contents

1 Introduction 1

2 White Matter Abnormalities in the Early Phase of Schizophrenia 19

2.1 White Matter Fibertracking in First-Episode Schizophrenia, Schizo-Affective Patients and Subjects at Ultra-High-Risk for Psychosis 21

2.2 Preliminary Evidence for Reduced Frontal White Matter Integrity in Subjects at Ultra-High-Risk for Psychosis 41

2.3 White Matter Connectivity and Psychosis in Ultra-High-Risk Subjects: a Diffusion Tensor Fiber Tracking Study 47

3 White Matter and Adolescent Cannabis Use 65

3.1 Recent-Onset Schizophrenia and Adolescent Cannabis Use: MRI Evidence for Structural Hyperconnectivity? 67

3.2 Cannabis Use and Callosal White Matter Structure and Integrity in Recent-Onset Schizophrenia 83

4 White Matter and Membrane Polyunsaturated Fatty Acids 103

4.1 Polyunsaturated Fatty Acids and Brain White Matter Anisotropy in Recent-Onset Schizophrenia: a Preliminary Study 105

5 Summary, Discussion & Conclusions **115**
5.1 Summary 117
5.2 General Discussion 125
5.3 Conclusions 135
5.4 References 139

6 Nederlandse samenvatting & conclusies **147**
6.1 Inleiding 149
6.2 Samenvatting van de resultaten 153
6.3 Conclusies 161

Dankwoord **165**

Curriculum vitae **171**

Publications **175**

Figures **181**

chapter 2

White Matter Abnormalities in the Early Phase of Schizophrenia

White Matter Fibertracking in First-Episode Schizophrenia, Schizo-Affective Patients and Subjects at Ultra-High-Risk for Psychosis 2.1

BD Peters, L de Haan, N Dekker, J Blaas, HE Becker, PM Dingemans, EM Akkerman, CB Majoie, T van Amelsvoort, GJ den Heeten, DH Linszen

Preliminary Evidence for Reduced Frontal White Matter Integrity in Subjects at Ultra-High-Risk for Psychosis 2.2

BD Peters, N Schmitz, PM Dingemans, TA van Amelsvoort, CB Majoie, GJ den Heeten, DH Linszen, L de Haan

White Matter Connectivity and Psychosis in Ultra-High-Risk Subjects: a Diffusion Tensor Fiber Tracking Study 2.3

BD Peters, PM Dingemans, N Dekker, J Blaas, E Akkerman, TA van Amelsvoort, CB Majoie, GJ den Heeten, DH Linszen, L de Haan

White Matter Fibertracking in First-Episode Schizophrenia, Schizo-Affective Patients and Subjects at Ultra-High-Risk for Psychosis

2.1

Bart D. Peters, Lieuwe de Haan, Nienke Dekker, Jorik Blaas, Hiske E. Becker, Peter M. Dingemans, Erik M. Akkerman, Charles B. Majoie, Therèse van Amelsvoort, Gerard J. den Heeten, Don H. Linszen

This chapter was published in:
Neuropsychobiology. 2008;58(1):19–28

Abstract

There is increasing evidence for white matter pathology in schizophrenia. The aim of this study was to examine whether white matter abnormalities found with diffusion tensor imaging (DTI) in previous schizophrenia studies are present in the early phase of the illness.

DTI was performed at 3 Tesla of ten male patients with a first (8) or second (2) psychotic episode of schizophrenia or schizo-affective disorder, ten male patients at ultra-high risk for psychosis with (pre)psychotic symptoms, and ten healthy controls. Fibertracts found abnormal in other DTI studies (uncinate and arcuate fasciculus, anterior and dorsal cingulum, subdivisions of the corpus callosum) were calculated and visualized; tract-specific measurements (fractional anisotropy and trace) were performed.

No differences were found between the healthy subjects and two patient groups.

These preliminary findings suggest that there is no white matter pathology of these association tracts detectable with DTI in the early stages of schizophrenic illness in males. Our findings are in contrast with DTI abnormalities found in some other first-episode studies. This discrepancy in findings may be related to differences in subject characteristics and DTI methodology. Possible effects of age, gender, level of education and illicit substance use on DTI findings in schizophrenia are discussed.

