Diffusion tensor imaging in the early phase of schizophrenia

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Chapter 2
White matter abnormalities in the early phase of schizophrenia

Diffusion tensor imaging findings in individuals at high risk of psychosis

Applying DTI fiber tracking of the uncinate and arcuate fasciculi, dorsal and anterior cingulate and subdivisions of the corpus callosum, we found no differences between subjects with an ultra-high-risk (UHR) of psychosis and healthy controls (Chapter 2.1; Peters et al. 2008), and no differences between UHR subjects with transition to psychosis at follow-up and subjects without transition (Chapter 2.3; Peters et al. 2010). In contrast, with voxel-based analysis (VBA) we found reduced FA in superior and middle parts of frontal white matter in UHR subjects (Chapter 2.2; Peters et al. 2009a).

VBA analysis in our UHR sample has also shown that transition to psychosis at follow-up was associated with lower FA values in the medial frontal lobes (compared to controls) and lateral to the right putamen and in the left superior temporal lobe (comparison within the UHR group) (Bloemen et al. 2009, not this thesis). The UHR subjects with transition to psychosis also showed higher FA in the left medial temporal lobe. These findings emphasize the power of VBA in exploratory analyses, providing target brain regions for testing hypotheses with region-of-interest or fiber tracking methods.

Karlsogt and colleagues (2009) found reduced FA in the arcuate fasciculus of UHR subjects, contrary to our findings, but analysis of the un-
cinate fasciculus and cingulum bundle was negative in their study as well. UHR samples are even more heterogeneous than schizophrenia samples. The subjects in the studies by Karlsgodt and colleagues included both males and females and had a somewhat younger age at DTI scanning. This difference in age may be especially important. A DTI study comparing adolescent-onset schizophrenia patients with young-adult patients found that the location of FA deficits differed between these groups, leading to the conclusion that white matter abnormalities may depend on the developmental stage at the time of illness onset (Kyriakopoulos et al. 2009).

DTI studies that investigated white matter in subjects with a genetic high risk, defined as having a first-degree relative with schizophrenia, found reduced FA in inferior frontal, posterior cingulate, angular white matter (Hoptman et al. 2008), in the anterior limb of the internal capsule (Muñoz Maniega et al. 2008), while increased FA was also found frontally and in the anterior cingulate (Hoptman et al. 2008). A study of young-adult monozygotic twins and first-degree relatives suggests that medial frontal lobe FA reductions reflect a genetic liability of schizophrenia (Camchong et al. 2009). The former two studies examined schizophrenia patients as well, and found more widespread FA reductions than in the high risk subjects, which is in accordance with our VBA study (Peters et al. 2009a) and suggests that FA abnormalities progress around the onset of psychosis. We emphasize here that the genetic high-risk subjects and the clinically UHR subjects are different groups, and do not necessarily fulfil each other’s criteria. Nonetheless, in an attempt to integrate the current DTI findings, there is some convergence of evidence that frontal abnormalities reflect a liability for schizophrenia, while temporal abnormalities are associated with psychosis, which is in line with functional brain imaging studies (Whalley et al. 2007). Age, genetic predisposition and clinical features may be important modifiers. In addition, gray matter alterations play a role in the transition to psychosis (Pantelis et al. 2003) particularly in the cingulate cortex (Fornito et al. 2008, Wood et al. 2008). At this moment we do not know how gray and white matter abnormalities interact. Further studies are needed to assess these interactions and examine how they relate to the risk and onset of psychosis.

Diffusion tensor imaging findings in individuals with a recent onset of schizophrenia

Similar to our analyses in UHR subjects, our DTI measurements with fiber tracking in patients with a first or second episode of schizophrenia or
schizoaffective disorder showed no abnormalities of the uncinate and arcuate fasciculi, dorsal and anterior cingulate, and subdivisions of the corpus callosum (Chapter 2.1; Peters et al. 2008). In contrast, VBA showed reduced FA in the parietal and temporal white matter and indications for frontal FA reductions, compared to healthy controls (Chapter 2.2; Peters et al. 2009a). This indicates that parietal and temporal abnormalities are associated with onset of the first psychosis.

