Structural brain abnormalities in first episode schizophrenia. Is it just illness?

Monica Rais

The studies described in this thesis were performed at the Rudolf Magnus Institute of Neuroscience, Department of Psychiatry, University Medical Center Utrecht, The Netherlands.

The studies which were part of the GROUP-project were supported by ZonMw (the Netherlands organisation for health research and development). Publication of this thesis was financially supported by the J.E. Jurriaanse Stichting.

ISBN: 978-94-6191-016-5

Printed by: Ipskamp drukkers BV, Enschede, the Netherlands

Stuctural brain abnormalities in first episode schizophrenia.
Is it just illness?

Structurele hersenafwijkingen bij eerste episode patiënten met schizofrenie.
Is het alleen maar ziekte?

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 27 oktober 2011 des ochtends te 10.30 uur

door

Monica Rais

geboren op 18 Juni 1975 te Cagliari, Italië

Promotoren:	Prof. dr. R.S. Kahn
	Prof. dr. H.E. Hulshoff Pol
Co-promotoren:	Dr. W. Cahn
	Dr. N.E.M. van Haren

A Maddalena, il mio primum movens.
Oltre la scienza, la ragione di tutto.

A papà e mamma.

A Maurizio.

Nullum magnum ingenium sine mixtura dementiae fuit.
(Seneca)

Contents

Chapter 1

Introduction

1. Introduction

The studies conducted in this thesis explore brain morphology abnormalities in first episode patients with schizophrenia and the relationship between (change in) morphological measures and possible confounding factors such as cannabis, antipsychotic medication and duration of illness.

1.2 Schizophrenia

Schizophrenia is a severe and progressive psychiatric brain disorder characterized by a disruption of thought processes, feelings and reality testing and perception. The lifetime risk to develop schizophrenia is estimated around 0.3-2 % with an average of approximately 0.7% (Saha et al., 2005; Tandon et al., 2008).

The illness was first described by Emil Kraepelin who clustered the symptoms of schizophrenia into one syndrome: "dementia praecox" (Kraepelin, 1913), underpinning both the relatively young age of onset and the clinical deterioration that characterize the course of the illness. After Kraepelin, Bleuler (Bleuler, 1923) named the disease schizophrenia from the Greek roots schizein (σχίζειν, "to split") and phren- (φρήν, φρεν-, "diafragm", "mind") referring to the disintegration of the personality observed in patients. He described the disease as "the group of schizophrenias", identifying a heterogeneous group of disorders with different aetiologies but similar clinical presentations.

Schizophrenia has an insidious onset and is preceded by a decline in functioning before the onset of the first psychotic episode. The first symptoms of schizophrenia occur typically in early adolescence. As described by Kraepelin, schizophrenia occurs mostly in early adulthood, on average earlier and more frequently (Aleman et al., 2003) in men (20-25 years) than in women (25-30 years) with a second smaller peak in females after age 45 (Goldstein and Levine, from Castle et al., 2000). The relatively young age of onset implies not only great subjective sufferance for the patient but also important social implications. Its symptoms interfere with the capacity to cope with the demands of daily life, particularly in those situations involving social interaction and decoding of social communication. Moreover, it interferes with the development of the patient (Sheitman et al., 1997), with his maturation, educational and occupational achievements, therefore, resulting in severely disrupted social skills and socioeconomic disadvantage.

In addition, schizophrenia can be fatal not only because of suicide (4-10%), homicide or other unnatural causes (Hiroeh et al., 2001), but also due to a poorer somatic condition and comorbidity. The average life expectancy for patients with schizophrenia is from 10 to 30 years shorter as compared to the general population due to high incidence for somatic comorbidity and higher prevalence of key risk factors for major causes of mortality in the general population such as overweight and obesity, hypertension, dyslipidemia, insulin resistance and hyperglycaemia, metabolic syndrome, smoking and substance abuse (Kaplan and Sadok, 2009).

1.2.1 | Symptoms and classification

Schizophrenia is a heterogeneous psychiatric syndrome characterized by different dimensions of symptoms. Positive symptoms refer to an excess of normal functioning (delusions, hallucinations and formal thought disorder) while negative symptoms reflect a loss of normal functioning (affective flattening, alogia, avolition and apathy, anhedonia and asociality, emotional withdrawal). Moreover, deficits in cognitive functions are frequently observed in patients with schizophrenia including problems with executive functioning (planning and organization of behaviour), attention, memory and concentration. Since the variety of presentation of the disease is large, making its course heterogeneous, different subtypes of schizophrenia have been defined. The most widely used standardized classification system for psychiatric symptoms mental disorders come from the American Psychiatric Association's "Diagnostic and Statistical manual of Mental Disorders-IV-TR" (DSM IV-TR) (American Psychiatric Association, 2000).
(See table 1).

Table 1 | Diagnostic Criteria for Schizophrenia, according to DSM-IV

A. Characteristic symptoms: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

1. Delusions
2. Hallucinations
3. Disorganized speech (e.g., frequent derailment or incoherence)
4. Grossly disorganized or catatonic behaviour
5. Negative symptoms, i.e., affective flattening, alogia, or avolition

B. Social/occupational dysfunction: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or, when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. Duration: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective and Mood Disorder exclusion: Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either (1) no major depressive episode, manic episode, or mixed episode have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. Substance/general medical condition exclusion: The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

F. Relationship to a Pervasive Developmental Disorder: If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

(Adapted from Diagnostic and Statistical Manual of Mental Disorders, 4th ed.)

1.2.2 | Aetiology and risk factors

The aetiology of schizophrenia is not completely understood. Family studies indicate that the genetic predisposition plays an important role. Studies investigating twin, adoption and family history underpin the evidence that the risk of developing schizophrenia is elevated in individuals having an affected family member, the closer the level of genetic relatedness the greater the risk to develop the illness (Gottesman and Bertelsen, 1989; Gottesman, 1991; McGuffin et al., 1995). Twin studies demonstrated a heritability of about 80% (Sullivan et al., 2003).

Interestingly, the fact that monozygotic twins have less than 100% concordance rates for schizophrenia suggests the role of environmental factors in the development of the illness. The neurodevelopmental hypothesis of schizophrenia suggests that a disruption of brain development underlies the development of the illness during adulthood.

A variety of specific environmental exposures have been implicated in the aetiology of schizophrenia: these include both biological and psychosocial risk factors during the different developing periods of the human being, from the antenatal period to the adolescence and early adulthood (Maki et al., 2005).

Older paternal age at conception together with maternal infections, severe nutritional deficiency, adverse life events experienced by the mother, obstetric and perinatal complications with foetal hypoxia and birth during late winter or early spring have been linked to an increased risk of developing schizophrenia (Kaplan and Sadok, 2009). Moreover, heterogeneous risk factors such as trauma, head injury, infection, together with social environmental factors such as parental separation or death during childhood, urbanicity and migration or socioeconomic status of the parents (Cantor-Graae, 2007) have been reported (for a review see Tandon et al., 2008).

Interestingly, cannabis use, particularly during adolescence, has been linked to an increased risk of developing schizophrenia (Torrey, 1988; Moore et al., 2007; for a review see Semple et al., 2005 and Tandon et al., 2008). Whether a direct cause-effect relationship or a precipitating effect in vulnerable individuals takes place is still debated. The association between cannabis and schizophrenia is well established but it remains unclear whether cannabis use precipitates schizophrenia or whether cannabis use is a form of self medication.

While genetic and environmental risk factors have been previously considered separately to clarify the aetiology of schizophrenia, it is now well accepted that the genetic and the environmental risk factors act in concert in the vulnerability for schizophrenia. Their role and interaction in the context of the pathophysiological mechanisms leading to the disease are the focus of current research (van Os and Murray, 2008a; van Os et al., 2008b).

1.3 Brain Imaging.

1.3.1 | MRI techniques.

Magnetic Resonance Imaging (MRI) is a medical technique used to visualize detailed internal structures, particularly tissues with many hydrogen nuclei and little density contrast, such as the brain, muscle and connective tissues. It makes use of the property of nuclear magnetic resonance to image the protons forming the nuclei of hydrogen atoms located in the water molecules inside the body. When a subject is placed in the magnetic field of the scanner some protons in the body will align with the field. A radio frequency pulse is used to excite the protons from their

resting state into a higher energy state in which they start to spin. When the field is turned off, the protons return to their original state with the emission of an electromagnetic signal that the scanner detects using a receiver coil. Different tissue types lead to differences in MR signal. The scanner determines from which location of the patient's body it receives the signals and, after integrating the information received, it creates a three dimensional image. The MR signal (and, therefore, the quality of the MRI scans) depends on magnetic field strength (expressed in Tesla, T). MRI is a safe procedure: brain scans are acquired in vivo without exposure to radiation and collateral effects.

After being acquired, the scans are processed with specific software: different brain areas can be segmented and partitioned into meaningful structures (intracranium, total brain, grey and white matter, third and lateral ventricles, cerebellum) to obtain a quantification of the volume of the different structures/tissues in the brain (Schnack et al., 2001a; Schnack et al., 2001b; Brouwer et al., 2010).

The majority of the MRI studies in schizophrenia employed a volumetric ROI approach. Although the anatomical validity of this techniques is high, the studies are time consuming and therefore do not allow for comparison of many brain regions or large subject groups. Moreover, they are sensitive to individual decision on anatomical boundaries of the ROI, possibly resulting in a higher risk of unreliable measurements.

Computational morphometrics, such as Voxel Based Morphometry (VBM) (Ashburner and Friston, 2000) allow the investigation of focal grey and white matter changes throughout the whole brain. VBM is a statistical analysis of the images on a voxel by voxel basis. It uses binary masks of grey and white matter which are blurred or smoothed resulting into grey or white matter density maps representing the local concentration of grey or white matter per voxel. After transforming all individual MR Images into a standardized coordinate system, differences between the mean densities for each voxel between groups can be calculated. Voxel based morphometry provides information about focal brain abnormalities instead of global volumetric measures.

Another approach to examine the localization of focal brain abnormalities is to quantify the thickness of the grey matter in specific regions of the human cerebral cortex (Davatzikos and Bryan, 1996; Thompson and Toga, 1996; Kabani et al., 2001; Fischl and Dale, 2000). Cortical thickness is determined by the size, density and arrangement of the neurons, neuroglia and nerve fibres. Cortical thinning is frequently regionally specific and can, therefore, provide information

for characterizing disease-specific neuroanatomical changes and could reflect cytoarchitectural abnormalities more specifically than brain volumes (Fischl and Dale, 2000; Kabani et al., 2001).

While structural MRI has been proven useful in examining and detecting grey matter abnormalities in schizophrenia, diffusion tensor imaging (DTI) allows for the investigation of white matter fibre bundles connecting different regions in the brain that cannot be measured with standard MRI.

White matter consists of large bundles of myelinated axons running in parallel enabling fast and efficient communication between distinct grey matter regions. DTI measures to what degree water diffusion is constraint by barriers such as myelin sheats, membranes of neuronal fibre tracts. Diffusion in white matter is anisotropic, which means that, in a given white matter voxel, axial diffusion is much greater than radial diffusion. Fractional anisotropy (FA) is a frequently used measure of the degree of diffusion and is a measure of white matter microstructure that may reflect organisation, fibre directional coherence and fibre integrity (Beaulieu, 2002). Especially in combination with magnetic transfer ratio (MTR), a putative measure of myelin concentration. FA and mean diffusivity (MD) give detailed information on the white matter microstructure.

1.3.2 | Early Brain Imaging studies.

Brain imaging techniques were used to study the brain of schizophrenia patients in vivo already in the early 1900's. Pneumoencepalography studies demonstrated brain abnormalities and (progressive) atrophic cerebral changes in patients with schizophrenia (Haug, 1962). In the 1970's Johnstone reported for the first time increased lateral ventricle volume in patients with chronic schizophrenia studied with computer assisted tomography (CT) (Johnstone et al., 1976). This study resulted into a proliferation of CT and post mortem studies showing enlarged ventricles in schizophrenia (for a review see Weinberger, 1984). Although the results of well matched case-control studies were not always consistent (for a review see Lewis, 1990), meta-analyses demonstrated an increased ventricle/brain ratio (Van Horn and McManus, 1992) and ventriculomegaly (Raz and Raz, 1990) in patients with schizophrenia.

1.3.3 | MRI studies in schizophrenia.

Magnetic Resonance Imaging (MRI) studies led to more definitive findings, suggesting that small and subtle brain abnormalities are involved in the pathophysiology of schizophrenia. Cross-sectional MRI studies in both early onset (for metanalyses see: Steen et al., 2006 and Vita et al., 2006) and chronic schizophrenia patients (for metanalysis see: Wright et al., 2000), have consistently demonstrated decreases in whole brain volume, in particular cortical grey and white

matter volume, with decreases in smaller brain structures such as the amygdala-hippocampus complex, frontal and temporal cortices and the insula, as well as increases in ventricular volume. A metanalysis of VBM studies (Honea et al., 2005) demonstrated reduced grey matter density in patients with schizophrenia as compared to healthy controls, most pronounced in the left superior temporal gyrus and the left medial temporal lobe.

Moreover, longitudinal studies conducted in recent-onset schizophrenia patients showed excessive brain volume decreases (DeLisi et al., 1995; DeLisi et al., 1997; Gur et al., 1998; DeLisi et al., 2004; Pantelis et al., 2005; Cahn et al., 2006; van Haren et al., 2008; Hulshoff Pol and Kahn, 2008) particularly in the frontal (Gur et al., 1998; Ho et al., 2003) and temporal (Kasai et al., 2003a; Kasai et al., 2003b) lobe, mainly attributable to a decrease in grey matter volume (Cahn et al., 2006; van Haren et al., 2007; van Haren et al., 2008). Interestingly, not only the grey matter volume decrease and ventricular increase appear to progress over time, but most (Lieberman et al., 1996; Davis et al., 1998; Mathalon et al., 2001; Lieberman et al., 2001; Cahn et al., 2002; Ho et al., 2003; Lieberman et al., 2005; van Haren et al., 2007; van Haren et al., 2008; for a review see Pantelis et al., 2005), but not all (DeLisi et al., 2004), studies report the largest brain volume decreases in patients with the poorest outcome.

The (global) grey matter changes in the brain of schizophrenia patients have been localized by studies reporting focal cortical thinning of frontal, temporal, parietal and occipital regions in chronic (Kuperberg et al., 2003) and first-episode (Narr et al., 2005a; Narr et al., 2005b) schizophrenia patients. These findings have consistently been replicated larger samples of patients in childhood onset (White et al., 2003; Greenstein et al., 2006), chronic (Nesvag et al., 2008; Goldman et al., 2009) and in a sample of patients across the adult age range (van Haren, 2011, in press).

While structural MRI has been proven tobe useful in detecting grey matter abnormalities in schizophrenia, Diffusion Tensor Imaging (DTI) techniques have been shown to be a useful technique to measure white matter integrity in schizophrenia, but findings are inconclusive possibly due to confounding factors such as clinical heterogeneity and differences in study methodologies (Kanaan et al., 2005).

Earlier studies reported reduced white matter integrity in patients with schizophrenia, particularly in the frontal lobe and its connection with the uncinate fasciculus, but results have been inconsistent (for a metanalyses see Kanaan et al., 2005; Kubicki et al., 2007; Ellison-Wright

and Bullmore, 2009). White matter tracts that have frequently been implicated in schizophrenia include the uncinate fasciculi, arcuate fasciculi, genu and splenium of the corpus callosum, inferior longitudinal fasciculi, superior longitudinal fasciculi and cingulum bundles (for a review see Kyriakopoulos et al., 2008).

1.3.4 | Brain morphology and confounding factors in schizophrenia.

Although neuroimaging studies consistently demonstrated brain volume alterations in patients with schizophrenia, confounding factors like age, IQ, duration of the illness, (ab-)use of antipsychotic medication, (illegal) drugs, alcohol and nicotine might partly explain these results. Interestingly, evidence from animal and human studies suggests that antipsychotic medication affects brain morphology. The direction of the effect is not consistent. A study in non-human primates showed that chronic, therapeutic-like daily exposure to either haloperidol or olanzapine antipsychotic is associated with a reduction of whole brain volume affecting both grey and white matter (Dorph-Petersen et al., 2005). Moreover, chronic exposure to haloperidol or olanzapine resulted in decreases in whole brain volume, particularly in the frontal cerebral cortex in rats, suggesting that antipsychotics have an effect on the morphological changes of the brain cortex (Vernon et al., 2011). Reviews of human studies point out that antipsychotic treatment might potentially contribute (possibly with different effects, including 'protective effects', being associated with different antipsychotics) to the morphological changes in the brain observed in psychosis (Navari and Dazzan, 2009; Moncrieff and Leo, 2010).

The relation between alcohol (ab-)use, illegal drugs, IQ and brain volume changes in schizophrenia is still debated. However, progressive brain volume loss over five years in the prefrontal and temporal cortices have been found in alcohol abusing healthy subjects (Pfefferbaum et al., 1998), and schizophrenia patients (Mathalon et al., 2003). To date, cigarette smoking has not been related to brain volume abnormalities (van Haren et al., 2010). Cannabis (ab-)use occurs in up to 50% of the patients with schizophrenia (Green et al., 2004; Boydell et al., 2006). A poor clinical and functional outcome has been consistently associated with cannabis use: with more positive symptoms (Bersani et al., 2002; Buhler et al., 2002; Grech et al., 2005; Dubertret et al., 2006; Mauri et al., 2006), an earlier disease onset (Veen et al., 2004) and an increased number of psychotic relapses or exacerbations (Linszen et al., 1994; Caspari, 1999; Grech et al., 2005) in cannabis-using patients as compared to non-using patients. Whether cannabis use is also associated with excessive decreases in brain volumes is unclear.

Finally, the association between brain volume and intelligence is of genetic origin (Posthuma et al., 2002). Prior studies in healthy subjects (Andreasen et al., 1993; Narr et al., 2007) and in schizophrenia patients (Toulopoulou et al., 2004; Antonova et al., 2005, for a review see Antonova et al., 2004) reported a relationship between IQ and brain volume.

1.4 Aim and outline of this thesis.

In this thesis we describe brain imaging studies investigating brain morphology and white matter integrity in patients with schizophrenia as compared to healthy comparison subjects and the relationship between abnormal brain volume, cortical thickness and white matter integrity and confounding factors such as cannabis use, medication intake, IQ, and illness duration.

In chapter 2 we compared global brain volume changes over five years in cannabis-using and non-using first episode patients with schizophrenia and healthy comparison subjects. The relation between progressive brain volume changes and outcome in cannabis-using patients as compared to non-using patients and healthy comparison subjects was investigated.

Chapter 3 describes cortical thickness changes over 5 years in the abovementioned sample in order to assess the cortical distribution of grey matter loss in cannabis-using patients with schizophrenia as compared to non-using patients.

In chapter 4 global brain volumes and cortical thickness were compared between never medicated first episode schizophrenia patients and healthy comparison subjects in order to assess whether brain abnormalities are already detectable at illness onset and before medication intake and are, thus, independent from its effects on brain morphology. In addiction, we investigated the relation between IQ and global brain volumes.

Chapter 5 describes a study comparing a group of medication naïve patients with healthy comparison subjects using a combination of DTI and MTI to assess the integrity of the major white matter fiber tracts. The aim of this study was to determine if there are disease-related differences in white matter that cannot be attributed to the use of antipsychotic medication.
Chapter 6 investigates the relation between duration of psychosis and brain volume changes in patients with schizophrenia.

Finally, chapter 7 provides a brief summary and discussion of the abovementioned studies including implications for future research.

Reference List

Aleman A., Kahn R.S., Selten J.P. (2003): Sex differences in the risk of schizophrenia: evidence from meta-analysis. Arch Gen Psychiatry 60:565-571.

American Psychiatric Association (2000): Diagnostic and Statistical Manual of Mental Disorders, 4th edition-Text Revision (DSM-IV-TR) ed. Washington DC, American psychiatric press.

Andreasen N.C., Flaum M., Swayze V., O'Leary D.S., Alliger R., Cohen G., Ehrhardt J., Yuh W.T. (1993): Intelligence and brain structure in normal individuals. Am J Psychiatry 150:130-134.

Antonova E., Kumari V., Morris R., Halari R., Anilkumar A., Mehrotra R., Sharma T. (2005): The relationship of structural alterations to cognitive deficits in schizophrenia: a voxel-based morphometry study. Biol Psychiatry 58:457-467.

Antonova E., Sharma T., Morris R., Kumari V. (2004): The relationship between brain structure and neurocognition in schizophrenia: a selective review. Schizophr Res 70:117-145.

Ashburner J., Friston K.J. (2000): Voxel-based morphometry--the methods. Neuroimage 11:805-821.

Basser P.J., Pierpaoli C. (1996): Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J Magn Reson B 111(3):209-19.

Beaulieu C. (2002): The basis of anisotropic water diffusion in the nervous system - a technical review. NMR Biomed 15:435-455.

Bersani G., Orlandi V., Kotzalidis G.D., Pancheri P. (2002): Cannabis and schizophrenia: impact on onset, course, psychopathology and outcomes. Eur Arch Psychiatry Clin Neurosci 252:86-92.

Bleuler E. (1923): Lehrbuch der psychiatry. 4th edition. Berlin Springer.

Boydell J., van Os J., Caspi A., Kennedy N., Giouroukou E., Fearon P., Farrell M., Murray R.M. (2006): Trends in cannabis use prior to first presentation with schizophrenia, in South-East London between 1965 and 1999. Psychol Med 36:1441-1446.

Brouwer R.M., Hulshoff Pol H.E., Schnack H.G. (2010): Segmentation of MRI brain scans using non-uniform partial volume densities. Neuroimage 49:467-477.

Buhler B., Hambrecht M., Loffler W., an der Heiden W., Hafner H. (2002): Precipitation and determination of the onset and course of schizophrenia by substance abuse--a retrospective and prospective study of 232 population-based first illness episodes. Schizophr Res 54:243-251.

Cahn W., Hulshoff Pol H.E., Lems E.B., van Haren N.E., Schnack H.G., van der Linden J.A., Schothorst P.F., van Engeland H., Kahn R.S. (2002): Brain volume changes in first-episode schizophrenia: a 1-year follow-up study. Arch Gen Psychiatry 59:1002-1010.

Cahn W., van Haren N.E., Hulshoff Pol H.E., Schnack H.G., Caspers E., Laponder D.A., Kahn R.S. (2006): Brain volume changes in the first year of illness and 5-year outcome of schizophrenia. Br J Psychiatry 189:381-382.

Cantor-Graae E. (2007): The contribution of social factors to the development of schizophrenia: a review of recent findings. Can J Psychiatry 52:277-286.

Caspari D. (1999): Cannabis and schizophrenia: results of a follow-up study. Eur Arch Psychiatry Clin Neurosci 249:45-49.

Davatzikos C., Bryan N. (1996): Using a deformable surface model to obtain a shape representation of the cortex. IEEE Trans Med Imaging 15:785-795.

Davis K.L., Buchsbaum M.S., Shihabuddin L., Spiegel-Cohen J., Metzger M., Frecska E., Keefe R.S., Powchik P. (1998): Ventricular enlargement in poor-outcome schizophrenia. Biol Psychiatry 43:783-793.

DeLisi L.E., Sakuma M., Maurizio A.M., Relja M., Hoff A.L. (2004): Cerebral ventricular change over the first 10 years after the onset of schizophrenia. Psychiatry Res 130:57-70.

DeLisi L.E., Sakuma M., Tew W., Kushner M., Hoff A.L., Grimson R. (1997): Schizophrenia as a chronic active brain process: a study of progressive brain structural change subsequent to the onset of schizophrenia. Psychiatry Res 74:129-140.

DeLisi L.E., Tew W., Xie S., Hoff A.L., Sakuma M., Kushner M., Lee G., Shedlack K., Smith A.M., Grimson R. (1995): A prospective follow-up study of brain morphology and cognition in first-episode schizophrenic patients: preliminary findings. Biol Psychiatry 38:349-360.

Dorph-Petersen K.A., Pierri J.N., Perel J.M., Sun Z., Sampson A.R., Lewis D.A. (2005): The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation: a comparison of haloperidol and olanzapine in macaque monkeys. Neuropsychopharmacology 30:1649-1661.

Dubertret C., Bidard I., Ades J., Gorwood P. (2006): Lifetime positive symptoms in patients with schizophrenia and cannabis abuse are partially explained by co-morbid addiction. Schizophr Res 86:284-290.

Ellison-Wright I., Bullmore E. (2009): Meta-analysis of diffusion tensor imaging studies in schizophrenia. Schizophr Res 108:3-10.

Fischl B., Dale A.M. (2000): Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A 97:11050-11055.

Goldman A.L., Pezawas L., Mattay V.S., Fischl B., Verchinski B.A., Chen Q., Weinberger D.R., Meyer-Lindenberg A. (2009): Widespread reductions of cortical thickness in schizophrenia and spectrum disorders and evidence of heritability. Arch Gen Psychiatry 66:467-477.

Goldstein, J.M., Levine R.R.J. (2000): Overview of sex differences in schizophrenia: where have we been and where are we do we go from here? In: Castle DJ, McGrath JJ, Kulkarni J, Women and Schizophrenia. Cambridge, MA: Cambridge University Press.

Gottesman I.I., Bertelsen A. (1989): Confirming unexpressed genotypes for schizophrenia. Risks in the offspring of Fischer's Danish identical and fraternal discordant twins. Arch Gen Psychiatry 46:867-872.

Gottesman, I.I. (1991): Schizophrenia Genesis-The origins of madness. New York, W.H. Freeman and Company.

Grech A., van Os J., Jones P.B., Lewis S.W., Murray R.M. (2005): Cannabis use and outcome of recent onset psychosis. Eur Psychiatry 20:349-353.

Green A.I., Tohen M.F., Hamer R.M., Strakowski S.M., Lieberman J.A., Glick I., Clark W.S. (2004): First episode schizophrenia-related psychosis and substance use disorders: acute response to olanzapine and haloperidol. Schizophr Res 66:125-135.

Greenstein D., Lerch J., Shaw P., Clasen L., Giedd J., Gochman P., Rapoport J., Gogtay N. (2006): Childhood onset schizophrenia: cortical brain abnormalities as young adults. J Child Psychol Psychiatry 47:1003-1012.

Gur R.E., Cowell P., Turetsky B.I., Gallacher F., Cannon T., Bilker W., Gur R.C. (1998): A follow-up magnetic resonance imaging study of schizophrenia. Relationship of neuroanatomical changes to clinical and neurobehavioral measures. Arch Gen Psychiatry 55:145-152.

Haug J.O. (1962): Pneumoencephalographic studies in mental disease. Acta Psychiatr Scand Suppl 38:1-104.

Hiroeh U., Appleby L., Mortensen P.B., Dunn G. (2001): Death by homicide, suicide, and other unnatural causes in people with mental illness: a population-based study. Lancet 358:2110-2112.

Ho B.C., Andreasen N.C., Nopoulos P., Arndt S., Magnotta V., Flaum M. (2003): Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. Arch Gen Psychiatry 60:585-594.

Honea R., Crow T.J., Passingham D., Mackay C.E. (2005): Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. Am J Psychiatry 162:2233-2245.

Hulshoff Pol H.E., Kahn R.S. (2008): What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. Schizophr Bull 34:354-366.

Johnstone E.C., Crow T.J., Frith C.D., Husband J., Kreel L. (1976): Cerebral ventricular size and cognitive impairment in chronic schizophrenia. Lancet 2:924-926.

Kabani N., Le Goualher G., MacDonald D., Evans A.C. (2001): Measurement of cortical thickness using an automated 3-D algorithm: a validation study. Neuroimage 13:375-380.

Kanaan R.A., Kim J.S., Kaufmann W.E., Pearlson G.D., Barker G.J., McGuire P.K. (2005): Diffusion tensor imaging in schizophrenia. Biol Psychiatry 58:921-929.

Kaplan en Sadok. (2009): Comprehensive textbook of psychiatry, ninth edition. Ed. Lippincott Williams and Wilkins.

Kasai K., Shenton M.E., Salisbury D.F., Hirayasu Y., Lee C.U., Ciszewski A.A., Yurgelun-Todd D., Kikinis R., Jolesz F.A., McCarley R.W. (2003a): Progressive decrease of left superior temporal gyrus grey matter volume in patients with first-episode schizophrenia. Am J Psychiatry 160:156-164.

Kasai K., Shenton M.E., Salisbury D.F., Hirayasu Y., Onitsuka T., Spencer M.H., Yurgelun-Todd D.A., Kikinis R., Jolesz F.A., McCarley R.W. (2003b): Progressive decrease of left Heschl gyrus and planum temporale grey matter volume in first-episode schizophrenia: a longitudinal magnetic resonance imaging study. Arch Gen Psychiatry 60:766-775.

Kraepelin E. (1913): Dementia praecox and paraphrenia. Edinburgh: E&S Livingstone.

Kubicki M., McCarley R., Westin C.F., Park H.J., Maier S., Kikinis R., Jolesz F.A., Shenton M.E. (2007): A review of diffusion tensor imaging studies in schizophrenia. J Psychiatr Res 41:15-30.

Kuperberg G.R., Broome M.R., McGuire P.K., David A.S., Eddy M., Ozawa F., Goff D., West W.C., Williams S.C., van der Kouwe A.J., Salat D.H., Dale A.M., Fischl B. (2003): Regionally localized thinning of the cerebral cortex in schizophrenia. Arch Gen Psychiatry 60:878-888.

Kyriakopoulos M., Vyas N.S., Barker G.J., Chitnis X.A., Frangou S. (2008): A diffusion tensor imaging study of white matter in early-onset schizophrenia. Biol Psychiatry 63(5):519-23

Le Bihan D., Breton E. (1985): Imagerie de diffusion in vivo par résonance magnétique nucléaire. Compte Rendus de l`Académie de Sciences Paris 301:1109-1112.

Lewis S.W. (1990): Computerised tomography in schizophrenia 15 years on. Br J Psychiatry Suppl :16-24.

Lieberman J., Chakos M., Wu H., Alvir J., Hoffman E., Robinson D., Bilder R. (2001): Longitudinal study of brain morphology in first episode schizophrenia. Biol Psychiatry 49:487-499.

Lieberman J.A., Alvir J.M., Koreen A., Geisler S., Chakos M., Sheitman B., Woerner M. (1996): Psychobiologic correlates of treatment response in schizophrenia. Neuropsychopharmacology 14:13S-21S.

Lieberman J.A., Tollefson G.D., Charles C., Zipursky R., Sharma T., Kahn R.S., Keefe R.S., Green A.I., Gur R.E., McEvoy J., Perkins D., Hamer R.M., Gu H., Tohen M. (2005): Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch Gen Psychiatry 62:361-370.

Linszen D.H., Dingemans P.M., Lenior M.E. (1994): Cannabis abuse and the course of recent-onset schizophrenic disorders. Arch Gen Psychiatry 51:273-279.

Maki P., Veijola J., Jones P.B., Murray G.K., Koponen H., Tienari P., Miettunen J., Tanskanen P., Wahlberg K.E., Koskinen J., Lauronen E., Isohanni M. (2005): Predictors of schizophrenia--a review. Br Med Bull 73-74:1-15.

Mathalon D.H., Pfefferbaum A., Lim K.O., Rosenbloom M.J., Sullivan E.V. (2003): Compounded brain volume deficits in schizophrenia-alcoholism comorbidity. Arch Gen Psychiatry 60:245-252.

Mathalon D.H., Sullivan E.V., Lim K.O., Pfefferbaum A. (2001): Progressive brain volume changes and the clinical course of schizophrenia in men: a longitudinal magnetic resonance imaging study. Arch Gen Psychiatry 58:148-157.

Mauri M., Volonteri L., De Gaspari I., Colasanti A., Brambilla M., Cerruti L. (2006): Substance abuse in first-episode schizophrenic patients: a retrospective study. Clin Pract Epidemol Ment Health 2:4.

McGuffin P., Owen M.J., Farmer A.E. (1995): Genetic basis of schizophrenia. Lancet 346:678-682.

Moncrieff J., Leo J. (2010): A systematic review of the effects of antipsychotic drugs on brain volume. Psychol Med 40:1409-1422.

Moore T.H., Zammit S., Lingford-Hughes A., Barnes T.R., Jones P.B., Burke M., Lewis G. (2007): Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet 370:319-328.

Narr K.L., Bilder R.M., Toga A.W., Woods R.P., Rex D.E., Szeszko P.R., Robinson D., Sevy S., Gunduz-Bruce H., Wang Y.P., DeLuca H., Thompson P.M. (2005a): Mapping cortical thickness and grey matter concentration in first episode schizophrenia. Cereb Cortex 15:708-719.

Narr K.L., Toga A.W., Szeszko P., Thompson P.M., Woods R.P., Robinson D., Sevy S., Wang Y., Schrock K., Bilder R.M. (2005b): Cortical thinning in cingulate and occipital cortices in first episode schizophrenia. Biol Psychiatry 58:32-40.

