WM areas of the patients were reported. Furthermore, they reported that only a subgroup of the patients suffered from more severe volume losses and that the losses were most pronounced at the early stage of the disorder. In addition to longitudinal studies FA changes associated to the progression of schizophrenia have been reported by many cross-sectional studies (Kochunov et al. 2013; Mori et al. 2007; Zhang et al. 2014). Some cross-sectional DTI studies have investigated the differences

between FEP and chronic schizophrenia patients as well as healthy controls, reporting most pronounced FA decrease in the chronic patients (Friedman et al. 2008; Kong et al. 2011).

However, many DTI studies, although reporting FA alterations in schizophrenia patients, have not found signs of progression (Kanaan, Picchioni, McDonald, Shergill & McGuire, 2017; Kelly et al. 2017; Zeng et al. 2016). As one explanation, these inconsistencies between the results have been speculated to be due to neuroprogression affecting only a sub-group of all the schizophrenia patients (Andreasen et al. 2016). Further explaining why neuroprogression is occurring, researchers have proposed the possibility of accelerated aging, illness related neurotoxic effect, antipsychotic medication or that the studies reporting progression might have included patients with poorer prognosis (Karlsgodt, 2016). Along with the issue of whether the progression of brain abnormalities in schizophrenia truly is illness related or not, another source of obscurity is the incoherent distribution of the WM changes reported.

5.2 The potential influence of antipsychotics

A prominent question in neuroimaging studies, perhaps strongly associating to the progression and regional variation of FA change between studies, is to what extent antipsychotic treatment influences the changes that occur in the brain structure. In vivo studies of the effects of antipsychotics particularly on the WM are somewhat limited. Some research findings are suggesting that antipsychotic medication may promote myelination by affecting oligodendrocytes (Walterfang, Velakoulis, Whitford & Pantelis, 2011). Respectively, in a study by Chandran & al. (2012), cuprizone induced demyelination in mice was reduced when they simultaneously received treatment with quetiapine, an anti-psychotic drug. These findings were shown with both MRI and histological measures. However, research has found evidence of antipsychotic treatment associating with a subtle decrease in both gray and WM volume in schizophrenia patients (Ho, Andreasen, Ziebell, Ronald, Pierson & Magnotta, 2011). As for DTI studies, Szeszko et al. (2014) have reported less FA reductions in parieto-occipital WM in schizophrenia patients after 12 weeks of antipsychotic treatment. In contrast, in many other DTI studies it is generally reported that there is no association between changes in FA scalars and antipsychotic treatment (Caprihan et al. 2015; Wang et al. 2013), including a recent meta-analysis (Kelly et al. 2017). In their review Kyriakopoulos et al. (2011) concluded that a degenerative effect of antipsychotic medication is possible but a rather minor one, as 32 of 40 cross-sectional studies reported no relationship

between antipsychotics and FA or MD indices. However, large-scale longitudinal studies are needed to further clarify whether antipsychotics have an effect on WM microstructure on a longer period, and to what extent.

6. Schizophrenia and other psychotic disorders

In most studies, schizophrenia has been compared with healthy controls. In some recent studies however, FA abnormalities in schizophrenia have also been compared with other psychotic disorders, such as schizophreniform disorder (Xiang et al. 2018), as well as bipolar disorder (Dong et al. 2017; Li et al. 2014; O'Donoghue, Holleran, Cannon & McDonald, 2017; Squarcina et al. 2017; Tønnesen et al. 2018), and also with closely related schizotypal personality disorder (Lener et al. 2015), reporting both overlapping and differences in WM changes between the disorders. Kochunov et al. (2013) analysed the diagnosis-by-age interaction in a group consisting of schizophrenia patients and healthy controls and in a group consisting of patients with major depressive disorder and healthy controls, reporting significantly accelerated age-related decline in FA only in schizophrenia group in comparison to controls. Furthermore, gray matter abnormalities have been compared between schizophrenia, schizoaffective and bipolar disorder, reporting volume reductions in overlapping regions in schizoaffective disorder and schizophrenia, but not in bipolar disorder (Amann et al. 2016). Notably many studies have included schizophrenia and schizoaffective disorder in the same diagnostic category (e.g. Antonius et al. 2011; Ardekani et al. 2003; Yao et al. 2013).

In general, non-schizophrenic psychotic disorders have not been considered as neuroprogressive disorders. However, in recent years, researchers have found evidence of bipolar disorder involving possible neurodegenerative processes. Volumetric reductions in gray matter associating with illness duration have been reported (Frey et al. 2008; Hallahan et al. 2010; Moorhead et al. 2007). Wollenhaupt-Aquiar et al. (2016) also found the bipolar patients' blood serum, especially in the late stage of the illness, to have a reducing effect on the neurite (that is, an axon or a dendrite) density and viability of neurons, when compared to healthy controls. In the field of DTI, studies have frequently reported FA decrease in bipolar patients when compared with healthy controls (Favre et al. 2019; Li et al. 2014). Studies that compared patients with schizophrenia and bipolar have found similar FA decreases between the disorders in frontal areas and corpus callosum for instance (Li et al. 2014; O'Donoghue et al. 2017). However, schizophrenia patients have often been

reported to either show trend level or significantly more pronounced FA decrease in comparison to patients with bipolar disorder (Anderson et al. 2013; Li et al. 2014; Mamah, Ji, Rutlin & Shimony, 2019; Sui et al. 2011; Tønnesen et al. 2018). Although schizophrenia and bipolar disorder with psychotic features have both been implicated as disconnection syndromes (Ji et al. 2019), progression of WM abnormalities has currently been held as a trait associating with schizophrenia (O'Donoghue et al. 2017). However, to this date DTI research about longitudinal WM changes in bipolar disorder has not been comprehensively conducted.

