Diffusion tensor imaging in the early phase of schizophrenia

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Conclusions

This thesis

From our DTI studies into brain white matter integrity in patients with a first or second psychotic episode of schizophrenia or related disorder, and in patients with an ultra-high risk of psychosis, we conclude the following:

1. There is no white matter pathology of the midsagittal parts of the corpus callosum, of anterior and dorsal parts of the cingulate, and of the uncinate and arcuate fasciculi, detectable with DTI in the early stage of schizophrenia or schizoaffective disorder or in the ultra-high-risk state of psychosis in males (Peters et al. 2008).

2. There is reduced fractional anisotropy in the frontal lobe of male patients with an ultra-high-risk for psychosis, and possibly in the early stage of schizophrenia, schizoaffective disorder. Frontal FA abnormalities may reflect a vulnerability for psychosis (Peters et al. 2009a).

3. There is reduced fractional anisotropy in the temporal and parietal lobes bilaterally in the early stage of schizophrenia, schizoaffective disorder. Together with the findings in point two this suggests that abnormalities in these areas are associated with onset of psychosis (Peters et al. 2009a).

4. Fractional anisotropy of the midsagittal parts of the corpus callosum, of anterior and dorsal parts of the cingulate, and of the uncinate and arcuate fasciculi, do not differ between male patients at ultra-high-risk of psychosis who develop a psychotic episode and ultra-high-risk patients who do not develop psychosis. Thus, white matter integrity in these white matter tracts appears not to
be disrupted before onset of psychosis, and fractional anisotropy in these tracts is not a biological marker of psychosis in ultra-high-risk patients (Peters et al. 2010).

5. Patients with a recent onset of schizophrenia or related disorder who have used cannabis during adolescence (before age 17) show increased fractional anisotropy in the bilateral uncinate fasciculus, anterior internal capsule and frontal white matter, compared to patients without adolescent cannabis use or healthy controls (Peters et al. 200b). Patients with a recent onset of schizophrenia who have used cannabis during early adolescence (before age 15) display normal FA values, while cannabis naïve patients may show reduced fractional anisotropy in the splenium of the corpus callosum, compared with patients with early-onset cannabis use (before age 15) and healthy controls (Dekker, Schmitz, Peters et al. 2010).

These findings indicate an association between early cannabis use and normal or enhanced white matter fractional anisotropy in recent-onset schizophrenia, and perhaps a more disturbed white matter microstructure in cannabis naïve schizophrenia patients. This supports the hypothesis that patients with schizophrenia and early cannabis use have different pathophysiological mechanisms than cannabis naïve patients or patients with late-onset cannabis use.

6. Total (poly)unsaturated fatty acid concentration in erythrocyte membranes is related to fractional anisotropy in the uncinate fasciculus. Unsaturated fatty acids may be necessary for the myelinating activity of oligodendrocytes or for myelin maintenance (Peters et al. 2009c).

General conclusions from DTI studies in the early phase of schizophrenia

At present there is substantial DTI data available on the early phase of schizophrenia from our and other research groups. Taking our results and the results of other studies together, DTI abnormalities in first-episode patients appear less robust than in chronic patients, suggesting that progression to more extensive abnormalities occurs after illness onset. There
are also indications for accelerated aging effects in schizophrenia. These findings suggest the possibility that early intervention may help to preserve white matter integrity. In both high-risk subjects as well as first-episode and chronic patients there is considerable variability among findings, and few genetic and environmental factors have been identified that may account for this. Sample differences in age, gender, substance use and variations in the neuregulin gene may play a role, as well as differences in DTI methodology. Found effects of cannabis on FA are inconsistent; cannabis may merely be associated with DTI alterations in schizophrenia and not itself affect white matter, and some results from basic and animal studies suggest that cannabis may even have neuroprotective properties. There seems little effect of medication in first-episode patients, but this needs more research. Functional consequences of DTI alterations are insufficiently studied as yet, but positive symptoms tend to be associated with local increases in FA. Because direct pathological comparisons are not available the underlying pathology of DTI abnormalities in schizophrenia remains speculative. Fewer studies have been performed on ultra-high-risk and genetically high-risk individuals, but there is some convergence in the results: frontal abnormalities may reflect a liability for schizophrenia, while temporal abnormalities are associated with psychosis.

Future research directions

Given the results and conclusions of this thesis, diffusion tensor imaging has shown to be a valuable tool in gaining more insight in the pathophysiology of schizophrenia. Nonetheless, many questions are still unanswered and further research is needed. A longitudinal design with at least three DTI measurements would be minimal to fill in the blanks in current knowledge. Individuals identified as having (ultra-) high-risk of psychosis should be scanned, then re-scanned twice at follow-up, after transition to psychosis has occurred in some individuals and at the end of the critical period after three years to assess the early course of DTI alterations. White matter regions conveying the risk of psychosis could be identified as well as those regions being affected by psychosis. The pathological specificity of these findings could be determined by comparing schizophrenia patients with various clinical presentations to one another and comparing them with other psychiatric disorders such as bipolar dis-
order. Genetic and other biological factors, for example membrane fatty acids (Peters et al. 2009c), adolescent cannabis use and type of antipsychotic medication (Bartzokis et al. 2009) could be taken into account together with clinical variables to clarify the determinants of DTI abnormalities and their functional consequences. DTI can be combined with other imaging modalities such as magnetization transfer imaging (MTI) and magnetic resonance spectroscopy (MRS)¹ to provide more insight in the white matter microstructure alterations causing DTI abnormalities in schizophrenia.

¹ MRS can detect spectra reflecting the concentrations of several compounds in the brain. Increases in choline-containing compounds in white matter may reflect increased myelin degradation or increased catabolism of membrane phospholipids in schizophrenia (Auer et al. 2001, Chang et al. 2007). Studies combining MRS and MTI have shown that MTI abnormalities may reflect decreased glutamate levels as measured by MRS, through prolonging T1-relaxation time (Wyckoff et al. 2003).