To date DTI studies have produced some evidence for widespread white matter abnormalities in first-episode patients (Hao et al. 2006, Federspiel et al. 2006, Price et al. 2007, Szeszko et al. 2008, Cheung et al. 2008, Karlsgodt et al. 2008, Gasparotti et al. 2009, Pérez-Iglesias et al. 2010, Peters et al. 2009a, Kawashima et al. 2009, Dekker et al. 2010) and chronic patients (Konrad and Winterer 2008), though findings are less consistent in the first-episode group. Six studies have shown no differences between patients and healthy individuals (Price et al. 2005, Peters et al. 2008, Friedman et al. 2008, Zou et al. 2008, Qiu et al. 2009, White et al. 2009a), and three studies found no FA abnormalities but did identify indications for abnormalities with other diffusion indices (Price et al. 2008, Chan et al. 2010, Mendelsohn et al. 2006). Most positive findings come from voxel-based analyses, while six out of fifteen fiber tracking or ROI analyses showed no abnormalities (Price et al. 2005, Peters et al. 2008, Friedman et al. 2008, Zou et al. 2008, Qiu et al. 2009, White et al. 2009a). Furthermore, for each fiber tract that was found to have reduced FA values there is at least one negative fiber tracking or ROI study, together with negative VBA studies.

The studies in antipsychotic drug-naive first-episode patients are of particular interest, showing FA reductions not attributable to antipsychotic medication (Cheung et al. 2008, Zou et al. 2008, Gasparotti et al. 2009). Data on the relation between DTI measures and clinical variables are sparse. Interestingly, three studies found positive correlations between FA and positive symptoms (Karlsgodt et al. 2008, Szeszko et al. 2008, Chan et al. 2010), which concurs with findings in chronic patients. Negative symptoms correlated negatively with FA in the uncinate fasciculus (Szeszko et al. 2008), and positive correlations were found for verbal learning/memory with FA in the uncinate fasciculus (Szeszko et al. 2008), for verbal working memory with FA in the arcuate fasciculus (Karlsgodt et al. 2008), and for spatial working memory with left thalamic FA (Qiu et al. 2009). The questions of where and when DTI abnormalities occur in the early phase of schizophrenia as well as what causes them are discussed in the general discussion below.
Chapter 3
White matter and adolescent cannabis use

With DTI, we found in recent-onset schizophrenia patients with cannabis use before age 17 (n = 24) increased FA in the bilateral uncinate fasciculus, anterior internal capsule and frontal white matter, compared to controls (n = 21) and patients without cannabis use before age 17 (n = 11) (Chapter 3.1; Peters et al. 2009b). The abnormalities were not related to lifetime doses of cannabis or other illicit drugs, and therefore we hypothesized that adolescent cannabis use is not a causative factor of FA alterations, but that cannabis users represent a subgroup of patients with distinct brain abnormalities, possibly with structural hyperconnectivity. One major limitation of our study was the polydrug use in the sample, and a general effect of cannabis use as opposed to specifically adolescent use could not be excluded. Therefore a second study compared patients with early cannabis use (< 15 years; n = 10) to patients with late cannabis use (> 17 years; n = 8) and cannabis naïve patients (n = 8), all without significant use of other substances (Chapter 3.2; Dekker, Schmitz, Peters et al. 2010). Cannabis-naïve patients showed significantly reduced FA values in the left splenium of the corpus callosum, compared to early-onset cannabis users and healthy controls (without significant cannabis or other substance use). One possible explanation for the difference in results described in Chapter 3.1 and Chapter 3.2 is that increases in FA may be subtle and require large sample sizes to detect them. Corroborating evidence for an association between increased FA and adolescent cannabis use comes from a study of cannabis users without major psychiatric illness (DeLisi et al. 2006). This study comprised a small sample as well, but subtle FA differences may be more difficult to detect in schizophrenia patients due to the combination of illness-related and cannabis-related processes. In larger samples of adolescents using both alcohol and cannabis, increased FA values were identified (Bava et al. 2009, De Bellis et al. 2008) in combination with reduced FA values in one of these studies (Bava et al. 2009). The functional consequences of increased FA were also assessed: increased occipital FA correlated positively with complex visuomotor sequencing, while increased anterior FA was negatively associated with verbal memory performance (Bava et al. 2010). The detrimental effects of frequent alcohol use on white matter integrity are well established (e.g. Pfefferbaum et al. 2006), suggesting that the increases in FA in the studies by Bava (2009) and De Bellis (2008) and colleagues may be related to
the adolescent cannabis use by their subjects. Adolescent cannabis use may enhance FA in several ways. First, there may be direct effects on white matter: cannabinoid receptor stimulation has been found to increase an oligodendrocyte transcription factor, augment the expression of myelin basic protein (Arévalo-Martín et al. 2007), and promote oligodendrocyte progenitor survival (Molina-Holgado et al. 2002). Secondly, increased FA may result from neuroadaptation compensating for cognitive impairments caused by cannabis use (Kanayama et al. 2004). Third, in line with our first results (chapter 3.1), De Bellis and colleagues (2008) suggested that increases in FA may reflect accelerated myelination in adolescence, which subsequently may elicit substance use.

