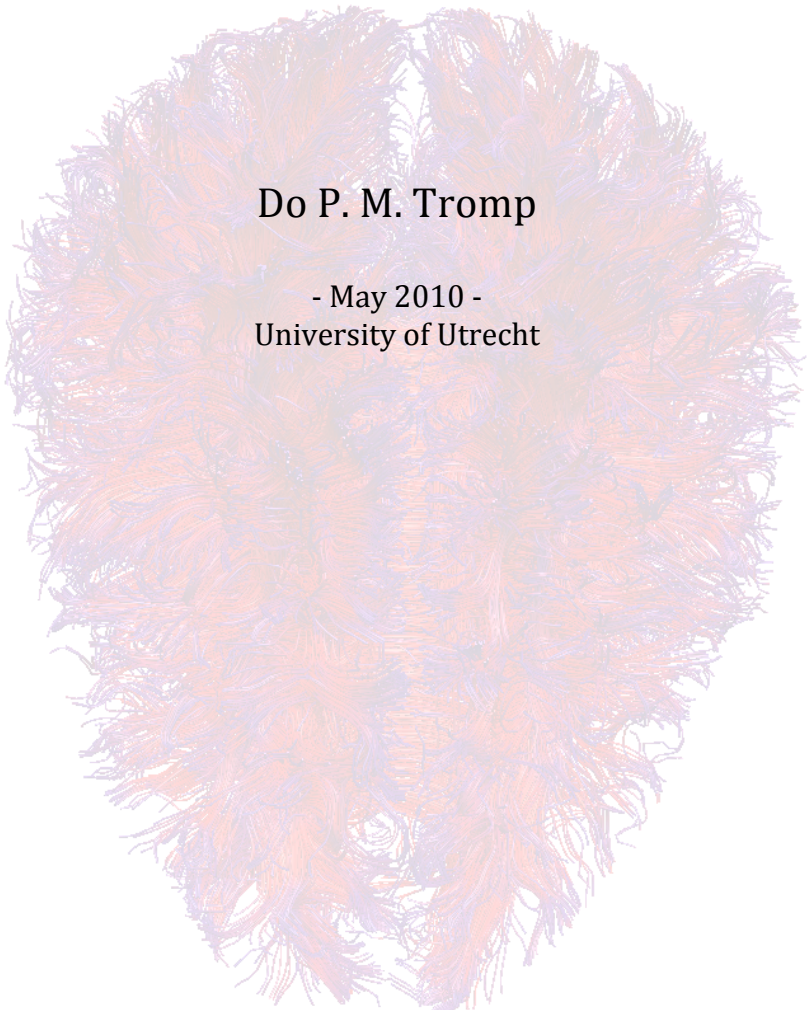
Current developments of white matter connectivity research in Schizophrenia

A study into voxel based versus track based DTI methodology



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Abstract

Research in schizophrenia has shown that structural brain abnormalities exist in patients with this disorder, but while imaging studies mostly pointed in the direction of gray matter changes, post-mortem studies were also finding abnormalities in neuronal cytoarchitecture and glial cells. These cells are highly important for the protection and formation of neuronal axons, and defective glial cells can lead to white matter changes. Newly developed MRI-methods such as diffusion tensor imaging (DTI) are able to investigate white matter changes in schizophrenia *in vivo*. DTI measures describe the magnitude and orientation of water diffusion and the shape of the diffusion profile and are often described with a scalar value named the fractional anisotropy (FA). When diffusion weighted images are analyzed there are two different techniques available to determine and compare group differences in region-specific FA variations. Voxel Based Morphometry analysis is the most straightforward method to look at group differences between FA values. It enables you to do whole brain analysis to indicate what regions have variations in FA values that exceed pure statistical chance. This means that it is a broad but coarse method. Tract-based analysis is a method that compares FA values of specific white matter fiber paths. An a priori region of interest is necessary to be able to use this method. This method increases the statistical power compared to VBM methods, which will allow for more sensitive detection of FA group differences. In this thesis both methods will be discussed, as well as the current developments in both fields in schizophrenia research. Furthermore research methods like scan protocol, voxel size, patient groups and VBM blurring will be compared to better understand contradicting or overlapping research results.

