Diffusion tensor imaging in the early phase of schizophrenia
Peters, B.D.

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Timing and progression of DTI abnormalities in schizophrenia

Two scenarios for the timing and progression of DTI abnormalities are feasible. First, FA abnormalities in schizophrenia may result from excessive aging effects observed in healthy people. Secondly, illness-related, possibly neurotoxic effects may take place around onset of the first psychotic symptoms. The first option suggests that age is the most important factor to take into account, while the second option suggests that age at onset and duration of illness have the most impact on DTI measures. Because age is closely related to duration of illness it is difficult to separate abnormal aging from illness-related effects. It is recalled here that FA shows a nonlinear upward pattern from childhood to adolescence (Schmithorst and Yuan 2010) and then downward into adulthood and old age (Sullivan and Pfefferbaum 2006).

Studies of adult schizophrenia patients found a greater FA decline with increasing age compared to healthy controls in the forceps major, inferior longitudinal fasciculus (Friedman et al. 2008, age range 18–80 years), genu of the corpus callosum (Carpenter et al. 2008, age range 18–78 years), widespread throughout the white matter (Mori et al. 2007, age range 22–59; White et al. 2009a, age range not reported), cingulate (Rosenberger et al. 2008, age range 20–50 years) and to a lesser extent uncinate fasciculus (Mandl et al. 2008; age range 20–41 years). This pronounced decline in the cingulum is of particular interest given the fact that FA decline in healthy individuals is found to start at the cingulum (Yoon et al. 2008). In addition, Mitelman and colleagues (2009, age range not reported) found that poor-outcome patients had lower baseline
anisotropy but tended to show less decline than good-outcome patients, suggesting that the most significant FA decreases in poor-outcome patients occur in an earlier phase of the illness. It is important to note that the age effects were not corrected for duration of illness in these studies.

Age of onset was not related to FA in the studies of Rosenberger (2008), Szeszko (2008) and Mandl (2008) and colleagues and not in the VBA analysis by Mori and colleagues (2007) though weakly related to mean FA of total white matter in this study. Studies comparing adolescent and chronic patients did identify effects of age of onset, and suggest that prefrontal FA deficits develop when illness onset occurs at a later age (Kyriakopoulos et al. 2009, Schneiderman et al. 2009).

Duration of illness was not related to FA in three samples (Kanaan et al. 2009a, age range 18–60 years; Mandl et al. 2008; White et al. 2009a), but was in two other samples (Mori et al. 2007, Carpenter et al. 2008), particularly in the genu of the corpus callosum. The strength of Carpenter’s study is that the correlations were corrected for age. It may be important here that in both Kanaan’s and Mandl’s studies the samples were fairly young (median age 27 years) with a much shorter duration of illness than in the other two studies.

In summary, the findings discussed above support an overall pattern of more severe and extensive abnormalities in chronic patients than in first-episode patients. There may be an acceleration of normal aging in schizophrenia, particularly in the cingulate. There are also indications for progression of illness-induced FA decreases after onset, independent of age effects, which may be most pronounced in the early course of poor-outcome patients (Mitelman et al. 2009). An effect of age of onset may only be detectable when onset occurs in adolescence, either suggesting a specific pathophysiology in adolescent-onset schizophrenia patients, or selective anatomical effects when psychosis hits during this critical phase of brain development. Although sample sizes were quite large in some studies, sample sizes may still have been too small in these studies to detect any nonlinear aging patterns. White matter volume shows a general increase into 40–50 years of age followed by a decrease in normal adults (e.g. Bartzokis et al. 2001), but not in schizophrenia patients (Bartzokis et al. 2003).
Anatomical location of DTI abnormalities: single lesion versus widespread


There may be methodological issues as well as sample differences involved in the variability of the findings. As described in the introduction, chronic schizophrenia patients with hallucinations displayed higher anisotropy values in the genu of the corpus callosum, cingulum and superior longitudinal fasciculus compared to healthy controls and patients without hallucinations (Hubl et al. 2004, Shergill et al. 2007, Seok et al. 2007). Other subgroups with distinct DTI abnormalities have not yet been identified. Given the fact that findings are inconsistent to date, the most appealing hypothesis seems to be that abnormalities vary according to genetic and environmental factors and the developmental stage in which these occur; these abnormalities may be superimposed on widespread abnormalities present in all patients, as suggested by Kanaan and colleagues (2009). As mentioned before, the problem of location variability can be approached by analyzing FA decreases that do not spatially overlap between patients and therefore do not appear in analyses of group-averaged images (White et al. 2009b). A notable report is a recent meta-analysis of VBA-DTI studies in chronic patients, which identified two consistent abnormal regions in deep left frontal white matter and deep temporal white matter (Ellison-Wright and Bullmore 2009). Such a meta-analysis of DTI studies in first-episode patients would be valuable,
but would not solve the problem. More research is needed on the genetic, environmental and clinical determinants of FA in the early stages of schizophrenia.