Since Kraepelin's formulation of psychosis as two distinct categories, dementia praecox and manic depression, there has been much debate about the classification of psychotic disorders. Traditional dichotomy has been challenged by many researchers. According to a study by Gandal et al. (2018), schizophrenia, bipolar disorder and autism all share specific gene expression patterns that are associated to astroglial activity and interference of synaptic processes. In addition to genetic load, environmental risk factors such as urbanicity, trauma and cannabis use also moderate the occurrence of symptoms shared by a variety of psychotic disorders. Based on symptomatic and biological overlap of psychotic disorders, Keshavan et al. (2011) have proposed a dimensional schizo-bipolar scale, for a novel classification of psychotic disorders, with schizophrenia on one end of the spectrum, bipolar disorder on the other and schizoaffective disorder in the middle. Further supporting the unitary spectrum model of psychosis, van Os and Guloksuz (2017) have suggested a possibility of bipolar disorder and schizophrenia stemming from a shared etiology, albeit having different expressions and outcomes depending on environmental and developmental factors. The question of the nosology of psychotic disorders indeed remains elusive. Whether schizophrenia and other psychoses share a similar trajectory in terms of WM pathology is a question this study aims to shed more light on.

7. Hypotheses

To further clarify whether WM changes in schizophrenia follow a different trajectory as other psychotic conditions, we compared schizophrenia patients with patients diagnosed with other psychotic disorders. In this study the group consisting of participants diagnosed with schizophrenia is called FES group (first episode schizophrenia) and the group consisting of participants diagnosed with other forms of psychotic disorder is called FEP group (first episode psychosis). Along the

results of several previous DTI studies, we predict that FES group will show decreases in FA in the 1-year follow-up measurement, as a sign of progressive worsening.

8. Materials and methods

8.1 Participants and clinical assessment

The data collection for the current study started in 2010. Patients were recruited from the Helsinki University's hospitals and outpatient clinics, after the patients' first contact with psychiatric care due to symptoms of psychosis. All patients included had their first episode of psychosis (FEP) and they were aged between 18 and 40. Psychosis was defined with the Brief Psychiatric Rating Scale Extended (BPRS-E) as having a score of 4 or more in the items assessing hallucinations or unusual thought content. Diagnostic interviews were conducted according to the Research Version of the Structured Clinical Interview for DSM-IV Disorders – Axis-I (SCID-I) by a psychologist or a research nurse. Diagnoses were made by a senior psychiatrist together with the interviewer. Medical records were used as a part of the diagnostic assessment. Clinical assessment was performed at baseline, 2-months and 1-year. For analysing the potential effect of antipsychotic medication on WM, medication dosage was expressed in equivalent doses of chlorpromazine (CPZ), calculated according to the method proposed by Leucht, Samara, Heres and Davis (2016). CPZ equivalent doses were calculated according to the current antipsychotic dosage of patients at baseline, 2 months and 1-year. Additionally, all CPZ equivalent values were summed together (CPZ-EQ sum), to estimate the effect of total antipsychotic medication. Clinical characteristics and the methods used in their assessment are shown in Table 1.

Participants included in this study (n=44) were split into two groups, participants diagnosed with schizophrenia (n=18) and participants diagnosed with other form of psychotic disorder (n=26). The latter diagnostic group consisted of participants with the following diagnoses: Psychotic disorder not otherwise specified (n=9), bipolar disorder (n=5), schizophreniform disorder (n=5), brief psychotic disorder (n=2), major depressive disorder with psychotic features (n=2), schizoaffective disorder with psychotic features (n=2) and obsessive compulsive disorder with psychotic features (n=1). Patients with previous psychotic episodes, substance-induced psychotic disorders and neurological disorders were excluded.

Group differences in clinical characteristic variables were tested with SPSS 25, using independent samples t-test, Mann Whitney U test or chi-square test depending on the variable type and their distribution. Difference in the baseline and follow-up scanning times were tested by subtracting the baseline age from the follow-up age and testing the mean difference of the variable with Mann Whitney U test.

Table 1 *Demographic and clinical characteristics of the sample including FES patients (n=18) and FEP patients (n=26).*

	FES patients n (%) or median and (interquartile range)	*FEP patients n (%) or median and (interquartile range)*	*Test statistic*	*P-value*
Age at BL	24.59 (4.8)	24.00 (7.16)	t = -5.43	0.590
Age at FU	25.64 (4.76)	25.08 (7.13)	U = 215	0.650
Sex (Female)	7/18 (38.90%)	10/26 (38.50%)	χ^2 = 0.84	0.772
GAF BL	33.50 (10.00)	40.00 (14.50)	U = 159	0.070
GAF FU	41.00 (20.00)	60.00 (22.25)	t = 3.30	**0.002**
BPRS BL Positive Symptoms	11.50 (5.00)	12.00 (3.50)	U = 207	0.655
BPRS FU Positive Symptoms	6.50 (5.00)	3.00 (6.75)	U = 146	**0.034**
BAI BL	10.00 (18.00)	13.00 (16.00)	U = 169	0.928
BAI FU	3.00 (3.50)	5.00 (16.25)	U = 91	0.565
BDI BL	10.00 (12.00)	7.00 (14.00)	U = 165	0.822
BDI FU	3.00 (11.00)	5.00 (15.00)	U = 73	0.332
OCI-R BL	14.00 (13.00)	14.00 (14.00)	t = 0.01	0.996
OCI-R FU	4.00 (8.00)	6.00 (10.50)	U = 89	0.508
Negative Symptoms BL	7.50 (3.50)	3.00 (4.25)	t = -4.71	**0.000**
Negative Symptoms FU	6.00 (7.75)	2.00 (4.00)	U = 116	**0.004**
CPZ-EQ BL	298.89 (228.75)	240.00 (335.63)	t = 0.75	0.940
CPZ-EQ 2 Months	300.00 (163.29)	198.41 (431.25)	t = 1.73	0.864
CPZ-EQ FU	300.00 (262.50)	150.00 (300)	U = 144	**0.030**
CPZ-EQ Sum	810.00 (475.00)	600.00 (968.13)	t = -0.63	0.532