Contents

Introduction

Schizophrenia is a devastating mental disorder; a study in 14 countries showed that active psychosis is ranked as being the most disabling condition after severe paralysis and dementia (Ustun et al., 1999). Despite hundred years of extensive research very little is known about the etiology of schizophrenia.

Research into the neuropathology of schizophrenia has identified a number of abnormalities. Most prominently is the ventricular enlargement of approximately 40% and decreased cerebral volume of 3% (Lawrie & Abukmeil, 1998; Harrison, 1999). To account for the volumetric changes research started to focus on cortical cytoarchitecture. This lead to the discovery that there are alterations in synaptic, dendritic and axonal organization in schizophrenic patients (Harrison, 1999).

Over the years a great amount of evidence has been collected concerning gray matter abnormalities (Wright et al., 2000; Shenton et al., 2001). A much smaller part of research focused on white matter changes although studies dating back to the early 1900's have been pointing in the direction of disrupted connectivity between the frontal and temporal lobes in schizophrenia (Kraepeling, 1919/1971; Bleuler, 1911). These ideas have been supported by recent studies showing reduced prefrontal white matter (Sanfilipo et al., 2000; Buchanan et al., 1998; Sigmundsson et al., 2001; Breier et al., 1992). This reduced prefrontal white matter volume is highly correlated with amygdala, hippocampus and temporal gyrus reductions (Wible et al., 1995; Lawrie & Abukmeil, 1998).

More indications to support an increased focus on white matter research in schizophrenia come from a multitude of methods showing abnormal myelin and oligodendrocytes. These methods vary from electron microscopy, post-mortem gene expression, animal models, gene association, neurophysiology to neuroimaging (Hakak et al., 2001; Uranova et al., 2001, 2004; Davis et al., 2003; Voineskos et al., 2010).

The development of diffusion tensor imaging (DTI) enabled the research of white matter integrity *in vivo*. DTI measures the magnitude and orientation of water diffusion. This is usually done in multiple directions to be able to calculate the tensor, which is a three dimensional representation of the water diffusion profile. Dense white matter tracks have highly anisotropic diffusion of water pointing in the direction of the fiber bundle, while gray matter has predominantly isotropic water diffusion.

The measure most commonly used to characterize directional diffusion is the fractional anisotropy (FA). This measure gives a value between 0 and 1 to indicate the fraction of diffusion that is in the longitudinal direction compared to the proportion of diffusion in both transverse directions.

There are two main methods to analyze diffusion images. The first and oldest is Voxel-Based Morphometry (VBM) analysis, which can do whole brain analysis. It is a voxelwise method to statistically compare local anisotropy values for the whole brain between different groups of subjects.

The second method is called tract-based analysis. This is the newest development in DTI methodology. It uses the more anisotropic tensors to form streamlines of tensors leading to estimations of white matter fiber tracks. A region of interest is used as seed region from where the fibers are traced. For each track mean FA values are calculated. These values per track can be compared across groups to investigate structural connectivity. Tractography proved to be useful in several studies that investigated other psychiatric disorders like epilepsy (Rodrigo et al., 2007), psychopathy (Craig et al., 2009), depression (Gutman et al., 2009) and autism (Barnea-Goraly et al., 2004). Fiber tractography is now also more frequently used in schizophrenia research.

This thesis will investigate how DTI has helped knowledge about white matter structure in schizophrenia forward. First we will look closer at the results of conventional magnetic resonance imaging (MRI) research in schizophrenia and how these results warrant more investigation of the structural integrity of white matter pathways. Next we will describe the techniques used in DTI and how this method can help to better explore the etiology of schizophrenia. Then we will discuss the research results of studies using VBM analysis in schizophrenia and studies using tract-based analysis in schizophrenia. We will finish with an overview of both methods, how the results overlap and differ, and what possible reasons there are for the different study results.

Schizophrenia Research

Background

Schizophrenia leads to a disordered perception of reality in patients. It is characterized by so-called positive and negative symptoms. Positive symptoms of schizophrenia exist of delusions, hallucinations and thought disorder. The negative symptoms consist of flat affect, reduced speech (alogia), reduced ability to experience happiness (anhedonia) and a lack of motivation (avolition). Symptoms usually start occurring around young adulthood and often last a lifetime. Both genetics and environment have been shown to influence the development of symptoms. The lifetime prevalence is around 4 out of 1000 (Bhugra, 2005).

