WHITE MATTERS

Diffusion Tensor Imaging in the Early Phase of Schizophrenia

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Diffusion Tensor Imaging in the Early Phase of Schizophrenia

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Introduction

In the studies involved in this thesis we employed the first-episode strategy to study the neurobiology of schizophrenia. First-episode patients offer the opportunity to study schizophrenia without confounding effects of illness and pharmacotherapy chronicity. We focused on brain white matter abnormalities as measured with MRI diffusion tensor imaging (DTI) in the context of the dysonnection hypothesis. Below we will discuss in more detail the research questions we posed in our studies.

Chapter 2 - White matter abnormalities in the early phase of schizophrenic illness.

The first question in our studies was whether white matter abnormalities as assessed with DTI are already present at clear illness onset, i.e. after onset of the first psychotic episode. If so this would support the assumption that these white matter abnormalities play a role in the primary pathophysiology, as opposed to being a result of secondary disease processes. A second question would then be when these white matter abnormalities occur (in early development, during adolescence or during the first psychotic episode). A third question that could be answered is whether white matter abnormalities have a predictive value of onset of schizophrenia. The prediction of schizophrenia is now a major topic in schizophrenia research, and holds the hope for early intervention and perhaps prevention. There is sufficient evidence that early intervention after onset of psychosis improves outcome in patients (Perkins et al. 2005). Furthermore, in individuals who have a high risk of developing schizophrenia early treatment before the first psychotic episode may prevent full development of the illness. At present, different sets of clinical criteria have proven valid in identifying individuals at ‘ultra-high risk’ of psychosis, including brief or attenuated psychotic symptoms (Yung et al. 2003, Lencz et al. 2003, Olsen and Rosenbaum 2006). These criteria define groups of help-seeking patients that show a 20-35% risk for psychosis within 1-2 years of follow-up in different independent international studies (Cannon et al. 2008, Ruhrmann et al. 2010).

In chapter two of this thesis we will describe the DTI studies we performed in patients with a recent onset of schizophrenia, and in subjects at ultra-high-risk of psychosis. We compared them with healthy controls, and furthermore we examined whether DTI white matter abnormalities were predictive of psychosis at clinical follow-up in the ultra-high-risk subjects.

Chapters 3 and 4 – Factors associated with white matter abnormalities in schizophrenic illness.

As schizophrenia is a multifactorial disorder, with a strong genetic basis interacting with environmental factors, multiple factors may independently or in synergy lead to white matter abnormalities. As stated above, while genetic research points to disturbances in myelin en oligodendrocyte genes, one can hypothesize about other factors involved white matter abnormalities, such as medication, substances abuse, pre- or perinatal complications, physical factors including diet, head trauma. In **chapter 3** we have examined the effects of cannabis use by our patients, particularly adolescent cannabis use, and **in chapter 4** the role of unsaturated fatty acid composition of cell membranes, which is presumed to be involved in the pathophysiology of schizophrenia (Peet 2006).

Cannabis: The major psychoactive ingredient of cannabis is delta-9-tetrahydrocannabinol and is known to cause transient psychotic symptoms in some healthy individuals (Castle and Murray 2004). Moreover, there is evidence that cannabis use is a partial causal risk factor for onset of schizophrenia (Moore et al. 2007). Cannabis use may play a role in the pathophysiology of psychosis by interacting with or aggravating pathological brain development in schizophrenia. We focus here particularly on cannabis use during adolescence as this is a critical period in brain development and there is evidence from subjects without major psychiatric illness that adolescent cannabis use has a negative effect on brain structure and function, such as verbal memory dysfunction (Pope et al. 2003), specific visual attention deficits (Ehrenreich et al. 1999), and larger percent white matter volume (Wilson et al. 2000). In contrast, a conventional MRI study found no effect of onset age of cannabis use on hippocampal volume (Tzilos et al. 2005). MRI studies in recent-onset schizophrenia patients with cannabis abuse found no differences in brain white matter volumes (Cahn et al. 2004, Szeszko et al. 2007). We applied DTI to determine whether there are microstructural white matter abnormalities associated with adolescent cannabis use in first-episode schizophrenia patients, which may not be detectable with conventional MRI.

(Poly)Unsaturated fatty acids:

Unsaturated fatty acids are essential constituents of the cell membranes in every body tissue, including of neurons in the brain. Decreased concentrations of unsaturated fatty acids, particularly polyunsaturated, have been identified in schizophrenia, *in vivo* in erythrocyte membranes of first-episode patients as well as post-mortem in brains of older patients. In a previous sample of recent-onset schizophrenia patients of our clinic reduced docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), and nervonic acid (NA) concentrations in

erythrocytes were found (Assies et al. 2001). In never-medicated first-episode patients DHA concentrations in erythrocytes were reduced (Kale et al. 2008, Reddy et al. 2004, Khan et al. 2002, Arvindakshan et al. 2003) as well as arachidonic (AA) and DPA (Khan et al. 2002, Arvindakshan et al. 2003, Reddy et al. 2004) and linoleic acid (LA) (Khan et al. 2002), whereas oleic acid (OA) was increased (Khan et al. 2002). Postmortem studies identified reduced DHA and AA, together with increased vaccenic (VA) and oleic acid (OA) in the orbitofrontal cortex (McNamara et al. 2007), and found reduced AA and LA in the caudate nucleus (Yao et al. 2000). Clinical trials of polyunsaturated fatty acid supplementation have suggested symptomatic improvement in schizophrenia, but the results of these studies are inconclusive (Joy et al. 2006). In individuals at high risk of psychosis fatty acid supplementation did decrease the risk of transition to psychosis (Amminger et al 2010).