Abbreviations: FES, first episode schizophrenia; FEP, first episode psychosis; FU, follow up; BL, baseline; GAF, global assessment of functioning; BPRS Positive symptoms, composite score of brief psychiatric rating scale items 10 (hallucinations), 11 (unusual thought content), 12 (bizarre behavior) and 15 (conceptual disorganisation)—before summing, the items were rescaled from 1—7 to 0—6, so that absence of symptoms would be 0; BAI, Beck anxiety inventory; BDI, Beck depression inventory; OCI-R, the obsessive-compulsive inventory; Negative symptoms, composite score of BPRS item 16 (blunted affect) and SANS (scale for the assessment of negative symptoms); CPZ-EQ, (Chlorpromazine equivalent dose of medication); CPZ Dose Equivalent Sum, all antipsychotic doses combined (BL + 2 Months + FU).

8.2 Image acquisition

DTI and T1-weighted image collection was done with a Siemens Skyra 3-T scanner (Siemens AG, Erlangen, Germany) with 32-channel head coil, at the AMI Centre of Aalto NeuroImaging, Aalto University. Image acquisition was done with two-dimensional spin-echo-planar-imaging-sequence. Diffusion sensitizing gradients (b = 1000 s/mm^2) were used to gather 64 non-collinear directions and 1 non-diffusion weighted image (b = 0 s/mm^2), in 58 axial slices without gaps. Voxel size was 1.88x1.88x3 mm. Repetition time (TR) of 9500 ms and echo time (TE) of 81 ms were used. T1-weighted images were collected using a magnetization-prepared rapid echo-sequence for 176 sagittal/192 transversal slices with voxel size of 1x1x1 mm. TR of 2530 ms and TE of 3.3–3.75 ms were used. Imaging was carried out at baseline and 1-year.

8.3 Preprocessing and analysis of DTI data

The preprocessing and statistical analysis of diffusion images were done using PANDA (Cui & al. 2013) pipeline tool for diffusion MRI (http://www.nitrc.org/projects/panda). Preprocessing involved resampling of the images, removing the skull, eddy-current correction, normalization and smoothing. To compare subjects, individual images need to be normalized into same space. This was done by registering individual FA images from their native space into the MNI-spaced standardized template and then calculating the diffusion metrics with the resulting warping transformations. As a default template PANDA uses FMRIB58_FA template, an average comprised of 58 high-quality FA images of males and females aged between 20 and 50. Images were normalized with 1-mm resolution, and images were smoothed using Gaussian kernel size of 6 mm to reduce registration error.

Whole brain voxel-wise analysis for the resulting FA data was carried out with Tract-Based Spatial Statistics (TBSS, [Smith, 2006]), part of the FSL toolbox (Smith, 2004). TBSS is one of the most commonly used methods for DTI analysis. TBSS is a fully automated procedure, that does not require predefinition of WM tracts of interest, but allows for statistical testing in all major tracts simultaneously. In short, TBSS first non-linearly aligns all subjects' FA images to the same target and then merges each of the aligned FA images to a "group FA skeleton", a common template representing the centres of major WM fibre bundles, common to all participants in general. Lastly, voxelwise statistics are carried out for the FA data in skeleton space (Smith & al. 2006).

Statistical tests for the whole brain analysis were performed using TBSS- randomise tool (FSL, version 4.1.2 http://www.fmrib.ox.ac.uk/fsl). TBSS- randomise is based on general linear modelling and uses permutation tests. In general linear modelling, the observed data, Y, at each voxel is represented as a linear combination of predictor variables, modelled in the design matrix X that corresponds with the experimental setting. Randomise estimates group differences by resampling the data labels of groups, with making minimal parametric assumptions. The number of permutations was 5000. Rather than assuming a known distribution, statistical significance is based on the permutation distribution and calculated directly from the test statistics obtained from the data (Nichols & Holmes, 2001). The family-wise-error corrected results were thresholded at $p < 0.05$. Cluster regions were specified with FSL's atlasquery tool, using John Hopkins University ICBM-DTI-81 WM Label Atlas (Mori, Wakana, Nagae-Poetscher & Van Zijl, 2005, p.276).

Whole-brain analyses were carried out with two-sample unpaired t-tests, for FA and MD, to compare the FES and FEP groups. As age and gender are well known to influence FA (Rathee, Rallabandi & Roy, 2016), they were included in the analyses as additional covariates as a standard procedure. T-tests were performed separately for baseline and follow-up data. The potential effect of medication was studied with correlation tests in SPSS 25, by using the extracted mean FA values and CPZ dose equivalent values. Spearman correlation tests were used between follow-up FA values and both follow up CPZ equivalent values and CPZ equivalent sum values. Also, a longitudinal skeleton, including baseline and follow-up images of both FES and FEP groups was formed in order to visualize the direction of FA changes.