Schizophrenia greatly influences the life of the patients; it has high comorbidity with other disorders like substance abuse, depression and anxiety disorders. It furthermore reduces the average lifespan with 10 years and can lead to unemployment, poverty and homelessness (Brown, Barraclough & Inskip, 2000). The negative symptoms are rated as the biggest source of disability.

Magnetic Resonance Imaging

Initial interest in schizophrenia in the early 20th century research got stuck on conflicting and null findings. This changed in 1976 when Johnstone discovered clear lateral ventricular enlargements using computerized tomography (CT) (Johnstone et al., 1976). This sparked renewed interest in the field and magnetic resonance imaging (MRI) techniques were specifically equipped to research local brain size abnormalities. Now there is a great database of MRI studies researching schizophrenia.

When combining the results of MRI studies they show the following findings; medial temporal lobe involvement, superior temporal gyrus involvement, inferior parietal lobe and subcortical brain involvement, specifically of the cerebellum, basal ganglia, corpus callosum and thalamus (Shenton et al., 2001). Also focal gray matter reductions have been reported in the amygdala, hippocampus, thalamus, frontal and temporal cortex (Hulshoff Pol et al., 2001; Wright et al., 2000). The most consistent locations that were found in imaging research are the left superior temporal gyrus and the left medial temporal lobe (Honea et al., 2005). In addition lateral ventricular enlargement is consistently found (Figure 1).

White matter changes were reported less often compared to gray matter changes, but deficits were found in a meta-analysis of Di, Chan and Gong (2009). They reported clusters of reduced white matter in the frontal lobe and the bilateral internal capsule. They also reported on deep temporal white matter changes. This is in accordance with research by Sigmundsson et al. (2001), they found changes in the left temporal lobe extending into the left frontal lobe.

Longitudinal studies have shown that there are progressive changes in specific brain areas like the frontal lobes and the left amygdala (Shenton et al., 2001; Hulshof Pol et al., 2001). This however does not take away that schizophrenia is

most likely a neurodevelopmental disorder (Shenton et al., 2001; Lewis & Levitt, 2002).

It seems that over 30 years of brain imaging in schizophrenia has foremost showed us that the disorder is not limited to a single brain region (Figure 2). Honea and colleagues (2005) show in their review that as many as 50 different brain regions are being reported. This has lead to the important conclusion that the disorder is most likely caused by a network of brain areas.

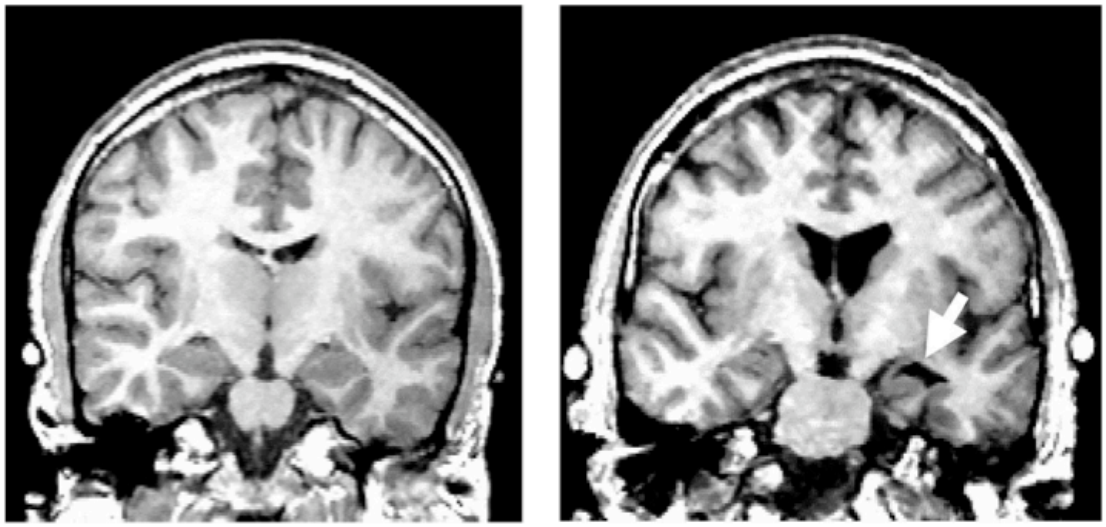

Figure 1. Coronal slice of a control (left panel) and a schizophrenic (right panel). Note the increased CSF in the left temporal horn (radiological view, i.e left=right), which surrounds the amygdala (see white arrow), and tissue reduction in the left superior temporal gyrus. The lateral ventricles are also enlarged in the patient image as can be seen by the black CSF regions in the center of the image (Shenton et al., 1992).