Narr K.L., Woods R.P., Thompson P.M., Szeszko P., Robinson D., Dimtcheva T., Gurbani M., Toga A.W., Bilder R.M. (2007): Relationships between IQ and regional cortical grey matter thickness in healthy adults. Cereb Cortex 17:2163-2171.

Navari S., Dazzan P. (2009): Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. Psychol Med :1-15.

Nesvag R., Lawyer G., Varnas K., Fjell A.M., Walhovd K.B., Frigessi A., Jonsson E.G., Agartz I. (2008): Regional thinning of the cerebral cortex in schizophrenia: effects of diagnosis, age and antipsychotic medication. Schizophr Res 98:16-28.

Pantelis C., Yucel M., Wood S.J., Velakoulis D., Sun D., Berger G., Stuart G.W., Yung A., Phillips L., McGorry P.D. (2005): Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. Schizophr Bull 31:672-696.

Pfefferbaum A., Sullivan E.V., Rosenbloom M.J., Mathalon D.H., Lim K.O. (1998): A controlled study of cortical grey matter and ventricular changes in alcoholic men over a 5-year interval. Arch Gen Psychiatry 55:905-912.

Posthuma D., De Geus E.J., Baare W.F., Hulshoff Pol H.E., Kahn R.S., Boomsma D.I. (2002): The association between brain volume and intelligence is of genetic origin. Nat Neurosci 5:83-84.

Raz S., Raz N. (1990): Structural brain abnormalities in the major psychoses: a quantitative review of the evidence from computerized imaging. Psychol Bull 108:93-108.

Saha S., Chant D., Welham J., McGrath J. (2005): A systematic review of the prevalence of schizophrenia. PLoS Med 2:e141.

Schnack H.G., Hulshoff Pol H.E., Baare W.F., Staal W.G., Viergever M.A., Kahn R.S. (2001a): Automated separation of grey and white matter from MR images of the human brain. Neuroimage 13:230-237.

Schnack H.G., Hulshoff H.E., Baare W.F., Viergever M.A., Kahn R.S. (2001b): Automatic segmentation of the ventricular system from MR images of the human brain. Neuroimage 14:95-104.

Semple D.M., McIntosh A.M., Lawrie S.M. (2005): Cannabis as a risk factor for psychosis: systematic review. J Psychopharmacol 19:187-194.

Sheitman B.B., Lee H., Strous R., Lieberman J.A. (1997): The evaluation and treatment of first-episode psychosis. Schizophr Bull 23:653-661.

Steen R.G., Mull C., McClure R., Hamer R.M., Lieberman J.A. (2006): Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. Br J Psychiatry 188:510-518.

Sullivan P.F., Kendler K.S., Neale M.C. (2003): Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch Gen Psychiatry 60:1187-1192.

Tandon R., Keshavan M.S., Nasrallah H.A. (2008): Schizophrenia, "just the facts" what we know in 2008. 2. Epidemiology and etiology. Schizophr Res 102:1-18.

Thompson P., Toga A.W. (1996): A surface-based technique for warping three-dimensional images of the brain. IEEE Trans Med Imaging 15:402-417.

Torrey E.F. (1988): Stalking the schizovirus. Schizophr Bull 14:223-229.

Toulopoulou T., Grech A., Morris R.G., Schulze K., McDonald C., Chapple B., Rabe-Hesketh S., Murray R.M. (2004): The relationship between volumetric brain changes and cognitive function: a family study on schizophrenia. Biol Psychiatry 56:447-453.

van Haren N.E., Hulshoff Pol H.E., Schnack H.G., Cahn W., Brans R., Carati I., Rais M., Kahn R.S. (2008): Progressive brain volume loss in schizophrenia over the course of the illness: evidence of maturational abnormalities in early adulthood. Biol Psychiatry 63:106-113.

van Haren N.E., Hulshoff Pol H.E., Schnack H.G., Cahn W., Mandl R.C., Collins D.L., Evans A.C., Kahn R.S. (2007): Focal grey matter changes in schizophrenia across the course of the illness: a 5-year follow-up study. Neuropsychopharmacology 32:2057-2066.

van Haren N.E., Koolschijn P.C., Cahn W., Schnack H.G., Hulshoff Pol H.E., Kahn R.S. (2010): Cigarette smoking and progressive brain volume loss in schizophrenia. Eur Neuropsychopharmacol 20:454-458.

van Haren N.E.M., Schnack H.G., Cahn W., van der Heuvel M., Lepage C., Collins L. Evans A., Hulshoff Pol H.E., Kahn R.S. (2011): Changes in cortical thickness across the course of the illness in schizophrenia. In press.

Van Horn J.D., McManus I.C. (1992): Ventricular enlargement in schizophrenia. A meta-analysis of studies of the ventricle:brain ratio (VBR). Br J Psychiatry 160:687-697.

van Os J., Murray R. (2008a): Gene-environment interactions in schizophrenia. Introduction. Schizophr Bull 34:1064-1065.

van Os J., Rutten B.P., Poulton R. (2008b): Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. Schizophr Bull 34:1066-1082.

Veen N.D., Selten J.P., van der Tweel I., Feller W.G., Hoek H.W., Kahn R.S. (2004): Cannabis use and age at onset of schizophrenia. Am J Psychiatry 161:501-506.

Vernon A.C., Natesan S., Modo M., Kapur S. (2011): Effect of chronic antipsychotic treatment on brain structure: a serial magnetic resonance imaging study with ex vivo and postmortem confirmation. Biol Psychiatry 69:936-944.

Vita A., de Peri L., Silenzi C., Dieci M. (2006): Brain morphology in first-episode schizophrenia: a meta-analysis of quantitative magnetic resonance imaging studies. Schizophr Res 82:75-88.

Weinberger D.R. (1984): Computed tomography (CT) findings in schizophrenia: speculation on the meaning of it all. J Psychiatr Res 18:477-490.

White T., Andreasen N.C., Nopoulos P., Magnotta V. (2003): Gyrification abnormalities in childhood- and adolescent-onset schizophrenia. Biol Psychiatry 54:418-426.

Wolff S.D., Balaban R.S. (1994): Magnetization transfer imaging: practical aspects and clinical applications. Radiology 192(3):593-9.

Wright I.C., Rabe-Hesketh S., Woodruff P.W., David A.S., Murray R.M., Bullmore E.T. (2000): Meta-analysis of regional brain volumes in schizophrenia. Am J Psychiatry 157:16-25.

Chapter 2

Excessive brain volume loss over time in cannabis-using first episode schizophrenia patients

Monica Rais | Wiepke Cahn | Neeltje E.M. van Haren | Hugo G. Schnack | Esther Caspers

Hilleke E. Hulshoff Pol | René S. Kahn

American Journal of Psychiatry 2008; 165: 490-496

Abstract

Cerebral grey matter volume reductions have been found to progress over time in schizophrenia, with larger decreases related to poorer outcome, which has also been associated with cannabis use in schizophrenia patients. Progressive grey matter changes in patients who use cannabis may be more extensive than in those who do not. Patients with recent-onset schizophrenia (N=51) and matched healthy subjects (N=31) were included. For all subjects, magnetic resonance imaging scans were obtained at inclusion (T0) and at 5-year follow-up (T5). Nineteen patients used cannabis but no other illicit drugs; 32 patients did not use any drugs during the 5-year follow-up. At T5, clinical outcome was measured. Cumulative amount of antipsychotic medication during the interval was calculated. At T0 and T5, total brain, grey and white matter, and lateral and third ventricle volumes were measured. Univariate analysis of covariance and pairwise comparisons were performed. Schizophrenia patients showed a larger grey matter volume decrease over time than healthy subjects. They also showed larger increases in lateral and third ventricle volumes than healthy subjects and patients who did not use cannabis during follow-up. This decrement was significantly more pronounced in the patients who continued to use cannabis. These differences could not be attributed to outcome or baseline characteristics. In conclusion, first-episode schizophrenia patients who use cannabis show a more pronounced brain volume reduction over a 5 year follow-up than patients with schizophrenia who do not use cannabis. These results may help explain some of the detrimental effects of cannabis use in schizophrenia.

Introduction

Although the neurobiological basis of schizophrenia is not yet fully understood (Mueser and McGurk, 2004), cross-sectional magnetic resonance imaging (MRI) studies in patients with schizophrenia have shown overall decreases in cortical grey and white matter volume and in smaller brain structures such as the amygdala-hippocampus complex, as well as volume increases in the lateral ventricles (Wright et al., 2000; Honea et al., 2005). Moreover, the grey matter volume decrease and ventricular increase appear to progress over time with most (Mathalon et al., 2001; Lieberman et al., 2005; Cahn et al., 2002; Ho et al., 2003; Lieberman et al., 2001; Davis et al., 1998; Lieberman et al., 1996; van Haren et al., 2007; van Haren et al., 2008), but not all (DeLisi et al., 2004), studies reporting the largest brain volume decreases in patients with the poorest outcome.

Of interest, poor clinical and functional outcome in schizophrenia has been consistently associated with cannabis use. Cannabis (ab-)use occurs in 28%–50% of patients with schizophrenia (Green et al., 2004; Boydell et al., 2006) , with those using cannabis having more positive (Dubertret et al., 2006; Buhler et al., 2002; Grech et al., 2005; Mauri et al., 2006; Bersani et al., 2002), but not negative (Dubertret et al., 2006; Grech et al., 2005; Bersani et al., 2002; Peralta and Cuesta, 1992; Compton et al., 2004) symptoms, an earlier disease onset (Veen et al., 2004), and an increased number of psychotic relapses or exacerbations (Grech et al., 2005; Linszen et al., 1994; Caspari, 1999) compared to nonusing patients. Thus, if brain volume changes over time are most prominent in the patients with a poor outcome, and poor outcome is associated with cannabis use, one would expect cannabis use to be associated with excessive decreases in brain volumes. However, no longitudinal studies examining the effect of cannabis use on brain changes in schizophrenia have been conducted to date. In a cross-sectional study, we found that brain volumes in cannabis-using patients with recent-onset schizophrenia did not differ from those of cannabis-naive patients (Cahn et al., 2004). This is consistent with the results of previous cross-sectional brain imaging studies comparing healthy subjects who use cannabis with those who do not (for a review see Quickfall and Crockford, 2006). Brain volume changes over time, however, may prove to be more sensitive in detecting the effect of cannabis on the brains of schizophrenia patients. Indeed, cross-sectional MRI studies have failed to predict outcome over time (Caspari, 1999), whereas longitudinal MRI studies show that an excessive decrease in grey matter volume during the early course of the illness is associated with poorer functioning 2 (Cahn et al., 2002) and 5 (Cahn et al., 2006) years later. Therefore, we hypothesized that in view of the deleterious effects of cannabis on clinical outcome and the reported relationship between outcome and

brain volume changes over time, cannabis-using patients with schizophrenia would show larger brain volume decreases over 5 years compared to nonusing patients and healthy comparison subjects.

Method

Subjects

Patients with first-episode schizophrenia (N=51) and healthy comparison subjects (N=31) recruited from the First-Episode Schizophrenia Research Program at the University Medical Center Utrecht, Utrecht, the Netherlands, were included in the study. The cohort was followed for a period of 5 years to examine the relationship between brain morphology, the use of cannabis, and outcome. In this subgroup, patients and comparison subjects were included when two MRI scans were available with an interval of approximately 5 years. All patients met the DSM-IV criteria for schizophrenia and did not report drug use other than cannabis during the scan interval.

Both at baseline and at follow-up, the subjects were physically healthy and did not have a history of head injury. At inclusion, the patients were assessed with the Comprehensive Assessment of Symptoms and History (Andreasen et al., 1992) by two trained raters who independently determined the diagnosis and achieved consensus afterward. All patients met the DSM-IV criteria for schizophrenia and did not report drug use other than cannabis during the scan interval. Severity of illness was measured with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Drug use was assessed with the Composite International Diagnostic Interview (CIDI) (Robins et al., 1988), and the information provided by the patient was confirmed by a relative. Random urine toxicology tests were performed throughout the study. Patients with a lifetime diagnosis of abuse or dependence of a substance other than cannabis (except nicotine) were excluded. Five years later (T5), all 51 patients were reassessed for diagnosis (the Comprehensive Assessment of Symptoms and History), the need for care [the Camberwell Assessment of Needs (Phelan et al., 1995)] and level of functioning (the Global Assessment of Functioning [GAF]), drug use (the CIDI), and symptom profile (the PANSS). The time interval between inclusion in the study at T0 and follow-up measurement at T5 is referred to as the scan interval.

At baseline (T0), 39 patients fulfilled DSM-IV criteria for schizophrenia, nine for schizophreniform disorder, one for schizoaffective disorder, and two for psychosis not otherwise specified; at T5, all 51 patients met DSM-IV criteria for schizophrenia. The number of days spent in the hospital

between T0 and T5 was recorded. In addition, every patient was monitored carefully for the amount and type of medication prescribed between T0 and T5. Nineteen patients used only cannabis and no other illicit drugs during the scan interval, and 32 patients did not use any illicit drugs during the scan interval. Of this latter group, 15 patients never used cannabis during their lifetime, and 17 patients stopped using cannabis before baseline.

At follow-up, information was obtained on the average number of alcohol consumptions per week. Two patients in the cannabis-using group and two patients in the nonusing group met the DSM-IV criteria for alcohol abuse, whereas no healthy comparison subjects met these criteria. The three groups did not differ significantly on average number of alcohol consumptions per week at follow-up. To calculate the cumulative dose of typical antipsychotic medication, a table from the Dutch National Health Service was used to derive haloperidol equivalents. The patients used only one antipsychotic at a time. For atypical antipsychotics, the respective pharmaceutical companies suggested how to convert the dose into haloperidol equivalents (clozapine, 40:1; olanzapine, 2.5:1; risperidone, 1:1; sulpiride, 170:1; quetiapine, 50:1; and sertindole, 2:1). The healthy comparison subjects were screened with the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (Endicott and Spitzer, 1978) and fulfilled criteria for "never mentally ill" both at baseline and follow-up. The groups were matched for sex, age, handedness, and socioeconomic status of their parents (expressed as the highest level of education completed by one of the parents). The healthy comparison subjects did not use any illicit substances before or during the study. After a complete description of the study to the subjects, written informed consent was obtained

MRI Procedures and Measurements

MRIs were acquired on a Philips NT (Best, the Netherlands) scanner operating at 1.5 T for all subjects. A three-dimensional fast field echo (TE=4.6 msec, TR=30 msec, flip angle=30°, field of view=256x256 mm^2) scan with 160–180 contiguous coronal 1.2-mm slices and a T2-weighted dual-echo turbo spin echo (TE1=14 msec, TE2=80 msec, TR=6,350 msec, flip angle=90°, field of view=256x256 mm^2) scan with 120 contiguous coronal 1.6-mm slices of the whole head were used for the quantitative measurements. Processing was done on the neuroimaging computer network of the Department of Psychiatry at the University Medical Center Utrecht. Processing procedures have been described before (Hulshoff Pol et al., 2002; van Haren et al., 2003). In short, all images were coded to ensure investigator blindness to subject identification and diagnosis; scans were put into Talairach frames without scaling and corrected for inhomogeneities in the magnetic field. Quantitative assessments of intracranial, total brain, grey and white matter of

the cerebrum, and lateral and third ventricle volumes were performed on the basis of histogram analyses and a series of mathematical morphology operators to connect all voxels of interest; they were validated previously (Schnack et al., 2001a; Schnack et al., 2001b).

Statistical Analysis

Data were examined for outliers and normality of the distribution. Duration of hospitalization, illness duration, and lateral ventricle volume at T0 were not normally distributed, so these quantities were logarithmically transformed. No further transformation was performed on the data. To assess whether the groups differed for demographic or clinical variables, multiple analyses of variance were conducted for noncategorical variables and chi-square analyses for categorical variables (Table 1).

Table 1 | Demographic and clinical data of the cannabis-using and non-using schizophrenia patients and healthy comparison subjects.

	Cannabis- N=32				**Cannabis+ N=19**				**Controls N=31**				
	Mean/N	SD	Range		Mean/N	SD	Range		Mean/N	SD	Range		Sig.
Sex, No. of subjects m/f	26/6				19/0				25/6				NS
Handedness, No. of subjects r/l/a	27/2/3				18/0/1				26/5/0				NS
Age, yrs	23.28	5.10	15.70	37.03	21.83	3.91	16.73	31	24.72	6.66	16.74	40.21	NS
Parental education level, yrs	12.77	6.66	6	17	13.32	3.59	6	17	13.68	2.83	10	17	NS
MRI interval, yrs	5.28	0.50	4.13	6.39	5.35	0.64	4.54	7.08	5.21	0.18	4.78	5.50	NS
Age first psychosis, yrs	22.54	4.94	14.24	36.63	20.53	3.93	16.45	29.64					NS
Duration of illness, days	350.61	388.07	9	1408	429	631.65	66	2866					NS
PANSS T0 positive	18.82	5.19	9	28.00	15.63	5.73	7	25					NS
PANSS T0 negative	19.29	4.90	10	30	17.06	4.75	8	24					NS
PANSS change positive*	-5.59	4.98	-17.00	4.00	-1.94	6.43	-15.00	12.00					0.043
PANSS change negative*	-6.15	6.25	-15.00	10.00	-1.00	7.21	-16.00	11.00					0.018
CAN T5 total – staff	8.87	5.34	0	20	11.94	7.60	0	24					NS
GAF T5	52.62	17.90	30	90	53.94	20.37	15	90					NS
Days of hospitalization	120.48	104.24	0	430	171.26	254.83	0	1062					NS
Cumulative antipsychotic medication T5 (mg eq. Haloperidol)	13711	6968	2966	30873	12302	5767	1511	20810					NS
Type antipsychotic medication before T0 (naive/typ/atyp/both)	14/13/1/4				7/6/2/4								NS
Type antipsychotic medication T0T5 (typ/atyp/both/missing)	0/13/18/1				0/7/11/1								NS
Duration of treatment at T0 (days)	77	126	0	483	119	142	0	413					NS

PANSS: Positive And Negative Syndrome Scale, CAN: Camberwell Assessment of Needs, GAF: Global Assessment of Functioning. *Significant differences were found between cannabis-using and non-using patients in change in positive symptoms (F=4.35; df= 42, 1; p=0.043) and change in negative symptoms (F=6.08; df=42, 1; p=0.018) over five years.

To assess whether baseline brain volumes differed between patients with first-episode schizophrenia who used cannabis during the interval, patients with first-episode schizophrenia who did not use cannabis during the interval, and healthy comparison subjects, univariate analyses of covariance were performed with brain volumes at T0 as dependent variable and group (cannabis-using, non-cannabis-using, healthy comparison) as independent variable. Intracranial volume, age, and gender served as covariates.

Since we hypothesized that changes in tissue volume are proportional to baseline tissue volume, percentage volume change during the scan interval was calculated by dividing the absolute volume change by volume at baseline multiplied by 100% ([(T5–T0)/T0]x100%) for each individual. To assess the difference in brain volume change between the groups, multiple general linear model univariate analyses of covariance were performed with percentage volume change as a dependent variable and group (cannabis-using, non-cannabis-using, healthy comparison) as an independent variable. Age at T0, gender, and intracranial volume served as covariates in all analyses. In case of significant findings, pairwise comparisons of main effects (least significant difference test) were performed.

To estimate clinical outcome in the different groups of patients, change in positive and negative symptoms over 5 years were quantified and baseline PANSS scores were subtracted from follow-up PANSS scores (PANSS T5 – PANSS T0).

In case of significant differences in volume change between the groups, we investigated the association between volume change and change in positive and negative symptom score between T0 and T5, score on the Camberwell Assessment of Need, and the GAF score at T5. All patients were included in multiple linear regression analyses with volume change as the dependent variable and clinical measure as the independent variable. Second, we repeated this analysis for each patient group separately.

Results

As shown in Table 1, the groups did not significantly differ with regard to sex, handedness, age, parental education, and scan interval.

At inclusion and follow-up, the cannabis-using subjects and the subjects not using cannabis did not differ significantly on positive and negative symptoms and type and cumulative amount of

medication during the interval. Cumulative duration of hospitalization did not differ significantly between the two patient groups. However, the subjects not using cannabis showed a small but significant improvement in positive and negative symptoms compared to the cannabis-using group over the follow-up interval. At inclusion, the cannabis-using and non-cannabis-using patients and healthy comparison subjects did not differ significantly on any of the brain volume measurements except for third ventricle volume at baseline, which was significantly larger in the non-cannabis-using group in relation to the healthy comparison subjects.

As shown in Table 2, a significant main effect for group was found for change in cerebral grey matter ($F=8.11$, $df=5, 76$, $p=0.001$), lateral ventricle ($F=3.87$, $df=5, 76$, $p<0.03$), and third ventricle ($F=4.04$, $df=5, 76$, $p<0.03$) volume over the 5-year follow-up. A tendency was found for total brain volume change ($F=2.78$, $df=5, 76$, $p<0.07$). No significant group effect was found for white matter volume changes.

Table 2 | Brain volumes at baseline and five year follow-up of schizophrenia patients who used and did not used cannabis

	subjects not using cannabis (N=32)				subjects using cannabis (N=19)				healthy comparison subjects (N=31)						
Brain Volume (ml)	**Baseline**		**5-year follow-up**		**Baseline**		**5-year follow-up**		**Baseline**		**5-year follow-up**				
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p
Intracranial	1512	145	1502	149	1491	134	1493	132	1557	152	1556	155			
Total brain	1324	125	1309	125	1308	111	1281	119	1368	131	1363	131	2.78	5,76	<0.07
Cerebral grey matter	695	60	664	64	685	68	635	58	707	73	694	64	8.11	5,76	0.001
Cerebral white matter	468	65	480	62	458	46	479	56	497	70	501	72	1.96	5,76	0.15
Lateral ventricles	16.44	9.79	17.73	10.43	13.70	7.23	16.11	7.85	15.99	10.36	16.76	11.12	3.87	5,76	<0.03
Third ventricle	0.92	0.34	0.98	0.41	0.87	0.33	1.01	0.34	0.74	0.29	0.74	0.29	4.04	5,76	<0.03

Pairwise comparisons showed significantly larger grey matter volume loss (Figure 1) over time in cannabis-using patients in relation to healthy comparison subjects (mean difference= –5.09%; standard error=1.28%, p<0.001) and versus patients not using cannabis (mean difference=–2.67%; standard error=1.21%, p=0.03) and in non-cannabis-using patients in relation to healthy comparison subjects (mean difference=–2.42%; standard error=1.02%, p<0.03).

Furthermore, cannabis-using patients showed a more pronounced lateral ventricle enlargement (Figure 2) over time in relation to healthy comparison subjects (mean difference=14.65%; standard error=5.34%, p=0.008) and compared to non-cannabis-using patients (mean difference=10.99%; standard error=5.05%, p<0.04).

Cannabis-using patients also showed a more pronounced third ventricle increase (Figure 3) in relation to healthy comparison subjects (mean difference=19.07%; standard error=6.87%, p=0.007) and patients not using cannabis (mean difference=14.89%; standard error=6.50%, p<0.03).

An increase in third and lateral ventricle volume during the interval was related to a higher Camberwell Assessment of Needs score; i.e., patients needed more help in daily life functioning (p<0.03 and p=0.006, respectively). Moreover, an increase in lateral ventricle volume was related to a lower GAF score (p=0.052). However, after dividing the patient group into cannabis-using and nonusing groups, no significant correlations with the clinical variables were present.

Figure 1

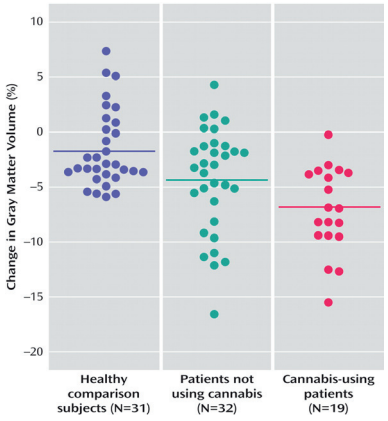


Figure 2

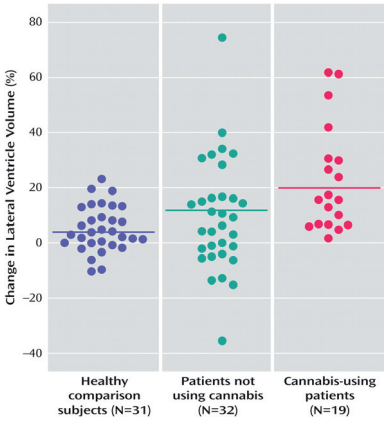


Figure 3

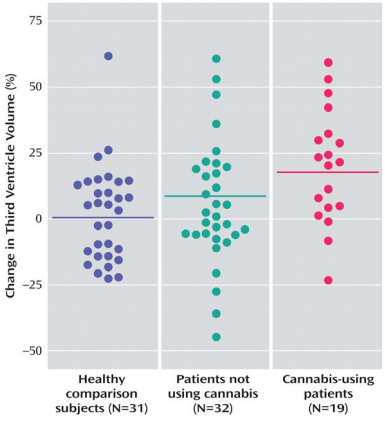


Figure 1 | Brain Volume Changes Over Time in Schizophrenia Patients and Healthy Comparison Subjects: Grey Matter Volume[a]

[a] The univariate comparison is significant (F=8.10, df=5, 76, p=0.001). Pairwise comparisons show the following: cannabis-using versus healthy comparison: p<0.001; cannabis-using versus non-cannabis-using: p=0.03; non-cannabis-using versus healthy comparison: p<0.03.

Figure 2 | Brain Volume Changes Over Time in Schizophrenia Patients and Healthy Comparison Subjects: Lateral Ventricle Volume[a]

[a] The univariate comparison is significant (F=3.90, df=5, 76, p<0.03). Pairwise comparisons show the following: cannabis-using versus healthy comparison: p=0.008; cannabis-using versus non-cannabis-using: p<0.04; non-cannabis-using versus healthy comparison: p=0.40.

Figure 3 | Brain Volume Changes Over Time in Schizophrenia Patients and Healthy Comparison Subjects: Third Ventricle Volume[a]

[a] The univariate comparison is significant (F=4.04, df=5, 76, p<0.03). Pairwise comparisons show the following: cannabis-using versus healthy comparison: p=0.007; cannabis-using versus non-cannabis-using: p<0.03; non-cannabis-using versus healthy comparison: p=0.45.

Discussion

This study finds that first-episode patients with schizophrenia who use cannabis show a more pronounced brain volume reduction over a 5-year follow-up (as expressed in lateral and third ventricle enlargement and grey matter loss) than patients with schizophrenia who do not use cannabis and compared to healthy subjects. Brain volume changes were measured over a 5-year interval in 19 first-episode schizophrenia patients who used cannabis during the interval, 32 first-episode schizophrenia patients who did not use cannabis during follow-up, and 31 cannabis-naive healthy subjects.

Finding progressive brain volume loss in schizophrenia patients, particularly of grey matter, is consistent with reports in high risk, first-episode, and chronic schizophrenia (for a review see Pantelis et al., 2005). Since most (Mathalon et al., 2001; Lieberman et al., 2005; Cahn et al., 2002; Ho et al., 2003; Lieberman et al., 2001; Davis et al., 1998; Lieberman et al., 1996; van Haren et al., 2007; van Haren et al., 2008), but not all (DeLisi et al., 2004), studies find this decrease to be related to outcome, one could argue that the excessive decrease, as found in the cannabis-using group, is related to their slightly poorer outcome as they had less improvement in symptoms than nonusers. However, it is unlikely that the excessive brain volume loss in the cannabis-using patients can be wholly attributed to poorer outcome since global functional outcome measures and the amount of days hospitalized during the follow-up period did not significantly differ between the patients who used and those who did not use cannabis.

No significant correlations were present between brain volume change and measures of symptomatic and functional outcome in either of the patient groups. This could be due to the relatively small number of subjects in each group, which reduces the power to find significant associations.

Of importance, the excessive brain volume loss in the cannabis-using group could not be attributed to differences in baseline characteristics, such as brain volume or clinical measures. Indeed, as reported previously (Cahn et al., 2004), the cannabis-using group did not display larger brain volume abnormalities at onset compared to the nonusing group (nor versus healthy subjects). Similarly, although medication has been reported to affect brain volume loss over time (Lieberman et al., 2005; Cahn et al., 2002; van Haren et al., 2007), the effects of medication cannot explain the excessive decrease in the cannabis-using patients since medication use over the follow-up period was qualitatively and quantitatively similar in both groups.

It could be argued that cannabis may amplify the pre-existent vulnerability to brain volume changes associated with schizophrenia. The mechanism by which cannabis may cause neuronal damage in schizophrenia patients remains unclear. It could either be a direct consequence of cannabis intake or occur as a consequence of psychotic symptoms in schizophrenia that are associated with cannabis use (Dubertret et al., 2006; Buhler et al., 2002; Grech et al., 2005; Mauri et al., 2006; Bersani et al., 2002). Indeed, it has been suggested that brain changes in the early stages of schizophrenia are the result of the "toxic" effect of the psychotic state (Lieberman et al., 2001). This would be consistent with our finding that the excessive brain volume decrease in the patients who continued to use cannabis was associated with less improvement in psychotic symptoms.

Since antipsychotic medication, especially atypical antipsychotic medication, has been suggested to attenuate the progressive brain changes in schizophrenia (Lieberman et al., 2005; Cahn et al., 2002; van Haren et al., 2007; Lieberman et al., 2001), excessive brain volume loss could also have been caused by noncompliance to antipsychotic medication in the cannabis-using patients. Indeed, it has been shown that patients who use cannabis are less compliant to prescribed antipsychotic medication (DeQuardo et al., 1994; Margolese et al., 2006). Of interest, our group showed more negative symptoms compared to those reported in an earlier longitudinal study by Grech et al. (Grech et al., 2005). One would expect that patients with more prominent negative symptoms and poor social skills are less capable of gaining access to illicit drugs. However, in the Netherlands, personal use of cannabis is not illegal. Therefore, it is relatively easy for patients, even for those with more prominent negative symptoms and more impaired social skills, to have access to the drug. For the same reason, patients might be more likely to provide reliable information about drug intake.

Several limitations of this study should be taken into consideration. First, the number of patients included was limited. Second, we did not include a healthy comparison group using cannabis. However, several cross-sectional studies have failed to demonstrate an association between cannabis use and brain volume loss in healthy subjects (for a review see Quickfall and Crockford, 2006). Third, the amount of cannabis used was estimated by the patients and their relatives. Although we are confident about whether a subject used or did not use cannabis, it is difficult to quantify the exposure because of differences in tetrahydrocannabinol (THC) content in cannabis cigarettes. Therefore, no information can be provided regarding a dose-response relationship between THC intake and brain volume change. Moreover, our study could not address the issue of direction of causality. In other words, it remains unclear whether brain volume loss results

in a greater risk for using cannabis or whether continuous use of cannabis leads to excessive brain volume loss. Finally, owing to limited statistical power, we did not correct for multiple comparisons.

In conclusion, this study found a progressive grey matter decrease in schizophrenia during the first 5 years of the illness, which was more pronounced in patients who continued using cannabis after illness onset compared to patients and healthy subjects who did not use cannabis during the follow-up period. The patients who continued to use cannabis showed a less pronounced improvement in positive and negative symptoms compared to nonusing patients. Although further studies need to be conducted to confirm whether the brain volume loss is a direct or an indirect effect of cannabis in schizophrenia, this study suggests that some of the detrimental effects of cannabis on the course of illness may be explained by its effect on the progression of brain changes in schizophrenia.

Reference List

Andreasen N.C., Flaum M., Arndt S. (1992): The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. Arch Gen Psychiatry 49:615-623.

Bersani G., Orlandi V., Kotzalidis G.D., Pancheri P. (2002): Cannabis and schizophrenia: impact on onset, course, psychopathology and outcomes. Eur Arch Psychiatry Clin Neurosci 252:86-92.

Boydell J., van Os J., Caspi A., Kennedy N., Giouroukou E., Fearon P., Farrell M., Murray R.M. (2006): Trends in cannabis use prior to first presentation with schizophrenia, in South-East London between 1965 and 1999. Psychol Med 36:1441-1446.

Buhler B., Hambrecht M., Loffler W., an der Heiden W., Hafner H. (2002): Precipitation and determination of the onset and course of schizophrenia by substance abuse--a retrospective and prospective study of 232 population-based first illness episodes. Schizophr Res 54:243-251.

Cahn W., Hulshoff Pol H.E., Caspers E., van Haren N.E., Schnack H.G., Kahn R.S. (2004): Cannabis and brain morphology in recent-onset schizophrenia. Schizophr Res 67:305-307.

Cahn W., Hulshoff Pol H.E., Lems E.B., van Haren N.E., Schnack H.G., van der Linden J.A., Schothorst P.F., van Engeland H., Kahn R.S. (2002): Brain volume changes in first-episode schizophrenia: a 1-year follow-up study. Arch Gen Psychiatry 59:1002-1010.