9. Results

The Mann Whitney U-test reported no significant age difference between the two patient groups ($U = 225.700$, $p = 0.877$). Unpaired t-test for baseline data with TBSS did not show significant differences. In the follow-up whole-brain analysis, group means differed significantly, FEP group showing larger FA in 5 clusters than the FES group (see Table 2.). P-values were modest, peak significance being $p = 0.044$. The group differences remained significant with and without the nuisance covariates in the analysis. Additionally, follow-up data were analysed for differences in MD, but no significant difference was found.

Table 2 *Results of the DTI analysis for 1-year follow-up group differences.*

Cluster Index	*Voxels*	*MIN p-value*	*MAX X (MNI)*	*MAX Y (MNI)*	*MAX Z (MNI)*
5	2232	0.044	14	1	-32
4	110	0.046	9	-30	49
3	92	0.049	-5	-10	45
2	78	0.048	3	-15	49
1	17	0.05	16	33	27

Note. Cluster index, number of cluster; Voxels, number of voxels in cluster; MIN p-value, minimum p-value within the cluster; MAX X/Y/Z, location of maximum intensity voxel

Specified cluster regions are shown in Table 3. The largest cluster contained 2232 voxels and overlapped with multiple anatomical regions. Averaged probabilities of significantly different voxels being part of a certain region within the selected atlas are also shown. The voxels that showed a statistically significant difference in the group means in the follow-up are visualised in figs. 1–2.

Table 3. *Cluster regions that showed a statistically significant difference between the FES and FEP groups at 1-year follow-up.*

Cluster 5.

Unclassified: 39.4 %

Posterior limb of internal capsule R: 15.5%

Superior corona radiata R: 13.0 %

Anterior limb of internal capsule R: 10 %

External capsule R: 6.9 %

Superior longitudinal fasciculus R: 6.8 %

Retrolenticular part of internal capsule R: 4.6 %

Superior fronto-occipital fasciculus (could be a part of anterior internal capsule) R: 1.3 %

Posterior corona radiata R: 1.25 %

Cerebral peduncle R: 0.8 %

Anterior corona radiata R: 0.4 %

Cluster 4.

Splenium of corpus callosum: 53.6 %

Unclassified: 43.6 %

Posterior corona radiata R: 2.7 %

Cluster 3.

Body of corpus callosum: 77.2 %

Splenium of corpus callosum: 22.8 %

Cluster 2.

Body of corpus callosum: 68.0 %

Splenium of corpus callosum: 32.0 %

Cluster 1.