Brain white matter consists for a large part of myelin, which is composed for 20% of proteins and 80% of lipids. All the major lipids in the brain are also present in myelin and the sphingolipid cerebroside is the most typical of myelin and its concentration is proportional to the brain myelin content (Sastry 1985). White matter has a high concentration of phospholipids amounting to about 7% of wet weight in humans. A large proportion of the phospholipid molecules in the myelin membrane are ethanolamine plasmalogens (EP), and another important phospholipid is sphingomyelin. Basic post-mortem studies in primates and humans have studied in detail the lipid-composition of white matter. Bourre and colleagues (1984) determined in rats that DHA constituted 5.8% of myelin and 5.1% of oligodendrocytes In white matter EP, OA and VA predominate in addition to AA and DHA (Sastry 1985). In primates relatively high concentrations of DHA and AA were identified in the cingulate white matter (Diau et al. 2005). In cerebellar white matter there are relatively high concentrations of VA and OA (Jamieson et al. 1999).

During early human brain development there is an increase in unsaturation of the fatty acid content of cerebroside, where the monounsaturated NA is the major component (Svennerholm and Ställberg-Stenhagen 1968). This process is about completed at two years of age. In infant sphingomyelin NA rises from 4% to 33% (Svennerholm and Vanier, 1973a) and is the major monounsaturated fatty acid (Martínez and Mougan 1998). In myelin EP, the polyunsaturated LA peaks between 4 months and 12 months of age, and then slowly diminished to old age (Svennerholm and Vanier 1978). Adrenic acid and OA are the predominant unsaturated fatty acids in EP postnatally and as myelination progresses OA increases significantly (Martínez and Mougan 1998). Similarly, Svennerholm and Vanier (1973b) found that during postnatal development, there is an increase of (mono)unsaturated fatty acids in white matter,

particularly of 18:1 (vaccenic and oleic acid) in EP, and that adrenic acid is the major acid from the 4th postnatal month, and at the age of two years it is twice as large as AA. Ställberg-Stenhagen and Svennerholm (1965) reported that 40% of white matter sphingomyelin is NA, but this is significantly reduced in dysmyelinating and demyelinating diseases. Martinez and Mougan (1999) found that in EP of infants with peroxisomal disorders, which are characterized by reduction in myelin volume, dysmyelination, or demyelination, DHA and AA were very significantly decreased, with DHA being the most affected. Adrenic acid was also decreased together with OA and DPA. In two children with metachromatic leucodystrophy reduced proportions of very long chain fatty acids (VLCFAs) in the sphingolipids were identified in frontal white matter (O'Brien 1964); in particular NA seemed reduced. Dietary supplementation with eicosapentaenoic acid (EPA) and DHA are found to improve white matter grade (Virtanen et al. 2008), and EPA is found to stimulate the expression of myelin proteins in rat brain (Salvati et al. 2008). Trapp and Bernsohn (1978) found in rats with essential fatty acid deficiency a decrease of LA in EP concomitant with morphological myelin changes, and supplementation with a source of LA showed a marked protective effect against experimental allergic encephalomyelitis, a model for acute multiple sclerosis (Selivonchick and Johnston 1975).

Thus, in schizophrenia reductions of the unsaturated fatty acids docosahexaenoic acid, docosapentaenoic acid, nervonic acid, arachidonic acid, and linoleic acid were found, whereas increases in oleic acid and vaccenic acid were also identified. These fatty acids are present in human and non-human brain white matter, and eicosapentaenoic acid, docosahexaenoic acid and linoleic acid are found to improve myelination in humans and rats in both the healthy state and in white matter disease.

Considering that the (poly)unsaturated acids showing alterations in erythrocytes and brains of schizophrenia patients are present in brain white matter, studying the relation between peripheral (poly)unsaturated acids and brain white matter anisotropy is of interest in schizophrenia. Indeed, Auer and colleagues (2001) concluded from a proton MRI spectroscopy (MRS) study measuring cholin in parietal white matter, together with other phosphorus MRS (31P-MRS) studies, that 'Elevated choline in line with 31P-MRS studies suggests increased myelin degradation thus further supporting a generalized membrane disorder in schizophrenic patients', and the authors suggested that '… direct correlations with measures of diffusion anisotropy or concentrations of highly unsaturated fatty acids in peripheral membranes may shed further light on the nature of these abnormalities'.

We conducted a pilot study to examine if erythrocyte membrane (poly)unsaturated fatty acid concentration is related to brain white matter anisotropy as measured with DTI.

Summary of results

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.

Karlsgodt and colleagues (2009) found reduced FA in the arcuate fasciculus of UHR subjects, contrary to our findings, but analysis of the uncinate 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 not 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 proteins 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.

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 disorder. 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)* to provide more insight in the white matter microstructure alterations causing DTI abnormalities in schizophrenia.

* 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).