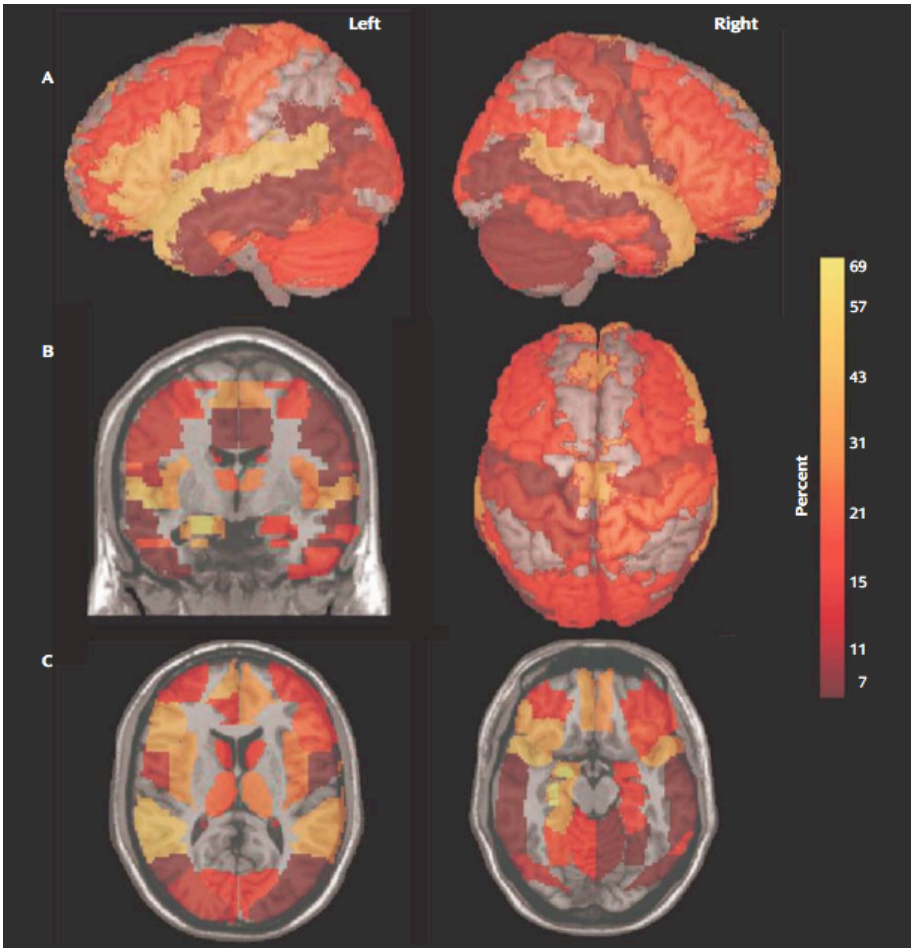

Figure 2. Brain regions in which significant volume deficits in patients with schizophrenia were reported in voxel-based morphometry MRI studies(n=15), by percentage of studies reporting the deficit (Honea et al., 2005)

Other research

Methods other than imaging have been used to investigate the etiology of schizophrenia as pointed out in the introduction. There are multiple neuroscientific disciplines researching schizophrenia, like electron microscopy, postmortem gene expression, animal models and gene association (Voineskos, 2009).

One of those studies was a post-mortem electron microscopy study (Uranova et al., 2001) investigating brain pathology in schizophrenia. This study reported signs of apoptosis and necrosis of oligodendroglial cells in the prefrontal area and caudate nucleus. A study by Budel and colleagues (2008) linked the Nogo-66 receptor gene to schizophrenia. This gene encodes an axonal protein which organizes myelin inhibition of axonal sprouting.

When the results of these and many other studies are taken together it shows dysregulation of myelin-associated gene expression, reduced oligodendroctye numbers and abnormalities of the myelin sheaths (Haroutunian & Davis, 2007). The reduced functionality of oligodendrocytes, which form the myelin sheath, can ultimately lead to reduced speed of conduction of neuronal signaling. When speed of signalling is disrupted the effect is reduced communication between brain areas.