Anterior corona radiata R: 82.4 %

Unclassified: 17.6 %

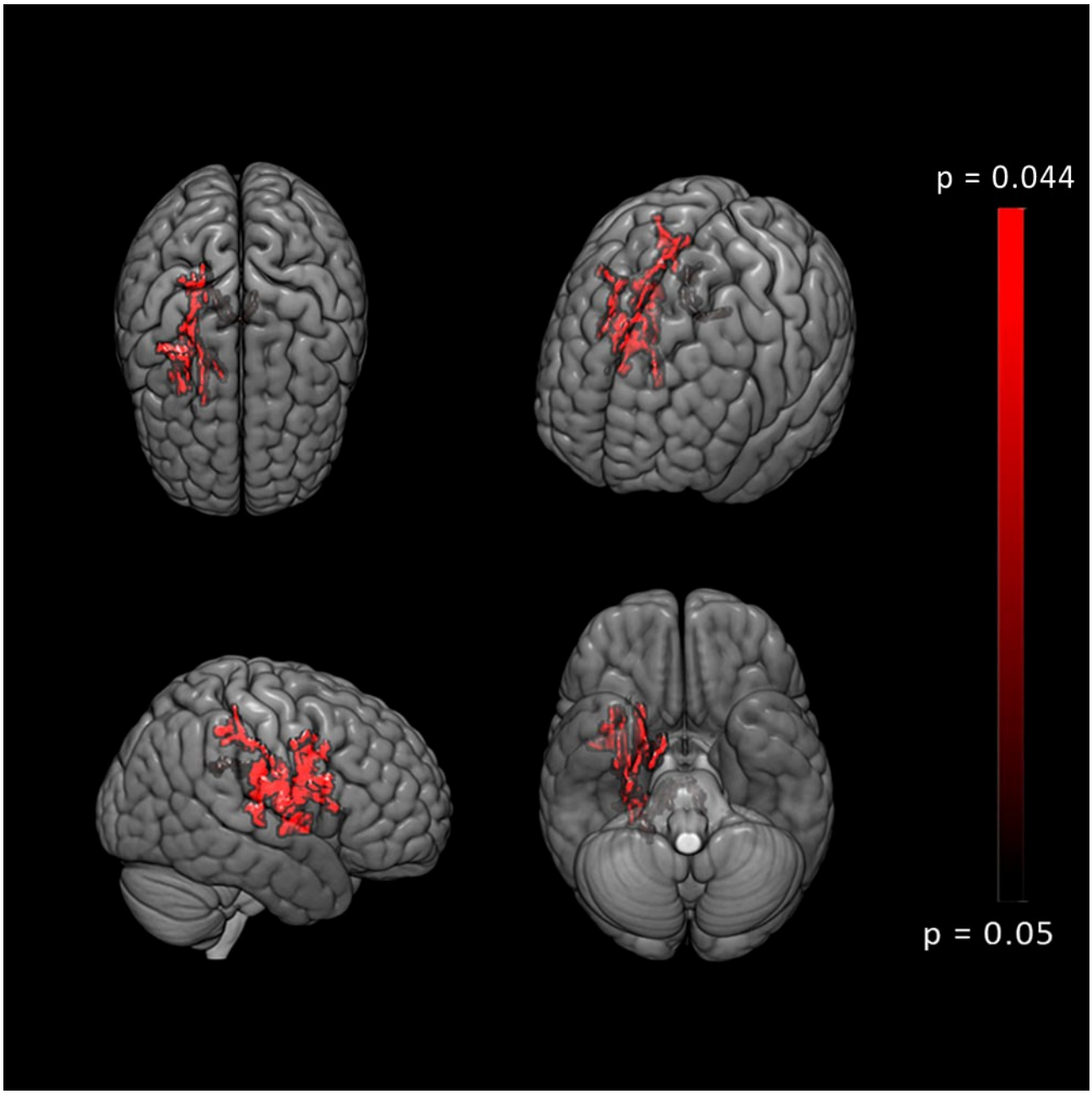

Figure 1 *Voxels with significantly higher FA in the FEP group compared to the FES group at 1-year follow-up.*

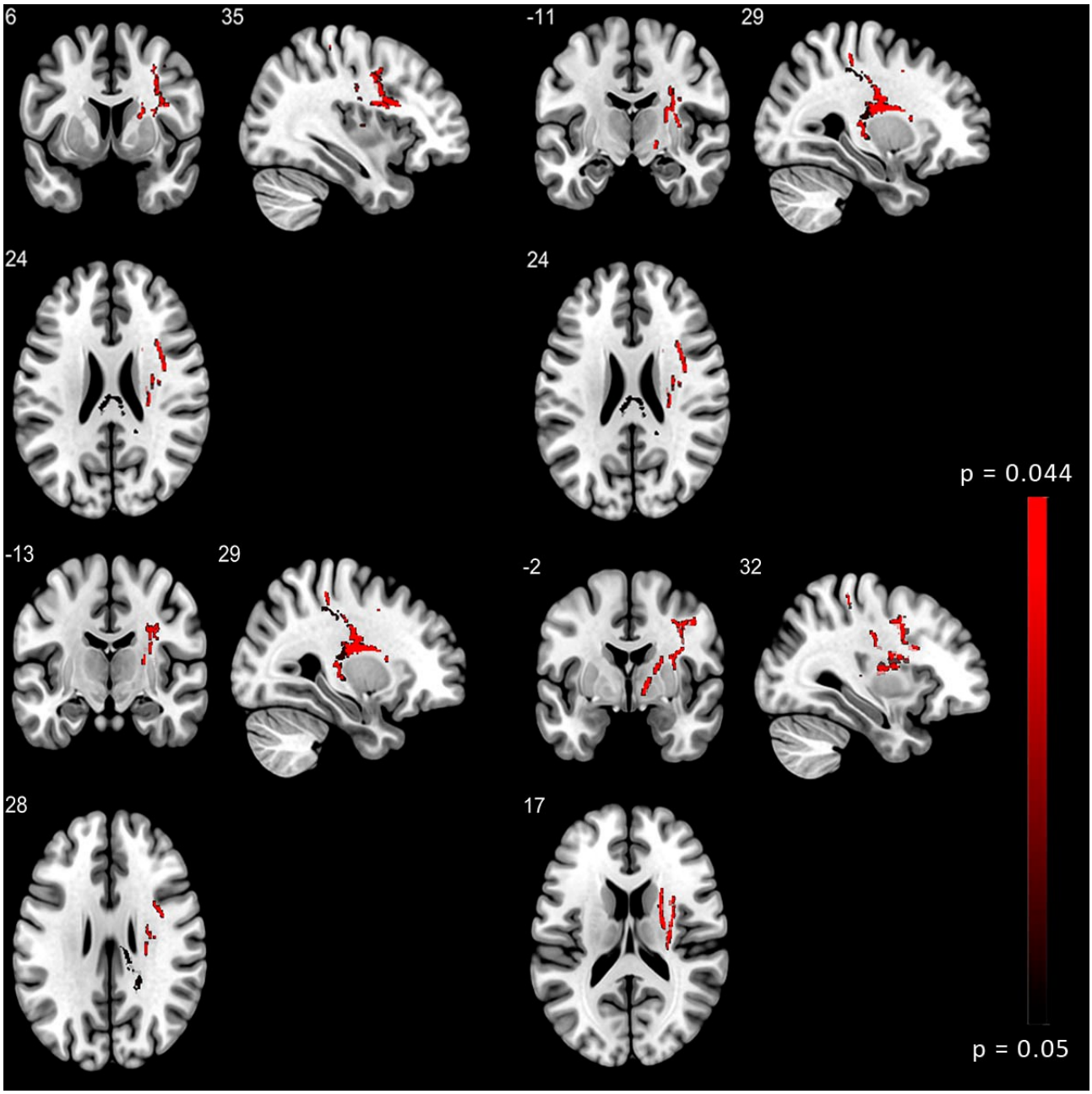

Figure 2 *Voxels with significantly higher FA in the FEP-group compared to the FES-group at 1-year follow-up.*

Longitudinal skeleton included the baseline and follow-up images of all the participants in the FES and FEP groups. Regions and the degree of FA change are visualised in in Fig. 3, in some of the most relevant tracts that showed group differences in the TBSS-analysis. FA mean values show decline in multiple regions in the FES group, steepest reduction being in right anterior corona radiata. Notably, in the FEP group none of the regions showed a declining FA trend.