2.1.1 Introduction

Abnormal brain development in schizophrenia is thought to lead to 'dysconnectivity' between brain areas associated with positive and negative symptom dimensions and cognitive dysfunctioning [1, 2, 3]. The neuroanatomical substrate for this dysconnectivity may be dysplastic white matter tracts as a result from abnormal development in utero [2], demyelination during adolescence [1, 3] and adulthood [3], or an arrest in the normal process of myelination during brain maturation in adolescence and middle age [3].

With diffusion tensor imaging (DTI), brain white matter structure can be assessed in a more detailed manner in vivo than with conventional MRI [4]. In DTI the magnetic resonance signal is made sensitive to the movement (or diffusion) of water molecules. A DTI index called fractional anisotropy is increased by myelination [5, 6], coherence of fibertracts [7], and by the structural integrity of fibers, their diameter and packing density [4].

Subjects at ultra high-risk (UHR) for conversion to psychosis are characterized by defined trait or state factors including attenuated or brief limited psychotic symptoms [8, 9, 10]. Studies in UHR subjects and first psychotic episode patients can provide insight in the early pathophysiological mechanisms in schizophrenia-like disorder. Eight DTI studies in patients with a recent onset of schizophrenia have been reported so far [11, 12, 13, 14, 15, 16, 17, 18] and have reported abnormalities in several white matter areas. To our knowledge, no DTI studies in UHR patients have been reported. One diffusion weighted study in first-degree relatives of schizophrenia patients found diffusion abnormalities in gray matter structures not detectable with conventional MRI [19]. In chronic schizophrenia patients, several DTI studies found reduced anisotropy in numerous brain regions [20, 21, 22, 23]. One study found also increased anisotropy in a subgroup of patients [24].

Many DTI studies in schizophrenia examined regions of interest (ROI) or used a voxel-by-voxel approach in gray-scale anisotropy images, in which it can be difficult to locate abnormalities to specific fibertracts. Advanced applications of DTI make it possible to calculate and visualize the probable trajectories of white matter fiber bundles (referred to as 'fibertracking'; [25]) and allow tract-specific measurements. To our knowledge, this is the first DTI study, which applies fibertracking to examine white matter tracts in UHR patients as well as patients with a first or second psychotic episode of schizophrenia or related disorder. Associ-

ation fibertracts connecting cortical regions may be primarily involved in schizophrenia [26] and we hypothesized that fractional anisotropy of association fibertracts, previously found to be abnormal in schizophrenia, would be altered in both patient groups compared to healthy controls. Furthermore, antipsychotic medication use is a major confounder in schizophrenia research and we hypothesized that there would be a positive correlation between duration and dose of antipsychotic treatment and white matter fractional anisotropy, as found previously [22, 23,]. Such a relation would be consistent with possible pro-myelination effects of some atypical antipsychotics, which have been found to increase brain neurosteroid and apolipoprotein D levels and blood lipid levels, which in turn are thought to stimulate myelination in the brain [3].

2.1.2 Methods

Subjects

This study was approved by the local and national medical ethics committees. Male patients diagnosed with a first or second psychotic episode of schizophrenia, schizo-affective disorder or schizophreniform disorder (referred to next as schizophrenia-like disorders) were recruited from the open-ward inpatient and day-care units of the Adolescent Clinic of the Academic Medical Center. These patients were approached when they were deemed clinically able to give informed consent. Ultra-high-risk patients were recruited from a naturalistic, longitudinal study program related to the Adolescent Clinic, with an 18 month follow-up. These patients are referred by mental health services. Inclusion criteria for these patients were defined according to criteria used in other studies [8, 9, 10]: attenuated psychotic symptoms (e.g. odd beliefs, paranoid ideation) or brief psychotic moments with spontaneous remission in less than one week; and/or a decline in functioning in the past year (30% reduction in Global Assessment of Functioning scale) plus a genetic risk (1^e degree relative with schizophrenia-like disorder or a schizotypal personality disorder); or two 2 'basic symptoms' (cognitive, perceptual, emotional and social disturbances; [10]). We included only males as white matter abnormalities may be gender-specific [27]. Male healthy control subjects were recruited through local advertisements and were matched for educational level, age and handedness.