The pathological substrate of DTI abnormalities in schizophrenia

As mentioned in the introduction, DTI abnormalities may reflect alterations in the degree of myelination, fiber number, fiber diameter or density, coherence of axons within fiber tracts, and the structural integrity of fibers. Post-mortem studies have identified white matter abnormalities in schizophrenia. These include microstructural myelin abnormalities (Uranova et al. 2001), reduced total length of nerve fibers (Marner et al. 2003), reduced fiber density or total fiber number in the corpus callosum and anterior commissure of female patients (Highley et al. 1999a, 1999b; note that another post-mortem study revealed greater fiber density in the fornix of male schizophrenia patients, suggested to reflect a myelination disturbance (Chance et al. 1999)). In contrast, Nasrallah (1982) and Casanova (1989) and colleagues reported no differences in the number of axons in the corpus callosum. We are not aware of combined DTI / post-mortem assessments in schizophrenia.

Studies combining DTI with other MRI modalities may provide more insight in the microstructural features underlying DTI abnormalities. Magnetization transfer imaging (MTI) indexes the exchange of magnetization between bound protons and free water, gives an indication of macromolecular integrity/concentration and is highly sensitive to myelin content (Kubicki et al. 2005). In middle-aged patients both MTI and FA decreases were noted in some fiber tracts, suggesting that the FA alterations in these tracts were myelin-related, while FA decreases in other tracts with normal MTI measures were suggestive of disturbed directional coherence of the fiber bundles (Kubicki et al. 2005). In a group of young adult patients a 1% increase in MTI signal was observed in the uncinate fasciculus, while FA was unaltered in the uncinate (Mandl et al. 2008). This was concluded possibly to reflect increased myelination compensating for frontal-temporal dysconnectivity. There was a decrease of FA with age not found with MTR, suggesting that decline in FA is not myelin-related in schizophrenia. It is important to recognize however,
that the magnetization transfer ratio (MTR) is not only determined by myelin content. MTI abnormalities may also result from prolonged T1 relaxation times due to a change in the free/bound water fraction, which, for instance, may result from changes in glial glutamate uptake (Wyckoff et al. 2003). Moreover, cerebral inflammation may reduce the MTR in white matter (Filippi and Rocca 2007) as well as reductions in axonal density: in multiple sclerosis hypointense lesions, which are characterized by severe axonal loss in addition to demyelination, have lower MTR values than isointense lesions (Filippi and Rocca 2007).

Thus, there are some indications from post-mortem studies for microstructural myelin abnormalities and reduced total length of nerve fibers in schizophrenia, and for reduced fiber density or total fiber number in female patients. Studies combining different MRI modalities concluded that DTI abnormalities reflect myelin alterations in some fiber bundles and disturbed directional coherence in other fiber tracts. These conclusions remain speculative because no MRI measure is specific for one microstructural feature.

Causal factors of DTI white matter abnormalities

Genetics. One DTI study specifically focused on genetic variation associated with DTI abnormalities in schizophrenia. The neuregulin gene is assumed to play a role in oligodendrocyte structure and function and myelination, and single nucleotide variations associated with an increased risk of psychosis were related to decreased white matter anisotropy in schizophrenia patients (Wang et al. 2009), which concurs with findings in healthy individuals (McIntosh et al. 2008).

Antipsychotic medication. Medication use is a major confounder in schizophrenia research. To our knowledge only one study specifically focused on the effects of antipsychotic medication on DTI measures and found no differences between chronically and briefly medicated patients (Kanaan et al. 2009). This is confirmed by the analyses of Szieszko and colleagues (2008). Similarly, Szieszko (2008) and White (2009a) and colleagues found no differences between medicated and antipsychotic naïve first-episode patients, though sample sizes were small. In our samples we found no significant correlations between FA and duration or dose of antipsychotic medication (Peters et al. 2008, Peters et al. 2009b), while
Szeszko and colleagues (2008) found FA of the arcuate to correlate positively with antipsychotic treatment duration. Thus, the effect of antipsychotics is insufficiently studied in first-episode patients, with current evidence suggesting no negative effect on FA in briefly medicated patients.