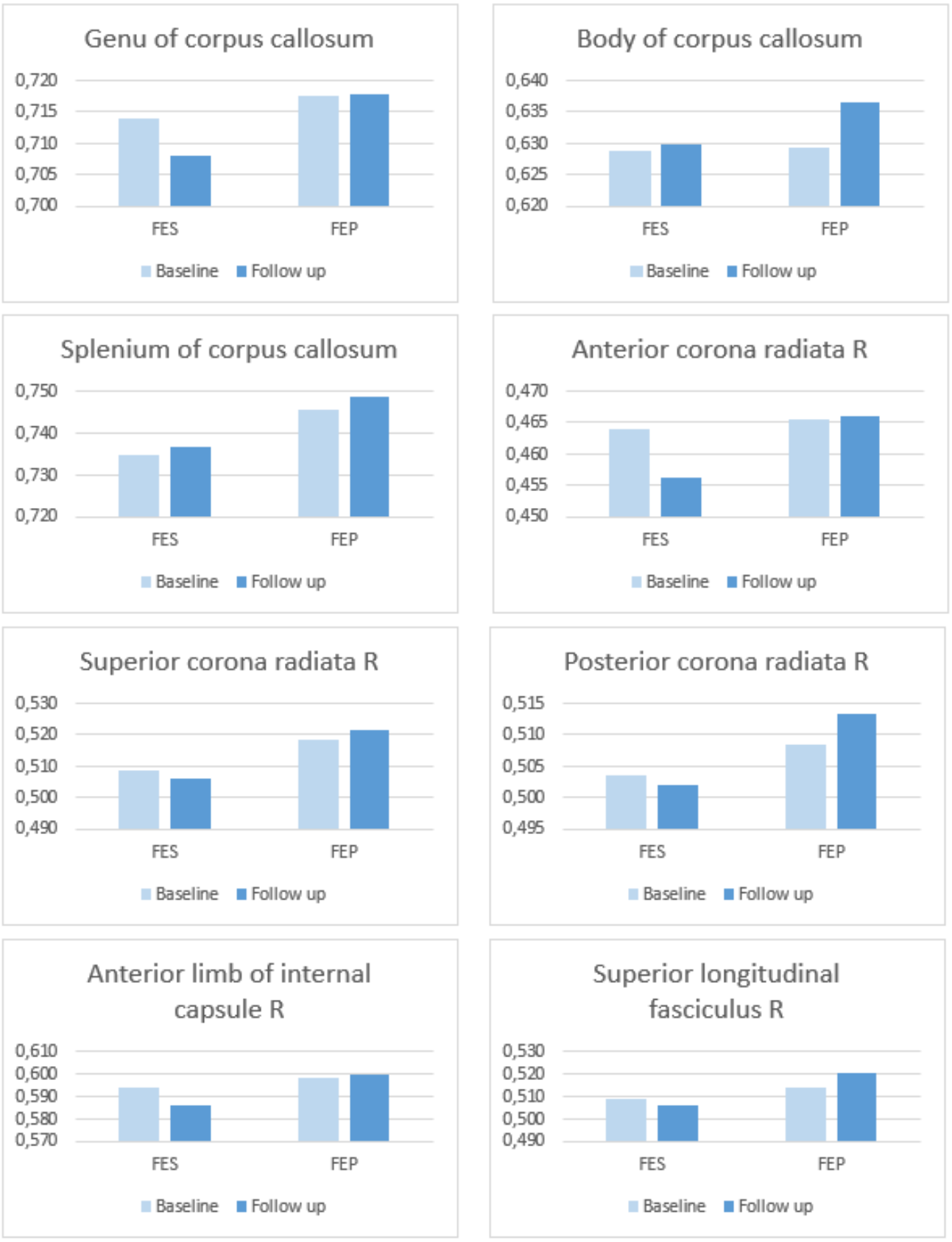

Figure 3 *Bar charts are mean FA-values extracted from a longitudinal TBSS-skeleton.*

Table 4 *Spearman correlations between antipsychotic medication dose equivalents and mean FA values from follow-up*

	CPZ 1-year		*CPZ sum*	
	Correlation	*sig. 2-tailed*	*Correlation*	*sig. 2-tailed*
ACR L	-0.067	0.667	0.212	0.177
ACR R	-0.049	0.750	0.187	0.236
PCR L	0.062	0.687	0.200	0.204
PCR R	-0.005	0.974	0.121	0.447
SCR L	0.213	0.166	0.430	**0.004**
SCR R	-0.058	0.709	0.162	0.305
Genu of CC	-0.034	0.826	0.101	0.524
Body of CC	-0.119	0.440	-0.020	0.901
Splenium of CC	-0.031	0.841	0.212	0.178
Fornix	-0.190	0.216	-0.353	**0.022**
ALIC L	-0.297	**0.050**	-0.089	0.577
ALIC R	-0.216	0.158	-0.001	0.993
PLIC L	0.022	0.885	0.230	0.143
PLIC R	-0.043	0.780	0.142	0.371
EC L	-0.070	0.653	0.067	0.675
EC R	-0.008	0.958	0.186	0.238
SLF L	0.120	0.439	0.290	0.062
SLF R	-0.130	0.400	0.026	0.870

Abbreviations: ACR, Anterior corona radiata; PCR, Posterior corona radiata; SCR, Superior corona radiata; CC, Corpus callosum; ALIC, Anterior limb of internal capsule; PLIC, Posterior limb of internal capsule; EC, External capsule; SLF, Superior longitudinal fasciculus.