In contrast to the above, the normal FA values found in patients with early cannabis use in Chapter 3.2 complies with the hypothesis of less structural brain abnormalities, and more functional derailment, in patients with cannabis use compared to patients who develop a psychotic disorder without using cannabis (Murray et al. 1992). The psychotic effects of cannabis are associated with its dopamine-stimulating effects (Linszen and van Amelsvoort 2007), and early cannabis use as opposed to later cannabis use may have more impact on dopamine neurotransmission as adolescence is a critical period in the development of the dopamine system (van Nimwegen et al. 2005). An association of cannabis use with less structural brain abnormalities is in line with findings of specific clinical characteristics of cannabis-using patients, such as better cognitive functioning early in the course of the illness (Stirling et al. 2003), less negative symptoms (Peralta et al. 1992, Bersani et al. 2002, Compton et al. 2004), better premorbid adjustment (Arndt et al. 1992), less incoherent speech (Rottanburg et al. 1982), fewer neurological soft signs (Bersani et al. 2002), and less qualitative MRI abnormalities (Scheller-Gilkey et al. 1999). An alternative explanation for lack of FA abnormalities in early cannabis-using patients is that cannabis may have neuroprotective effects and these effects could mitigate any neurodevelopmental white matter abnormalities in schizophrenia. This hypothesis is supported by DTI findings in adolescents without a psychiatric disorder: while adolescent binge drinking of alcohol was associated with FA decreases in several fiber tracts, these effects were partially attenuated in adolescents with both binge drinking and cannabis use (Jacobus et al. 2009). Neuroprotective effects of cannabis may result from its ability to reduce glutamatergic excitotoxicity (van der Stelt et al. 2002) in combination with its antioxidant properties (Hampson et al. 1998, van der Stelt et al. 2002). Findings are inconsistent however and reduced FA values (Ashtari et al. 2009) as well
as normal FA values (Arnone et al. 2008) have been found in cannabis-using adolescents without major psychiatric illness. The age of this latter sample was somewhat older than in our own study and the other studies; the effects of adolescent cannabis use may diminish with time.

In summary, at present there is some evidence that adolescent cannabis use is associated with preserved or even enhanced diffusion anisotropy in white matter, both in schizophrenia patients as well as individuals without major psychiatric illness. However, substantial inconsistencies are still present, and the following interpretations should be considered as preliminary. Schizophrenia patients with adolescent cannabis use may represent a separate subgroup with distinct DTI white matter abnormalities, possibly reflecting hyperconnectivity, or rather less DTI abnormalities. DTI effects may involve direct effects of cannabis on myelination, neuroadaptive mechanisms compensating for compromised neuropsychological functioning, as well as neuroprotective properties of cannabis; alternatively, increased FA may precede adolescent cannabis use. Future studies should further assess the relation between adolescent cannabis use and white matter anisotropy, its time course and functional consequences.

Chapter 4
White matter and membrane polyunsaturated fatty acids

In our pilot study described in chapter four, we found a correlation between fractional anisotropy of the uncinate fasciculus and total concentration of (poly)unsaturated fatty acids (PUFAs) in erythrocyte membranes of twelve patients with a recent onset of schizophrenia or related disorder. This finding supports the hypothesis that PUFA abnormalities may be implicated in white matter abnormalities in schizophrenia. This effect on myelin appeared to be region specific, as only one of the six regions of interest showed a correlation with PUFA concentration. The exact mechanism through which PUFA abnormalities affect white matter microstructure is unclear. White matter and myelin are rich in PUFAs, for instance DHA constitutes 5.8% of myelin and 5.1% of oligodendrocytes (Bourre et al. 1984). PUFAs may be important in myelin formation, or myelin maintenance. Dietary supplementation with eicosapentaenoic acid (EPA) was found to stimulate the expression of myelin pro-
teins in rat brain (Salvati et al. 2008). Magnetic resonance spectroscopy results indicate that PUFA disturbances in schizophrenia may cause a generalized cell membrane dysfunction and this may have a role in myelin degradation (Auer et al. 2001). Our finding needs replication or falsification in a larger sample. Furthermore, examining the separate effect of individual mono- and polyunsaturated fatty acids is of interest; this was not feasible in our pilot study due to the small sample size.