Methodological issues

Diffusion tensor imaging

There are multiple DTI acquisition and post-processing schemes. As discussed earlier, DTI uses a rather weak effect, the diffusion of free water, to analyze the local orientation of fibrous structures. To extract fiber bundles from these data, fiber tracking is necessary. In classic fiber tracking, the main diffusion direction is determined in each voxel, and following the path of these diffusion directions creates a fiber bundle which consists of a multitude of axons. There are several algorithms available to perform fiber tracking, ranging from simple step-by-step Euler integration of the main diffusion direction, to more complicated tensor-line methods with higher-order integration steps. When two physical fiber bundles cross, a simple diffusion tensor cannot fully capture the information of both bundles, making tracking and connectivity analysis challenging. A naïve Euler method, that locally follows the single strongest diffusion direction cannot cope properly with fiber crossings, as in these voxels no single fiber direction is best followed. Higher-order methods such as HOT-lines can better distinguish these situations, and allow the tracking to continue through these areas (Hlawitschka and Scheuermann 2005). Recently, more advanced acquisition schemes have been proposed to combat this weakness, such as High-Angular Resolution Diffusion Imaging (HARDI) (Tuch et al. 1999), but these are still experimental and often need more scanning time or have additional hardware requirements. In general, crossing fibers will cause a decrease in the fractional anisotropy within a voxel. When comparing tractography results, it is important to know that each tracking method has a number of free parameters, such as stopping conditions (below which anisotropy value or under which other conditions should a fiber be considered terminated). By and large three methods of analyzing DTI images can be applied: voxel based analysis (VBA), region-of-interest (ROI) analysis and fiber tracking. All have advantages and disadvantages. VBA’s strength is the automated analysis of
the whole brain so abnormal regions can be identified without a priori hypotheses. On the other hand, false-positive findings are a possible limitation, as well as the margin of error in intersubject registration of the images, and difficulties in ascribing abnormalities to specific fiber tracts. In our VBA study (Peters et al. 2009a) the frontal white matter abnormalities in the schizophrenia patients did not survive cluster-level correction and should therefore be considered preliminary. These problems are diminished when applying tract-based spatial statistics (TBBS), where images are fitted to an ‘FA skeleton.’ There is a trend for VBA studies to find FA decreases, while ROI and fiber tracking studies more often produce negative results in first-episode patients. Hypothesis testing would preferably be done with fiber tracking, and VBA studies may have optimal value when combined with fiber tracking analysis to confirm the found abnormalities. High-field strength imaging can increase resolution, while isotropic voxels are preferred for fiber tracking; voxel size should be identical between subjects (Kim et al. 2006).

During our data-analyses in Chapter 2.3 it came to our attention that voxel size was not identical between subjects, and average voxel size differed significantly between groups. Moreover, FA correlated negatively with voxel size. In chapter 2.3 this proved an essential factor in our results: increased FA in the anterior cingulate of UHR subjects resulted from their smaller voxel size. Therefore, we explored the possible effects of different voxel sizes in our other studies. In Chapter 2.1 voxel size was significantly smaller in the UHR subjects and nonsignificantly larger in the first-episode patients (due to some patients with large voxel sizes; most patients had smaller voxel sizes). We repeated the analyses with voxel size as a covariate, and the results remained virtually unchanged. In Chapter 2.2, the same subjects were studied as in Chapter 2.1. The decreases in FA found in the UHR subjects can not be explained by their smaller voxel sizes, which produce increased FA values. Nonetheless, if voxel size would have been ‘normal’ more FA reductions may have been identified in the UHR subjects. In the first-episode patients the larger voxel size may have contributed to their FA reductions, although the difference in voxel size between first-episode patient and controls was not significant. Thus, it cannot be excluded that in chapter 2.2 the voxel size differences may have caused a dephasing between the UHR and first-episode patients, where actual DTI differences may have been more similar in these groups. This would derogate our conclusion that additional DTI abnormalities occur around onset of the first psychosis. On the other hand, it would confirm the conclusion that white matter DTI abnormalities are not ex-
tensive in first-episode patients. Of note, in our fiber tracking analyses we did not observe that the FA values of the larger voxels of the schizophrenia patients were lower than the FA values of the (larger) voxels of the healthy controls. In Chapter 3.1 voxel size was not an issue because in the 1.5 T acquisitions voxel size was maintained identical across subjects. Regarding our analyses in Chapter 3.2, voxel size of the patients was larger than voxel size of the controls, though this was not statistically significant. In addition, voxel size was not similar across the three patient groups: patients with cannabis use before age 15 had about the same average voxel size as the controls, but voxel sizes were nonsignificantly larger in the patients with cannabis use after age 17 and the cannabis naive patients. Regarding possible effects of this on our results, the slightly larger voxel size in the cannabis naive patients may have contributed to their decreased FA values in the corpus callosum. Also, there may have been increases in FA in the patients with cannabis use after age 17 which were obscured by the larger voxel sizes. Nonetheless, our conclusion in chapter 3.2 that early cannabis use is associated with intact white matter integrity remains unchanged.