Correlation analysis revealed significant associations between CPZ dose equivalent sum values and two regions, fornix ($r = -0.353$, $p = 0.022$) and left superior corona radiata ($r = 0.430$, $r = 0.004$). Also, correlation between 1-year follow-up CPZ dose equivalent values and left anterior limb of internal capsule was almost significant ($r = -0.297$, $p = 0.050$).

10. Discussion

As a novel finding, the results of this study imply WM alterations in schizophrenia to follow a different trajectory in comparison to other psychotic disorders. The correlation analyses further demonstrated that the FA changes in the FES group were not associated to antipsychotic medication. The absence of significant differences in WM at baseline, and FA decrease in the FES group in comparison to the FEP group at follow-up offer evidence against the steep view of schizophrenia as the end state of abnormal neurodevelopmental processes. To a large degree, the regions with differing FA in the FES group are the same as the regions established in many other studies, including the largest meta-analysis so far (Kelly et al. 2017) that compared schizophrenia patients at illness onset to healthy controls (Caprihan et al. 2015; Wang et al. 2013; Zhang et al. 2014). The results of this study support the findings made by the previously mentioned studies, that microstructural changes in corticothalamic, frontotemporal and interhemispheric WM tracts might play a central role in schizophrenia. However, conclusions must be made cautiously, which is discussed further below.

According to previous and the current research, particularly anterior corona radiata and corpus callosum seem to show pronounced impairment in schizophrenia. As the current study only compared group differences in the FA, the possible effects of symptoms or behavioural and lifestyle changes to the progression of tract hypoconnectivity remain unanswered. However, as positive and negative symptoms are the core symptoms of schizophrenia, which differed significantly between the two groups follow-up measurements in the current study, their relation to the progressive change in the WM tracts is worth speculating.

Anterior corona radiata includes projections from internal capsule to areas of frontal lobe, and the frontal lobe especially is known to associate with many functional and structural alterations in schizophrenia (Mubarik & Tohid, 2016). Previous DTI research has implicated anterior corona radiata to have major relevance for information processing, as there has been reports of associations between anterior corona radiata FA and e.g. intellectual performance and social functioning (Koshiyama et al. 2018), attention (Stave, De Bellis, Hooper, Woolley, Chang & Chen, 2017) and also with the severity of delusions (Nakaaki et al, 2013). Ćurčić-Blake et al. (2013) found lower FA in schizophrenia patients with auditory hallucinations when compared to patients without hallucinations in several regions including bilateral anterior corona radiata as well as

posterior parts of corpus callosum by comparing schizophrenia patients with and without hallucinations. Auditory connectivity via the corpus callosum has been demonstrated to be relevant for the normal processing of verbal stimuli (Steinman, Meier, Nolte, Engel, Leicht & Mulert, 2017; Tantillo et al. 2016) and is also implicated to associate with auditory hallucinations in schizophrenia patients. Researchers have frequently reported interhemispheric dysconnectivity associating to verbal hallucinations, albeit the specific part of corpus callosum affected has varied (Ćurčić-Blake et al. 2013; Hudl et al. 2004). In addition to corpus callosum, Zhang et al. (2016) reported positive symptoms to associate with hypoconnectivity in superior longitudinal fasciculus, anterior limb of internal capsule and external capsule, tracts that yielded significant differences between the groups also in the current study.

Nevertheless, a link between the worse course of symptoms or functioning and brain abnormalities in schizophrenia has not been established by research so far. This study corroborates the neuroprogression hypothesis more clearly, however, without conflicting with the neurodevelopmental hypothesis. Of these two, the progression of brain abnormalities remains as the vaguer aspect of the illness. Concerning neuroprogression previous research has already discussed multiple possible explanations, such as neurotoxicity caused by psychotic episode, effect of accelerated aging, antipsychotic medication or cohort bias where a sample of patients with poorer prognosis has been included into the studies (Peters & Karlsgodt, 2015). Myelination, myelination related genes and oligodendroglia and their impairment in schizophrenia has also been highlighted as another possible explanation (Andreasen et al. 2011). Nonetheless, as research has shown, progression seems to occur in some cases. Accordingly, considering current evidence schizophrenia is perhaps best understood as a developmental disorder, that may involve continuing neural changes after the illness onset.

Although many aspects of the progression of the WM anomalies remain unanswered, the findings may have important clinical implications. Further delineating the sub-group with progressive brain abnormalities would have relevance for both diagnostic measuring and classification of the disorder. For the purpose of identifying patients with neuroprogressive schizophrenia as well as separating other diverging patient groups, WM markers could have potential utility in the future. Researchers have already begun the efforts of subtyping schizophrenia patients based on WM data. For instance, by using an unsupervised factorization technique Arnedo et al. (2015) identified four distinct patterns of decreased FA associating with certain clinical symptoms in schizophrenia

patients. Sun et al. (2015) found two separate patterns of WM decrease in FEP schizophrenia patients, one that was affecting more globally and was also associated with negative symptoms and the other affecting mainly in the left superior longitudinal fasciculus. Currently MRI-based subtyping seems to be a growing topic of discussion also in the field of psychiatric disorders in general (Huang, Gong, Sweeney & Biswal, 2019; Ivleva, Turkozer & Sweeney, 2019).