Diffusion Tensor Imaging

The diffusion tensor

The goal of diffusion tensor imaging is to measure the diffusion profile of water in the brain to obtain information on the tissue's microstructure. This is done using a conventional MRI scanner. A series of scans is made with different diffusion gradient directions. If water particles diffuse during a scan in the direction of the diffusion gradient then the MR signal from these water particles attenuates. This reduction in signal strength is proportional to the level of diffusion. When this is done in 6 directions and up it is possible to calculate the direction of the diffusion.

Besides the direction of water diffusion you can also measure the magnitude of the diffusion, when these two properties are combined a so-called tensor can be calculated which is often represented using an ellipsoid. Water in gray matter diffuses in all directions equally, thus having ellipsoids that are more ball shaped reflecting isotropic diffusion. While water in and around white matter tracks can only diffuse in the same direction as the fibers, parallel to the track, these ellipsoids are more cigar-shaped (Figure 3) reflecting anisotropic diffusion.

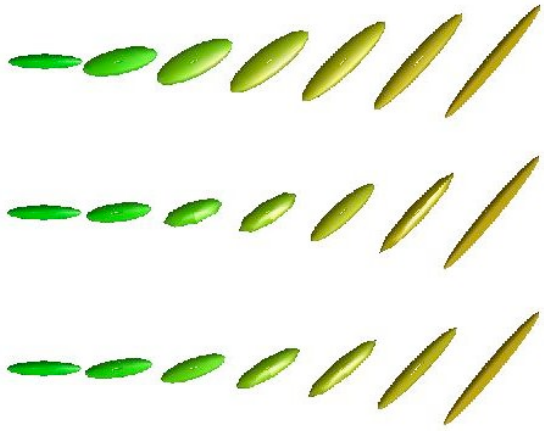

Figure 3. Ellipsoids with varying degrees of isotropy, magnitude and direction

Tensor values allow for calculation of scalars to describe the anisotropy of the diffusion. The one most frequently used is Fractional Anisotropy (FA), which is the fraction of the tensor magnitude that can be ascribed to the anisotropic diffusion (Basser et al., 1995). Values range from 0 to 1, with 0 meaning perfect isotropy and 1 indicating ideal linear diffusion.

Fiber direction on 2D images is often visualized using color encoded fiber orientation maps, where left-right is shown in red, anterior-posterior in green and superior-inferior in blue. An example with the fiber path names is shown in Figure 4.