Cahn W., van Haren N.E., Hulshoff Pol H.E., Schnack H.G., Caspers E., Laponder D.A., Kahn R.S. (2006): Brain volume changes in the first year of illness and 5-year outcome of schizophrenia. Br J Psychiatry 189:381-382.

Caspari D. (1999): Cannabis and schizophrenia: results of a follow-up study. Eur Arch Psychiatry Clin Neurosci 249:45-49.

Compton M.T., Furman A.C., Kaslow N.J. (2004): Lower negative symptom scores among cannabis-dependent patients with schizophrenia-spectrum disorders: preliminary evidence from an African American first-episode sample. Schizophr Res 71:61-64.

Davis K.L., Buchsbaum M.S., Shihabuddin L., Spiegel-Cohen J., Metzger M., Frecska E., Keefe R.S., Powchik P. (1998): Ventricular enlargement in poor-outcome schizophrenia. Biol Psychiatry 43:783-793.

DeLisi L.E., Sakuma M., Maurizio A.M., Relja M., Hoff A.L. (2004): Cerebral ventricular change over the first 10 years after the onset of schizophrenia. Psychiatry Res 130:57-70.

DeQuardo J.R., Carpenter C.F., Tandon R. (1994): Patterns of substance abuse in schizophrenia: nature and significance. J Psychiatr Res 28:267-275.

Dubertret C., Bidard I., Ades J., Gorwood P. (2006): Lifetime positive symptoms in patients with schizophrenia and cannabis abuse are partially explained by co-morbid addiction. Schizophr Res 86:284-290.

Endicott J., Spitzer R.L. (1978): A diagnostic interview: the schedule for affective disorders and schizophrenia. Arch Gen Psychiatry 35:837-844.

Grech A., van Os J., Jones P.B., Lewis S.W., Murray R.M. (2005): Cannabis use and outcome of recent onset psychosis. Eur Psychiatry 20:349-353.

Green A.I., Tohen M.F., Hamer R.M., Strakowski S.M., Lieberman J.A., Glick I., Clark W.S. (2004): First episode schizophrenia-related psychosis and substance use disorders: acute response to olanzapine and haloperidol. Schizophr Res 66:125-135.

Ho B.C., Andreasen N.C., Nopoulos P., Arndt S., Magnotta V., Flaum M. (2003): Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. Arch Gen Psychiatry 60:585-594.

Honea R., Crow T.J., Passingham D., Mackay C.E. (2005): Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. Am J Psychiatry 162:2233-2245.

Hulshoff Pol H.E., Schnack H.G., Bertens M.G., van Haren N.E., van der Tweel I., Staal W.G., Baare W.F., Kahn R.S. (2002): Volume changes in grey matter in patients with schizophrenia. Am J Psychiatry 159:244-250.

Kay S.R., Fiszbein A., Opler L.A. (1987): The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13:261-276.

Lieberman J., Chakos M., Wu H., Alvir J., Hoffman E., Robinson D., Bilder R. (2001): Longitudinal study of brain morphology in first episode schizophrenia. Biol Psychiatry 49:487-499.

Lieberman J.A., Alvir J.M., Koreen A., Geisler S., Chakos M., Sheitman B., Woerner M. (1996): Psychobiologic correlates of treatment response in schizophrenia. Neuropsychopharmacology 14:13S-21S.

Lieberman J.A., Tollefson G.D., Charles C., Zipursky R., Sharma T., Kahn R.S., Keefe R.S., Green A.I., Gur R.E., McEvoy J., Perkins D., Hamer R.M., Gu H., Tohen M. (2005): Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch Gen Psychiatry 62:361-370.

Linszen D.H., Dingemans P.M., Lenior M.E. (1994): Cannabis abuse and the course of recent-onset schizophrenic disorders. Arch Gen Psychiatry 51:273-279.

Margolese H.C., Carlos N.J., Tempier R., Gill K. (2006): A 12-month prospective follow-up study of patients with schizophrenia-spectrum disorders and substance abuse: changes in psychiatric symptoms and substance use. Schizophr Res 83:65-75.

Mathalon D.H., Sullivan E.V., Lim K.O., Pfefferbaum A. (2001): Progressive brain volume changes and the clinical course of schizophrenia in men: a longitudinal magnetic resonance imaging study. Arch Gen Psychiatry 58:148-157.

Mauri M., Volonteri L., De Gaspari I., Colasanti A., Brambilla M., Cerruti L. (2006): Substance abuse in first-episode schizophrenic patients: a retrospective study. Clin Pract Epidemol Ment Health 2:4.

Mueser K.T., McGurk S.R. (2004): Schizophrenia. Lancet 363:2063-2072.

Pantelis C., Yucel M., Wood S.J., Velakoulis D., Sun D., Berger G., Stuart G.W., Yung A., Phillips L., McGorry P.D. (2005): Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. Schizophr Bull 31:672-696.

Peralta V., Cuesta M.J. (1992): Influence of cannabis abuse on schizophrenic psychopathology. Acta Psychiatr Scand 85:127-130.

Phelan M., Slade M., Thornicroft G., Dunn G., Holloway F., Wykes T., Strathdee G., Loftus L., McCrone P., Hayward P. (1995): The Camberwell Assessment of Need: the validity and reliability of an instrument to assess the needs of people with severe mental illness. Br J Psychiatry 167:589-595.

Quickfall J., Crockford D. (2006): Brain neuroimaging in cannabis use: a review. J Neuropsychiatry Clin Neurosci 18:318-332.

Robins L.N., Wing J., Wittchen H.U., Helzer J.E., Babor T.F., Burke J., Farmer A., Jablenski A., Pickens R., Regier D.A. (1988): The Composite International Diagnostic Interview. An epidemiologic Instrument suitable for use in conjunction with different diagnostic systems and in different cultures. Arch Gen Psychiatry 45:1069-1077.

Schnack H.G., Hulshoff Pol H.E., Baare W.F., Staal W.G., Viergever M.A., Kahn R.S. (2001a): Automated separation of grey and white matter from MR images of the human brain. Neuroimage 13:230-237.

Schnack H.G., Hulshoff H.E., Baare W.F., Viergever M.A., Kahn R.S. (2001b): Automatic segmentation of the ventricular system from MR images of the human brain. Neuroimage 14:95-104.

van Haren N.E., Cahn W., Hulshoff Pol H.E., Schnack H.G., Caspers E., Lemstra A., Sitskoorn M.M., Wiersma D., van den Bosch R.J., Dingemans P.M., Schene A.H., Kahn R.S. (2003): Brain volumes as predictor of outcome in recent-onset schizophrenia: a multi-center MRI study. Schizophr Res 64:41-52.

van Haren N.E., Hulshoff Pol H.E., Schnack H.G., Cahn W., Brans R., Carati I., Rais M., Kahn R.S. (2008): Progressive brain volume loss in schizophrenia over the course of the illness: evidence of maturational abnormalities in early adulthood. Biol Psychiatry 63:106-113.

van Haren N.E., Hulshoff Pol H.E., Schnack H.G., Cahn W., Mandl R.C., Collins D.L., Evans A.C., Kahn R.S. (2007): Focal grey matter changes in schizophrenia across the course of the illness: a 5-year follow-up study. Neuropsychopharmacology 32:2057-2066.

Veen N.D., Selten J.P., van der Tweel I., Feller W.G., Hoek H.W., Kahn R.S. (2004): Cannabis use and age at onset of schizophrenia. Am J Psychiatry 161:501-506.

Wright I.C., Rabe-Hesketh S., Woodruff P.W., David A.S., Murray R.M., Bullmore E.T. (2000): Meta-analysis of regional brain volumes in schizophrenia. Am J Psychiatry 157:16-25.

Chapter 3

Cannabis use and progressive cortical thickness loss in areas rich in CB1 receptors during the first five years of schizophrenia

Monica Rais | Neeltje E.M. van Haren | Wiepke Cahn | Hugo G. Schnack | Claude Lepage

D. Louis Collins | Alan C. Evans | Hilleke E. Hulshof-Pol | René S. Kahn

European Neuropsychopharmacology 2010; 20: 855-865.

Abstract

Cerebral grey matter volume reductions are progressive in schizophrenia, with larger grey matter volume decreases associated with cannabis use. It is unknown whether this grey matter loss is globally distributed over the entire brain or more pronounced in specific cortical brain regions. Fifty-one patients with recent-onset schizophrenia and 31 matched healthy subjects were included. For all subjects, magnetic resonance imaging scans were obtained at inclusion and at 5-year follow-up. Nineteen patients (ab-)used cannabis but no other illicit drugs; 32 patients and the healthy comparison subjects did not use any drugs during the 5-year follow-up. At follow-up, clinical outcome was measured. To evaluate the local differences in cortical thickness change over five years between the two groups regression analysis was carried out over the cortical surface. At inclusion cortical thickness did not differ between patients and controls and between cannabis-using and non-using patients. Over the follow-up period we found excessive thinning of the right supplementary motor cortex, inferior frontal cortex, superior temporal gyrus, angular gyrus, occipital and parietal lobe in patients relative to controls after controlling for cannabis use. Patients who used cannabis showed additional thinning in the left dorsolateral prefrontal cortex (DLPFC), left anterior cingulate cortex (ACC) and left occipital lobe as compared to those patients that did not use cannabis during the scan interval. First-episode schizophrenia patients who use cannabis show a more pronounced cortical thinning than non-using patients in areas known for their high density of CB1 receptors, such as the ACC and the DLPFC.

Introduction

Structural brain imaging studies have consistently demonstrated brain volume abnormalities in schizophrenia, with increases in ventricular volumes as well as decreases in cortical grey and white matter volumes (for review see Honea et al., 2005 and Wright et al., 2000). Longitudinal studies show that brain volume diminishes more extensively in patients relative to controls, with most (Van Haren et al., 2007; van Haren et al., 2008; Rais et al., 2008; for a review see Pantelis et al., 2005), but not all (DeLisi et al., 2004), studies reporting the largest brain volume loss in patients with the poorest outcome.

Interestingly, cannabis use has been associated with poor clinical and functional outcome in schizophrenia. This finding is relevant since cannabis (ab-)use is common in schizophrenia, occurring in up to half of the patients (Boydell et al., 2006), with cannabis-using patients showing more positive (Bersani et al., 2002; Buhler et al., 2002; Dubertret et al., 2006; Grech et al., 2005; Mauri et al., 2006), but not negative (Bersani et al., 2002; Compton et al., 2004; Dubertret et al., 2006; Grech et al., 2005; Peralta and Cuesta, 1992), symptoms, an earlier disease onset (Veen et al., 2004) and increased number of psychotic relapses or exacerbations (Caspari, 1999; Grech et al., 2005; Linszen et al., 1994) compared with non-using patients. In view of the reported relationship between poor outcome and progressive brain volume loss (van Haren et al., 2007; van Haren et al., 2008; Rais et al., 2008; for a review see Pantelis et al., 2005), it could be expected that patients abusing cannabis show larger brain volume loss over time than patients who do not. Indeed, we recently reported more overall grey matter loss and excessive ventricle enlargement over five years in cannabis-using first-episode schizophrenia patients compared with non-using patients and healthy comparison subjects (Rais et al., 2008). However, since that study only examined global brain structures such as the cerebrum and ventricles, it is unknown whether this grey matter loss is globally distributed over the entire brain or more pronounced in specific brain regions. The grey matter volume is principally represented in the cerebral cortex. It can be defined as the product of the cortical thickness and the cortical surface. Therefore, to investigate whether it is indeed particular cortical areas that are vulnerable to the effects of cannabis use change in cortical thickness over five years was compared between cannabis-using and non-using schizophrenia patients.

To our knowledge this is the first longitudinal study analyzing cortical thickness in cannabis-using schizophrenia patients as compared to non-using patients and healthy comparison subjects.

Experimental procedures

Subjects

Patients with first-episode schizophrenia (N=51) recruited from the First-Episode Schizophrenia Research Program at the University Medical Center Utrecht, Utrecht, The Netherlands, and healthy comparison subjects (N=31) were included in the study. The study received approval of the local ethical committee. Two MRI scans were obtained with an interval of approximately 5 years. This group of subjects has been described in more detail previously (Rais et al., 2008).

In short, both at inclusion (T0) and follow-up (T5), the patients were assessed with the Comprehensive Assessment of Symptoms and History (Andreasen et al., 1992) by two trained raters who independently determined the diagnosis and achieved consensus afterward; severity of illness was measured with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and drug use was assessed with the Composite International Diagnostic Interview (CIDI) (Robins et al., 1988). Patients with a lifetime diagnosis of abuse or dependence of a substance other than cannabis (except nicotine) were excluded. The time interval between inclusion in the study at T0 and follow-up measurement at T5 is referred to as the scan interval. At T5, all 51 patients met DSM-IV criteria for schizophrenia. Nineteen patients used only cannabis and no other illicit drugs during the scan interval, and 32 patients did not use any illicit drugs during the scan interval. Of this latter group, 15 patients never used cannabis during their lifetime, and 17 patients stopped using cannabis before baseline.

At follow-up, information was obtained on the average number of alcohol consumptions per week. Two patients in the cannabis-using group and two patients in the non-using group met the DSM-IV criteria for alcohol abuse, whereas no healthy comparison subjects met these criteria. The three groups did not differ significantly on average number of alcohol consumptions per week at follow-up. To calculate the cumulative dose of typical antipsychotic medication, a table from the Dutch National Health Service was used to derive haloperidol equivalents. The patients used only one antipsychotic at a time. For atypical antipsychotics, the respective pharmaceutical companies suggested how to convert the dose into haloperidol equivalents (clozapine, 40:1; olanzapine, 2.5:1; risperidone, 1:1; sulpiride, 170:1; quetiapine, 50:1; and sertindole, 2:1).

The healthy comparison subjects fulfilled criteria for “never mentally ill” both at baseline and follow-up. The healthy comparison subjects did not use any illicit substances before or during the study. The groups were matched for sex, age, handedness, and socioeconomic status of their parents (expressed as the highest level of education completed by one of the parents). After a complete description of the study to the subjects, written informed consent was obtained.

MRI procedures and measurements

Brain scans were acquired on a Philips NT (Best, The Netherlands) scanner operating at 1.5 T for all subjects. A three-dimensional fast field echo (TE=4.6 ms, TR=30 ms, flip angle=30°, field of view=256×256 mm^2) scan with 160–180 contiguous coronal 1.2-mm slices and a T2-weighted dual-echo turbo spin echo (TE1=14 ms, TE2=80 ms, TR=6350 ms, flip angle=90°, field of view=256×256 mm^2) scan with 120 contiguous coronal 1.6-mm slices of the whole head were used for the quantitative measurements (Hulshoff Pol et al., 2001).

Processing was done on the neuroimaging computer network of the Department of Psychiatry at the University Medical Center Utrecht. Processing procedures have been described before (Hulshoff Pol et al., 2002; van Haren et al., 2003).

In short, all images were coded to ensure investigator blindness to subject identification and diagnosis; scans were put into Talairach orientation without scaling and corrected for intensity non-uniformity artifacts (Sled et al., 1998). Intensity histogram analysis on the T1 image yielded thresholds for separating brain tissue from cerebrospinal fluid and, within the brain, grey matter from white matter. Grey and white matter segments were created by applying these thresholds to the images (Schnack et al., 2001). These segments were used as input for an advanced neural net classifier (Zijdenbos et al., 2002).

To analyze the cortical thickness, the CLASP algorithm designed at the McConnell Brain Imaging Centre of the Montreal Neurological Institute was employed (Kabani et al., 2001; Kim et al., 2005; MacDonald et al., 2000).

A 3D surface comprising 81,920 polygons per hemisphere was fitted to the white matter/grey matter intersection, which created the inner surface of the cortex which was then expanded out to fit the grey matter/cerebrospinal fluid intersection, thereby creating the outer cortical surface. Cortical thickness was estimated by taking the distance between the two surfaces such that each of the 81,924 vertices of the polygons on the outer surface had a counterpart vertex on the inner surface. Each subject's thickness measurements were smoothed across the surface using a 20 mm surface-based blurring kernel (Chung and Taylor, 2004). This method of blurring improves the chances of detecting population differences, but also follows the curvature of the surface to preserve any anatomical boundaries within the cortex.

For each subject, change in cortical thickness (T5–T0) was calculated for every vertex in individual space, then transformed to the ICBM template. The surfaces of each subject were registered to an average surface created from 152 healthy subjects aged 18–40 years (ICBM 152) (Lyttelton et al., 2007), allowing comparison of cortical thickness locally between subjects.

Statistical analysis

Demographic and clinical data

Data were examined for outliers and normality of the distribution.

To assess whether the groups differed on demographic or clinical variables, multiple analyses of variance were conducted for non-categorical variables and chi-square analyses for categorical variables (Table 1).

To estimate clinical outcome in the different groups of patients, change in positive and negative symptoms over 5 years was quantified by subtracting baseline PANSS scores from follow-up PANSS scores (PANSS T5–PANSS T0).

Group differences in cortical thickness

To evaluate the differences in cortical thickness change over five years between the two groups a vertex-by-vertex analysis was carried out.

In each vertex group differences in baseline cortical thickness and in cortical thickness change were calculated by using regression analyses with diagnosis (patient–control), cannabis use (yes–no), age and sex as covariates. Baseline cortical thickness and cortical thickness change respectively were included in the analysis as dependent variable. This produced F-statistics at each vertex, one for the effect of diagnosis (thus corrected for the effect of cannabis use), one for the effect of cannabis use (in patients only), one for the effect of age, and one for the effect of sex. In our previous paper (Rais et al., 2008) we showed decreased grey matter volumes in patients in general relative to controls and in cannabis-using patients relative to non-using patients. Therefore, we adjusted for multiple comparisons using a False Discovery Rate (FDR) of alpha=0.10 (one-tailed). Statistical maps were created showing significant differences in cortical thickness (change) between patients and healthy comparison subjects and between cannabis-using patients and non-using patients.

Table 1 | Demographic and clinical data of the cannabis-using and non-using schizophrenia patients and healthy comparison subjects.

	Cannabis- N=32				Cannabis+ N=19				Controls N=31				
	Mean/N	SD	Range		Mean/N	SD	Range		Mean/N	SD	Range		Sig.
Sex, No. of subjects m/f	26/6				19/0				25/6				NS
Handedness, No. of subjects r/l/a	27/2/3				18/0/1				26/5/0				NS
Age, yrs	23.28	5.10	15.70	37.03	21.83	3.91	16.73	31	24.72	6.66	16.74	40.21	NS
Parental education level, yrs	12.77	6.66	6	17	13.32	3.59	6	17	13.68	2.83	10	17	NS
MRI interval, yrs	5.28	0.50	4.13	6.39	5.35	0.64	4.54	7.08	5.21	0.18	4.78	5.50	NS
Age first psychosis, yrs	22.54	4.94	14.24	36.63	20.53	3.93	16.45	29.64					NS
Duration of illness, days	350.61	388.07	9	1408	429	631.65	66	2866					NS
PANSS T0 positive	18.82	5.19	9	28.00	15.63	5.73	7	25					NS
PANSS T0 negative	19.29	4.90	10	30	17.06	4.75	8	24					NS
PANSS change positive*	-5.59	4.98	-17.00	4.00	-1.94	6.43	-15.00	12.00					0.043
PANSS change negative*	-6.15	6.25	-15.00	10.00	-1.00	7.21	-16.00	11.00					0.018
CAN T5 total – staff	8.87	5.34	0	20	11.94	7.60	0	24					NS
GAF T5	52.62	17.90	30	90	53.94	20.37	15	90					NS
Days of hospitalization	120.48	104.24	0	430	171.26	254.83	0	1062					NS
Cumulative antipsychotic medication T5 (mg eq. Haloperidol)	13711	6968	2966	30873	12302	5767	1511	20810					NS
Type antipsychotic medication before T0 (naive/typ/atyp/both)	14/13/1/4				7/6/2/4								NS
Type antipsychotic medication T0T5 (typ/atyp/both/missing)	0/13/18/1				0/7/11/1								NS
Duration of treatment at T0 (days)	77	126	0	483	119	142	0	413					NS

PANSS: Positive And Negative Syndrome Scale, CAN: Camberwell Assessment of Needs, GAF: Global Assessment of Functioning. *Significant differences were found between cannabis-using and non-using patients in change in positive symptoms (F=4.35; df= 42, 1; p=0.043) and change in negative symptoms (F=6.08; df=42, 1; p=0.018) over five years.

For those cortical areas that showed significant differences between cannabis-using patients, non-using patients or between patients and controls the most significant vertex was identified visually using the cortical surface viewer Brain-view developed at the Montreal Neurological Institute.

To evaluate the differences in mean cortical thickness change over the whole cortex between the patients and healthy comparison subjects and between cannabis-using and non-using patients a linear regression analysis was carried out with diagnosis (patient–control), cannabis use (yes–no), age and sex as covariates.

To assess the correlation between cortical thickness change (in peak vertices only) and change in positive and negative symptoms in first-episode patients with schizophrenia multiple regressions were performed with cortical thickness change (most significant vertex) as dependent variable and age, sex and change in positive and negative symptoms as independent variable.

Furthermore, to exclude possible effect of alcohol abuse, the main analysis was repeated excluding the four patients with alcohol abuse during the interval.

Results

Demographic and clinical data have been described previously (Rais et al., 2008) and are briefly reported in Table 1. The groups did not significantly differ with regard to sex, handedness, age, level of parental education, and duration of scan interval.

At inclusion and follow-up, the cannabis-using patients and those not using cannabis did not differ significantly on positive and negative symptoms and type and cumulative amount of medication during the scan interval. Cumulative duration of hospitalization during the scan interval did not differ significantly between the two patient groups. However, the subjects not using cannabis showed a small but significant improvement in positive and negative symptoms compared with the cannabis-using group over the follow-up interval.

Mean cortical thickness decrease over the whole cortex was significantly more pronounced in patients as compared to healthy subjects over both the right (mean [sd]: controls: −0.0028 [0.014] mm; patients: −0.014 [0.014] mm; t=−2.74; df=4, 81; p=0.008.) and left (mean: controls: −0.003 [0.014] mm; patients: −0.016 [0.015] mm; t=−2.5; df=4,81; p=0.014) hemisphere. No

significant differences in mean global cortical thickness change were found between cannabis-using and non-using patients. No significant increases in cortical thickness were found between patients and healthy subjects and between cannabis-using and non-using patients.

At inclusion, focal cortical thickness did not differ significantly between schizophrenia patients and healthy comparison subjects and between cannabis-using and non-using patients.

Figure 1 shows the statistical difference map of the cortical thickness change over time in the patient group, corrected for the effect of cannabis use, as compared to the healthy comparison subjects at a corrected threshold of F>8.16 ($p<0.005$; FDR corrected at alpha=0.10). Cortical thinning in patients was most apparent in the right supplementary motor cortex (SMC), right inferior frontal cortex, right superior temporal gyrus and angular gyrus, right occipital lobe (cuneus) and right parietal lobe (postcentral gyrus) (see Table 2).

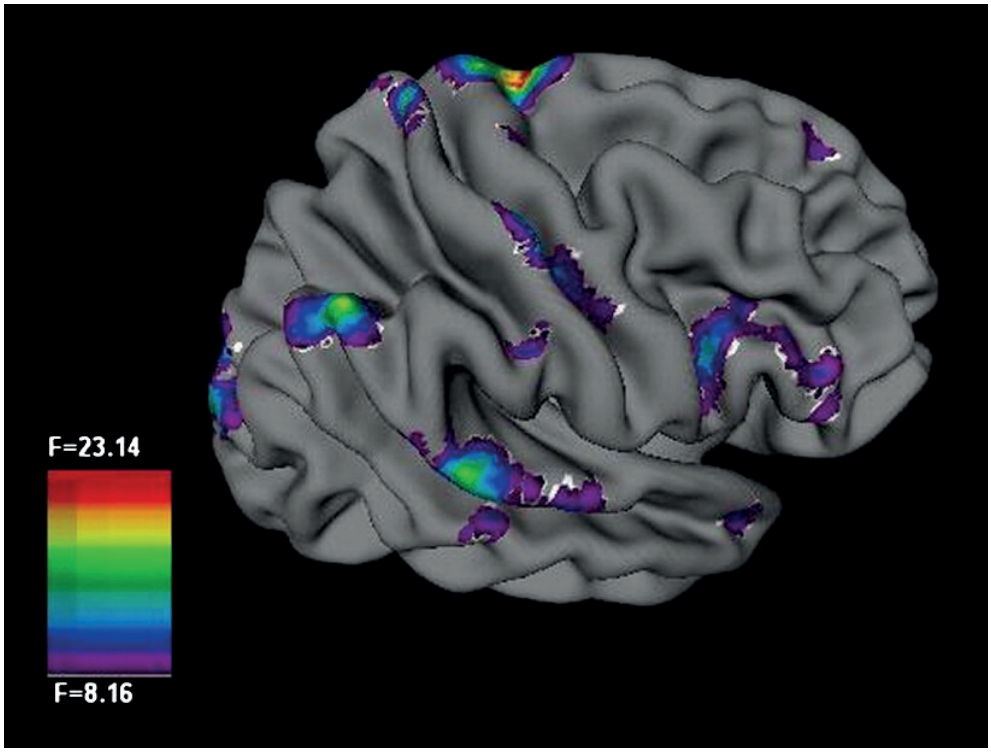


Figure 1 | Lateral view of the right hemisphere of the statistical map comparing patients with schizophrenia and healthy comparison subjects on cortical thickness change over five years after FDR correction. Colored areas indicate the areas where the cortical thickness was significantly decreased in first-episode patients with schizophrenia (in red see right supplementary motor cortex).

Table 2 | Difference in cortical thickness change over five years in patients vs. healthy comparison subjects and in cannabis-using schizophrenia patients vs. non-using patients.

	Difference (in mm)	Df	F	P
Right SMC	-0.0622	81, 4	23.14	$7.3x10^{-6}$
Right IFC	-0.0203		14.18	$3.2x10^{-4}$
Right OL	-0.0146		18.06	$5.8x10^{-5}$
Right STG	-0.0335		19.32	$3.4x10^{-5}$
Right AG	-0.0271		17.44	$7.6x10^{-5}$
Right PL	-0.033		18.44	$5.1x10^{-5}$
Left DLPFC	-0.0292		17.6	$7.2x10^{-5}$
Left ACC	-0.0221		18.78	$4.4x10^{-5}$
Left OL	-0.0256		18.79	$4.4x10^{-5}$

SMC: supplementary motor cortex; IFC: inferior frontal cortex; OL: occipital lobe; STG: superior temporal gyrus; AG: angular gyrus; PL: parietal lobe; DLPFC: dorsolateral prefrontal cortex, ACC: anterior cingulate cortex, OL: occipital lobe

Figure 2 shows statistical difference maps of the cortical thickness change over five years in the cannabis-using patients as compared to the non-using patients at a corrected threshold of F>9.2 ($p<0.003$; FDR corrected at alpha=0.10). Cortical thinning was most prominent in patients who used cannabis during the scan interval compared with patients who did not use cannabis in the left dorsolateral prefrontal cortex (DLPFC); in the left anterior cingulate cortex (ACC) and in the left occipital lobe (see Table 2). Figures 3 and 4 and show cortical thickness changes (10^{-2}mm) over time, over the right (A) and left (B) hemisphere respectively in first-episode schizophrenia patient vs. healthy comparison subjects (Fig. 3A and B) and in cannabis-using patients vs. non-using patients (Fig. 4A and B).

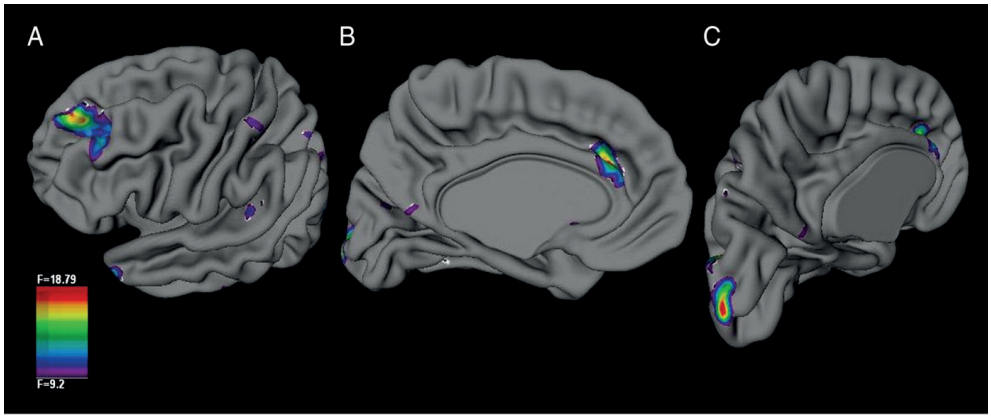


Figure 2 | View of the left hemisphere of the statistical map comparing cannabis-using patients and non-using patients with schizophrenia on cortical thickness change over five years after FDR correction. Colored areas indicate the areas where cortical thickness was significantly decreased in cannabis-using patients. A) Lateral view: left dorsolateral prefrontal cortex; B) medial view: left anterior cingulate cortex; C) posterior view: left occipital lobe.

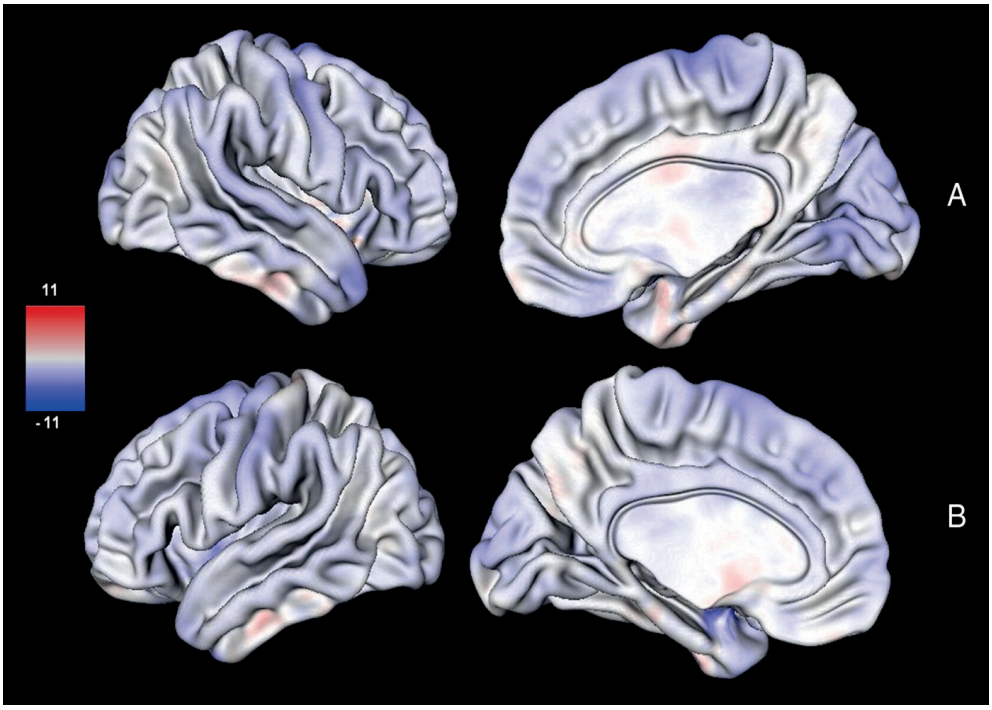


Figure 3 | View of the right (A) and left (B) hemisphere comparing patients with schizophrenia and healthy comparison subjects on cortical thickness change (10^{-2} mm) over five years. Blue areas indicate the areas of cortical thinning over time in first-episode patients with schizophrenia relative to controls. Red areas are areas showing excessive thickening in patients relative to controls.