Table 2.1.2: White Matter Diffusion Tensor Measurements in Four Association Fibertracts

	First-episode Patients (N=10) mean ± SD	Ultra-High-Risk Patients (N=10) mean ± SD	Healthy Controls (N=10) mean ± SD	F	df	p
Uncinatus						
Fractional anisotropy				0.15	2	0.86
left	0.479 ±0.050	0.477 ±0.044	0.477 ±0.053			
right	0.467 ±0.034	0.494 ±0.044	0.485 ±0.041			
Trace				0.35	2	0.71
left	0.248 ±0.014	0.249 ±0.008	0.244 ±0.009			
right	0.245 ±0.006	0.239 ±0.007	0.245 ±0.005			
Arcuatus						
Fractional anisotropy				(analyzed with uncinatus)		
left	0.503 ±0.031	0.501 ±0.029	0.508 ±0.035			
right	0.502 ±0.046	0.505 ±0.025	0.503 ±0.027			
Trace				(analyzed with uncinatus)		
left	0.226 ±0.013	0.225 ±0.008	0.228 ±0.006			
right	0.224 ±0.011	0.222 ±0.009	0.266 ±0.007			
Cingulum						
Fractional anisotropy				1.21	2	0.31
dorsal left	0.536 ±0.072	0.572 ±0.053	0.561 ±0.043			
dorsal right	0.498 ±0.049	0.563 ±0.049	0.516 ±0.043			
anterior left	0.483 ±0.060	0.498 ±0.055	0.496 ±0.047			
anterior right	0.437 ±0.063	0.480 ±0.060	0.409 ±0.049			
Trace				0.92	2	0.41
dorsal left	0.250 ±0.028	0.245 ±0.012	0.243 ±0.010			
dorsal right	0.243 ±0.016	0.232 ±0.009	0.242 ±0.007			
anterior left	0.254 ±0.032	0.247 ±0.009	0.240 ±0.011			
anterior right	0.248 ±0.024	0.238 ±0.014	0.245 ±0.011			

the FA distribution along the tract was skewed in the patients, which is thought to represent reduced FA in the core of the tract. In accordance with another first-episode study [13] we found no abnormalities in the genu or splenium of the corpus callosum. In contrast, Cheung et al. did find reduced FA in the splenium of the corpus callosum in medication-naive first-episode patients [16].

There may be several explanations for this discrepancy in findings between DTI studies in young-adult patients with schizophrenia-like disorder. First, the lack of differences between patients and controls in our

Table 2.1.2: (continued)

	First-episode Patients (N=10) mean ± SD	Ultra-High-Risk Patients (N=10) mean ± SD	Healthy Controls (N=10) mean ± SD	F	df	p
Corpus Callosum						
Fractional anisotropy				1.67	2	0.21
splenium	0.680 ±0.028	0.706 ±0.018	0.680 ±0.020			
posterior truncus	0.551 ±0.029	0.553 ±0.045	0.542 ±0.029			
anterior truncus	0.558 ±0.040	0.568 ±0.033	0.564 ±0.027			
genu	0.624 ±0.038	0.651 ±0.039	0.638 ±0.029			
Trace				2.66	2	0.09
splenium	0.287 ±0.017	0.285 ±0.014	0.291 ±0.014			
posterior truncus	0.320 ±0.011	0.312 0.027	0.332 ±0.014			
anterior truncus	0.309 ±0.017	0.295 ±0.020	0.298 ±0.023			
genu	0.284 ±0.019	0.280 ±0.017	0.292 ±0.025			

study may result from lack of power due to the small sample size. However, one first-episode study finding differences included ten patients [11], whereas the study finding no differences included twenty patients [13].

Secondly, level of education of the subjects may be an important confounder, although subjects were matched carefully on educational level. In our study, seven out of ten first-episode patients and seven out of ten UHR patients had received education at a Bachelor's or Master's level. A structural MRI study in first-episode patients with a high level of education found no differences compared with healthy controls in cerebral white matter volume [43], while other first-episode studies did [44, 45]. High educational level has been associated with good outcome [46, 47], which in turn has been associated with a relative lack of brain abnormalities at illness presentation [48] and in the course of the illness [49]. Educational level was not mentioned in four of the first-episode or recent-onset DTI studies [11, 13, 14, 15], and was somewhat higher in controls in one study [12]. Parental socio-economic status or years of education was matched in three studies [16, 17, 18].