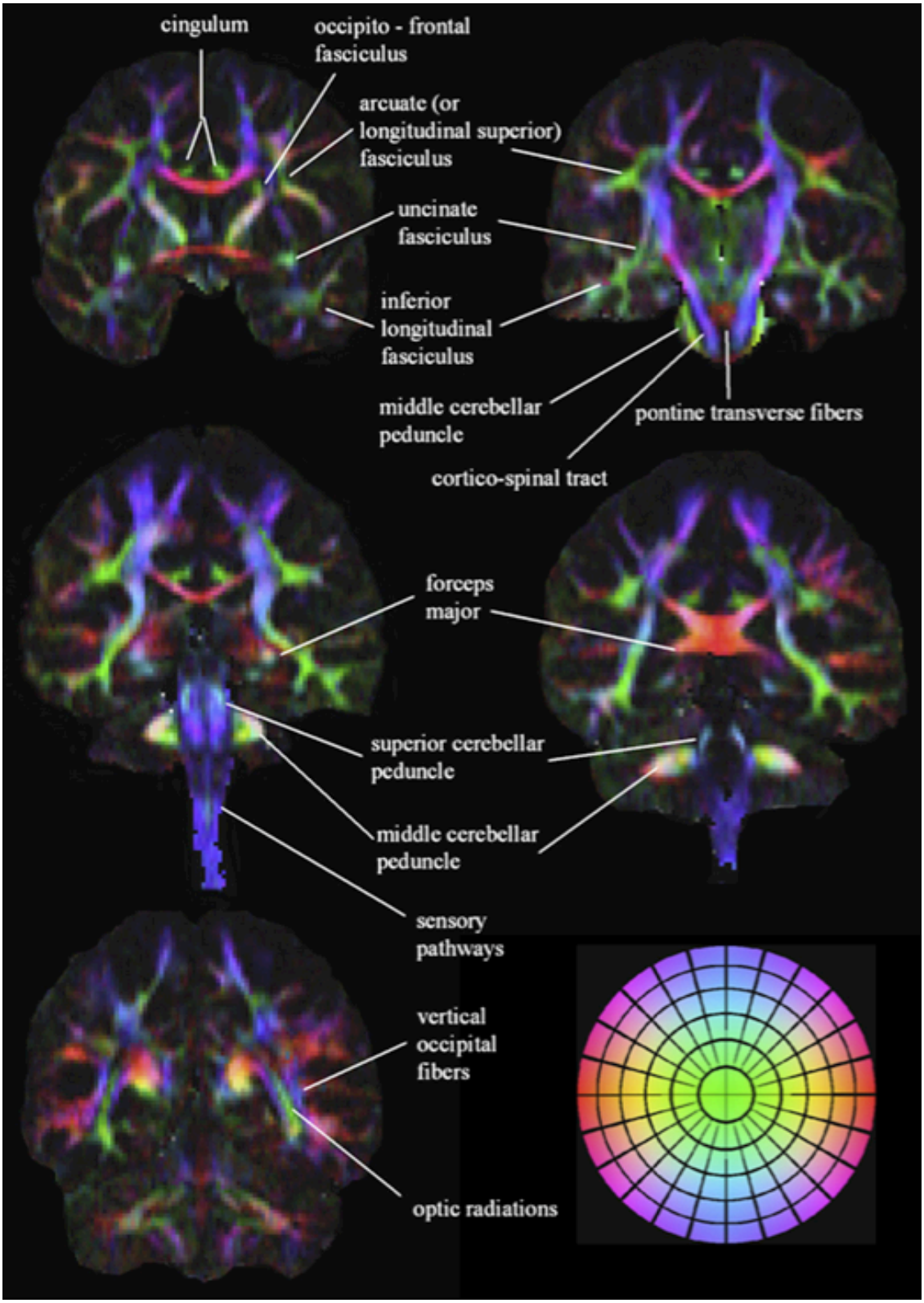

Figure 4. Color coded fiber orientation maps, color wheel visualizes how direction corresponds to color (Pajevic and Pierpaoli, 1999).

Voxel Based Morphometry

When diffusion images are analyzed using voxel based morphometry (VBM) statistics are conducted on a voxel-by-voxel basis. The diffusion images of each subject are registered into a standard space in which voxelwise statistics are carried out. This method allows for whole brain comparison between populations and can therefore be used in more exploratory setups.

A problem with this method is that it relies on normalization across subjects to allow for cross group comparison. Nonlinear registration will influence the original data and alignment inaccuracies may introduce errors into the data, two problems that are hard to solve. Furthermore to compensate for imperfect spatial normalization images have to be smoothed with a Gaussian filter, the degree of smoothing can influence the results further (Concha, Gross & Beaulieu ,2005; Jones et al., 2005; Assaf & Pasternak, 2008).

Tract-based Analysis

Tractography is a method to track fibers. Tract-based analysis uses tractography to show subtle differences between groups of subjects. Broadly speaking there are two ways of tractography, deterministic and probabilistic.

Deterministic tractography

Diffusion tensors can be visualized in 3D tensor fields as shown in Figure 5. This tensor field can be used to calculate line propagation; this method is called deterministic tractography. A seed point is chosen from which the maximal diffusion direction of each tensor will be followed. Thus revealing the macroscopic structure of white matter fiber pathways, like the uncinate fasciculus as in Figure 6.

Fiber propagation ends when anisotropy drops below pre-specified FA levels, often around FA values of 0.2, to stop propagation in gray matter or ambiguous areas. Propagation also ends when the change of angle is larger than the pre-set threshold; this is to avoid unfeasible turns and to stop tracks running back into itself (Mori & van Zijl, 2002; Jones, 2008).

A problem of this method is that as the fiber tracking propagates along the tensors errors accumulate. A reason for this is that with each step a choice has to be made about what neighboring tensor the fiber tract will follow. A solution is to use a multiple region of interest (ROI) approach. This means that more than one seed area is used to do the fiber tracking (Mori & van Zijl, 2002).