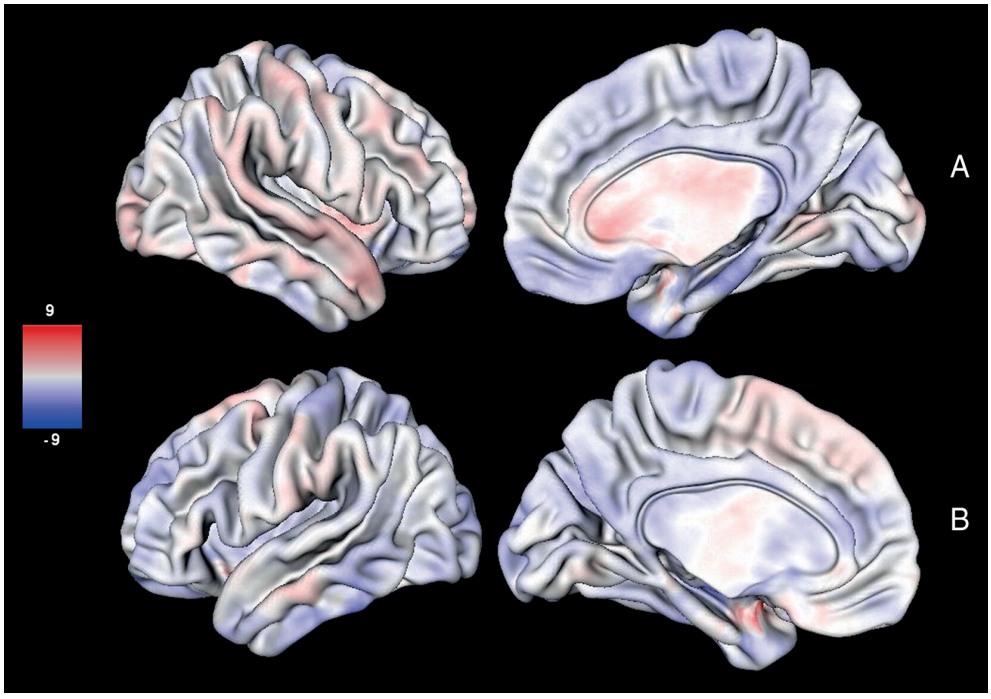


Figure 4 | View of the right (A) and left (B) hemisphere comparing cannabis-using patients and non-using patients with schizophrenia on cortical thickness change (10^{-2} mm) over five years. Blue areas indicate the areas of cortical thinning over time in cannabis-using patients relative to non-using patients with schizophrenia. Red areas are areas showing excessive thickening in cannabis-using compared to non-using patients.

In the patient group, a negative correlation was found between change in the negative symptoms and changes in the DLPFC (B=−0.17; t=−2.06; p=0.05) and in the occipital lobe (B=−0.167; t=−2.78; p=0.01).

Finally, two patients with alcohol abuse during follow-up were included in each patient group (can+ and can−). The exclusion of these patients did not influence the results of the main analysis.

Discussion

This five year longitudinal study investigated differences in cortical thickness change in 19 first-episode schizophrenia patients who used cannabis during the scan interval, 32 first-episode schizophrenia patients who did not and 31 cannabis-naïve healthy comparison subjects. We found that while the three groups did not differ in cortical thickness at baseline, after controlling for cannabis use, relative to controls schizophrenia patients showed excessive thinning of the

right supplementary motor cortex (SMC), right inferior frontal cortex, right superior temporal gyrus and angular gyrus, right occipital lobe (cuneus) and parietal lobe (postcentral gyrus). In patients who used cannabis additional excessive thinning was found in the left dorsolateral prefrontal cortex (DLPFC), left anterior cingulate cortex (ACC) and left occipital lobe as compared to those patients that did not use cannabis during the scan interval. These findings suggest that the excessive thinning of the left DLPFC, ACC and the cortex of the occipital lobe are probably related to the use of cannabis.

Importantly, these findings could not be explained by differences in cortical thickness at baseline. As mean cortical thinning was significantly more pronounced in patients as compared to controls, this might explain the excessive loss of grey matter volume in these patients. However, no mean cortical thinning was found in cannabis-using patients as compared to non-using patients.

Although our study is the first to examine the relationship between cannabis use and cortical thickness change over time in schizophrenia, our results are consistent with two previous cross-sectional MRI studies, in a comparable number of subjects as our sample, reporting grey matter deficits in the posterior (Bangalore et al., 2008) and anterior cingulate cortex (Szeszko et al., 2007) in cannabis-using first-episode schizophrenia patients as compared to non-using patients and healthy subjects. In addition, functional MRI studies have reported an association between exposure to cannabis and changes in brain activity in the prefrontal cortex and anterior cingulate in healthy subjects (for reviews see Martin-Santos et al., 2009 and Quickfall and Crockford, 2006). Also consistent with our findings, exposure to cannabis has been associated with cognitive impairments via altered neural transmission in the prefrontal cortex (for a review see Egerton et al., 2006). Since dysfunction of the DLPFC (Baare et al., 1999; Gur et al., 2000; Kuperberg and Heckers et al., 2000; Wible et al., 2001) and ACC (Szeszko et al., 2000) have been found to be related to the negative symptoms and cognitive impairment in schizophrenia, the cortical thinning in the DLPFC and ACC in the cannabis-using patients may be functionally relevant. Indeed, we found less improvement in the negative symptoms in the cannabis-using patients as compared to those who did not use cannabis. Moreover, change in the negative symptoms was associated with changes in the dorsolateral prefrontal cortex and in the occipital lobe suggesting that improvement of the negative symptoms over time was associated less loss of thickness in the DLPFC and occipital lobe. These data suggest an association between more pronounced negative symptoms and thinner cortex in these areas, irrespective of the use of cannabis. Unfortunately, we did not examine cognitive function in this sample.

The mechanism by which cannabis might be related to excessive cortical thinning in schizophrenia patients remains unclear. It could either be a direct consequence of cannabis intake or occur as a consequence of (psychotic) symptoms that have been found to be associated with cannabis use (Bersani et al., 2002; Buhler et al., 2002; Dubertret et al., 2006; Grech et al., 2005; Mauri et al., 2006).

Interestingly, increased cerebrospinal fluid (CSF) levels of endogenous cannabinoids have been reported in patients with schizophrenia suggesting a possible role for (changes in the) endocannabinoid signaling system in the pathogenesis of schizophrenia (Koethe et al., 2009; Leweke et al., 1999; Leweke et al., 2007). Moreover, in post-mortem studies both DLPFC and ACC have not only been identified as being rich in cannabinoid (CB1) receptors in the brains of healthy individuals (Eggan and Lewis, 2007; Freund et al., 2003; Glass et al., 1997; Iversen, 2003) but also show increased density of these receptors in brain tissue of schizophrenia patients, irrespective of cannabis use (Dean et al., 2001; Zavitsanou et al., 2004). It has previously been hypothesized (Freedman, 2008) that the brain tissue loss due to cannabis use in schizophrenia patients (Rais et al., 2008) is a consequence of the CB1 receptors no longer protecting the brain against excitotoxic events. Indeed, CB1 receptors, when physiologically activated via endogenous cannabinoids are thought to protect the brain from excitotoxic injuries (Kim et al., 2006; Marsicano et al., 2003). However, while endogenous cannabinoids play a role in the physiological regulation of the neural activity in the PFC, exogenous cannabinoids might disrupt the physiological neural transmission in the PFC via the non-specific activation of the CB1 receptors (for a review see Egerton et al., 2006). Thus, a desensitization of the CB1 receptor by exogenous cannabinoids might lead to further loss of inhibition and consequently impair the neuroprotective effect of the endocannabinoid system. In fact, recent studies in animals demonstrated that stimulation of CB1 receptors enhance the glutamatergic and dopaminergic transmission in the prefrontal cortex via the reduction of GABA transmission (Pistis et al., 2002; for a review see Egerton et al., 2006), thereby increasing brain activation of glutamate and dopamine. Interestingly, individuals with schizophrenia might be particularly vulnerable to excitotoxic damage, especially in the DLPFC and ACC. Not only are these regions particularly rich in CB1 receptors in individuals with schizophrenia (Dean et al., 2001; Zavitsanou et al., 2004), a diminished inhibitory function of the GABA-ergic system in the DLPFC and ACC (Hashimoto et al., 2008) and a higher level of baseline activation in the DLPFC have also been reported in schizophrenia patients as compared to healthy controls (Tregellas et al., 2007; Tregellas et al., 2009).

Evidence for a direct effect of cannabis on the brain is also provided by studies reporting raised serum concentrations of Nerve Growth Factor (NGF) (Jockers-Scherubl et al., 2003) and Brain Derived Neurotrophic Factor (BDNF) (Jockers-Scherubl et al., 2004) in cannabis-using schizophrenia patients. Since NGF and BDNF are released as a consequence of neuronal damage, it was speculated that the higher levels of these neurotrophins were a sign of cannabis-induced neurotoxicity in schizophrenia patients.

Alternatively, the excessive thinning in the cannabis-using patients could be explained as an indirect consequence of cannabis use. It has been suggested that brain changes in the early stages of schizophrenia are the result of the "toxic" effect of the psychotic state (Lieberman et al., 2001), and it is well known that cannabis-using patients have a poorer clinical outcome as compared to non-using patients (Bersani et al., 2002; Buhler et al., 2002; Caspari, 1999; Dubertret et al., 2006; Grech et al., 2005; Linszen et al., 1994; Mauri et al., 2006; Baeza et al., 2009; Gonzalez-Pinto et al., 2009). Evidence that this is possibly causally related to the effects of cannabis is provided by the finding that the clinical and functional outcome improves in those patients who cease cannabis use after illness onset (Baeza et al., 2009; Gonzalez-Pinto et al., 2009). Indeed, in our study the cannabis-using patients showed less improvement of positive and negative symptoms over five years as compared to the non-using patients. In other words, during the scan interval cannabis-using patients probably have been in a psychotic state longer than non-using patients and consequently may show larger decreases in brain volume over time.

Whether or not brain volume abnormalities are the consequence of antipsychotic medication intake is controversial (for a review see Navari and Dazzan, 2009). In our study both patient groups were matched on amount and type of medication used during the scan interval. Thus, it is unlikely that the cortical thinning in the cannabis-using patients might be related to the effect of antipsychotic medication.

Finding cortical thinning in the occipital lobe in cannabis-using patients as compared to non-using patients was unexpected and it has not been reported in previous studies on cannabis-using subjects. Nevertheless two previous cross-sectional studies reported cortical thinning of occipital regions in chronic (Kuperberg et al., 2003) and first-episode (Narr et al., 2005b) schizophrenia patients.

The excessive cortical thinning in the supplementary motor cortex, inferior frontal cortex, parietal, temporal and occipital lobe of schizophrenia patients relative to controls are in line with

previous reports of cortical thinning in childhood onset (Greenstein et al., 2006; White et al., 2003), first-episode (Narr et al., 2005a; Narr et al., 2005b), and chronic (Kuperberg et al., 2003; Nesvag et al., 2008) schizophrenia patients. Also, previous cross-sectional volumetric studies report reduced SMC volume in schizophrenia patients as compared to normal controls (Exner et al., 2006; Suzuki et al., 2005).

Nevertheless, unlike the results reported in most cross-sectional studies in first-episode schizophrenia patients showing cortical thinning in prefrontal, temporal, parietal, occipital and cingulate cortices (Narr et al., 2005a; Narr et al., 2005b) we could not demonstrate cortical thinning at baseline in patients as compared to healthy subjects. However, these differences in the results might probably be attributed to differences in sample size.

Some limitations need to be addressed. First, the number of subjects included was limited as a consequence of including only first-episode schizophrenia patients who used only cannabis and no other drugs. Secondly, based on our previous findings (Rais et al., 2008) of global loss of grey matter volume in the same sample, we chose to adjust for multiple comparisons with a one-tailed test. However, a global loss of grey matter volume does not completely exclude the possibility of finding local cortical thickness increases. Nevertheless, in our sample, there were no significant focal cortical thickness increases neither in patients as compared with healthy subjects neither in cannabis-using patients as compared with non-using patients. Thirdly, our study could not address the direction of causality and cannot therefore show whether a direct effect of cannabis use is causing the excessive cortical thinning or if those patients with excessive cortical thinning are more vulnerable to continue cannabis use. Moreover, since a healthy comparison cannabis-using group was not included, it remains unclear whether the cortical thinning in the DLPFC and ACC is a consequence of cannabis use per se or of the interaction between cannabis and schizophrenia. However, the higher density of CB1 receptors in the DLPFC and ACC reported in schizophrenia patients (Dean et al., 2001; Zavitsanou et al., 2004) might suggest that these regions might be particularly vulnerable to the effect of cannabis. Moreover, in our sample, the areas showing cortical thinning in schizophrenia patients irrespective of cannabis use are dissimilar to those that are related to the use of cannabis. This suggests that the effect of cannabis on the brain of schizophrenia patients is distinct from that of the illness itself.

Although results of previous sMRI studies in healthy subjects using cannabis have been contradictory (for review see Martin-Santos et al., 2009 and Quickfall and Crockford, 2006), a recent region of interest study reported dose-related hippocampal and amygdala structural

abnormalities in long-term healthy cannabis users, suggesting a possible direct neurotoxic effect of cannabis on the healthy human brain (Yucel et al., 2008). However, it cannot be excluded that the subjects with lower grey matter volume in these areas were also those more prone to use cannabis. Finally, no information could be provided regarding a dose–response relationship between delta-9-tetrahydrocannabinol (THC) intake and thinning of the cerebral cortex as this information was not available.

In conclusion, this study found progressive cortical thinning in the DLPFC and ACC, areas rich in CB1 receptors, in cannabis-using schizophrenia patients, but not in patients who did not use cannabis. Our results suggest that in the first-episode schizophrenia patients who continue to use cannabis after illness onset, it is particularly those cortical regions that are rich in CB1 receptors that are vulnerable to excessive cortical thinning. Interestingly, it is also these areas that are related to the negative symptoms and to poorer cognitive functioning in schizophrenia, providing a morphological explanation for the detrimental effects of cannabis in schizophrenia.

Reference List

Andreasen N.C., Flaum M., Arndt S. (1992): The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. Arch Gen Psychiatry 49:615-623.

Baare W.F., Hulshoff Pol H.E., Hijman R., Mali W.P., Viergever M.A., Kahn R.S. (1999): Volumetric analysis of frontal lobe regions in schizophrenia: relation to cognitive function and symptomatology. Biol Psychiatry 45:1597-1605.

Baeza I., Graell M., Moreno D., Castro-Fornieles J., Parellada M., Gonzalez-Pinto A., Paya B., Soutullo C., de la Serna E., Arango C. (2009): Cannabis use in children and adolescents with first episode psychosis: influence on psychopathology and short-term outcome (CAFEPS study). Schizophr Res 113:129-137.

Bangalore S.S., Prasad K.M., Montrose D.M., Goradia D.D., Diwadkar V.A., Keshavan M.S. (2008): Cannabis use and brain structural alterations in first episode schizophrenia--a region of interest, voxel based morphometric study. Schizophr Res 99:1-6.

Bersani G., Orlandi V., Kotzalidis G.D., Pancheri P. (2002): Cannabis and schizophrenia: impact on onset, course, psychopathology and outcomes. Eur Arch Psychiatry Clin Neurosci 252:86-92

Boydell J., van Os J., Caspi A., Kennedy N., Giouroukou E., Fearon P., Farrell M., Murray R.M. (2006): Trends in cannabis use prior to first presentation with schizophrenia, in South-East London between 1965 and 1999. Psychol Med 36:1441-1446.

Buhler B., Hambrecht M., Loffler W., an der Heiden W., Hafner H. (2002): Precipitation and determination of the onset and course of schizophrenia by substance abuse--a retrospective and prospective study of 232 population-based first illness episodes. Schizophr Res 54:243-251.

Caspari D. (1999): Cannabis and schizophrenia: results of a follow-up study. Eur Arch Psychiatry Clin Neurosci 249:45-49.

Chung M.K., Taylor J. (2004): Diffusion smoothing on brain surface via finite element method. Biomedical Imaging: Nano to Macro, 2004 IEEE International Symposium 1:432-435.

Compton M.T., Furman A.C., Kaslow N.J. (2004): Lower negative symptom scores among cannabis-dependent patients with schizophrenia-spectrum disorders: preliminary evidence from an African American first-episode sample. Schizophr Res 71:61-64.

Dean B., Sundram S., Bradbury R., Scarr E., Copolov D. (2001): Studies on [3H]CP-55940 binding in the human central nervous system: regional specific changes in density of cannabinoid-1 receptors associated with schizophrenia and cannabis use. Neuroscience 103:9-15.

DeLisi L.E., Sakuma M., Maurizio A.M., Relja M., Hoff A.L. (2004): Cerebral ventricular change over the first 10 years after the onset of schizophrenia. Psychiatry Res 130:57-70.

Dubertret C., Bidard I., Ades J., Gorwood P. (2006): Lifetime positive symptoms in patients with schizophrenia and cannabis abuse are partially explained by co-morbid addiction. Schizophr Res 86:284-290.

Egerton A., Allison C., Brett R.R., Pratt J.A. (2006): Cannabinoids and prefrontal cortical function: insights from preclinical studies. Neurosci Biobehav Rev 30:680-695.

Eggan S.M., Lewis D.A. (2007): Immunocytochemical distribution of the cannabinoid CB1 receptor in the primate neocortex: a regional and laminar analysis. Cereb Cortex 17:175-191.

Exner C., Weniger G., Schmidt-Samoa C., Irle E. (2006): Reduced size of the pre-supplementary motor cortex and impaired motor sequence learning in first-episode schizophrenia. Schizophr Res 84:386-396.

Freedman R. (2008): Cannabis, inhibitory neurons, and the progressive course of schizophrenia. Am J Psychiatry 165:416-419.

Freund T.F., Katona I., Piomelli D. (2003): Role of endogenous cannabinoids in synaptic signaling. Physiol Rev 83:1017-1066.

Glass M., Dragunow M., Faull R.L. (1997): Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. Neuroscience 77:299-318.

Gonzalez-Pinto A., Alberich S., Barbeito S., Gutierrez M., Vega P., Ibanez B., Haidar M.K., Vieta E., Arango C. (2009): Cannabis and First-Episode Psychosis: Different Long-term Outcomes Depending on Continued or Discontinued Use. Schizophr Bull .

Grech A., van Os J., Jones P.B., Lewis S.W., Murray R.M. (2005): Cannabis use and outcome of recent onset psychosis. Eur Psychiatry 20:349-353.

Greenstein D., Lerch J., Shaw P., Clasen L., Giedd J., Gochman P., Rapoport J., Gogtay N. (2006): Childhood onset schizophrenia: cortical brain abnormalities as young adults. J Child Psychol Psychiatry 47:1003-1012.

Gur R.E., Cowell P.E., Latshaw A., Turetsky B.I., Grossman R.I., Arnold S.E., Bilker W.B., Gur R.C. (2000): Reduced dorsal and orbital prefrontal grey matter volumes in schizophrenia. Arch Gen Psychiatry 57:761-768.

Hashimoto T., Bazmi H.H., Mirnics K., Wu Q., Sampson A.R., Lewis D.A. (2008): Conserved regional patterns of GABA-related transcript expression in the neocortex of subjects with schizophrenia. Am J Psychiatry 165:479-489.

Honea R., Crow T.J., Passingham D., Mackay C.E. (2005): Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. Am J Psychiatry 162:2233-2245.

Hulshoff Pol H.E., Schnack H.G., Bertens M.G., van Haren N.E., van der Tweel I., Staal W.G., Baare W.F., Kahn R.S. (2002): Volume changes in grey matter in patients with schizophrenia. Am J Psychiatry 159:244-250.

Hulshoff Pol H.E., Schnack H.G., Mandl R.C., van Haren N.E., Koning H., Collins D.L., Evans A.C., Kahn R.S. (2001): Focal grey matter density changes in schizophrenia. Arch Gen Psychiatry 58:1118-1125.

Iversen L. (2003): Cannabis and the brain. Brain 126:1252-1270.

Jockers-Scherubl M.C., Danker-Hopfe H., Mahlberg R., Selig F., Rentzsch J., Schurer F., Lang U.E., Hellweg R. (2004): Brain-derived neurotrophic factor serum concentrations are increased in drug-naive schizophrenic patients with chronic cannabis abuse and multiple substance abuse. Neurosci Lett 371:79-83.

Jockers-Scherubl M.C., Matthies U., Danker-Hopfe H., Lang U.E., Mahlberg R., Hellweg R. (2003): Chronic cannabis abuse raises nerve growth factor serum concentrations in drug-naive schizophrenic patients. J Psychopharmacol 17:439-445.

Kabani N., Le Goualher G., MacDonald D., Evans A.C. (2001): Measurement of cortical thickness using an automated 3-D algorithm: a validation study. Neuroimage 13:375-380.

Kay S.R., Fiszbein A., Opler L.A. (1987): The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13:261-276.

Kim J.S., Singh V., Lee J.K., Lerch J., Ad-Dab'bagh Y., MacDonald D., Lee J.M., Kim S.I., Evans A.C. (2005): Automated 3-D extraction and evaluation of the inner and outer cortical surfaces using a Laplacian map and partial volume effect classification. Neuroimage 27:210-221.

Kim S.H., Won S.J., Mao X.O., Jin K., Greenberg D.A. (2006): Molecular mechanisms of cannabinoid protection from neuronal excitotoxicity. Mol Pharmacol 69:691-696.

Koethe D., Giuffrida A., Schreiber D., Hellmich M., Schultze-Lutter F., Ruhrmann S., Klosterkotter J., Piomelli D., Leweke F.M. (2009): Anandamide elevation in cerebrospinal fluid in initial prodromal states of psychosis. Br J Psychiatry 194:371-372.

Kuperberg G., Heckers S. (2000): Schizophrenia and cognitive function. Curr Opin Neurobiol 10:205-210.

Kuperberg G.R., Broome M.R., McGuire P.K., David A.S., Eddy M., Ozawa F., Goff D., West W.C., Williams S.C., van der Kouwe A.J., Salat D.H., Dale A.M., Fischl B. (2003): Regionally localized thinning of the cerebral cortex in schizophrenia. Arch Gen Psychiatry 60:878-888.

Leweke F.M., Giuffrida A., Koethe D., Schreiber D., Nolden B.M., Kranaster L., Neatby M.A., Schneider M., Gerth C.W., Hellmich M., Klosterkotter J., Piomelli D. (2007): Anandamide levels in cerebrospinal fluid of first-episode schizophrenic patients: impact of cannabis use. Schizophr Res 94:29-36.

Leweke F.M., Giuffrida A., Wurster U., Emrich H.M., Piomelli D. (1999): Elevated endogenous cannabinoids in schizophrenia. Neuroreport 10:1665-1669.

Lieberman J., Chakos M., Wu H., Alvir J., Hoffman E., Robinson D., Bilder R. (2001): Longitudinal study of brain morphology in first episode schizophrenia. Biol Psychiatry 49:487-499.

Linszen D.H., Dingemans P.M., Lenior M.E. (1994): Cannabis abuse and the course of recent-onset schizophrenic disorders. Arch Gen Psychiatry 51:273-279.

Lyttelton O., Boucher M., Robbins S., Evans A. (2007): An unbiased iterative group registration template for cortical surface analysis. Neuroimage 34:1535-1544.

MacDonald D., Kabani N., Avis D., Evans A.C. (2000): Automated 3-D extraction of inner and outer surfaces of cerebral cortex from MRI. Neuroimage 12:340-356.

Marsicano G., Goodenough S., Monory K., Hermann H., Eder M., Cannich A., Azad S.C., Cascio M.G., Gutierrez S.O., van der Stelt M., Lopez-Rodriguez M.L., Casanova E., Schutz G., Zieglgansberger W., Di Marzo V., Behl C., Lutz B. (2003): CB1 cannabinoid receptors and on-demand defense against excitotoxicity. Science 302:84-88.

Martin-Santos R., Fagundo A.B., Crippa J.A., Atakan Z., Bhattacharyya S., Allen P., Fusar-Poli P., Borgwardt S., Seal M., Busatto G.F., McGuire P. (2009): Neuroimaging in cannabis use: a systematic review of the literature. Psychol Med :1-17.

Mauri M., Volonteri L., De Gaspari I., Colasanti A., Brambilla M., Cerruti L. (2006): Substance abuse in first-episode schizophrenic patients: a retrospective study. Clin Pract Epidemol Ment Health 2:4.

Narr K.L., Bilder R.M., Toga A.W., Woods R.P., Rex D.E., Szeszko P.R., Robinson D., Sevy S., Gunduz-Bruce H., Wang Y.P., DeLuca H., Thompson P.M. (2005a): Mapping cortical thickness and grey matter concentration in first episode schizophrenia. Cereb Cortex 15:708-719.

Narr K.L., Toga A.W., Szeszko P., Thompson P.M., Woods R.P., Robinson D., Sevy S., Wang Y., Schrock K., Bilder R.M. (2005b): Cortical thinning in cingulate and occipital cortices in first episode schizophrenia. Biol Psychiatry 58:32-40.

Navari S., Dazzan P. (2009): Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. Psychol Med :1-15.

Nesvag R., Lawyer G., Varnas K., Fjell A.M., Walhovd K.B., Frigessi A., Jonsson E.G., Agartz I. (2008): Regional thinning of the cerebral cortex in schizophrenia: effects of diagnosis, age and antipsychotic medication. Schizophr Res 98:16-28.

Pantelis C., Yucel M., Wood S.J., Velakoulis D., Sun D., Berger G., Stuart G.W., Yung A., Phillips L., McGorry P.D. (2005): Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. Schizophr Bull 31:672-696.

Peralta V., Cuesta M.J. (1992): Influence of cannabis abuse on schizophrenic psychopathology. Acta Psychiatr Scand 85:127-130.

Pistis M., Ferraro L., Pira L., Flore G., Tanganelli S., Gessa G.L., Devoto P. (2002): Delta(9)-tetrahydrocannabinol decreases extracellular GABA and increases extracellular glutamate and dopamine levels in the rat prefrontal cortex: an in vivo microdialysis study. Brain Res 948:155-158.

Quickfall J., Crockford D. (2006): Brain neuroimaging in cannabis use: a review. J Neuropsychiatry Clin Neurosci 18:318-332.

Rais M., Cahn W., van Haren N., Schnack H., Caspers E., Hulshoff Pol H., Kahn R. (2008): Excessive brain volume loss over time in cannabis-using first-episode schizophrenia patients. Am J Psychiatry 165:490-496.

Robins L.N., Wing J., Wittchen H.U., Helzer J.E., Babor T.F., Burke J., Farmer A., Jablenski A., Pickens R., Regier D.A., . (1988): The Composite International Diagnostic Interview. An epidemiologic Instrument suitable for use in conjunction with different diagnostic systems and in different cultures. Arch Gen Psychiatry 45:1069-1077.

Schnack H.G., Hulshoff Pol H.E., Baare W.F., Staal W.G., Viergever M.A., Kahn R.S. (2001): Automated separation of grey and white matter from MR images of the human brain. Neuroimage 13:230-237.

Sled J.G., Zijdenbos A.P., Evans A.C. (1998): A nonparametric method for automatic correction of intensity nonuniformity in MRI data. IEEE Trans Med Imaging 17:87-97.

Suzuki M., Zhou S.Y., Takahashi T., Hagino H., Kawasaki Y., Niu L., Matsui M., Seto H., Kurachi M. (2005): Differential contributions of prefrontal and temporolimbic pathology to mechanisms of psychosis. Brain 128:2109-2122.

Szeszko P.R., Bilder R.M., Lencz T., Ashtari M., Goldman R.S., Reiter G., Wu H., Lieberman J.A. (2000): Reduced anterior cingulate gyrus volume correlates with executive dysfunction in men with first-episode schizophrenia. Schizophr Res 43:97-108.

Szeszko P.R., Robinson D.G., Sevy S., Kumra S., Rupp C.I., Betensky J.D., Lencz T., Ashtari M., Kane J.M., Malhotra A.K., Gunduz-Bruce H., Napolitano B., Bilder R.M. (2007): Anterior cingulate grey-matter deficits and cannabis use in first-episode schizophrenia. Br J Psychiatry 190:230-236.

Tregellas J.R., Davalos D.B., Rojas D.C., Waldo M.C., Gibson L., Wylie K., Du Y.P., Freedman R. (2007): Increased hemodynamic response in the hippocampus, thalamus and prefrontal cortex during abnormal sensory gating in schizophrenia. Schizophr Res 92:262-272.

Tregellas J.R., Ellis J., Shatti S., Du Y.P., Rojas D.C. (2009): Increased hippocampal, thalamic, and prefrontal hemodynamic response to an urban noise stimulus in schizophrenia. Am J Psychiatry 166:354-360.

van Haren N.E., Cahn W., Hulshoff Pol H.E., Schnack H.G., Caspers E., Lemstra A., Sitskoorn M.M., Wiersma D., van den Bosch R.J., Dingemans P.M., Schene A.H., Kahn R.S. (2003): Brain volumes as predictor of outcome in recent-onset schizophrenia: a multi-center MRI study. Schizophr Res 64:41-52.

van Haren N.E., Hulshoff Pol H.E., Schnack H.G., Cahn W., Brans R., Carati I., Rais M., Kahn R.S. (2008): Progressive brain volume loss in schizophrenia over the course of the illness: evidence of maturational abnormalities in early adulthood. Biol Psychiatry 63:106-113.

van Haren N.E., Hulshoff Pol H.E., Schnack H.G., Cahn W., Mandl R.C., Collins D.L., Evans A.C., Kahn R.S. (2007): Focal grey matter changes in schizophrenia across the course of the illness: a 5-year follow-up study. Neuropsychopharmacology 32:2057-2066.

Veen N.D., Selten J.P., van der Tweel I., Feller W.G., Hoek H.W., Kahn R.S. (2004): Cannabis use and age at onset of schizophrenia. Am J Psychiatry 161:501-506.

White T., Andreasen N.C., Nopoulos P., Magnotta V. (2003): Gyrification abnormalities in childhood- and adolescent-onset schizophrenia. Biol Psychiatry 54:418-426.

Wible C.G., Anderson J., Shenton M.E., Kricun A., Hirayasu Y., Tanaka S., Levitt J.J., O'Donnell B.F., Kikinis R., Jolesz F.A., McCarley R.W. (2001): Prefrontal cortex, negative symptoms, and schizophrenia: an MRI study. Psychiatry Res 108:65-78.

Wright I.C., Rabe-Hesketh S., Woodruff P.W., David A.S., Murray R.M., Bullmore E.T. (2000): Meta-analysis of regional brain volumes in schizophrenia. Am J Psychiatry 157:16-25.

Yucel M., Solowij N., Respondek C., Whittle S., Fornito A., Pantelis C., Lubman D.I. (2008): Regional brain abnormalities associated with long-term heavy cannabis use. Arch Gen Psychiatry 65:694-701.

Zavitsanou K., Garrick T., Huang X.F. (2004): Selective antagonist [3H]SR141716A binding to cannabinoid CB1 receptors is increased in the anterior cingulate cortex in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 28:355-360.

Zijdenbos A.P., Forghani R., Evans A.C. (2002): Automatic “pipeline” analysis of 3-D MRI data for clinical trials: application to multiple sclerosis. IEEE Trans Med Imaging 21:1280-1291.

Chapter 4

Brain volume reductions in medication naïve patients with schizophrenia in relation to IQ

Monica Rais | Wiepke Cahn | Hugo G. Schnack | Hilleke E. Hulshoff Pol

René S. Kahn | Neeltje E.M. van Haren

(submitted for publication)

Abstract

Global brain abnormalities such as brain volume loss and grey and white matter deficits are consistently reported in first episode schizophrenia patients and may already be detectable in the very early stages of the illness. Whether these changes are dependent of medication use or IQ is still debated.

Magnetic Resonance Imaging (MRI) scans were obtained for 20 medication naïve patients with first episode schizophrenia and 26 matched healthy subjects. Volume measures of total brain grey and white matter, third and lateral ventricles and cortical thickness were obtained. Differences between the groups were investigated, taking into account the effect of intelligence.

Medication naïve patients showed statistically significant reductions in whole brain volume and cerebral grey and white matter volume together with lateral ventricle enlargement as compared to healthy subjects. IQ was significantly lower in patients as compared to controls and was positively associated to brain and white matter volume in the whole group. A negative correlation was found between whole brain volume and total score on the general subscale of the PANSS. No significant differences in cortical thickness were found between the groups.

Our findings suggest that brain abnormalities are present at illness onset, are not related to medication and are related to IQ and general symptoms of the illness.

Introduction

Cross-sectional magnetic resonance imaging (MRI) studies in early onset schizophrenia patients have consistently demonstrated decreases in whole brain volume, in particular grey matter volume, as well as increases in ventricular volume (for metanalyses see: Steen et al., 2006; Vita et al., 2006). The volume loss can at least partly be explained by cortical thinning in frontotemporal cortices (Schultz et al., 2010), anterior cingulate cortex (Fornito et al., 2008) and the right insular cortex (Roiz-Santianez et al., 2010).

These findings convincingly show that brain abnormalities are already present in the early stages of the illness; however, it is still unclear whether these changes are influenced by factors related to the illness such as the use of antipsychotic medication (Navari and Dazzan, 2009; Moncrieff and Leo, 2010) or other confounders such as level of education or IQ (Narr et al., 2007). To rule out an effect of medication, studies in never medicated patients are needed. So far, findings of these studies have been inconsistent. Chua et al. (Chua et al., 2007) reported grey and white matter reductions after correcting for whole brain volume in 26 medication naïve patients as compared to 38 healthy controls. Others failed to find any global brain volume difference between 38 patients and 43 controls (Ebdrup et al., 2010), while we only found enlargement of the third ventricle (Cahn et al., 2002) in 20 medication naive patients with schizophrenia as compared to 20 controls. Despite little evidence for loss in global brain volumes, studies do report cortical thickness reductions in medication naive patients, primarily in the prefrontal cortex (Narr et al., 2005a; Narr et al., 2005b; Venkatasubramanian et al., 2008) but also in the temporal, parietal and occipital cortices (Narr et al., 2005a; Narr et al., 2005b). Based on these findings, subtle brain abnormalities appear to be present, at least in focal areas of the cortical mantle at the onset of the illness.