In Chapter 4 voxels size was not relevant as these analyses involved correlations between FA and fatty acid levels.

Of particular interest is the use of different diffusion indices to infer the underlying substrate of DTI abnormalities. Reduced fractional anisotropy with normal mean diffusivity could point to disordered neuronal architecture rather than compromised myelination (Kanaan et al. 2009b). Furthermore, a measure derived from DTI referred to as transverse diffusivity shows a higher correlation with myelin than FA (Gulani et al. 2001) and indicated in one study that increased MTI was not due to an increase in myelin content (Mandl et al. 2008). Also, applying a high b-value (the strength of the magnetic diffusion gradient) has been suggested to produce a diffusion weighted signal which represents intra-axonal diffusion more specifically than fractional anisotropy, which is also influenced by diffusion in other tissue compartments, e.g. glial tissue, as well. Mendelsohn and colleagues (2006) found frontal diffusion abnormalities in first-episode patients with high b-values, while FA measures were unaltered.

Clinical characteristics of patients

We studied male subjects only as white matter structure is found to differ between males and females. Particularly the corpus callosum seems influ-
enced by gender in schizophrenia patients, with more pronounced abnormalities in females as noted in DTI (Price et al. 2007) and post-mortem studies (Highley et al. 1999a). Therefore the lack of abnormalities in chapters 2.1 en 2.3 may have been partly due to the inclusion of males only. In contrast, Gasparotti et al. (2009) found that lower mean FA values in the splenium were possibly stronger in males. Most DTI studies performed by others have included both male and female subjects. Although inclusion of males only can be considered a limitation of our studies, it has also a clear advantage to exclude confounding effects of gender. Future studies should take gender into account to clarify its effect.

A strength of our studies is the narrow age range of the included subjects, while some other studies have a broad age range of their participants. In light of the described age effects in DTI measures narrower ranges are preferred. Duration of illness varied in our samples, and was moderate to short in chapters 2.1/2.2 and 3.2 respectively, but fairly long on average in the patients of chapter 3.1. Duration of illness has been related to lower FA values and therefore short durations of illness within a narrow range are preferable. In other studies illness duration varied from short to long, and was comparable to the variation in our studies.

Educational level was well-matched in our samples, and a significant number of our patients were highly educated. Educational level (or premorbid IQ) is sometimes not addressed or not successfully matched between patients and controls in other studies, while group differences in this variable could affect results. We have hypothesized that the high level of education in our patients may have played a role in the relative lack of DTI abnormalities (chapter 2.1, Peters et al. 2008).

An important limitation of our studies are the small sample sizes. Therefore our negative studies in chapters 2.1 and 2.3 cannot confirm the null-hypothesis, we can only conclude there is insufficient evidence to reject it. We did calculate in chapter 2.3 from the effect sizes that fairly large sample sizes would have been required to detect significant differences. The correlation between FA and (poly)unsaturated fatty acids in chapter 4.1 was one-tailed and did not survive bonferroni correction.

Lastly, some of our and other studies combined schizophrenia and schizoaffective patients, and considering the clinical and neurobiological differences between these patients (e.g. Morris et al. 2009) examining them separately would be of interest.