Third, a gender effect may be involved. We included males only and the seven DTI studies showing abnormalities included both males and fe-

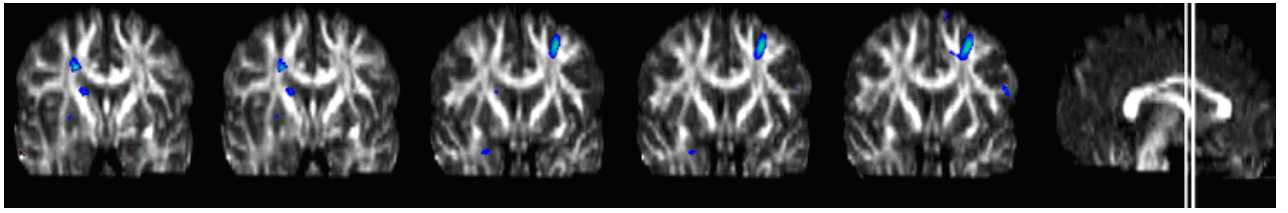

Figure 2.2.1: Significant fractional anisotropy differences between ultra-high-risk subjects and healthy controls.

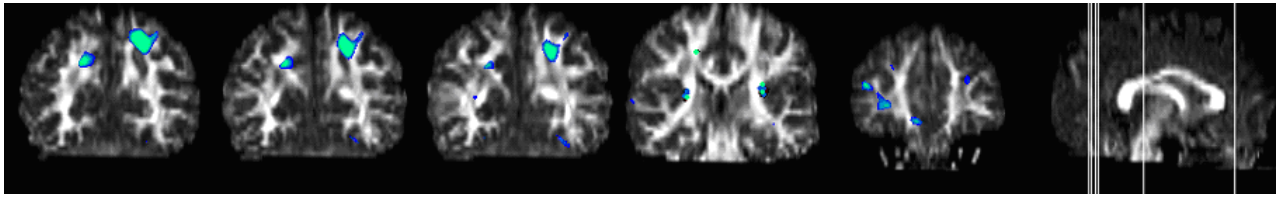

Figure 2.2.2: Significant fractional anisotropy differences between schizophrenia patients and healthy controls.

Legend: Clusters of decreased FA are overlaid on a FA image. There were no areas of increased FA in UHR or schizophrenia subjects. Left is left-hemisphere, right is right-hemisphere.

2.2.1 References

Cannon, T.D., Thompson, P.M., van Erp, T.G., Toga, A.W., Poutanen, V.P., Huttunen, M., Lonnqvist, J., Standerskjold-Nordenstam, C.G., Narr, K.L., Khaledy, M., Zoumalan, C.I., Dail, R., Kaprio, J. , 2002. Cortex mapping reveals regionally specific patterns of genetic and disease-specific gray-matter deficits in twins discordant for schizophrenia. Proc. Natl. Acad. Sci. USA 99, 3228-33.

Jessen, F., Scherk, H., Träber, F., Theyson, S., Berning, J., Tepest, R., Falkai, P., Schild, H.H., Maier, W., Wagner, M., Block, W., 2006. Proton magnetic resonance spectroscopy in subjects at risk for schizophrenia. Schizophr. Res. 87, 81-88.

Hoptman, M.J., Nierenberg, J., Bertisch, H.C., Catalano, D., Ardekani, B.A., Branch, C.A., Delisi, L.E., 2008. A DTI study of white matter microstructure in individuals at high genetic risk for schizophrenia. Schizophr. Res. 106, 115-124.

Klosterkötter, J., Ruhrmann, S., Schultze-Lutter, F., Salokangas, R.K., Linszen, D., Birchwood, M., Juckel, G., Morrison, A., Vázquèz-Barquero, J.L., Hambrecht, M., Von Reventlow, H., 2005. The European Prediction of Psychosis Study (EPOS): integrating early recognition and intervention in Europe. World Psychiatry 4, 161-167.

Miller, T.J., McGlashan, T.H., Rosen, J.L., Somjee, L., Markovich, P.J., Stein, K., Woods, S.W., 2002. Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: preliminary evidence of interrater reliability and predictive validity. Am. J. Psychiatry 159, 863-865.

Muñoz Maniega, S., Lymer, G.K., Bastin, M.E., Marjoram, D., Job, D.E., Moorhead, T.W., Owens, D.G., Johnstone, E.C., McIntosh, A.M., Lawrie, S.M., 2008. A diffusion tensor MRI study of white matter integrity in subjects at high genetic risk of schizophrenia. Schizophr. Res. 106, 132-9.

Pantelis, C., Yücel, 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.