Apart from medication, level of general cognitive function may confound the differences in brain volume between schizophrenia patients and healthy individuals. Whole brain and grey matter volume has been found to be related to IQ in patients with schizophrenia (Baare et al., 1999; Toulopoulou et al., 2004; Antonova et al., 2005; for a review see Antonova et al., 2004) as well as in healthy subjects (Andreasen et al., 1993; Narr et al., 2007) The association between brain volume and intelligence is of genetic origin (Posthuma et al., 2002).

In most studies, patients do not obtain the same level of education as the control group, while the groups are otherwise matched for age, gender and parental level of education or socioeconomic

status. Indeed, decline of cognitive function in subjects who later develop schizophrenia is present a decade before the onset of the first psychotic symptoms (van Oel et al., 2002) and precedes the onset of schizophrenia by many years (Reichenberg et al., 2010; for a meta-analysis see Woodberry et al., 2008).

We set out to recruit a sample of antipsychotic-naive first episode schizophrenia patients and healthy subjects to assess whether the brain abnormalities (global volumes and cortical thickness) are already present before the intake of antipsychotic medication and to investigate how the brain abnormalities are related to IQ.

Method

Patients with first-episode non affective psychosis (n=20), recruited from the GROUP study at the University Medical Center Utrecht, Utrecht, the Netherlands, and 26 healthy comparison subjects were included in the study. The study received approval of the local ethical committee. After complete description of the study to the subjects, written informed consent was obtained. Subjects were physically healthy and did not have a history of head injury. All subjects were assessed with the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992) by two trained raters who independently determined the diagnosis and achieved consensus afterwards. Drug use was assessed using the Composite International Diagnostic Interview (CIDI) (Robins et al., 1988). Information was obtained on the average number of alcohol consumptions per week during the month prior MRI scan and lifetime. Two patients and two healthy comparison subjects met the DSM-IV criteria for alcohol abuse during the month preceding the MRI scan, whereas five patients and four healthy comparison subjects met these criteria lifetime. The two groups did not differ significantly on average number of alcohol consumptions per week.

In the patient group, severity of illness was measured with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and the duration of untreated psychosis (DUP) was calculated. Moreover, the Intelligence Quotient (IQ) of each subject was estimated based on four subtests of the Dutch version of the Wechsler Adult Intelligence Scale (WAIS) (Information, Arithmetics, Block design and digit symbol coding). At baseline (T0), 19 patients fulfilled DSM IV criteria for schizophrenia, and one for schizoaffective disorder. All patients were antipsychotic-naive at inclusion. The healthy comparison subjects fulfilled criteria for “never mentally ill”. The groups were matched for sex, age, handedness and socioeconomic status of their parents (expressed as the highest level of education completed by one of the parents).

MRI procedures and measurements

Imaging and processing

Structural magnetic resonance imaging (MRI) scans of the whole brain were obtained on a 1.5T Achieva scanner (Philips, Best, The Netherlands). A three-dimensional T1-weighted coronal spoiled-gradient echo scan of the whole head (256x256 matrix, TE=4.6 ms, TR=30 ms, flip angle=30 degrees, 160–180 contiguous slices; 1x1x1.2 mm^3 voxels, field-of-view = 256 mm/70%) was acquired. Furthermore, a single-shot EPI (echo planar imaging) scan was made as part of a diffusion tensor imaging (DTI)-series (SENSE factor 2.5; flip angle 90 degrees; 60 transverse slices of 2.5 mm; no gap; 128 x 96 acquisition matrix; FOV 240 mm; TE=78 ms) together with a magnetization transfer imaging (MTI) scan (60 transverse slices of 2.5 mm; no gap; 128x96 acquisition matrix; FOV 240 mm; flip angle 8 degrees; TE=4.5 ms; TR=37.5 ms).

Processing was done on the computer network of the Department of Psychiatry at the University Medical Center Utrecht. All images were coded to ensure investigator blindness to subject identification and diagnosis.

Volumetric processing

Our imaging protocol made use of T2-weighted contrast of the DTI-B0 and MTI-series for segmentation of the intracranial volume. The DTI-B0 and MTI images were superimposed onto the T1-weighted image to remove non-brain tissue voxels, as described previously (Peper et al., 2008). The T1-weighted images were automatically put into Talairach orientation without scaling, by registering them to a model brain. The translation and rotation parameters of this registration were then applied to the intracranial segment (Maes et al., 1997). The intracranial segment served as a mask for all further segmentation steps. The T1-weighted images were corrected for field inhomogeneities using the N3 algorithm (Sled et al., 1998). Our automatic image processing pipeline was used for segmentation of total brain, grey (GM) and white matter (WM) of the whole brain (Brouwer et al., 2010). In short, pure GM and WM intensities were directly estimated from the image. The amounts of pure and partial volume voxels were modelled in a non-uniform partial volume density, which is fitted to the intensity histogram. Expected tissue fractions, based on the pure intensities and the partial volume density, were subsequently computed in each voxel within the cerebrum. Grey and white matter volumes were calculated by summating the fractions of grey and white matter over all voxels. Total brain volume was calculated by adding the grey and white matter segments.

Lateral and third ventricle and cerebellum volumes were assessed. The software included histogram analysis, mathematical morphology operations, and anatomical knowledge-based rules to connect all voxels of interest, as was validated before (Schnack et al., 2001). The intracranial mask, ventricle and cerebellum segments were visually checked and edited if necessary.

Cortical thickness

To compute cortical thickness, the binarized GM and WM segments were used as input for the custom implementation of the CLASP algorithm designed at the McConnell Brain Imaging Centre of the Montreal Neurological Institute (MacDonald et al., 2000; Kabani et al., 2001; Kim et al., 2005). A 3D surface comprising 81,920 polygons per hemisphere was fitted to the white matter/grey matter intersection, which created the inner surface of the cortex which was then expanded to fit the grey matter/cerebrospinal fluid intersection, thereby creating the outer cortical surface. Cortical thickness was estimated by taking the distance between the two surfaces such that each of the 81,924 vertices of the polygons on the outer surface had a counterpart vertex on the inner surface. Each subject's thickness measurements were smoothed across the surface using a 20 mm surface-based blurring kernel (Chung and Taylor, 2004). This method of blurring improves the chances of detecting population differences, but also follows the curvature of the surface to preserve any anatomical boundaries within the cortex. For each subject, cortical thickness was calculated for every vertex in individual space, and then transformed to the ICBM template. The surfaces of each subject were registered to an average surface created from 152 healthy subjects aged 18-40 years (ICBM 152) (Lyttelton et al., 2007), allowing comparison of cortical thickness locally between subjects.

Statistical Analysis

Demographic and clinical data

To assess whether the groups differed on demographic or clinical variables, multiple analyses of variance (ANOVA) were conducted for non-categorical variables (including IQ) and chi-square analyses for categorical variables (Table 1).

Group differences in brain volumes and IQ

To assess whether brain volumes differed between medication naive patients and healthy comparison subjects, multiple regression analyses were performed with brain volumes as dependent variable and group (schizophrenia patient, healthy comparison), intracranial volume, age, and sex as independent variables. Also, using Pearson product-moment correlations the

Table 1 | Demographic and clinical data of the medication naïve first-episode (FE-MN) patients with schizophrenia and healthy comparison subjects.

	FE-MN Patients N=20				Healthy Comparison Subjects N=26						
	Mean/N	SD	Range		Mean/N	SD	Range		df	F/X^2	Sig
Sex, No. of subjects m/f	15/5				17/9				1	0.49	0.36
Handedness, No. of subjects r/l/a	18/2/0				23/2/1				2	0.84	0.66
Age, yrs	24.39	5.14	18.62	41.21	23.70	4.15	17.64	36.90	45, 1	0.25	0.61
Parental education level, yrs	13.72	4.01	10	17	14.12	2.41	10	17	43, 1	0.17	0.69
Education, yrs	12.05	2.04	9	15	14.27	1.66	11	17	44, 1	16.10	<0.001
Education, highest level	5.16	2.09	2	8	7.23	1.03	4	8	44, 1	19.29	<0.001
IQ*	88.94	17.26	68	128	113.62	10.87	94	140	43, 1	33.91	<0.001
Alcohol Units at Inclusion	7.20	16.65	0	70	7.62	9.10	0	35	45, 1	0.01	0.91
Alcohol Units lifetime	18.30	26.61	0	100	14.08	29.54	0	150	45, 1	0.25	0.62
DSM Alcohol at inclusion (yes/no)	2/18				2/24				1	0.08	0.59
DSM Alcohol LT (yes/no)	5/15				4/22				1	0.66	0.33
Hard drugs LT (yes/no)	2/18				2/24				1	0.78	0.59
Hard drugs at inclusion (yes/no)	1/19				1/25				1	0.85	0.69
Cannabis LT (yes/no)	9/11				4/22				1	0.03	0.03
Cannabis at inclusion (yes/no)	6/14				1/25				1	0.01	0.02
Nicotine (yes/no)	13/7				7/19				1	0.01	0.01
Panss Positive	17.60	6.76									
Panss Negative	17.00	5.71									
Panss General	34.75	8.93									

*IQ not available for two patients

association between global brain volume (corrected for age, sex and intracranial volume) and IQ was investigated, both in the total sample as well as per group.

Group differences in cortical thickness

First, group differences in mean cortical thickness were calculated by using regression analyses with diagnosis (patient-control), age and sex as covariates.

To evaluate the differences in focal cortical thickness between the groups a vertex-by-vertex analysis was carried out. In each vertex, group differences in cortical thickness were calculated by using regression analyses with diagnosis (patient-control), age and sex as covariates. This produced t-statistics at each vertex, one for the effect of diagnosis, one for the effect of age, and one for the effect of sex. We adjusted for multiple comparisons using a False Discovery Rate (FDR=0.05, two-tailed). Statistical maps were created showing significant differences in cortical thickness between patients and healthy comparison subjects. Statistical maps were visualized using the cortical surface viewer Brain-view developed at the Montreal Neurological Institute.

Association with clinical variables

To exclude effect of alcohol, cannabis or nicotine use all analyses were repeated with respectively alcohol ab(use) (yes/no or units per week in the period of most frequent use), cannabis use (yes/no), or nicotine use (yes/no) as covariate. In patients only, the clinical relevance of the brain volume abnormalities is investigated. In case of significant differences in brain volume or cortical thickness between patients and controls, the relationship with positive and negative symptom score (PANSS) was investigated. Multiple regression analyses were done adding brain volume or cortical thickness (in the most significant peak vertices) as the dependent variable, the clinical measure, age, sex, and IC (only in case of global brain volumes) as independent variable.

Results

Demographic and clinical data

As shown in Table 1, the groups did not differ significantly with regard to sex, handedness, age, and socioeconomic status (estimated by the highest level of education reached by one of the parents). Moreover, no differences were found on alcohol or hard-drugs (ab-)use lifetime and during the 12 months preceding the MRI scan.

A significantly higher number of schizophrenia patients had a DSM diagnosis of cannabis misuse/abuse as compared to the healthy subjects.

The patient group had a significantly lower IQ as compared to the healthy comparison subjects (IQpatients= 88.94 [sd=17.26]; IQcontrols= 113.62 [sd=10.87]).

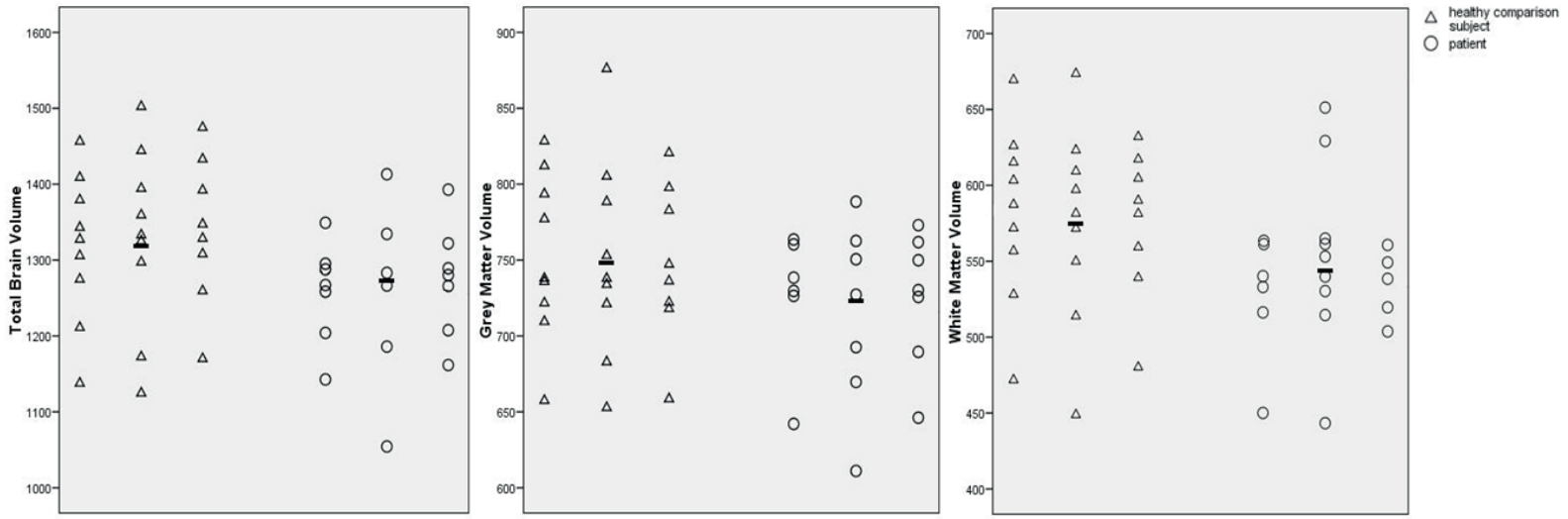
Group differences in brain volumes

As shown in table 2 and figure 1, a significant decrease in whole brain volume (b=-41.1 ml, t(41)=-3.65, p=0.001) was found in medication naive first episode schizophrenia patients as compared to healthy controls. In addition, both grey and white matter volume were decreased in patients as compared to controls (GM: b=-16.0 ml, t(41)=-2.03, p=0.05; WM: b=-25.1 ml, t(41)=-2.59, p=0.01). Furthermore, a significant lateral ventricle enlargement was found in patients as compared to controls (b=7.1 ml, t(41)=2.36, p=0.02).

Table 2 | Brain volumes in first episode medication naïve (FE-MN) patients with schizophrenia (N=20) and healthy comparison subjects

	FE-MN Patients N=20		**Healthy Comparison Subjects N=26**				
	Mean (ml)	SD	Mean (ml)	SD	b	t(41)	Sig.
Intracranial Volume	1517.97	115.44	1550.18	118.17			
Whole Brain Volume	1263.05	85.58	1327.38	102.34	-41.1	-3.65	0.001
Gray Matter Volume	721.92	48.44	750.32	55.96	-16.0	-2.03	0.05
White Matter Volume	541.13	47.85	577.05	55.83	-25.1	-2.59	0.01
Lateral Ventricle Volume	18.63	14.50	13.34	7.35	7.1	2.36	0.02
Third Ventricle Volume	0.89	0.39	0.80	0.33	0.15	1.47	0.14
Mean cortical thickness	Mean (mm)	SD	Mean (mm)	SD	B	t(41)	P
Left	2.9	0.08	2.9	0.06	-0.02	-0.71	0.47
Right	3.0	0.12	2.9	0.12	-0.02	-0.56	0.58

Figure 1 | Brain volume in first episode medication naïve schizophrenia patients and healthy comparison subjects:



Both whole brain volume as well as white matter volume were positively associated with IQ in the whole group (whole brain: r=0.33; p=0.03; white matter: r=0.31; p=0.04). Lateral ventricle volume was negatively correlated with IQ (r=-0.35; p=0.02). No significant correlations were found between IQ and brain volume in the separate groups.
Excluding one patient with an IQ below 70 did not change these findings.

Group differences in cortical thickness

Finally, as shown in table 2, no significant differences in mean or focal cortical thickness were found between schizophrenia patients and healthy comparison subjects.

Association with clinical variables

Adding alcohol, cannabis or nicotine use as covariate did not change the direction of the effects for total brain, grey and white matter volume.

A negative correlation was found between whole brain volume and total score on the general subscale of the PANSS (b=-2.2; t(15)=-2.52; p=0.02) while the correlation with white matter volume reached trend level (WM: b=-1.2; t(15)=-1.98; p=0.07). These correlations indicate that a smaller volume is associated with higher level of symptoms.

Discussion

This cross-sectional structural MRI study compared global brain volumes and cortical thickness between 20 first episode medication-naive schizophrenia patients and 26 healthy comparison subjects. Our main finding is a reduction of whole brain volume in medication naive patients as compared to matched healthy controls, which can be explained by reductions in both grey as well as white matter. In addition, a significant increase in lateral ventricles volume was found.

Our data suggests that brain abnormalities are indeed present at the onset of the illness and that they are not related to the effect of antipsychotic medication. Evidence from animal and human studies suggests that antipsychotic medication affects brain morphology. The direction of the effect is not consistent. A study in non-human primates showed that chronic, therapeutic-like daily exposure to either haloperidol or olanzapine antipsychotic is associated with a reduction of whole brain volume affecting both grey and white matter (Dorph-Petersen et al., 2005). Reviews of human studies point out that antipsychotic treatment might potentially contribute (possibly with different effects, including 'protective effects', being associated with different

antipsychotics) to the morphological changes in the brain observed in psychosis (Navari and Dazzan, 2009; Moncrieff and Leo, 2010).

That brain volume decrease is present at illness onset and is not a consequence upon the intake of antipsychotic medication is consistent with structural MRI studies in high risk subjects. Many of those converting to psychosis not only have more pronounced neuroanatomical abnormalities before the first psychotic episode but also show further changes in grey (Pantelis et al., 2003; Borgwardt et al., 2007; for a review see Pantelis et al., 2005) and possibly white matter volume (Walterfang et al., 2008) after psychosis onset (for a review and meta analysis see Smieskova et al., 2010). Interestingly, Ziermans et al. (Ziermans et al., 2010) showed progressive whole brain and white matter volume loss in unmedicated ultra high risk subjects converting to psychosis compared to non-converters and control groups.

Whether the decrease in whole brain volume we find in medication naive patients is indeed a global effect or is the result of the volume loss in specific regions of interest (ROIs) is difficult to answer from this study. We could not detect a significant focal loss of cortical thickness; however, the size of our sample limits the statistical power to find effects in such measurements. Previous MRI studies in medication naive schizophrenia patients have reported decreased volumes of cortical and subcortical ROIs, such as the pituitary (Upadhyaya et al., 2007), the caudate nucleus (Keshavan et al., 1998; Corson et al., 1999; Ebdrup et al., 2010), the entorhinal cortex and the parahippocampal gyrus (Joyal et al., 2002; Prasad et al., 2004a; Prasad et al., 2004b), the thalamus (Gur et al, 1998), the amygdala (Joyal et al, 2003), the corpus callosum (Keshavan et al., 2002) and the hippocampus (Ebdrup et al., 2010). In addition, Venkatasubramanian et al. (Venkatasubramanian et al., 2008) and Narr et al. (Narr et al., 2005a; Narr et al., 2005b) showed cortical thickness decreases in frontal and temporal areas in relatively large sample of first episode patients. However, in the patient sample of Narr (Narr et al., 2005a; Narr et al., 2005b) only 39 out of 72 patients were medication naive, while the remainder was minimally treated.

In our earlier MRI study in medication naive patients with schizophrenia we reported no differences between patients and controls in global (and subcortical) brain structures, except for an enlargement of the third ventricle. Surprisingly, the patients, although suffering from schizophrenia, had an IQ (IQ=109) comparable to that of the healthy comparison subjects (IQ=114). This might indicate that their premorbid IQ was actually higher as compared to that of the controls, assuming that a slower premorbid cognitive development is predictive for the onset of schizophrenia (Reichenberg et al., 2010).

In the current study patients had a significantly lower IQ than healthy comparison subjects (IQ=89 and IQ=114, respectively), despite matching the sample on socioeconomic status of the parents. Not only did we find evidence for lower intellectual performance just after onset of the psychosis, patients also had a lower level and less years of education, which indicates a poorer cognitive development before onset (see table 1). In agreement with prior studies in healthy subjects (Andreasen et al., 1993; Narr et al., 2007) and schizophrenia patients (Toulopoulou et al., 2004; Antonova et al., 2005); for a review see (Antonova et al., 2004) we also found a relationship between IQ and brain volume, irrespective of diagnosis. Thus, it may be argued that the smaller brain volume in schizophrenia at the onset of psychosis is related to their abnormal cognitive development prior to the onset of psychosis.

In addition, higher PANSS scores in the general psychopathology scale were correlated to a smaller whole brain volume in the patients only.

Several limitations of this study should be taken into consideration. First the number of subjects included was limited. This might account for not finding statistical difference in cortical thickness between first episode patients and healthy comparison subjects. In addition, our patients and controls were not matched on nicotine and lifetime and present cannabis (ab-)use. However, correcting our analysis for nicotine or cannabis use did not change the direction of our findings.

In conclusion, we showed that whole brain volume is decreased in medication naive first episode patients, due to smaller grey as well as white matter volumes. This smaller brain volume could be partially explained by the (lowered) IQ and general psychopathology symptom severity in the patients. This finding suggests that brain abnormalities are present at illness onset, are independent of medication and related to the cognitive and general symptoms of the illness.

Reference List

Andreasen N.C., Flaum M., Arndt S. (1992): The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. Arch Gen Psychiatry 49:615-623.

Andreasen N.C., Flaum M., Swayze V., O'Leary D.S., Alliger R., Cohen G., Ehrhardt J., Yuh W.T. (1993): Intelligence and brain structure in normal individuals. Am J Psychiatry 150:130-134.

Antonova E., Kumari V., Morris R., Halari R., Anilkumar A., Mehrotra R., Sharma T. (2005): The relationship of structural alterations to cognitive deficits in schizophrenia: a voxel-based morphometry study. Biol Psychiatry 58:457-467.

Antonova E., Sharma T., Morris R., Kumari V. (2004): The relationship between brain structure and neurocognition in schizophrenia: a selective review. Schizophr Res 70:117-145.

Baare W.F., Hulshoff Pol H.E., Hijman R., Mali W.P., Viergever M.A., Kahn R.S. (1999): Volumetric analysis of frontal lobe regions in schizophrenia: relation to cognitive function and symptomatology. Biol Psychiatry 45:1597-1605.

Borgwardt S.J., Riecher-Rossler A., Dazzan P., Chitnis X., Aston J., Drewe M., Gschwandtner U., Haller S., Pfluger M., Rechsteiner E., D'Souza M., Stieglitz R.D., Radu E.W., McGuire P.K. (2007): Regional grey matter volume abnormalities in the at risk mental state. Biol Psychiatry 61:1148-1156.

Brouwer R.M., Hulshoff Pol H.E., Schnack H.G. (2010): Segmentation of MRI brain scans using non-uniform partial volume densities. Neuroimage 49:467-477.

Cahn W., Hulshoff Pol H.E., Bongers M., Schnack H.G., Mandl R.C., van Haren N.E., Durston S., Koning H., van der Linden J.A., Kahn R.S. (2002): Brain morphology in antipsychotic-naive schizophrenia: a study of multiple brain structures. Br J Psychiatry Suppl 43:s66-s72.

Chua S.E., Cheung C., Cheung V., Tsang J.T., Chen E.Y., Wong J.C., Cheung J.P., Yip L., Tai K.S., Suckling J., McAlonan G.M. (2007): Cerebral grey, white matter and csf in never-medicated, first-episode schizophrenia. Schizophr Res 89:12-21.

Chung M.K., Taylor J. (2004): Diffusion smoothing on brain surface via finite element method. Biomedical Imaging: Nano to Macro, 2004 IEEE International Symposium 1:432-435.

Corson P.W., Nopoulos P., Andreasen N.C., Heckel D., Arndt S. (1999): Caudate size in first-episode neuroleptic-naive schizophrenic patients measured using an artificial neural network. Biol Psychiatry 46:712-720.

Dorph-Petersen K.A., Pierri J.N., Perel J.M., Sun Z., Sampson A.R., Lewis D.A. (2005): The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation: a comparison of haloperidol and olanzapine in macaque monkeys. Neuropsychopharmacology 30:1649-1661.

Ebdrup B.H., Glenthoj B., Rasmussen H., Aggernaes B., Langkilde A.R., Paulson O.B., Lublin H., Skimminge A., Baare W. (2010): Hippocampal and caudate volume reductions in antipsychotic-naive first-episode schizophrenia. J Psychiatry Neurosci 35:95-104.

Fornito A., Yucel M., Wood S.J., Adamson C., Velakoulis D., Saling M.M., McGorry P.D., Pantelis C. (2008): Surface-based morphometry of the anterior cingulate cortex in first episode schizophrenia. Hum Brain Mapp 29:478-489.

Gur, R.E., Maany, V., Mozley, P.D., Swanson, C., Bilker, W. & Gur, R.C. (1998): Subcortical MRI volumes in neuroleptic-naive and treated patients with schizophrenia. American Journal of Psychiatry **155**, 1711-1717.

Joyal, C.C., Laakso, M.P., Tiihonen, J., Syvalahti, E., Vilkman, H., Laakso, A. Alakare, B., Räkköläinen, V., Salokangas, R.K., Hietala, J. (2003): The amygdala and schizophrenia: a volumetric magnetic resonance imaging study in first-episode, neuroleptic-naive patients. Biological Psychiatry 54, 1302-1304.

Joyal C.C., Laakso M.P., Tiihonen J., Syvalahti E., Vilkman H., Laakso A., Alakare B., Rakkolainen V., Salokangas R.K., Hietala J. (2002): A volumetric MRI study of the entorhinal cortex in first episode neuroleptic-naive schizophrenia. Biol Psychiatry 51:1005-1007.

Kabani N., Le Goualher G., MacDonald D., Evans A.C. (2001): Measurement of cortical thickness using an automated 3-D algorithm: a validation study. Neuroimage 13:375-380.

Kay S.R., Fiszbein A., Opler L.A. (1987): The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13:261-276.

Keshavan M.S., Diwadkar V.A., Harenski K., Rosenberg D.R., Sweeney J.A., Pettegrew J.W. (2002): Abnormalities of the corpus callosum in first episode, treatment naive schizophrenia. J Neurol Neurosurg Psychiatry 72:757-760.

Keshavan M.S., Rosenberg D., Sweeney J.A., Pettegrew J.W. (1998): Decreased caudate volume in neuroleptic-naive psychotic patients. Am J Psychiatry 155:774-778.

Kim J.S., Singh V., Lee J.K., Lerch J., Ad-Dab'bagh Y., MacDonald D., Lee J.M., Kim S.I., Evans A.C. (2005): Automated 3-D extraction and evaluation of the inner and outer cortical surfaces using a Laplacian map and partial volume effect classification. Neuroimage 27:210-221.

Lyttelton O., Boucher M., Robbins S., Evans A. (2007): An unbiased iterative group registration template for cortical surface analysis. Neuroimage 34:1535-1544.

MacDonald D., Kabani N., Avis D., Evans A.C. (2000): Automated 3-D extraction of inner and outer surfaces of cerebral cortex from MRI. Neuroimage 12:340-356.

Maes F., Collignon A., Vandermeulen D., Marchal G., Suetens P. (1997): Multimodality image registration by maximization of mutual information. IEEE Trans Med Imaging 16:187-198.

Moncrieff J., Leo J. (2010): A systematic review of the effects of antipsychotic drugs on brain volume. Psychol Med 40:1409-1422.

Narr K.L., Bilder R.M., Toga A.W., Woods R.P., Rex D.E., Szeszko P.R., Robinson D., Sevy S., Gunduz-Bruce H., Wang Y.P., DeLuca H., Thompson P.M. (2005a): Mapping cortical thickness and grey matter concentration in first episode schizophrenia. Cereb Cortex 15:708-719.

Narr K.L., Toga A.W., Szeszko P., Thompson P.M., Woods R.P., Robinson D., Sevy S., Wang Y., Schrock K., Bilder R.M. (2005b): Cortical thinning in cingulate and occipital cortices in first episode schizophrenia. Biol Psychiatry 58:32-40.

Narr K.L., Woods R.P., Thompson P.M., Szeszko P., Robinson D., Dimtcheva T., Gurbani M., Toga A.W., Bilder R.M. (2007): Relationships between IQ and regional cortical grey matter thickness in healthy adults. Cereb Cortex 17:2163-2171.

Navari S., Dazzan P. (2009): Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. Psychol Med :1-15.

Pantelis C., Velakoulis D., McGorry P.D., Wood S.J., Suckling J., Phillips L.J., Yung A.R., Bullmore E.T., Brewer W., Soulsby B., Desmond P., McGuire P.K. (2003): Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. Lancet 361:281-288.

Pantelis C., Yucel M., Wood S.J., Velakoulis D., Sun D., Berger G., Stuart G.W., Yung A., Phillips L., McGorry P.D. (2005): Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. Schizophr Bull 31:672-696.

Peper J.S., Brouwer R.M., Schnack H.G., van Baal G.C., van Leeuwen M., van den Berg S.M., Delemarre-Van de Waal H.A., Janke A.L., Collins D.L., Evans A.C., Boomsma D.I., Kahn R.S., Hulshoff Pol H.E. (2008): Cerebral white matter in early puberty is associated with luteinizing hormone concentrations. Psychoneuroendocrinology 33:909-915.

Posthuma D., De Geus E.J., Baare W.F., Hulshoff Pol H.E., Kahn R.S., Boomsma D.I. (2002): The association between brain volume and intelligence is of genetic origin. Nat Neurosci 5:83-84.

Prasad K.M., Patel A.R., Muddasani S., Sweeney J., Keshavan M.S. (2004a): The entorhinal cortex in first-episode psychotic disorders: a structural magnetic resonance imaging study. Am J Psychiatry 161:1612-1619.

Prasad K.M., Rohm B.R., Keshavan M.S. (2004b): Parahippocampal gyrus in first episode psychotic disorders: a structural magnetic resonance imaging study. Prog Neuropsychopharmacol Biol Psychiatry 28:651-658.

Reichenberg A., Caspi A., Harrington H., Houts R., Keefe R.S., Murray R.M., Poulton R., Moffitt T.E. (2010): Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: a 30-year study. Am J Psychiatry 167:160-169.

Robins L.N., Wing J., Wittchen H.U., Helzer J.E., Babor T.F., Burke J., Farmer A., Jablenski A., Pickens R., Regier D.A., . (1988): The Composite International Diagnostic Interview. An epidemiologic Instrument suitable for use in conjunction with different diagnostic systems and in different cultures. Arch Gen Psychiatry 45:1069-1077.

Roiz-Santianez R., Perez-Iglesias R., Quintero C., Tordesillas-Gutierrez D., Mata I., Ayesa R., Sanchez J.M., Gutierrez A., Sanchez E., Vazquez-Barquero J.L., Crespo-Facorro B. (2010): Insular cortex thinning in first episode schizophrenia patients. Psychiatry Res .

Schnack H.G., Hulshoff H.E., Baare W.F., Viergever M.A., Kahn R.S. (2001): Automatic segmentation of the ventricular system from MR images of the human brain. Neuroimage 14:95-104.

Schultz C.C., Koch K., Wagner G., Roebel M., Schachtzabel C., Gaser C., Nenadic I., Reichenbach J.R., Sauer H., Schlosser R.G. (2010): Reduced cortical thickness in first episode schizophrenia. Schizophr Res 116:204-209.

Sled J.G., Zijdenbos A.P., Evans A.C. (1998): A nonparametric method for automatic correction of intensity nonuniformity in MRI data. IEEE Trans Med Imaging 17:87-97.

Smieskova R., Fusar-Poli P., Allen P., Bendfeldt K., Stieglitz R.D., Drewe J., Radue E.W., McGuire P.K., Riecher-Rossler A., Borgwardt S.J. (2010): Neuroimaging predictors of transition to psychosis--a systematic review and meta-analysis. Neurosci Biobehav Rev 34:1207-1222.

Steen R.G., Mull C., McClure R., Hamer R.M., Lieberman J.A. (2006): Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. Br J Psychiatry 188:510-518.

Toulopoulou T., Grech A., Morris R.G., Schulze K., McDonald C., Chapple B., Rabe-Hesketh S., Murray R.M. (2004): The relationship between volumetric brain changes and cognitive function: a family study on schizophrenia. Biol Psychiatry 56:447-453.