Recognizing the important role of WM related abnormalities in schizophrenia and the possibility of their progressively worsening trajectory may have relevance for treatment as well. Research has already addressed the potential of treatments that may enhance myelination. Administration of polyunsaturated fatty acids (PUFAs), parts of cell membrane phospholipids that have a role in myelin formation have been suggested as a potential supplementary treatment for psychotic disorders (Karlsgodt, 2016; Peters & Karlsgodt, 2015). There is some evidence of such interventions reducing the symptoms of schizophrenia patients (Bozzatello, Rocca, Mantelli & Bellino, 2019; Peet, Brind, Ramchand, Shah & Vankar, 2001). PUFAs could potentially provide a low-cost supplementary treatment approach with no noteworthy side-effects (Schlögelhofer et al. 2014), but the evidence so far is mixed (Bozzatello et al. 2019). More promising results have been achieved in studies with individuals at high-risk of psychosis, whose risk of transitioning to psychosis was reduced by PUFAs (Amminger et al. 2010; Amminger et al. 2015). Thus, it has been indicated that the potential treatment advantage of PUFAs may be dependent of the myelination stage of patients and limited to early stages of schizophrenia rather than chronic stage of the disorder (Karlsgodt, 2016; Bozzatello et al. 2019). The potential treatment advantage of PUFAs and their specific association to WM abnormalities in schizophrenia as well as other treatment options remain to be further studied.

11. Limitations and future directions

There are some limitations in the current study to consider. One of the main limitations is that only patients with psychotic disorders were compared. Although the occurrence of global WM FA decrease in schizophrenia in comparison with healthy controls is well established by previous research, the present study lacked healthy controls as a reference to FA changes observed in both patient groups. Furthermore, healthy brains would serve as an essential reference in the analysis for establishing a link between schizophrenia and progression of the FA abnormalities. To further study the possibility of progression, larger samples would also be required. Albeit the current

study suggests a progressive decline in schizophrenia patients' FA, the FEP group consisted of patients with various diagnoses. Therefore, there is a possibility of considerable heterogeneity between subjects in the FEP group. To study further this possibility, future studies should concentrate to compare a FES group against a more homogeneous diagnostic group, e.g. patients with schizoaffective disorder or patients with bipolar disorder with psychotic features, in a longitudinal setting.

In the current study the potential effect of the CPZ values on the FA values was examined with correlations. However, a more optimal method to confirm that the antipsychotic medication had not influenced the FA change during one year at all, would have been to include the CPZ values into the analysis as a covariate. Also, the variance of negative and positive symptom scores and their potential influence on the FA values was not examined in the current study. On that account, the possibility of differences in negative symptom, hallucination and/or CPZ dose scores explaining decline in FA in the FES group at least partly, cannot be omitted. For future research, a good direction would be to longitudinally compare FEP groups with high and low scores on hallucination and negative symptom scores, and their effect on the FA during the course of the illness. Concerning the symptom profile and neuroprogression of schizophrenia patients, another important research question for future research to address would be, which part of the patient group exhibits signs of progressive brain anomalies.

One of the other limitations in this study is that the main analyses were carried out in a repeat cross-sectional setting. With the results of the current analyses, the trajectory of the potential neuroprogression can be described only referentially. A two-way mixed effect ANOVA, an available option for modelling repeated-measures data for two groups in general linear model, was not used because it requires a compound symmetric structure within the subject's brain data and cannot account for the repeated-measures correlation, and thus would provide an inaccurate analysis. Longitudinal statistical design would further allow for more accurate examination of the potential effect of medication and symptom severity on the disease trajectory. One of the shortcomings of the TBSS- pipeline used in this study is that it uses subjects' FA values to perform both the preprocessing steps and the statistics for analysis. For boosting accuracy, especially in a longitudinal test design, a registration method that uses the information of the whole diffusion tensor rather than just FA, such as DTI-TK- toolkit, is reported to result in higher specificity and reliability (Keihaninejad et al. 2013). Furthermore, for avoiding any interpolation asymmetries in

the processing of longitudinal DTI data, the unbiased pipeline that creates a within-subject template is recommended (Keihaninejad et al. 2013).

There are also some interpretational issues concerning the TBSS method and the diffusion scalars used. TBSS registration aligns individual subjects' locally maximum FA value in the perpendicular directions at each point of the skeleton to the voxels in the major tissue structures, therefore focusing on the largest WM tracts. However, when voxels outside larger WM tracts are examined, it might be challenging to delineate whether the change in FA is caused by a change within the tract or a difference in tract thickness. WM regions where tracts cross or converge further cause difficulties in determining the true value of the scalar used (Smith et al. 2006). There are also some uncertainties associated with DTI scalars to be aware of. In addition to myelination, FA is sensitive to many other tissue features, such as fiber density, fiber organisation and axon diameter. Therefore, the relationship between tissue anatomy and DTI scalar is never straightforward, but rather associated with multiple — and sometimes opposing — factors (Scholz, Tomassini & Johansen-Berg, 2014).

12. Conclusions

The results of this study indicate schizophrenia to follow a different disease trajectory in terms of WM FA changes, compared to a group of patients with other psychotic disorders. WM abnormalities in schizophrenia also imply a worsening trend over time, which may not be associated to the antipsychotic treatment, supporting the view that schizophrenia involves ongoing microstructural alterations in the WM after the onset of the psychosis. The results further highlight the potentially important role of corticothalamic, frontotemporal and interhemispheric WM tracts in the etiology of schizophrenia. Future investigations should focus on comparing a FES group against a homogenous group of FEP patients in a longitudinal setting, with controlling the antipsychotic medication and taking the degree of symptom severity into account.

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