Upadhyaya A.R., El-Sheikh R., MacMaster F.P., Diwadkar V.A., Keshavan M.S. (2007): Pituitary volume in neuroleptic-naive schizophrenia: a structural MRI study. Schizophr Res 90:266-273.

van Oel C.J., Sitskoorn M.M., Cremer M.P., Kahn R.S. (2002): School performance as a premorbid marker for schizophrenia: a twin study. Schizophr Bull 28:401-414.

Venkatasubramanian G., Jayakumar P.N., Gangadhar B.N., Keshavan M.S. (2008): Automated MRI parcellation study of regional volume and thickness of prefrontal cortex (PFC) in antipsychotic-naive schizophrenia. Acta Psychiatr Scand 117:420-431.

Vita A., de Peri L., Silenzi C., Dieci M. (2006): Brain morphology in first-episode schizophrenia: a meta-analysis of quantitative magnetic resonance imaging studies. Schizophr Res 82:75-88.

Walterfang M., McGuire P.K., Yung A.R., Phillips L.J., Velakoulis D., Wood S.J., Suckling J., Bullmore E.T., Brewer W., Soulsby B., Desmond P., McGorry P.D., Pantelis C. (2008): White matter volume changes in people who develop psychosis. Br J Psychiatry 193:210-215.

Woodberry K.A., Giuliano A.J., Seidman L.J. (2008): Premorbid IQ in schizophrenia: a meta-analytic review. Am J Psychiatry 165:579-587.

Ziermans T.B., Schothorst P.F., Schnack H.G., Koolschijn P.C., Kahn R.S., van Engeland H., Durston S. (2010): Progressive Structural Brain Changes During Development of Psychosis. Schizophr Bull .

Chapter 5

Altered white matter connectivity in never-medicated patients with schizophrenia

Monica Rais* | René C.W. Mandl* | G. Caroline M. van Baal | Neeltje E.M. van Haren

Wiepke Cahn | René S. Kahn | Hilleke E. Hulshoff Pol

**these authors contributed equally to the paper.*

(submitted for publication)

Abstract

Numerous diffusion tensor imaging (DTI) studies have implicated white matter brain tissue abnormalities in schizophrenia. However, the vast majority of these studies included patient populations that use anti-psychotic medication. Previous research showed that medication intake can affect brain morphology and the question therefore arises to what extent the reported white matter aberrations can be attributed to the disease rather than to the use of medication. In this study we included 16 medication-naive patients with schizophrenia and compared them to 23 healthy controls to exclude anti-psychotic medication use as a confounding factor. For each subject DTI scans and magnetic transfer imaging (MTI) scans were acquired. A new fiber-based analysis was used that combines fractional anisoptropy (FA), mean diffusivity (MD) and magnetic transfer ratio (MTR) to examine group differences in 12 major white matter fiber bundles. Significant group differences in combined FA, MD, MTR values were found for the right uncinate fasciculus and the left arcuate fasciculus. Additional analysis revealed that the largest part of both tracts showed an increase in MTR in combination with an increase in MD for patients with schizophrenia. We interpret these group-related differences as disease related axonal or glial aberrations that cannot be attributed to anti-psychotic medication use.

Introduction

Schizophrenia is a devastating illness, which not only affects grey matter tissue in the human brain but also its white matter tissue (for a review see Shenton, 2010). White matter consists of large bundles of myelinated axons running in parallel enabling fast and efficient communication between distinct grey matter regions. Modern magnetic resonance imaging (MRI) techniques such as diffusion tensor imaging (DTI) (Le Bihan en Breton, 1985) and magnetization transfer imaging (MTI) (Wolff and Balaban, 1994) allow one to non-invasively study various aspects of the microstructure of these connecting white matter fiber bundles. On the basis of DTI scans fractional anisotropy (FA) (Brasser and Pierpaoli, 1996) and mean diffusivity (MD) can be computed, which provide information on the directionality and density of the axons (Beaulieu, 2002). The magnetic transfer ratio (MTR) can be derived from the MTI scans to measure macromolecule (e.g. myelin) concentrations. Although FA, MD and MTR are not completely independent, they do measure different aspects of the fiber bundle.

White matter tracts that have frequently been implicated in schizophrenia include the uncinate fasciculi, arcuate fasciculi, genu and splenium of the corpus callosum, inferior longitudinal fasciculi, superior longitudinal fasciculi and cingulum bundles (for a review see Kyriakopoulos et al., 2008). So far, most DTI studies have only included patients on medication. This may be problematic since antipsychotic medication has been suggested to affect results (Navari and Dazzan, 2009). One way to exclude this confounding factor is to compare medication-naive patients with schizophrenia to healthy volunteers. To date, only two DTI studies investigated the white matter's microstructure in medication naive schizophrenia patients (Cheung et al., 2008; Gasparotti et al., 2009), suggesting the involvement of the splenium of the corpus callosum. These studies used an ROI analysis and/or voxel-based analysis. Both methods, however, are not optimal to detect small but consistent disease-related differences in the signal that occur along complete fiber bundles (Jones, 2008). To detect this type of disease-related differences, so-called fiber-based analysis is a more sensitive method that averages FA over complete fiber bundles. However, by simply averaging the measured signal one ignores the fact that the signal changes considerably along the fiber bundle and that effect sizes may differ for various signal levels. Here we introduce a new method of fiber-based analysis that is based on (Mandl et al., 2008) and which uses the concept of the average fiber (Gerig et al., 2004; Mandl et al., 2010). This new method differs from conventional fiber-based analysis in two ways. First, in order to take signal variations along the fiber bundle into account, an F-statistic to test for group is done separately per average fiber point. If there are no group differences then the F-values for the points of an

average fiber will follow an F-distribution. Significant deviations from the F-distribution can then be detected using the Kolmogorov-Smirnov test. Second, the FA, MD and MTR are combined in one single analysis (by using a MANOVA as a per average fiber point F-statistic) because these three measures all serve as an index of white matter integrity and may therefore be dependent to a certain degree. This new method is more sensitive than conventional fiber-based analysis because a part of the within-variation (i.e. the variation of values along the fiber) is removed and the degrees of freedom are increased (while correcting for the partial dependency between FA, MD and MTR). Consequently, this new fiber-based analysis allows us to elicit subtle disease-related changes found in (large parts of) the fiber bundles.

In this study, we compared a group of 16 medication-naive patients with 23 healthy volunteers using a combination of DTI and MTI to assess the integrity of the major white matter fiber tracts. The aim of this study is to determine if there are disease-related differences in white matter that are independent of the use of anti-psychotic medication.

Method

Patients with first-episode non affective psychosis (n=16), recruited from the Genetic Risk and Outcome of Psychoses (GROUP) study at the University Medical Center Utrecht, Utrecht, the Netherlands, and 23 healthy comparison subjects were included in the study. The study received approval of the local ethical committee. After complete description of the study to the subjects, written informed consent was obtained. Subjects were physically healthy and did not have a history of head injury. All subjects were assessed with the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al, 1992) by two trained raters who independently determined the diagnosis and achieved consensus afterwards. Drug use was assessed using the Composite International Diagnostic Interview (CIDI) (Robins et al., 1998). Information was obtained on the average number of alcohol consumptions per week during the month prior MRI scan and lifetime. Two patients and two healthy comparison subjects met the DSM-IV criteria for alcohol abuse during the month preceding the MRI scan, whereas five patients and four healthy comparison subjects met these criteria lifetime. The two groups did not differ significantly on average number of alcohol consumptions per week, neither in the last months as well as lifetime. In the patient group, severity of illness was measured with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and the duration of untreated psychosis (DUP) was calculated. Moreover, the Intelligence Quotient (IQ) of each subject was estimated based on four subtests of the Dutch version of the Wechsler Adult Intelligence Scale (WAIS) (Information, Arithmetics,

Block design and digit symbol coding). All patients fulfilled DSM IV criteria for schizophrenia and were antipsychotic-naive at inclusion. The healthy comparison subjects fulfilled criteria for "never mentally ill" (Pfohl et al., 1995). As shown in table 1, the groups were matched for sex, age, handedness and socioeconomic status of their parents (expressed as the highest level of education completed by one of the parents).

Table 1. | Demographic and clinical data of the medication naive first-episode (FE-MN) patients with schizophrenia and healthy comparison subjects.

	FE-MN Patients N=16		**Healthy Comparison Subjects N=23**	
	Mean/N	SD	Mean/N	SD
Sex, No. of subjects m/f	13/3		14/9	
Handedness, No. of subjects r/l/a	14/2/0		20/2/1	
Age, yrs	23.37	3.49	22.81	3.10
Parental education level, yrs	14.38	2.36	14.00	2.49
Education, yrs*	11.53	1.89	14.17	1.75
IQ[a]*	87.53	15.39	113.26	10.74
Alcohol Units at Inclusion	8.75	18.39	8.13	9.50
Alcohol Units lifetime	21.56	28.87	14.91	31.23
DSM Alcohol at inclusion (yes/no)	2/14		2/21	
DSM Alcohol LT (yes/no)	5/11		4/19	
Hard drugs at inclusion (yes/no)	1/15		0/23	
Hard drugs LT (yes/no)	2/14		1/22	
Cannabis at inclusion (yes/no)*	5/11		0/23	
Cannabis LT (yes/no)*	8/8		3/20	
Nicotine (yes/no)*	12/4		7/16	
Panss Positive	16.69	7.07		
Panss Negative	17.13	4.91		
Panss General	35.38	9.60		
Illness duration (m) [b]	22.24	35.63		
Duration of untreated illness (m) [c]	86.49	49.20		

* $p<0.05$

[a] IQ not available for one patients

[b] Time between onset of first psychotic symptoms and MRI scan

[c] Time between prodromal symptoms and MRI scan

Acquisition and post processing have been described in detail (Mandl et al., 2010). In short, for each subject a three-dimensional T1-weighted coronal (spoiled-gradient) echo scan (256×256 matrix; TE=4.6 ms; TR=30 ms; flip angle=30 degrees; 160-180 contiguous slices; total scan duration 405-456 s; 1×1×1.2 mm^3 voxels; FOV=256 mm/70%; parallel imaging applied in both phase-encoding directions with SENSE-factor=1.5), two DTI scans (32 diffusion-weighted volumes with different non-collinear diffusion directions with b-factor=1000 s/mm^2 and 8 diffusion unweighted volumes with b-factor=0 s/mm^2; parallel imaging SENSE factor 2.5; flip angle 90 degrees; 60 slices of 2.5 mm; no slice gap; 96×96 acquisition matrix; reconstruction matrix 128×128; FOV 240 mm; TE=88 ms; TR=9822 ms; no cardiac gating; total scan duration 296 s per scan) and a three-dimensional MTR scan (transverse; 2 volumes, 60 slices of 2.5 mm; 128×128 acquisition matrix; FOV 240 mm; flip angle 8 degrees; TE=3.7 ms; TR=37.5 ms; SENSE factor 2.5; MT prepulse at second volume with off-resonance prepulse frequency offset 1100 Hz, 620 degrees, three-lobe sync-shaped; total scan duration 394 s) were collected.

After simultaneous correction for motion and gradient-induced distortions (Andersson and Shake, 2002) the diffusion tensors were computed per voxel (Chang et al., 2005) followed by the computation of the FA and the MD. The MTR was computed per voxel from the MTI scan using the following formula: MTR=(S0-Sp)/S0, where S0 is the first volume (without magnetization prepulse) and Sp is the second volume (with magnetization prepulse). For within-subject registration purposes, the linear transformations were computed between the diffusion unweighted (b=0 s/mm^2) volume of the post-processed DTI scan and T1-weighted image and between the first volume of the MTI scan both using mutual information as similarity metric. In addition, for each subject a nonlinear transformation was computed between the T1-weighted scan and a study-specific model brain (Boos et al., 2011).

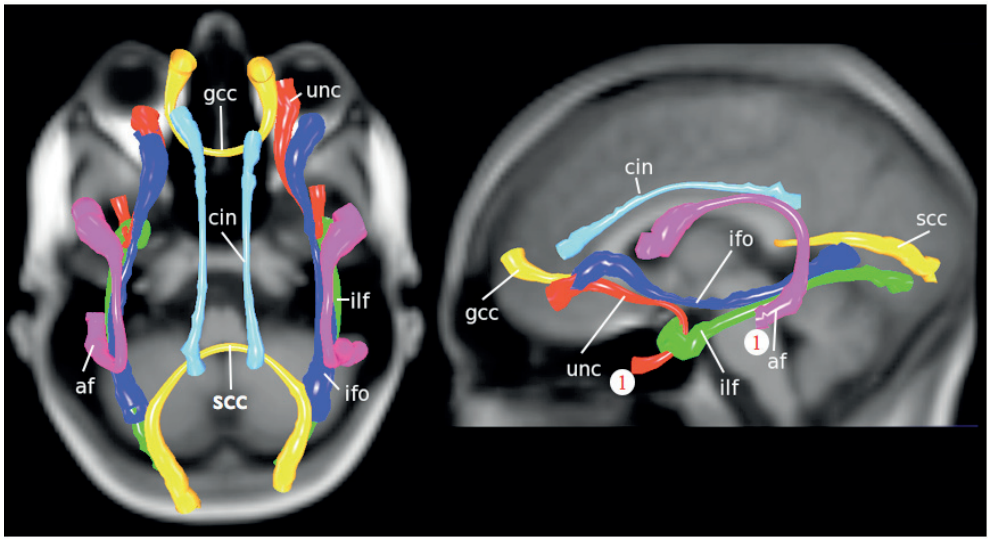
Fiber tracking and fiber bundle selection

A multiple ROI fiber bundle selection approach (Wakana et al., 2004) was used to select the fiber tracts of interest (figure 1) where the reconstruction of the tracts was performed in native space and the selection and analysis of the tracts was performed in model space.

In the first step, all possible tracts in brain were reconstructed individually in native space using the diffusion tensor images with an in-house implementation of the fiber assignment by continuous tracking (FACT) algorithm (Mori et al., 1999) with the following parameter settings: 8 seed-points per voxel, minimum FA=0.1, maximum angle=45 degrees, maximum average angle with neighbouring voxels=45 degrees. Next, the points of the reconstructed tracts were labelled

with the corresponding FA and MTR values after which the tracts were warped into the model space.

FIGURE 1 | Average fiber bundles



The average fiber bundles used in the fiber-based analysis are the af: arcuate fasciculus; unc: uncinate fasciculus; gcc: genu of corpus callosum; scc: splenium of corpus callosum; ilf: inferior longitudinal fasciculus; cin: cingulum tract. The beginning of the tracts for which the analysis results are shown in figure 2 denoted by "1" (in red).

In the second step, the ROIs that were needed to select the tracts were manually delineated on a study-specific model brain as described by Boos et al. (Boos et al., in preparation).

Computation of average fibers

We computed an average fiber in model space for the selected fiber bundles for each individual subject. In short, first a spline representation of the shape of the original reconstructed fiber tracts was created. This spline was then divided into 2 mm regular intervals starting from the centre of the spline. This centre was defined by the geometric centre of the midpoint coordinates of all tracts of the fiber bundle perpendicularly projected onto the spline. For each of these points we defined planes that are perpendicular to the spline. These planes were used to resample the original reconstructed fiber tracts. Each plane was cross-sectioned with the original tracts of the fiber bundle. The cross-sectional coordinates were averaged to form the coordinate of the average fiber in this plane. For each separate plane the MTR and FA values of the cross-sectional coordinates of the original tracts were averaged to produce the average FA and MTR values for that plane. Note that averaging was done over the reconstructed tracts in model space and did

not incorporate resampling of the original voxel data. The average cross-sectional coordinates of all the planes together with the corresponding average FA and MTR values then formed the average fiber.

Average fiber statistics

With conventional fiber-based analysis the FA (or MD or MTR) values are averaged over the bundle assuming that possible group effects are consistently found along the complete (or at least large parts of) fiber bundle. This approach ignores the fact that these values may vary considerably along the bundle and that group effects may vary accordingly. Moreover, the relation between the FA, MD and MTR may vary as well for different parts of the bundles. The major advantage of using the concept of the average fiber is that there is a per point (i.e. points of the average fiber) correspondence between subjects and therefore allows for a point-by-point comparison between groups along the complete bundle. By applying a statistical test per point and then combining these results for all average fiber points one eliminates the within fiber variance. In addition, one can apply statistical tests (e.g. MANOVA) per point that search for an optimal contrast of FA, MD and MTR values revealing group-differences. In this study we apply a MANOVA for each point of an average fiber with FA, MD and MTR as dependent variables yielding an F-value. If no group effect is present then all the F-values for all points along the average bundle should follow an F-distribution. Using the Kolmogorov-Smirnov test we then test if the measured distribution deviates significantly from an F-distribution. If this is the case, then a post-hoc analysis is warranted to assess the nature of the group differences. To deal with possible dependencies between the measurements along a tract we computed a correction factor for the degrees of freedom using the singular value decomposition of the covariance matrix of the raw measurements (Nyholt, 2004). This correction factor was computed separately for the FA, MD and MTR measurements and the average of these correction factors was used to compute the corrected degrees of freedom. In the MANOVA group was added as independent variable while age, sex, handedness, lifetime alcohol abuse, alcohol abuse at inclusion, lifetime hard drugs abuse, hard drug abuse at inclusion, lifetime cannabis abuse and cannabis abuse at inclusion were used as covariates. Finally the Bonferroni correction for multiple comparisons was used to correct for the number of fiber bundles that were tested.

Clustering

In the post-hoc analysis the MANOVA contrasts (FA, MD and MTR) of all average fiber points were clustered based on the signs of the FA, MD and MTR mean group differences. Eight combinations are possible (for example, FA patients smaller than (<) FA controls, MD patients greater or equal

than (≥) MD controls, MTR patients < MTR controls). Some of these combinations are consistent with biophysical differences. For instance, in case of an increase in myelination, regions on the fiber bundle where the axons run highly in parallel (i.e. have a high FA value) are expected to increase in FA and MTR, and decrease in MD. However, for regions with low FA an increase in myelin would also lead to an increase MTR and a decrease MD but only lead to a very small increase (if any) in FA. This because it would alter the diffusion profile equally in all directions and would therefore alter the size of the diffusion profile but not its shape. It was previously pointed out (Mandl et al, 2010) that the interpretation of the MTR is complicated by the fact that the MTI acquisition as used in this study has a considerable T1-weighting. As a consequence, an increase in MTR may not only reflect an increase in macromolecule content but could also be caused by a prolonged T1, for instance due to an increase in free bulk water. In combination with MD, however, it is possible to determine which of the two possible mechanisms is most likely. If an increase in MTR is accompanied by a decrease in MD then this would point in the direction of increased macromolecule content while an increase in MD would suggest an increase in bulk water. The effect of increasing free bulk water on FA is not straight forward as this depends on the actual shape of the increase.

We defined 4 separate clusters that could be linked with increase/decrease in myelination or with an increase/decrease in bulk water. Cluster #1 is formed by those fiber points for which FA patients < FA controls, MD patients ≥ MD controls, MTR patients < MTR controls and is consistent with a disease-related decrease in myelin. Cluster #2 is formed by MD patients ≥ MD controls, MTR patients ≥ MTR controls which is consistent with a disease-related increase of free bulk water. We note that for this cluster we do not consider effects in FA as the effects of a change in free bulk water on FA are not univocal. Cluster #3 is formed by FA patients ≥ FA controls, MD patients < MD controls, MTR patients ≥ MTR controls --- the opposite of cluster #1 --- and is consistent with a disease-related increase of myelin. Finally, cluster #4 is formed by MD patients < MD controls, MTR patients < MTR controls and is consistent with a disease-related decrease of free bulk water --- the opposite of cluster #2.

Results

From the twelve fiber tracts that were tested using the Kolmogorov-Smirnov test (table 2) only significant group-related differences were found for the right uncinate fasciculus (D+=0.3592, degrees of freedom=34, p<0.0006) and the left arcuate fasciculus (D+=0.3145, degrees of freedom=36, p<0.00005). Additional cluster analysis (figure 2) revealed that for both tracts the largest cluster is cluster #2 (table 3) reflecting an increase in both MTR and MD in patients with schizophrenia.

TABLE 2 | Tract results

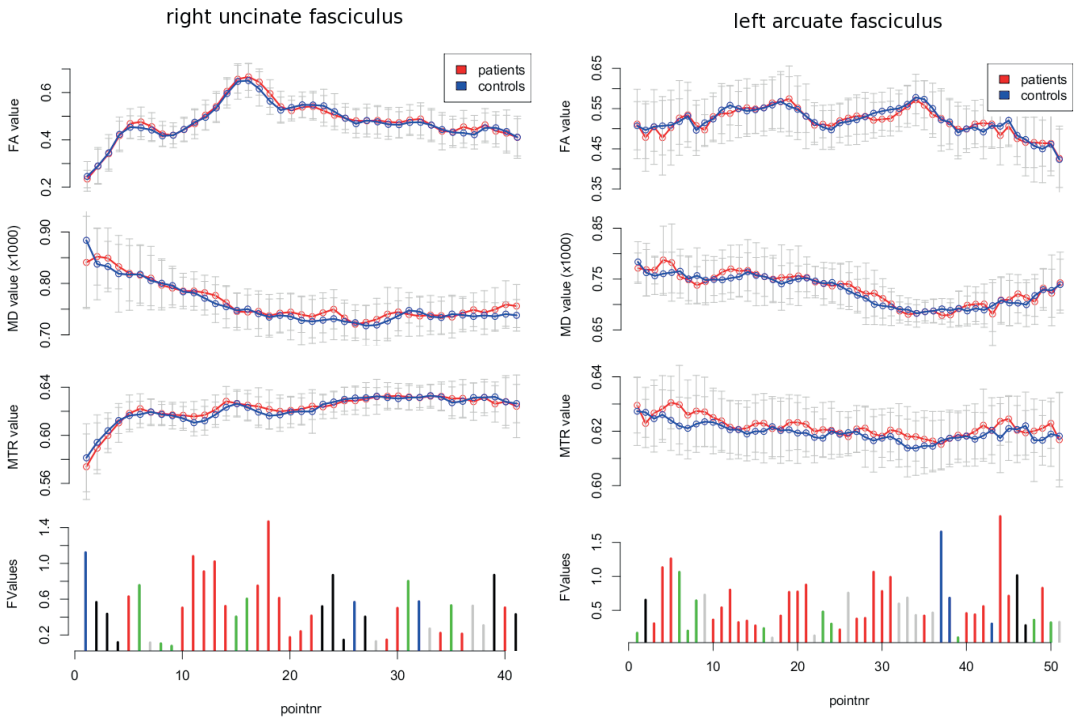
Tract	KS-test D+	Corrected degrees of freedom	P
Genu	0.0213	36	0.96
Splenium	0.0339	61	0.85
Arcuate left	0.3145	36	0.0006*
Arcuate right	0.0717	35	0.67
Cingulum left	0.0675	40	0.66
Cingulum right	0.2432	35	0.013
Uncinate left	0.2128	32	0.047
Uncinate right	0.3592	34	0.00005*
ILF left	0.0578	41	0.73
ILF right	0.1264	42	0.24
IFO left	0.0601	44	0.70
IFO right	0.0695	48	0.60

* significant after Bonferroni correction for multiple comparisons

TABLE 3 | Fiber bundle clustering.

tract	Cluster nr	Cluster size	avg anova F-value for clusters (FA, MD, MTR)
arcuate left	1	3	(0.31, 0.75, 0.87)
	2	26	(0.59, 0.73, 0.73)
	3	10	(0.21, 0.68, 0.89)
	4	3	(0.20, 1.93, 0.07)
uncinate right	1	9	(0.57, 0.84, 0.51)
	2	17	(0.38, 0.52, 1.65)
	3	7	(0.32, 0.68, 1.69)
	4	3	(0.27, 0.75, 0.55)

FIGURE 2 | Clustering results



Discussion

We compared a group of sixteen medication-naive schizophrenia patients with twenty-three healthy comparison subjects (matched for age, sex and handedness) on measures of white matter fiber integrity using a new fiber-based analysis method. This analysis combines three different indices of fiber integrity (FA, MD, MTR) allowing the elucidation of subtle disease-related differences.

Significant group differences were found for the right unciate fasciculus and the left arcuate fasciculus, representing increased MD and MTR in patients relative to controls. These findings are consistent with earlier reports showing abnormalities in both white matter fiber bundles in patients who are in the early stages of schizophrenia (de Weijer et al., in press; Federspiel et al., 2006; Kawashima et al, 2009; Perez-Iglesias et al., 2010; Peters et al., 2009; Price et al; 2008; Rotarska-Jagiela et al., 2009; Szeszko et al., 2008). In addition, increased MTR in patients with schizophrenia has been reported previously for the right uncinate fasciculus (Mandl et al., 2010) and the arcuate fasciculi (de Weijer et al., in press). The increases in MTR reported in (Mandl et

al., 2010) were not accompanied by increases in FA and consequently we hypothesized that 1) the increase in MTR represented an increase in macromolecular content in the right uncinate fasciculus or 2) the increase in MTR reflected an increase in free bulk water because the MTI acquisition as used here is to a certain extent sensitive to changes in T1. Such an increase in free bulk water can be linked to axonal or glial abnormalities (Flynn et al., 2003). Indeed, the results of the post-hoc analysis (Table 3) show that for both the left arcuate fasciculus and the right uncinate fasciculus the group-related differences are predominantly found in fiber points that are part of cluster #2. Cluster #2 is formed by all average fiber points for which there is a disease-related increase in both MTR and MD. This is consistent with an increase in bulk water. Therefore, the results from this study confirm abnormalities in the right uncinate fasciculus and left arcuate bundle and add that these cannot be explained by medication intake.

Additional quantitative T1 measurements in future studies may help to further elucidate the underlying mechanisms of the observed MTR changes.

The main limitation of this study is the small size of the population. However, the need to investigate special groups of patients, often with a low incidence, is necessary in order to learn more about the disease and underscores the need for new highly sensitive analysis methods as introduced in this study. This new fiber-based analysis has a number of advantages over existing methods such as voxel-based morphometry (VBM) (Ashburner and Friston, 2000), conventional fiber-based analysis or tract-based spatial statistics (TBSS) (Smith et al., 2006). With VBM all subjects are transformed into a common stereotaxic space typically followed by the application of a blurring kernel to reduce the effects of inter-subject variability. A disadvantage of VBM analysis for DTI data is that the outcome greatly depends on the choice of the size of the blurring kernel (Jones et al., 2005). Another disadvantage is that, due to the large number of statistical tests performed (one test per voxel), a large correction for multiple comparisons is needed reducing the method's sensitivity. TBSS addresses both problems by considering only those voxels that are part of a so-called white matter skeleton computed for each individual subject. The skeleton not only allows for a one-to-one voxel correspondence between subjects, therefore eliminating the need for the use of a blurring kernel, but also reduces the number of voxels to be tested and hence reducing the multiple comparison correction factor. However, both VBM and TBSS perform statistical tests per voxel --- a suboptimal approach in terms of sensitivity--- to search for subtle disease-related effects that occur along complete fiber tracts. Conventional fiber-based analysis performs group comparisons over measurements averaged along complete fiber tracts and is, in that respect, optimal to detect such subtle effects. By simply averaging the measurements

along the tract it does not take into account that group effects may be different for different parts of the tract. This is particularly important when different types of measurements (e.g. FA, MD and MTR) are combined in a MANOVA-like approach. The new method introduced here does recognize that the relationship between the different types of measurements may vary along the tract allowing for the detection of more complex group differences. The advantage of the basic clustering method used in the post-hoc analysis is that we could link a number of these clusters to possible physiological disease-related differences. Future work will include the incorporation of more sophisticated clustering algorithms to obtain a better one-to-one mapping between clusters and physiology.

Our findings implicate that the previously reported increase in MTR in medicated patients with schizophrenia in the right uncinate fasciculus (Mandl et al., 2010) and the left arcuate fasciculus (de Weijer et al., in press) is also present in medication naive patients. The results of the cluster analysis suggest that the MTR increase, which is accompanied by an increase in MD, reflects axonal or glial abnormalities rather than an increase in myelin.

In conclusion, our findings show that white matter microstructure in the brain, specifically in the left arcuate fasciculus and the right uncinate fasciculus is altered early in the disease process in schizophrenia and cannot be explained by the use of antipsychotic medication.

References

Andersson J.L., Skare S. (2002): A model-based method for retrospective correction of geometric distortions in diffusion-weighted EPI. Neuroimage 16(1):177-99.

Andreasen N.C., Flaum M., Arndt S. (1992): The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. Arch Gen Psychiatry 49(8):615-23.

Ashburner J., Friston K.J. (2000): Voxel-based morphometry--the methods. Neuroimage 11(6 Pt 1):805-21.

Basser P.J., Pierpaoli C. (1996): Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J Magn Reson B 111(3):209-19.

Beaulieu C. (2002): The basis of anisotropic water diffusion in the nervous system - a technical review. NMR Biomed 15(7-8):435-55.

Boos H.B., Cahn W., van Haren N.E., Derks E.M., Brouwer R.M., Schnack H.G., Hulshoff Pol H.E., Kahn R.S. (2011): Focal And Global Brain Measurements in Siblings of Patients With Schizophrenia. Schizophr Bull.

Boos H.B.M., Mandl R.C.W., van Haren N.E.M., Cahn W., van Baal G.C.M., Kahn R.S., Hulshoff Pol H.E. (in preparation): Tract-based diffusion tensor imaging in patients with schizophrenia and their non-psychotic siblings.

Chang L.C., Jones D.K., Pierpaoli C. (2005): RESTORE: robust estimation of tensors by outlier rejection. Magn Reson Med 53(5):1088-95.

Cheung V., Cheung C., McAlonan G.M., Deng Y., Wong J.G., Yip L., Tai K.S., Khong P.L., Sham P., Chua S.E. (2008): A diffusion tensor imaging study of structural dysconnectivity in never-medicated, first-episode schizophrenia. Psychol Med 38(6):877-85.

de Weijer A.D., Mandl R.C.W., Diederen K.M.J., Neggers S.W.F., Kahn R.S., Hulshoff Pol H.E., Sommer I.E.C. (In press): Microstructural alterations of the arcuate fasciculus in schizophrenia patients with frequent auditory verbal hallucinations. Schziophrenia Research.

Federspiel A., Begre S., Kiefer C., Schroth G., Strik W.K., Dierks T. (2006): Alterations of white matter connectivity in first episode schizophrenia. Neurobiol Dis 22(3):702-9.

Flynn S.W., Lang D.J., Mackay A.L., Goghari V., Vavasour I.M., Whittall K.P., Smith G.N., Arango V., Mann J.J., Dwork A.J. Falkai P., Honer W.G. (2003): Abnormalities of myelination in schizophrenia detected in vivo with MRI, and post-mortem with analysis of oligodendrocyte proteins. Mol Psychiatry 8(9):811-20.

Gasparotti R., Valsecchi P., Carletti F., Galluzzo A., Liserre R., Cesana B., Sacchetti E. (2009): Reduced fractional anisotropy of corpus callosum in first-contact, antipsychotic drug-naive patients with schizophrenia. Schizophr Res 108(1-3):41-8.

Gerig G., Gouttard S., Corouge I. (2004): Analysis of brain white matter via fiber tract modeling. Conf Proc IEEE Eng Med Biol Soc 6:4421-4.

Jones D.K. (2008): Studying connections in the living human brain with diffusion MRI. Cortex 44(8):936-52.

Jones D.K., Symms M.R., Cercignani M., Howard R.J. (2005): The effect of filter size on VBM analyses of DT-MRI data. Neuroimage 26(2):546-54.

Kawashima T., Nakamura M., Bouix S., Kubicki M., Salisbury D.F., Westin C.F., McCarley R.W., Shenton M.E. (2009): Uncinate fasciculus abnormalities in recent onset schizophrenia and affective psychosis: a diffusion tensor imaging study. Schizophr Res 110(1-3):119-26.

Kay S.R., Fiszbein A., Opler L.A. (1987): The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13(2):261-76.

Kyriakopoulos M., Vyas N.S., Barker G.J., Chitnis X.A., Frangou S. (2008): A diffusion tensor imaging study of white matter in early-onset schizophrenia. Biol Psychiatry 63(5):519-23.

Le Bihan D., Breton E. (1985): Imagerie de diffusion in vivo par résonance magnétique nucléaire. Compte Rendus de l`Académie de Sciences Paris 301:1109-1112.

Mandl R.C., Schnack H.G., Luigjes J., van den Heuvel M.P., Cahn W., Kahn R.S., Hulshoff Pol H.E. (2010): Tract-based analysis of magnetization transfer ratio and diffusion tensor imaging of the frontal and frontotemporal connections in schizophrenia. Schizophr Bull 36(4):778-87.

Mandl R.C.W., Schnack H.G.S., Zwiers M.P., van der Schaaf A., Kahn R.S., Hulshoff Pol H.E. (2008): Functional Diffusion Tensor Imaging: Measuring Task-Related Fractional Anisotropy Changes in the Human Brain along White Matter Tracts. PLos ONE 3(11):e3631. doi:10.1371/journal.pone.0003631.

Mori S., Crain B.J., Chacko V.P., van Zijl P.C. (1999): Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Ann Neurol 45(2):265-9.

Navari S., Dazzan P. (2009): Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. Psychol Med 39(11):1763-77.

Nyholt D.R. (2004): A simple correction for multiple testing for single-nucleotide polymorphisms in linkage disequilibrium with each other. Am J Hum Genet 74(4):765-9.

Perez-Iglesias R., Tordesillas-Gutierrez D., Barker G.J., McGuire P.K., Roiz-Santianez R., Mata I., de Lucas E.M., Quintana F., Vazquez-Barquero J.L., Crespo-Facorro B. (2010): White matter defects in first episode psychosis patients: a voxelwise analysis of diffusion tensor imaging. Neuroimage 49(1):199-204.

Peters B.D., de Haan L., Vlieger E.J., Majoie C.B., den Heeten G.J., Linszen D.H. (2009): Recent-onset schizophrenia and adolescent cannabis use: MRI evidence for structural hyperconnectivity? Psychopharmacol Bull 42(2):75-88.

Pfohl B., Blum N., Zimmerman M. (1995): Structured Interview for DSMIV Personallity: SIDP-IV. Iowa City: University of Iowa,.

Price G., Cercignani M., Parker G.J., Altmann D.R., Barnes T.R., Barker G.J., Joyce E.M., Ron M.A. (2008): White matter tracts in first-episode psychosis: a DTI tractography study of the uncinate fasciculus. Neuroimage 39(3):949-55.

Robins L.N., Wing J., Wittchen H.U., Helzer J.E., Babor T.F., Burke J., Farmer A., Jablenski A., Pickens R., Regier D.A. (1988): The Composite International Diagnostic Interview. An epidemiologic Instrument suitable for use in conjunction with different diagnostic systems and in different cultures. Arch Gen Psychiatry 45:1069-1077.

Rotarska-Jagiela A., Oertel-Knoechel V., DeMartino F., van de Ven V., Formisano E., Roebroeck A., Rami A., Schoenmeyer R., Haenschel C., Hendler T., Maurer K., Vogeley K., Linden D.E.J. (2009): Anatomical brain connectivity and positive symptoms of schizophrenia: a diffusion tensor imaging study. Psychiatry Res 174(1):9-16.

Shenton M.E., Whitford T.J., Kubicki M. (2010): Structural neuroimaging in schizophrenia: from methods to insights to treatments. Dialogues Clin Neurosci 12(3):317-32.

Smith S.M., Jenkinson M., Johansen-Berg H., Rueckert D., Nichols T.E., Mackay C.E., Watkins K.E., Ciccarelli O., Cader M.Z., Matthews P.M., Behrens T.E.J. (2006): Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 31(4):1487-505.

Szeszko P.R., Robinson D.G., Ashtari M., Vogel J., Betensky J., Sevy S., Ardekani B.A., Lencz T., Malhotra A.K., McCormack J., Miller R., Lim K.O., Gunduz-Bruce H., Kane J.M., Bilder R.M. (2008): Clinical and neuropsychological correlates of white matter abnormalities in recent onset schizophrenia. Neuropsychopharmacology 33(5):976-84.

Wakana S., Jiang H.Y., Nagae-Poetscher L.M., van Zijl P.C.M., Mori S. (2004): Fiber tract based atlas of human white matter anatomy. Radiology 230(1):77-87.

Wolff S.D., Balaban R.S. (1994): Magnetization transfer imaging: practical aspects and clinical applications. Radiology 192(3):593-9

Chapter 6

Psychosis and brain volume changes during the first five years of schizophrenia

Wiepke Cahn | Monica Rais | Pien Sigter | Neeltje E.M. van Haren | Esther Caspers

Hilleke E. Hulshoff Pol | Zhida Xu, Hugo G. Schnack | René S. Kahn

Eur.Neuropsychopharmacology 2009;19: 147-151.

Abstract

The underlying mechanisms explaining brain volume changes in schizophrenia are not yet understood, but psychosis might be related to these changes. Forty-eight patients with first-episode schizophrenia underwent Magnetic Resonance Imaging brain scanning at inclusion and after five years. An association was found between longer duration of psychosis, larger grey matter volume decrease and larger ventricular volume increase. These findings strongly suggest that psychosis contributes to brain volume reductions found in schizophrenia.

Background

It is well-established that structural brain changes are present in schizophrenia (Wright et al., 2000). Furthermore, longitudinal neuroimaging studies have shown that these brain volume changes are progressive, not only in the early course (Pantelis et al., 2005) but also in the later stages of schizophrenia (Hulshoff Pol and Kahn, 2008). It remains unclear what causes these brain volume reductions over time in schizophrenia. Some have implicated factors such as medication (Gur et al., 1998; Cahn et al., 2002; Lieberman et al., 2005; van Haren et al., 2007), stress (Pariante et al., 2005) and co-morbid cannabis use (Rais et al., 2008), but others suggest the progressive brain volume reductions to be primarily related to the core symptoms of schizophrenia (Lieberman et al., 2001).

As psychotic symptoms play a central role in schizophrenia, it has been suggested that brain volume loss over time could be attributable to the "toxic" effects of the psychotic state on the brain (Lieberman, 1999; McGlashan, 2006; Seok et al., 2005). For instance, abnormal excitatory amino acid neurotransmission in glutamatergic systems might cause cellular cell damage and death (Olney and Farber, 1995) and could result in grey matter volume reduction. Nevertheless, clinical evidence of an association between psychosis and brain volume changes in schizophrenia is lacking.

Interestingly, recent longitudinal imaging studies in first-episode schizophrenia report associations of brain volume decreases with poor outcome (Cahn et al., 2002; Milev et al., 2003; Lieberman et al., 2005; Cahn et al., 2006; Nakamura et al., 2007).

However, it is unclear what aspects of the illness outcome drive this association. In light of the hypothesis that psychosis itself is related to the progressive brain changes, one could postulate that the longer the patient is actively psychotic, the larger the brain loss over time. So far, no study has specifically examined the relation between duration of psychosis and brain volume change over time.

To the best of our knowledge, this is the first longitudinal MRI study to examine the relationship between brain volume changes over time and duration of psychosis, estimated by using various rating scales and close investigation of the medical records.

Methods

Subjects

Patients were recruited from The First Episode Schizophrenia Research Program at the University Medical Center, Utrecht, The Netherlands. The original cohort consisted of 126 patients with a first psychotic episode. The current study included patients who had an MRI at inclusion (T0) and after five years (T5), a diagnosis of schizophreniform disorder, schizoaffective disorder and schizophrenia at T5 and sufficient data to identify the course of psychotic symptoms over time.

Forty-eight patients (male n=41; female n=7) with a mean age (sd) of 23.39 (4.20) years old, met the criteria for inclusion. All provided written informed consent. Diagnosis was assessed with the Comprehensive Assessment of Symptoms and History Schizophrenia (Andreasen et al., 1992) leading to a DSMIV diagnosis of schizophrenia (n=42), schizoaffective disorder (n=5) and schizophreniform disorder (n=1).

Both at inclusion and follow-up sociodemographic, illness and treatment data were gathered with a case record form. Courses of illness data were collected retrospectively at follow-up using patient report prompted by key data and all other possible sources of information, including data from a shortened version of the Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS) at T5 (Hafner et al., 1992) and from the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987), that was gathered over the illness course. Furthermore a careful examination of the medical records was carried out and the treating psychiatrist and/or key worker were interviewed. Total duration of psychosis (Ps) was defined as a period in which the patient had experienced delusions, hallucinations or conceptual disorganization, which interfered with daily life. These symptoms had to be severe enough to obtain a score of 4 (moderate) or higher on the PANSS. Psychosis remitted (Prem) was defined as psychotic symptoms severe enough to obtain a score of 3 (mild) on the PANSS. Total duration of psychotic symptoms was defined as Ps+Prem. Psychotic recovery (Prec) was defined as questionable or no psychotic symptoms (PANSS score of 2 or less). Mean duration of Ps in months [sd] was 24.33 [24.80], Prem was 15.50 [20.56] months, Ps+Prem was 39.83 [25.52] months and Prec was 21.47 [26.20] months. At T0 patients had a mean [sd] positive PANSS score of 17.04 [5.70], negative PANSS score of 17.50 [5.29] and general PANSS score of 35.45 [9.05] and at T5 a mean [sd] positive PANSS score of 14.02 [6.07], negative PANSS score of 13.58 [6.67] and general PANSS score of 27.20 [9.83]. Between T0 and T5 patients had taken a mean cumulative amount of antipsychotic medication [sd] of 11,906 mg [1458] haloperidol equivalents.

MRI procedures

MRI brain scans were acquired on a 1.5 T Philips NT scanner at inclusion (T0) and after five years (T5) with a mean (sd) MRI interval of 61.30 (7.11) months. All images were corrected for inhomogeneities in the magnetic field according to the method described by Sled (Sled et al., 1998). In-house developed software was used to measure total brain, grey and white matter, cerebellar, lateral and third ventricle volumes. Images were checked, corrected manually if necessary. For a description of MRI procedure and segmentation see Schnack (Schnack et al., 2001) and Hulshoff Pol (Hulshoff Pol et al., 2002). For mean (sd) global brain volumes see Table 1.

Table 1 | Global brain volumes (cm^3) at inclusion (T0) and five-year follow-up (T5) and brain volume change (%)

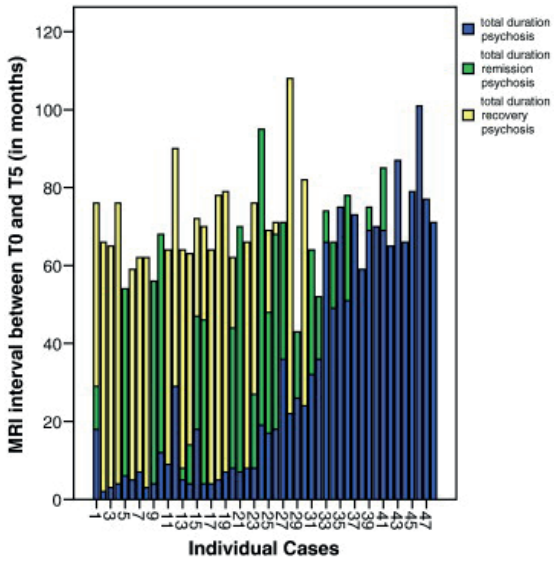
	T0		**T5**		**(T0 – T5)**
	Volume	sd	Volume	sd	%
Total brain	1321.09	123.62	1310.04	122.59	−0.84
Grey matter	688.33	61.58	659.67	56.69	−4.16
White matter	469.16	62.68	483.54	66.16	3.07
Cerebellum	149.04	14.01	151.22	13.91	1.46
Lateral ventricles	14.86	8.80	16.14	9.38	8.61
Third ventricle	0.85	0.32	0.88	0.37	3.53

Statistical analyses

Figure 1 show the duration of psychosis in months per patient. Brain volume measures and clinical data were normally distributed. The absolute volume change over time per subject was calculated for all brain volumes by subtracting the volume at baseline from the volume at follow-up (T5−T0). The percentage volume change during the scan interval was calculated for each individual by dividing the absolute volume change by volume at baseline multiplied by 100% ([(T5−T0)/T0]∗100%). This method was used to control for possible volume change caused by psychosis prior to inclusion, particularly as the data on the duration of psychosis before the first MRI was less reliable than the data gathered during the follow-up period. Linear regression analyses were performed to examine the relation between the total duration of psychosis (Ps), total duration of psychotic symptoms (Ps+Prem) and percentage of brain volume change over time. Ps and Ps+Prem separately entered the analyses as predictor variables and percentage of volume change of the different brain structures entered the analyses as dependent variables. Intracranial volume, age and gender served as covariates. To examine whether the brain volume changes were specifically related to psychotic symptoms and not to negative symptoms, the

same analyses were conducted with PANSS negative symptom score at T5 as covariate. As antipsychotic medication might also influence the progressive brain volume changes the same analyses were done with cumulative antipsychotic medication as covariate.

Figure 1 | Per patient (n=48) the total duration of psychosis, psychotic remission and recovery of psychosis during the follow-up period in months.



To examine whether scanner drift over time altered the results Pearson's correlations were performed between the date of MRI and the percentage of volume change and the date of MRI was added as covariate in all the analyses.

Results

Total duration of psychosis was significantly related to the percentage of volume change in grey matter (b=−0.05%/month, p=0.05), lateral ventricle (b=0.37%/month, p<0.01) and third ventricle (b=0.38%/month, p=0.02). At trend level there was a relation between the duration of psychosis and the percentage of total brain volume change (b=−0.02%/month, p=0.09). There was no significant association between psychosis, percentage of volume change in white matter (b=−0.01%/month, p=0.69) and in cerebellum (b=−0.01%/month, p=0.37).

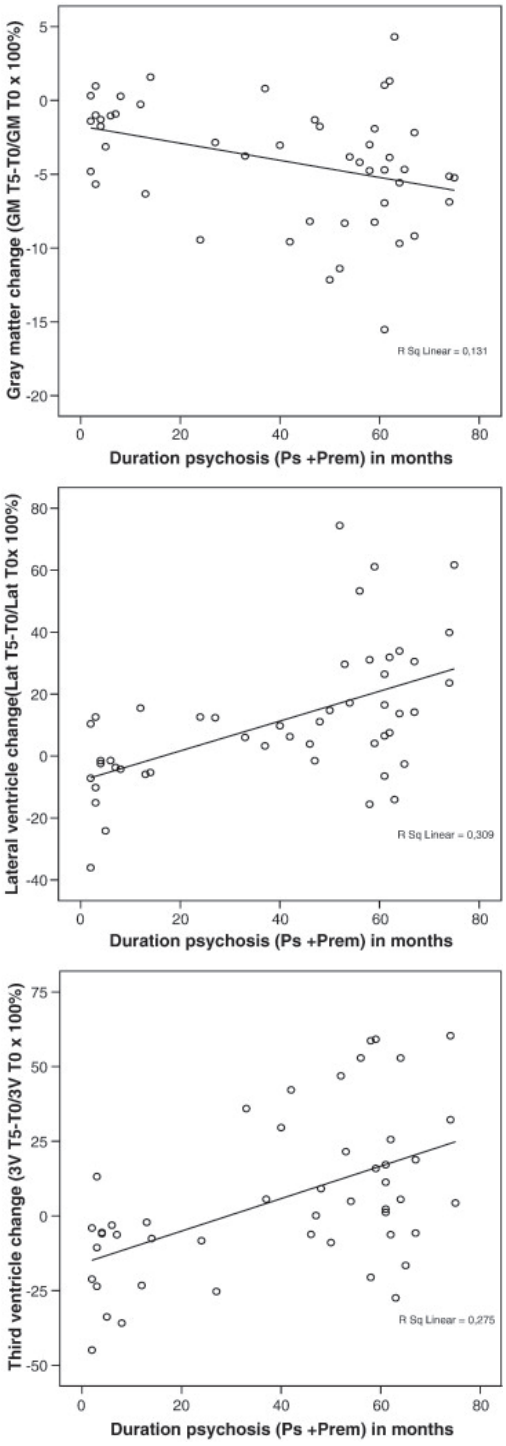
Total duration of psychotic symptoms (Ps+Prem) was significantly related to the percentage of volume decrease in total brain (b=−0.03%/month, p=0.02), grey matter (b=−0.06%/month, p=0.01) and cerebellar volume (b=−0.03%/month, p=0.05) and the percentage of volume increase in lateral ventricle (b=0.44%/month, p<0.0001) and third ventricle (b=0.54%/month, p<0.0001) (see Figure 2). There was no significant relationship between the duration of psychosis and the percentage of white matter volume change (b=−0.01%/month, p=0.69). The results remained significant for lateral and third ventricle volume by adding the total negative score at T5 as covariate in the analyses. The results did not change by adding cumulative antipsychotic medication as covariate, except for the percentage of grey matter volume change and total duration of psychosis (b=−0.04%/month, p=0.08). There were no associations between the date of MRI and the percentage of volume change nor did the results change by adding the date of MRI as covariate in the analyses.

Conclusion

This five-year longitudinal MRI study investigated the relationship between psychosis and brain volume change in 48 first episode patients with schizophrenia. We found associations between grey matter volume loss, lateral and third ventricle volume increase, longer duration of psychosis. Longer duration of psychotic symptoms was further associated with greater decreases in total brain and cerebellar volume. These findings suggest that psychosis contributes to the brain volume changes reported in schizophrenia in longitudinal studies (Pantelis et al., 2003; Hulshoff Pol and Kahn, 2008).

This is the first study examining the longitudinal relationship between active psychosis and change in brain volume in schizophrenia. Our finding of an association between grey matter volume loss and length of active psychosis (despite treatment) is in agreement with cross-sectional studies

Figure 2 | Total duration of psychotic symptoms (months) and percentage of brain grey matter, lateral and third ventricle volume change between inclusion (T0) and after five years of follow-up (T5).



reporting larger grey matter loss in relation to a longer duration of untreated psychosis prior to brain volume assessment (Lappin et al., 2006; Takahashi et al., 2007). Moreover, a one-year longitudinal MRI study in ultra high risk subjects found larger decreases in grey matter in the left parahippocampal, fusiform, orbitofrontal, and the cingulate gyri in the subjects who became psychotic as compared to those who did not (Pantelis et al., 2005). In that study volume decrease in the cerebellum was similar in both groups. However, our results agree with those of Nopoulos (Nopoulos et al., 2001) who reported in a cross-sectional MRI study an association between a reduced cerebellar volume and psychotic symptoms.

Our study cannot resolve whether psychosis causes brain volume reductions or whether a longer duration of psychosis is the consequence of these brain changes. This issue can only be addressed in a long-term study that assesses brain volume change in patients randomized to treatments that are expected to lead to differences in the duration of psychosis (e.g. comparing brain changes in patients randomized to long acting injectable or oral medication).

Some limitations should be considered by interpreting the results of this present study. First, most of the information on the duration of psychosis was obtained retrospectively. Monthly prospective PANSS ratings would have given a more accurate assessment of the psychosis. Second, this study only examined global, and not regional, changes in brain volumes. Third, there was a preponderance of male patients, so the results might be different for female patients with schizophrenia.

In summary, this five-year longitudinal MRI study shows that in the first five years of schizophrenia brain volume loss is related to the time patients are actively psychotic. Our finding strongly suggests that the progressive brain changes in schizophrenia (Hulshoff Pol and Kahn, 2008) are part and parcel of the schizophrenic illness and, more specifically, are related to the psychotic aspects of it.

Reference List

Andreasen N.C., Flaum M., Arndt S. (1992): The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. Arch Gen Psychiatry 49:615-623.

Cahn W., Hulshoff Pol H.E., Lems E.B., van Haren N.E., Schnack H.G., van der Linden J.A., Schothorst P.F., van Engeland H., Kahn R.S. (2002): Brain volume changes in first-episode schizophrenia: a 1-year follow-up study. Arch Gen Psychiatry 59:1002-1010.

Cahn W., van Haren N.E., Hulshoff Pol H.E., Schnack H.G., Caspers E., Laponder D.A., Kahn R.S. (2006): Brain volume changes in the first year of illness and 5-year outcome of schizophrenia. Br J Psychiatry 189:381-382.

Gur R.E., Cowell P., Turetsky B.I., Gallacher F., Cannon T., Bilker W., Gur R.C. (1998): A follow-up magnetic resonance imaging study of schizophrenia. Relationship of neuroanatomical changes to clinical and neurobehavioral measures. Arch Gen Psychiatry 55:145-152.

Hafner H., Riecher-Rossler A., Hambrecht M., Maurer K., Meissner S., Schmidtke A., Fatkenheuer B., Loffler W., van der Heiden W. (1992): IRAOS: an instrument for the assessment of onset and early course of schizophrenia. Schizophr Res 6:209-223.

Hulshoff Pol H.E., Kahn R.S. (2008): What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. Schizophr Bull 34:354-366.

Hulshoff Pol H.E., Schnack H.G., Bertens M.G., van Haren N.E., van der Tweel I., Staal W.G., Baare W.F., Kahn R.S. (2002): Volume changes in grey matter in patients with schizophrenia. Am J Psychiatry 159:244-250.

Kay S.R., Fiszbein A., Opler L.A. (1987): The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13:261-276.

Lappin J.M., Morgan K., Morgan C., Hutchison G., Chitnis X., Suckling J., Fearon P., McGuire P.K., Jones P.B., Leff J., Murray R.M., Dazzan P. (2006): Grey matter abnormalities associated with duration of untreated psychosis. Schizophr Res 83:145-153.

Lieberman J., Chakos M., Wu H., Alvir J., Hoffman E., Robinson D., Bilder R. (2001): Longitudinal study of brain morphology in first episode schizophrenia. Biol Psychiatry 49:487-499.

Lieberman J.A. (1999): Is schizophrenia a neurodegenerative disorder? A clinical and neurobiological perspective. Biol Psychiatry 46:729-739.

Lieberman J.A., Tollefson G.D., Charles C., Zipursky R., Sharma T., Kahn R.S., Keefe R.S., Green A.I., Gur R.E., McEvoy J., Perkins D., Hamer R.M., Gu H., Tohen M. (2005): Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch Gen Psychiatry 62:361-370.

McGlashan T.H. (2006): Is active psychosis neurotoxic? Schizophr Bull 32:609-613.

Milev P., Ho B.C., Arndt S., Nopoulos P., Andreasen N.C. (2003): Initial magnetic resonance imaging volumetric brain measurements and outcome in schizophrenia: a prospective longitudinal study with 5-year follow-up. Biol Psychiatry 54:608-615.

Nakamura M., Salisbury D.F., Hirayasu Y., Bouix S., Pohl K.M., Yoshida T., Koo M.S., Shenton M.E., McCarley R.W. (2007): Neocortical grey matter volume in first-episode schizophrenia and first-episode affective psychosis: a cross-sectional and longitudinal MRI study. Biol Psychiatry 62:773-783.

Nopoulos P.C., Ceilley J.W., Gailis E.A., Andreasen N.C. (2001): An MRI study of midbrain morphology in patients with schizophrenia: relationship to psychosis, neuroleptics, and cerebellar neural circuitry. Biol Psychiatry 49:13-19.

Olney J.W., Farber N.B. (1995): Glutamate receptor dysfunction and schizophrenia. Arch Gen Psychiatry 52:998-1007.

Pantelis C., Velakoulis D., McGorry P.D., Wood S.J., Suckling J., Phillips L.J., Yung A.R., Bullmore E.T., Brewer W., Soulsby B., Desmond P., McGuire P.K. (2003): Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. Lancet 361:281-288.

Pantelis C., Yucel M., Wood S.J., Velakoulis D., Sun D., Berger G., Stuart G.W., Yung A., Phillips L., McGorry P.D. (2005): Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. Schizophr Bull 31:672-696.

Pariante C.M., Dazzan P., Danese A., Morgan K.D., Brudaglio F., Morgan C., Fearon P., Orr K., Hutchinson G., Pantelis C., Velakoulis D., Jones P.B., Leff J., Murray R.M. (2005): Increased pituitary volume in antipsychotic-free and antipsychotic-treated patients of the AEsop first-onset psychosis study. Neuropsychopharmacology 30:1923-1931.

Rais M., Cahn W., van Haren N., Schnack H., Caspers E., Hulshoff Pol H., Kahn R. (2008): Excessive brain volume loss over time in cannabis-using first-episode schizophrenia patients. Am J Psychiatry 165:490-496.

Schnack H.G., Hulshoff Pol H.E., Baare W.F., Staal W.G., Viergever M.A., Kahn R.S. (2001): Automated separation of grey and white matter from MR images of the human brain. Neuroimage 13:230-237.

Seok J.B., Kwon J.S., Yoon K.S., Lee C., Youn T., Moon C.H., Yoon K.C. (2005): Functional imaging evidence of the relationship between recurrent psychotic episodes and neurodegenerative course in schizophrenia. Psychiatry Res 139:219-228.

Sled J.G., Zijdenbos A.P., Evans A.C. (1998): A nonparametric method for automatic correction of intensity nonuniformity in MRI data. IEEE Trans Med Imaging 17:87-97.

Takahashi T., Suzuki M., Tanino R., Zhou S.Y., Hagino H., Niu L., Kawasaki Y., Seto H., Kurachi M. (2007): Volume reduction of the left planum temporale grey matter associated with long duration of untreated psychosis in schizophrenia: a preliminary report. Psychiatry Res 154:209-219.

van Haren N.E., Hulshoff Pol H.E., Schnack H.G., Cahn W., Mandl R.C., Collins D.L., Evans A.C., Kahn R.S. (2007): Focal grey matter changes in schizophrenia across the course of the illness: a 5-year follow-up study. Neuropsychopharmacology 32:2057-2066.

Wright I.C., Rabe-Hesketh S., Woodruff P.W., David A.S., Murray R.M., Bullmore E.T. (2000): Meta-analysis of regional brain volumes in schizophrenia. Am J Psychiatry 157:16-25.

Chapter 7

Concluding words

Summary and discussion

The studies described in the previous chapters explored (change in) brain structure in first episode patients with schizophrenia and the effect of confounding factors, such as cannabis, antipsychotic medication and duration of illness. In this final chapter a summary and discussion of the main findings are provided.

Cannabis

Chapter 2 and **chapter 3** describe the effects of cannabis use and clinical outcome on progressive change in global brain volumes and cortical thickness during the first five years of illness in first episode schizophrenia.

In chapter 2 the effect of cannabis (ab-)use on brain morphology change over time was addressed. Brain volume changes were measured over a 5-year follow-up interval in 19 first episode patients who used cannabis during the interval, 32 first episode patients who did not use cannabis during follow-up, and 31 cannabis-naive healthy subjects. Total brain, grey and white matter, lateral and third ventricle volumes were measured at inclusion and after 5 years. This study suggests that first episode patients with schizophrenia who use cannabis show a more pronounced brain volume reduction over a 5-year follow-up as compared to non-using patients and healthy comparison subjects. In addition, those patients who continued to use cannabis showed less improvement in positive and negative symptoms compared to non-using patients.

The mechanism by which cannabis may cause brain volume loss in schizophrenia patients remains unclear. It could either be a direct consequence of cannabis intake or occur as a consequence of the "toxic effect" (Lieberman et al., 2001) of the psychotic symptoms in schizophrenia that are associated with cannabis use (Dubertret et al., 2006; Buhler et al., 2002; Grech et al., 2005; Mauri et al., 2006; Bersani et al., 2002). This would be consistent with our finding that the excessive brain volume decrease in the patients who continued to use cannabis was associated with less improvement in psychotic symptoms. Moreover, since (atypical) antipsychotic medication has been suggested to attenuate the progressive brain changes in schizophrenia (Lieberman et al., 2005; Cahn et al., 2002; van Haren et al., 2007; Lieberman et al., 2001; Navari and Dazzan, 2009; Moncrieff and Leo, 2010) excessive brain volume loss could also be explained by non-compliance to antipsychotic medication in the cannabis-using group. Indeed, it has been shown that patients who use cannabis are less compliant to prescribed antipsychotic medication (DeQuardo et al., 1994; Margolese et al., 2006).

Based on these findings we emphasise that some of the detrimental effects of cannabis on the course of schizophrenia may be explained by its effect on the progression of brain changes in schizophrenia.

The study described in chapter 2, however, could not address whether the reported grey matter loss is widespread over the entire brain or more pronounced in specific brain regions. Since the grey matter volume is principally represented in the cerebral cortex, the effect of cannabis exposure after onset of schizophrenia on cortical thickness changes over a five year follow-up was assessed in the same sample of patients in the study reported in **chapter 3**.

Although schizophrenia patients showed widespread excessive thinning along the cerebral cortex, those patients who used cannabis showed additional excessive thinning in the left dorsolateral prefrontal cortex (DLPFC), left anterior cingulate cortex (ACC) and left occipital lobe as compared to those patients who did not use cannabis during the scan interval. Interestingly, these areas have not only been identified as being rich in cannabinoid (CB1) receptors in healthy individuals (Glass et al., 1997; Iversen, 2003; Freund et al., 2003; Eggan and Lewis, 2007) but also show a more pronounced density of these receptors in the cerebral tissue of schizophrenia patients, irrespective of cannabis use (Dean et al., 2001; Zavitsanou et al., 2004).

Furthermore, the results described in chapter 3 are similar to those of two previous cross-sectional studies reporting grey matter deficits in the posterior (Bangalore et al., 2008) and anterior cingulate cortex (Szeszko et al., 2007) in cannabis-using first-episode schizophrenia patients and to those of functional MRI studies reporting changes in brain activity in the prefrontal cortex and anterior cingulate gyrus in healthy subjects (for review see Quickfall and Crockford, 2006 and Martin-Santos et al., 2009).

In conclusions, we suggest that in first-episode patients with schizophrenia who continue to use cannabis after illness onset, it is particularly those cortical regions that are rich in CB1 receptors that are vulnerable to excessive cortical thinning. Interestingly, it is also these areas that are related to the negative symptoms and to poorer cognitive functioning in schizophrenia, providing a morphological explanation for the detrimental effects of cannabis after illness onset.

Antipsychotic medication

In the cross-sectional studies presented in **chapter 4** and **chapter 5** global brain volumes and white matter structure were investigated in antipsychotic naive patients. In **chapter 4** we

compared global brain volumes and cortical thickness between 20 first episode medication-naive schizophrenia patients and 26 healthy comparison subjects to assess whether brain abnormalities are already present before the intake of antipsychotic medication and to investigate how the brain abnormalities are related to IQ. The main finding of this study is a reduction of whole brain volume in medication naive patients relative to controls, which can be explained by reductions in both grey and white matter. In addition, a significant increase in lateral ventricles volume was found. These data suggest that brain abnormalities are indeed present at the onset of the illness and that they are not related to the effect of antipsychotic medication.

That brain volume decrease is present at illness onset and is not a consequence upon the intake of antipsychotic medication is consistent with structural MRI studies in high risk subjects. Many of those converting to psychosis not only have more pronounced neuroanatomical abnormalities before the first psychotic episode but also show further changes in grey (Pantelis et al., 2003; Borgwardt et al., 2007; for a review see Pantelis et al., 2005) and possibly white matter volume (Walterfang et al., 2008) after psychosis onset (for a review and meta analysis see Smieskova et al., 2010). Moreover, our results are consistent to those of Ziermans and colleagues (Ziermans et al., 2010) showing progressive whole brain and white matter volume loss in unmedicated ultra high risk subjects converting to psychosis compared to non-converters and control groups.

Interestingly, our patients had a significantly lower IQ and level of education than healthy comparison subjects. Moreover, a relationship between IQ and brain volume, irrespective of diagnosis, was found. It might be argued that the smaller brain volume in schizophrenia at the onset of psychosis is related to the abnormal cognitive development prior to the onset of psychosis.

In the conclusion, we suggest that brain abnormalities are present at illness onset, are independent of medication and could be partially explained by the (lowered) IQ and general psychopathology symptom severity in the patients.

In **chapter 5** diffusion tensor imaging (DTI) techniques were used to measure fractional anisotropy (FA), mean diffusivity (MD) and magnetic transfer ratio (MTR) to study white matter structure in medication naive patients.

Numerous DTI studies have implicated white matter brain tissue abnormalities in schizophrenia. However, the vast majority of these studies included patient populations that use anti-psychotic

medication. Therefore, the question arises to what extent the reported white matter aberrations can be attributed to the disease rather than to the use of medication. In this study we included 16 medication-naive patients with schizophrenia and compared them to 23 healthy controls to exclude anti-psychotic medication use as a confounding factor. For each subject DTI scans and magnetic transfer image (MTI) scans were acquired. A new fiber-based analysis was used that combines fractional anisoptropy (FA), mean diffusivity (MD) and magnetic transfer ratio (MTR) to examine group differences in 12 major white matter fiber bundles. Significant group differences in combined FA, MD, MTR values were found for the right uncinate fasciculus and the left arcuate fasciculus. Additional analysis revealed that the largest part of both tracts showed an increase in MTR in combination with an increase in MD for patients with schizophrenia. Our findings implicate that the previously reported increase in MTR in medicated patients with schizophrenia in the right uncinate fasciculus (Mandl et al, 2010) and the left arcuate fasciculus (De Weijer et al., in press) is also present in medication naive patients.

In conclusion, our findings show that white matter microstructure in the brain, specifically in the left arcuate fasciculus and the right uncinate fasciculus is altered early in the disease process in schizophrenia and cannot be attributed to the effects of antipsychotic medication.

Duration of psychosis

The five-year longitudinal structural MRI study described in **chapter 6** investigated the relation between brain volume change over time in 48 first episode patients with schizophrenia and the duration of psychosis. Associations were found between grey matter volume loss, lateral and third ventricle volume increase and longer duration of psychosis. Moreover, longer duration of psychotic symptoms was also associated with greater decreases in total brain and cerebellar volume. These findings suggest that psychosis contributes to the brain volume changes reported in schizophrenia in longitudinal studies (Pantelis et al., 2003; Hulshoff Pol and Kahn, 2008).

Whether psychosis causes brain volume reductions or whether a longer duration of psychosis is the consequence of these brain changes remains unclear.

In conclusion, this five-year longitudinal MRI study shows that in the first five years of schizophrenia brain volume loss is related to the time patients are actively psychotic, suggesting that the progressive brain volume changes in schizophrenia (Hulshoff Pol and Kahn., 2008) are intrinsic to the schizophrenic illness and, more specifically, are related to the psychotic aspects of it.

Final remarks and conclusions

In the preceding chapters of this thesis structural magnetic resonance imaging studies exploring the role of confounding factors in the onset of morphological brain abnormalities in patients with first episode schizophrenia were described. Although the effect of confounding factors on brain morphology in patients with schizophrenia remains debated, the studies described in this thesis underpin that (some) brain morphological alterations are intrinsic to schizophrenia, even in the early stages of the illness, before medication effect took place. Moreover, not only brain alterations in schizophrenia are progressive, but they are more pronounced in those patients with a lower IQ, longer duration of psychosis and in those patients that keep (ab-)using cannabis after illness onset. This indicates that factors, other than illness, can possibly play an important role in the progression of the brain abnormalities associated with schizophrenia. These findings underpin the need to recognize, in future studies, those factors that are likely to affect brain morphology acting as confounders and threatening the validity of the studies, to better understand the causality relation/direction between illness and brain morphology changes.

In conclusion, the field is currently dominated by the debate on the effects of antipsychotic medication intake on brain volume abnormalities in schizophrenia patients. However, the results of the studies reported in this thesis provide convincing evidence that other important factors, such as cannabis use and duration of psychosis also exert their influence on a vulnerable brain such as the brain of a schizophrenia patient.

Reference List

Bangalore S.S., Prasad K.M., Montrose D.M., Goradia D.D., Diwadkar V.A., Keshavan M.S. (2008): Cannabis use and brain structural alterations in first episode schizophrenia--a region of interest, voxel based morphometric study. Schizophr Res 99:1-6.

Bersani G., Orlandi V., Kotzalidis G.D., Pancheri P. (2002): Cannabis and schizophrenia: impact on onset, course, psychopathology and outcomes. Eur Arch Psychiatry Clin Neurosci 252:86-92.

Borgwardt S.J., Riecher-Rossler A., Dazzan P., Chitnis X., Aston J., Drewe M., Gschwandtner U., Haller S., Pfluger M., Rechsteiner E., D'Souza M., Stieglitz R.D., Radu E.W., McGuire P.K. (2007): Regional grey matter volume abnormalities in the at risk mental state. Biol Psychiatry 61:1148-1156.

Buhler B., Hambrecht M., Loffler W., an der Heiden W., Hafner H. (2002): Precipitation and determination of the onset and course of schizophrenia by substance abuse--a retrospective and prospective study of 232 population-based first illness episodes. Schizophr Res 54:243-251.

Cahn W., Hulshoff Pol H.E., Lems E.B., van Haren N.E., Schnack H.G., van der Linden J.A., Schothorst P.F., van Engeland H., Kahn R.S. (2002): Brain volume changes in first-episode schizophrenia: a 1-year follow-up study. Arch Gen Psychiatry 59:1002-1010.

Dean B., Sundram S., Bradbury R., Scarr E., Copolov D. (2001): Studies on [3H]CP-55940 binding in the human central nervous system: regional specific changes in density of cannabinoid-1 receptors associated with schizophrenia and cannabis use. Neuroscience 103:9-15.

DeQuardo J.R., Carpenter C.F., Tandon R. (1994): Patterns of substance abuse in schizophrenia: nature and significance. J Psychiatr Res 28:267-275.

de Weijer AD, Mandl RCW, Diederen KMJ, Neggers SWF, Kahn RS, Hulshoff Pol HE, Sommer IEC. (In press): Microstructural alterations of the arcuate fasciculus in schizophrenia patients with frequent auditory verbal hallucinations. Schziophrenia Research.

Dubertret C., Bidard I., Ades J., Gorwood P. (2006): Lifetime positive symptoms in patients with schizophrenia and cannabis abuse are partially explained by co-morbid addiction. Schizophr Res 86:284-290.

Eggan S.M., Lewis D.A. (2007): Immunocytochemical distribution of the cannabinoid CB1 receptor in the primate neocortex: a regional and laminar analysis. Cereb Cortex 17:175-191.

Freund T.F., Katona I., Piomelli D. (2003): Role of endogenous cannabinoids in synaptic signaling. Physiol Rev 83:1017-1066.

Glass M., Dragunow M., Faull R.L. (1997): Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. Neuroscience 77:299-318.

Grech A., van Os J., Jones P.B., Lewis S.W., Murray R.M. (2005): Cannabis use and outcome of recent onset psychosis. Eur Psychiatry 20:349-353.

Hulshoff Pol H.E., Kahn R.S. (2008): What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. Schizophr Bull 34:354-366.

Iversen L. (2003): Cannabis and the brain. Brain 126:1252-1270.

Lieberman J., Chakos M., Wu H., Alvir J., Hoffman E., Robinson D., Bilder R. (2001): Longitudinal study of brain morphology in first episode schizophrenia. Biol Psychiatry 49:487-499.

Lieberman J.A., Tollefson G.D., Charles C., Zipursky R., Sharma T., Kahn R.S., Keefe R.S., Green A.I., Gur R.E., McEvoy J., Perkins D., Hamer R.M., Gu H., Tohen M. (2005): Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch Gen Psychiatry 62:361-370.

Mandl RC, Schnack HG, Luigjes J, van den Heuvel MP, Cahn W, Kahn RS, Hulshoff Pol HE. (2010): Tract-based analysis of magnetization transfer ratio and diffusion tensor imaging of the frontal and frontotemporal connections in schizophrenia. Schizophr Bull 36(4):778-87.

Margolese H.C., Carlos N.J., Tempier R., Gill K. (2006): A 12-month prospective follow-up study of patients with schizophrenia-spectrum disorders and substance abuse: changes in psychiatric symptoms and substance use. Schizophr Res 83:65-75.

Martin-Santos R., Fagundo A.B., Crippa J.A., Atakan Z., Bhattacharyya S., Allen P., Fusar-Poli P., Borgwardt S., Seal M., Busatto G.F., McGuire P. (2009): Neuroimaging in cannabis use: a systematic review of the literature. Psychol Med :1-17.

Mauri M., Volonteri L., De Gaspari I., Colasanti A., Brambilla M., Cerruti L. (2006): Substance abuse in first-episode schizophrenic patients: a retrospective study. Clin Pract Epidemol Ment Health 2:4.

Moncrieff J., Leo J. (2010): A systematic review of the effects of antipsychotic drugs on brain volume. Psychol Med 40:1409-1422.

Navari S., Dazzan P. (2009): Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. Psychol Med :1-15.

Pantelis C., Velakoulis D., McGorry P.D., Wood S.J., Suckling J., Phillips L.J., Yung A.R., Bullmore E.T., Brewer W., Soulsby B., Desmond P., McGuire P.K. (2003): Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. Lancet 361:281-288.

Pantelis C., Yucel M., Wood S.J., Velakoulis D., Sun D., Berger G., Stuart G.W., Yung A., Phillips L., McGorry P.D. (2005): Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. Schizophr Bull 31:672-696.

Quickfall J., Crockford D. (2006): Brain neuroimaging in cannabis use: a review. J Neuropsychiatry Clin Neurosci 18:318-332.

Smieskova R., Fusar-Poli P., Allen P., Bendfeldt K., Stieglitz R.D., Drewe J., Radue E.W., McGuire P.K., Riecher-Rossler A., Borgwardt S.J. (2010): Neuroimaging predictors of transition to psychosis--a systematic review and meta-analysis. Neurosci Biobehav Rev 34:1207-1222.

Szeszko P.R., Robinson D.G., Sevy S., Kumra S., Rupp C.I., Betensky J.D., Lencz T., Ashtari M., Kane J.M., Malhotra A.K., Gunduz-Bruce H., Napolitano B., Bilder R.M. (2007): Anterior cingulate grey-matter deficits and cannabis use in first-episode schizophrenia. Br J Psychiatry 190:230-236.

van Haren N.E., Hulshoff Pol H.E., Schnack H.G., Cahn W., Mandl R.C., Collins D.L., Evans A.C., Kahn R.S. (2007): Focal grey matter changes in schizophrenia across the course of the illness: a 5-year follow-up study. Neuropsychopharmacology 32:2057-2066.

Walterfang M., McGuire P.K., Yung A.R., Phillips L.J., Velakoulis D., Wood S.J., Suckling J., Bullmore E.T., Brewer W., Soulsby B., Desmond P., McGorry P.D., Pantelis C. (2008): White matter volume changes in people who develop psychosis. Br J Psychiatry 193:210-215.

Zavitsanou K., Garrick T., Huang X.F. (2004): Selective antagonist [3H]SR141716A binding to cannabinoid CB1 receptors is increased in the anterior cingulate cortex in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 28:355-360.

Ziermans T.B., Schothorst P.F., Schnack H.G., Koolschijn P.C., Kahn R.S., van Engeland H., Durston S. (2010): Progressive Structural Brain Changes During Development of Psychosis. Schizophr Bull .

Chapter 8

Nederlandse samenvatting

De studies die zijn beschreven in dit proefschrift onderzochten (veranderingen in) hersenstructuren bij eerste episode patiënten met schizofrenie en het effect van confounders, zoals cannabis, antipsychotische medicatie en ziekteduur.

Cannabis

In Hoofdstuk 2 en Hoofdstuk 3 is een antwoord gezocht op de vraag of cannabisgebruik en klinische prognose een effect hebben op de progressieve veranderingen in de globale hersenvolumes en de corticale dikte tijdens de eerste vijf jaar van schizofrenie.

In Hoofdstuk 2 werd het effect van cannabis gebruik op veranderingen in hersenvolumes over tijd onderzocht. Het sample bestond uit 19 eerste episode cannabis gebruikende patiënten, 32 niet-gebruikende patiënten en 31 gezonde niet-gebruikende controles.

Kort na het ontwikkelen van de eerste psychotische episode kregen patiënten met schizofrenie een MRI scan waarmee hersenvolumes bepaald konden worden. Vijf jaar later werden de patiënten opnieuw gescand en werden veranderingen in hersenvolume gemeten.

De bevindingen uit deze studie suggereren dat eerste episode patiënten die cannabis blijven gebruiken na het ontstaan van schizofrenie vertonen een grotere afname van het grijze stof volume en een toename van de laterale en derde ventrikels volume tijdens de 5-jaar follow-up in vergelijking met niet-gebruikende patiënten en gezonde controles. Bovendien, toonden cannabis-gebruikende patiënten een slechter klinisch beloop (kleinere verbeteringen over tijd in de positieve en negatieve symptomen) in vergelijking met de niet-gebruikende patiënten.

Het is nog onduidelijk hoe cannabis hersenvolumeverlies in patiënten met schizofrenie beïnvloedt. Enerzijds zou het een directe consequentie van cannabisgebruik kunnen zijn of anderzijds een consequentie van de “toxiciteit” van de psychotische symptomen die met cannabisgebruik geassocieerd zijn. Bovendien, hebben eerdere studies aangetoond dat (atypische) antipsychotica de progressieve hersenveranderingen in schizofrenie kunnen vertragen en dat cannabis gebruikende patiënten minder medicatie trouw zijn dan niet-gebruikende patiënten. Het is mogelijk dat de afname in hersenvolume verklaard zou kunnen worden door de lage medicatie compliance in de cannabis gebruikende groep.

In de conclusie van dit hoofdstuk benadrukten we de schadelijke effecten van cannabis zowel op het verloop van de ziekte en als mogelijke verklaring voor de progressieve hersenafwijkingen in schizofrenie.

De studie beschreven in Hoofdstuk 2, kon niet uitwijzen of de gerapporteerde grijze stof afname gelijkmatig was verspreid over de hersenen of meer in specifieke hersengebieden.

In Hoofdstuk 3 werd de relatie tussen lokale grijze stof en blootstelling aan cannabis bij eerste episode patiënten met schizofrenie onderzocht met behulp van corticale dikte metingen.

Hoewel patiënten met schizofrenie een algemeen verspreide verdunning over de hersencortex vertoonden, lieten de cannabis gebruikende patiënten grotere verdunningen zien in de linker dorsolaterale prefrontale cortex, linker anterior cingulate cortex en linker occipitale cortex ten opzichte van niet-gebruikende patiënten. Deze gebieden zijn niet alleen rijk aan cannabinoïden (CB1) receptoren in de normale populatie, maar hebben ook een hogere dichtheid van CB1 receptoren in de hersenen van patiënten met schizofrenie, ongeacht cannabis gebruik.

In de conclusie, suggereren wij dat in eerste episode patiënten die cannabis blijven gebruiken na het ontstaan van schizofrenie, vooral de corticale gebieden met de grootste dichtheid van CB1 receptoren gevoelig zijn voor corticale verdunning.

Antipsychotica

Hoofdstuk 4 en Hoofdstuk 5 beschrijven de uitkomsten van een cross-sectionele studie waarin globale hersenvolumes en witte stof zijn onderzocht in medicatie naïeve eerste episode patiënten met schizofrenie.

Het doel van de studie beschreven in Hoofdstuk 4 was om te onderzoeken of verschillen in hersenvolume en -dikte al in eerste episode patiënten met schizofrenie aanwezig zijn vóórdat er gestart wordt met het gebruik van antipsychotische medicatie. Tevens werd de relatie tussen de volume- en diktemetingen en IQ onderzocht.

De belangrijkste bevinding van deze studie is een afname van grijze en witte stof, en een volume toename van de laterale ventrikels in de patiënten groep. Groter hersenvolmeverlies was geassocieerd met een lager IQ. Deze bevindingen suggereren dat de structurele hersenveranderingen al daadwerkelijk aanwezig zijn bij het ontstaan van de ziekte en niet alleen gerelateerd zijn aan effecten van antipsychotica. Bovendien werd de afname in hersenvolume gedeeltelijk verklaard door een lager IQ en de ernst van de algemene psychopathologie bij patiënten ten opzichte van gezonde controles.

De gerapporteerde afname van witte stof volume in patiënten met schizofrenie is consistent met veel Diffusion Tensor Imaging (DTI) studies die veranderingen in de (micro-)structuur van de witte stof hebben aangetoond in schizofrenie. Echter, de meeste studies hebben patiëntenpopulaties geïncludeerd die al antipsychotica gebruikten. Hierdoor blijft het onduidelijk in welke mate de gerapporteerde witte stof veranderingen geassocieerd zijn met schizofrenie en welke met medicatiegebruik. Om medicatie effecten op de hersenmorfologie uit te sluiten hebben we met DTI de microstructurele eigenschappen van witte stof onderzocht in medicatie naïeve patiënten. In deze studie, beschreven in Hoofdstuk 5, hebben we 16 medicatie naïeve patiënten met schizofrenie geïncludeerd, samen met 23 gezonde controle controles.

Een nieuwe “fiber-gebaseerde” analyse werd gebruikt om verschillen in 12 belangrijke witte stof banen te onderzoeken in de twee groepen. Deze analyse combineert fractional anisoptropy (FA), mean diffusivity (MD) and magnetic transfer ratio (MTR). Significante verschillen in de FA, MD, MTR waardes werden gevonden in de rechter uncinate fasciculus en de linker arcuate fasciculus. Onze bevindingen laten zien dat eerder gerapporteerde toenames in MTR in de rechter uncinate fasciculus en de linker arcuate fasciculus van medicatie gebruikende patiënten ook aantoonbaar zijn in patiënten die nog geen antipsychotica hebben gebruikt.

We concludeerden dat de microstructuur van de witte stof, vooral in de linker arcuate fasciculus en rechter uncinate fasciculus afwijkend is in de beginstadia van schizofrenie en niet volledig is toe te schrijven aan de effecten van antipsychotica.

Psychoseduur

De 5-jaar longitudinale structurele MRI studie beschreven in Hoofdstuk 6 onderzocht de relatie tussen volumeveranderingen en de (totale) duur van psychose over vijf jaar in 48 eerste episode patiënten met schizofrenie. Afnames in totaal brein en grijze stof volume en een toename van de volumes van de derde en laterale ventrikels waren geassocieerd met een langere duur van de psychotische klachten.

Tot slot, laat deze longitudinale MRI studie zien dat in de eerste vijf jaar van de ziekte, afnames in hersenvolumes gerelateerd zijn aan de totale psychoseduur. Tevens suggeren de resultaten van deze studie dat de progressieve hersenveranderingen intrinsiek zijn aan schizofrenie en vooral gerelateerd zijn aan de psychotische aspecten daarvan.

Slot opmerkingen en conclusies

Samenvattend, de studies beschreven in dit proefschrift onderzochten de rol van confounders in het ontstaan van morfologische hersenafwijkingen bij eerste episode patiënten met schizofrenie.

Hoewel het effect van confounders op hersenmorfologie (nog) niet geheel duidelijk is, tonen de studies beschreven in de voorafgaande hoofdstukken dat (tenminste enkele) hersenveranderingen intrinsiek zijn aan schizofrenie, ook in de beginstadia van de ziekte voordat de effecten van medicatiegebruik hebben plaats gevonden.

Bovendien zijn niet alleen de hersenafwijkingen in schizofrenie progressief, maar ze zijn groter in patiënten met een lager IQ, een langere ziekteduur, en in die patiënten die cannabis (blijven) gebruiken na het ontstaan van de ziekte

Dit duidt erop dat factoren, anders dan de ziekte zelf, een belangrijke rol spelen in het progressieve verloop van de hersenafwijkingen die geassocieerd zijn met schizofrenie.

Deze bevindingen onderstrepen de noodzaak van het (h)erkennen, in toekomstige studies, van confoundende factoren die de hersenmorfologie beïnvloeden en die een bedreiging vormen voor de validiteit van de studies.

Dankwoord

Dankwoord

Tijdens de afgelopen jaren heb ik met veel mensen samengewerkt om dit proefschrift tot stand te laten komen. Zij hebben onder andere ervoor gezorgd dat ik altijd met enthousiasme en plezier naar het werk ben gegaan! Daarvoor wil ik ze hartelijk danken!

Allereerst gaat mijn dank uit naar alle **patiënten en controles** die aan deze studies hebben meegewerkt. Ik bewonder het doorzettingsvermogen en bereidheid om deel te nemen aan het onderzoek!

In het bijzonder dank ik mijn promotoren: **prof. dr. R.S. Kahn** en **prof. dr. H.E. Hulshoff Pol**.
Beste René, het was een eer om vanuit Italië naar Nederland te mogen komen om onder uw begeleiding onderzoek te doen. Ik heb de regelmatige afspraken altijd als zeer stimulerend ervaren, niet alleen omdat ik dan (echt!) mijn deadlines moest respecteren, maar omdat uw charisma, enthousiasme voor de wetenschap, nieuwsgierigheid, doeltreffende kritiek, stijl en acute humor aanstekelijk zijn! Ik heb veel van u geleerd en ik heb, dankzij uw begeleiding, me op verschillende gebieden kunnen ontwikkelen. Na onze regelmatige contacten kreeg ik altijd het gevoel dat het goed zou komen! Mijn dank hiervoor.

Beste Hilleke, ik heb altijd veel plezier gehad aan onze supervisiecontacten! Het was niet alleen wetenschappelijk leerzaam en stimulerend (nooit een keer ben ik jouw deur uit gestapt zonder een nieuwe analyse in gedachten om meer informatie uit de data uit te halen!), maar ook zeer gezellig en persoonlijk.

Mijn co-promotoren: **dr. W. Cahn** en **dr. N.E.M. van Haren**.
Beste Wiepke, bij jou is het helemaal begonnen! Ik “hoor” nog je woorden in mijn hoofd: “you have to do what makes you happy!”. Toen besloot ik om een sprong in het diepe te maken en naar Nederland te komen om onderzoek te doen. Hier heb ik nog nooit (echt!) spijt van gekregen! Ik heb op verschillende momenten veel steun aan jou ervaren. Ik bewonder vanaf het begin je capaciteiten om patiënten (en AIO’s) te motiveren voor onderzoek en je stimulerende houding.

Lieve Neeltje, er zijn geen woorden om jou op een adequate manier te kunnen bedanken. Vanaf dag één, toen ik aan de slag ging met mijn eerste IC, wist ik dat je de “golden standard” was. In de afgelopen jaren heb ik kunnen ervaren waarom dit ook zeer terecht is. Het is niet alleen zeer stimulerend en leerzaam om met jou samen te werken, zonder je hulp, steun, tips, bereikbaarheid, intelligentie en snelle feedback had dit proefschrift niet tot stand kunnen komen.

Ik heb veel van jou geleerd (vooral dat statistiek heel boeiend kan zijn en dat ook een clinicus kan denken in SPSS termen!). Tijdens het laatste jaar heb ik moeilijke momenten gehad, je had altijd een woord van troost en begrip waardoor ik nooit het idee heb gehad dat het niet goed zou komen. Ik ben jou zeer dankbaar.

“A good friend will come and bail you out of jail. A true friend will be sitting next to you saying, “Damn…that was fun!”: mijn paranimfen, **Heleen en Cédric**.

Lieve Heleen, leuk dat ik jouw paranimf kon zijn en geweldig dat je nu achter mij wil staan! We hebben veel tijd samen doorgebracht in de laatste jaren, veel gekletst, veel gesnoept, gereisd (lees: congressen & huwelijken), veel gelachen maar ook veel gehuild. Altijd samen, altijd naast elkaar. En als de ene lachte de ander daarvan kon genieten. Als de ene huilde, de ander ernaast was met een hand op de schouder (en een chocolaatje altijd klaar!). Ik vind het zo geweldig dat je mijn vriendin bent!

Lieve **Cé**, wat heb ik je gemist in de laatste jaren in het UMCU! Niet alleen je technische eigenschappen (ook zeer gemist) maar je (pittige) humor, je bereidheid om voor de ander tijd te maken, de ijsjes in de “achtertuin van het ziekenhuis” en je gevoel voor “het kletsen” (wat in een man een zeer aangename eigenschap is!). Ik ben blij dat je mijn paranimf wil zijn!

Mijn (historische) kamergenoten: **Ahmet, Jeroen** (get yourself the no-machine!) **én Kim** (wat leuk jullie te zien groeien tot een gezinnetje), **Sander en Marloes**. Ik heb met veel plezier met jullie een kamer gedeeld en genoten van de veel nuttige en (vooral) onnuttige discussies en speculaties! **Sander**, een Italiaan is (genetisch) een grammaticale freak! Je bent de enige die mij ooit (in duidelijke grammaticale termen) het verschil kon uitleggen tussen “hen” en “hun”. Ik zal je hiervoor eeuwig dankbaar zijn!

Voor de (niet alleen) technische en statistische ondersteuning ben ik ook dank verschuldig aan **René (Mandl)**, **Rachel (Brouwer)**, **Caroline** en **Eske**, samen met **Vincent** (je wordt gemist!) en **Yumas**.

Hugo, in de eerste jaren van mijn onderzoek hebben wij vaak samen geluncht. Wat mis ik onze gesprekken van toen! Het ging over alle mogelijke onderwerpen: (Italiaanse) politiek, literatuur, klinisch werken en onderzoek, hoe je een perfecte espresso maakt, waar kan je leuke workshops in Toscane doen. Het was altijd boeiend! Het eerste boek van een Nederlandse auteur wat ik

heb gelezen kreeg ik een keer van jou. Het was prachtig en is nu een van mijn favoriete boeken. Niet alleen hiervoor wil ik jou bedanken, maar ook voor je steun, kennis, tips, voor het lezen en nauwkeurig corrigeren van mijn manuscripten, voor je opbouwende scherpe kritiek. Ik heb veel respect voor wat je doet.

Alle **co-auteurs** wil ik bedanken voor hun bijdrage aan de totstandkoming van de artikelen die in dit proefschrift staan.

Mijn **collega's onderzoekers** dank ik voor de leuke tijd, gesprekken, lunches, interesse, hulp en vriendschap. In het bijzonder: **Astrid** (het wordt tijd om weer samen naar een voorstelling in Amsterdam gaan!), **Esther** (je staat altijd klaar voor een ander, dank voor je fijne vriendschap), **Geartsje**, **Jiska**, **Joost**, **Kuan**, **Maartje**, **Marcel**, **Maria**, **Marieke**, **Martijn**, **Mechteld**, **Miriam**, **Rachel** (wat leuk om een kamer "met zijn vieren" te delen in Colorado!), **Sarah**, **Sjoerd**, **Tamar**, **Thomas**, **Tim**, **Valérie** en de **collega's van kantoortuin 1, 2 en 3**.

In de laatste jaren van mijn promotietraject heb ik onderzoek gecombineerd met klinisch werk. Dit had nooit kunnen gebeuren zonder de steun van velen! Daarvoor wil ik alle **assistenten psychiatrie** (sommigen zijn inmiddels al psychiaters) van het UMC Utrecht bedanken. In het bijzonder mijn dank aan Mirte en Saskia voor de leuke samenwerking, collegialiteit en vriendschap!

Niet alleen de collega arts–assistenten, maar ook de supervisoren en werkbegeleiders hebben bijgedragen aan de (nodige steun voor de) totstandkoming van dit proefschrift. In het bijzonder **dr. Jaap Wijkstra** (die mij de "wet van Lasagna" geleerd heeft, en die mij steeds subtiel stimuleert om aan het uitspreken van de letter "U" te gaan werken) en **dr. Marco Boks**. Beste Marco, met jou ben ik plotseling terug in de klinische wereld gestapt na vele jaren onderzoek. Wat een enthousiasme! Ik herinner onze supervisiemomenten als zeer plezierig (ook omdat het vaak over onderzoek ging!), vol humor en (auto-)ironie (wat in dit vak een kunst moet zijn)! Je kunt je interesse, enthousiasme, nieuwsgierigheid en kennis op een zeer aangename manier aan de ander overdragen, wat ik als zeer motiverend heb ervaren. Mijn dank gaat uiteraard naar **alle werkbegeleiders en supervisoren van het UMC Utrecht**, voor de steun en het begrip. Ik heb, inmiddels, geleerd dat het combineren van onderzoek en klinisch werk een kunst is.

Daarnaast ben ik ook dank verschuldigd aan mijn supervisoren en werkbegeleiders van het St. Antonius Ziekenhuis: **Rolf**, dank je voor je begeleiding, de vrijheid en de ironie. **Sina**, ik bewonder je betrokkenheid en interesse in de ander. Tijdens mijn stage op de PCD ben ik nóóit een keer met tegenzin op mijn werk gekomen!

Uiteraard wil ik ook **Annet, Henk, Jan, Jean** (la tua supervisione in Italiano é fantastica!), **Leonie** en **Nicole** bedanken: wat leuk om met jullie samen te werken! **Danielle** & **Ingrid**, dank voor de gezelligheid, ik heb veel met jullie genoten!

Ook wil ik de **MRI-laboranten** bedanken: **Gerrit, Jürgen, Esther, Niels** en alle anderen die aan het schizofrenie onderzoek meegeholpen hebben (ik zal nóóit de gezellige scan-weekends vergeten). **Joyce,** wat een fijn mens ben jij, ik hoop snel een keer weer samen te kunnen lunchen! **Paula** wil ik bedanken voor de fijne samenwerking en de humor!

Emmy, Elly en Tjen. Een instituut binnen de afdeling psychiatrie! Altijd klaar om alle AIOS, AGIKO, AIO's te ondersteunen met een vleugje persoonlijke betrokkenheid!

De **secretaresses van balie 34B** wil ik ook bedanken, evenals de mensen van de **IT hersenen** voor hun hulp met de (vele) conflicten met technologie.

Tot slot kom ik bij diegenen die mij in mijn persoonlijke leven door dik en dun gesteund hebben en die mij zo dierbaar zijn.

Ed ora arrivo a coloro che mi hanno affiancato nei momenti di gioia e di tristezza e che tanto mi sono cari.

Francesca e **Vincenzo** senza i quali l'avventura olandese non sarebbe mai cominciata! **Massimo**. **Luisa**, grazie per l'ottimismo! Le vipere: **Alice, Cristina, Dina, Ida, Laura, Manuela, Monica, Nicoletta e Paola**: anche grazie al vostro sostegno e ai momenti di leggerezza che mi concedo con voi son riuscita a portare a termine questo progetto. E ora che é concluso, mi ritiro nella comune e vi aspetto. **Marina** (ora tocca a te), **Ad** én **Peggy** (wat fijn dat jullie er zijn, hopelijk lukt het nu om elkaar vaker te zien!).

Ook dank aan **Klaas, Netty, Erik**, en (mijn lieve broertje) **Niels**. Hopelijk willen jullie in de toekomst naast mij blijven lopen.

Infine **Gioia** (la mia P.A. preferita!), grazie per il buon umore e l'affetto.

Naturalmente un ringraziamento speciale alla mia famiglia che da sempre mi sostiene e stimola con affetto e imperturbabile fiducia!

Marinella, Gigi, Manuela, Mariasole e **Maddalena,** grazie per tanti anni condivisi con affetto e per la fiducia nelle mie capacità.
Zio Giuliano, Zia Mariolina e **Massimiliano**, che tanto significano per me.
Maria Grazia, grazie per l'amicizia speciale di cui ci fai dono.

Ma soprattutto voglio ringraziare **papà e mamma**: per gli anni insieme, le rinunce, l'amore, il sostegno, la pazienza, la curiosità, lo stimolo a migliorarsi e l'instancabile fiducia. Mi mancate tanto. **Matteo, Emanuela** e la piccola **Elisa**, vi voglio bene.

Bert, het is niet makkelijk geweest maar ik zou "het avontuur" op hetzelfde manier nog een keer doen! Dank voor je liefde, je geduld en je steun, maar vooral voor het delen van vele jaren met een moeilijk mens als ik ben!

Tot slot, lieve **Maddalena:** mijn leven samengevat in een klein, wonderlijk, gek mens! Vederti crescere e condividere la vita con te é la gioia e la gratificazione piú grande. Grazie, perchè, insieme a te, divento ogni giorno la persona che ho sempre desiderato essere.

List of Publications

List of publications

Rais M., Mandl R.C.W., van Baal G.C.M., van Haren N.E.M., Cahn W., Kahn R.S., Hulshoff Pol H.E. (2011). Altered white matter connectivity in never-medicated patients with schizophrenia. (submitted for publication)

Rais M., Cahn W., Schnack H.G., Hulshoff Pol H.E., Kahn R.S., Van Haren N.E.M. (2011). Brain volume reductions in medication naïve patients with schizophrenia in relation to IQ. (Submitted for publication)

Rais M., van Haren N.E., Cahn W., Schnack H.G., Lepage C., Collins L., Evans A.C., Hulshoff Pol H.E., Kahn R.S. (2010). Cannabis use and progressive cortical thickness loss in areas rich in CB1 receptors during the first five years of schizophrenia. Eur Neuropsychopharmacol 20:855-865.

Cahn W., Rais M., Stigter F.P., van Haren N.E., Caspers E., Hulshoff Pol H.E., Xu Z., Schnack H.G., Kahn R.S. (2009). Psychosis and brain volume changes during the first five years of schizophrenia. Eur Neuropsychopharmacol 19:147-151.

Rais M., Cahn W., Van Haren N., Schnack H., Caspers E., Hulshoff Pol H., Kahn R. (2008). Excessive brain volume loss over time in cannabis-using first-episode schizophrenia patients. Am J Psychiatry 165:490-496.

van Haren, NE, Pol, HE, Schnack, HG, Cahn, W, Brans, R, Carati, I, Rais, M, and Kahn, R.S. (2008). Progressive brain volume loss in schizophrenia over the course of the illness: evidence of maturational abnormalities in early adulthood. Biol. Psychiatry; 1:106-13

Curriculum Vitae

Curriculum Vitae

Monica Rais werd op 18 juni 1975 geboren te Cagliari, Italië. In 1994 behaalde zij het gymnasium diploma aan het “Liceo Ginnasio Siotto Pintor” te Cagliari. Aansluitend studeerde zij Geneeskunde aan de Universitá degli Studi di Cagliari, Italie. In 2004 begon zij als promovenda bij het Rudolf Magnus Instituut voor Neurowetenschappen, afdeling Volwassenen Psychiatrie van het Universitair Medisch Centrum (UMC) Utrecht. Onder de supervisie van Prof. Dr. R.S. Kahn en Prof. Dr. H.E. Hulhoff Pol heeft zij onderzoek gedaan naar hersenstructuren bij patiënten met eerste episode schizofrenie, hetgeen heeft geleid tot dit proefschrift. Sinds 2006 is zij, naast haar werk als onderzoekster, werkzaam als psychiater in opleiding in het UMC Utrecht.