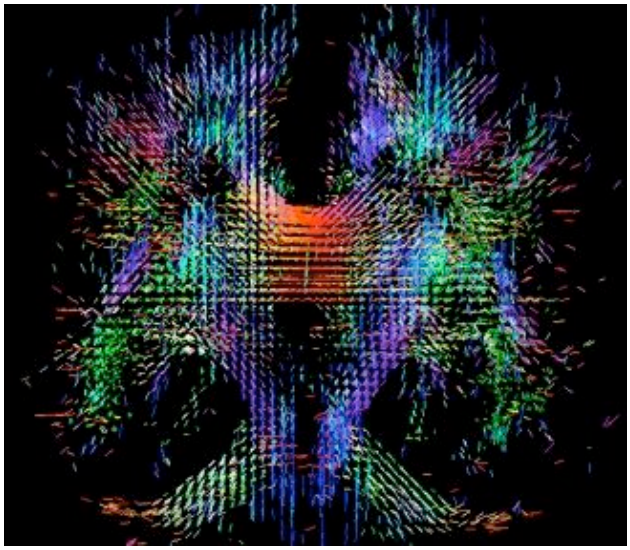

Figure 5. Field of color-coded diffusion tensor ellipsoids

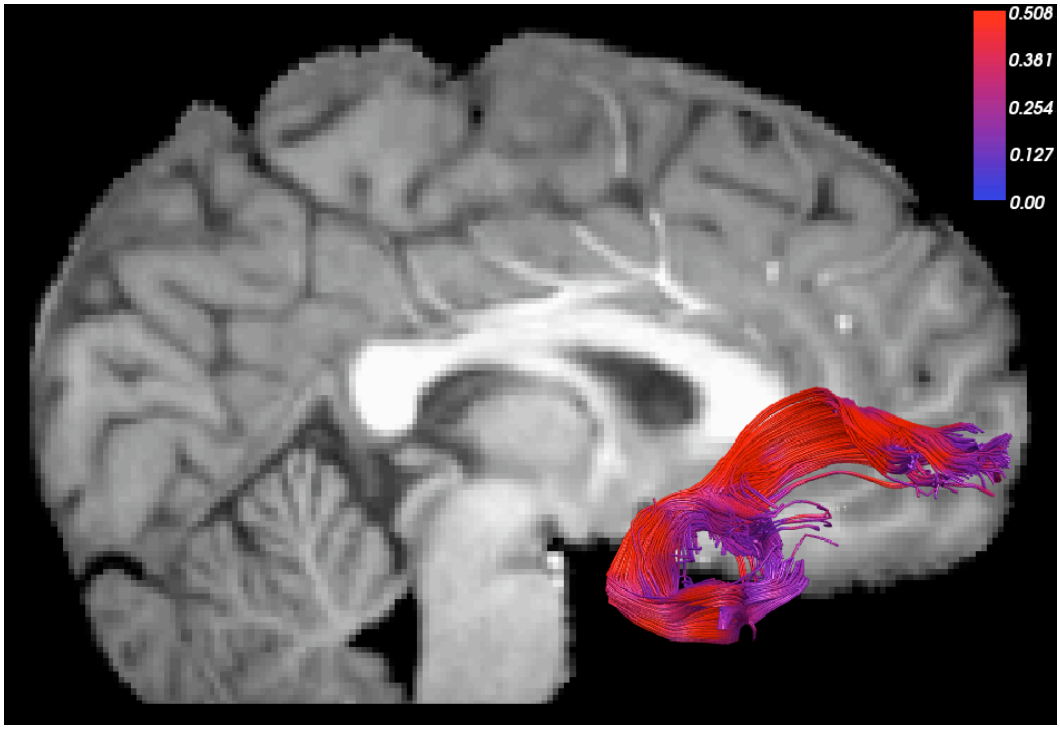

Figure 6. 3D view of the right UF, red is higher FA, blue is lower FA

Probabilistic tractography

Another algorithm for tractography is probabilistic fiber tracking. This method gives the probability of two ROI's being connected or the probability of fiber track existence between subjects (see Figure 7). In this method a large number of pathways are calculated from one seed point, and the end result shows for each voxel the probability of connectivity to the seed point (Behrens et al., 2003).

For probabilistic tractography there is no cut off point associated with FA value, though there is a cut off for angular deviation, tracking can also stop when it reaches areas it visited before.

The disadvantages of probabilistic algorithms are similar to the problems associated with deterministic tractography. Tracking errors, especially when caused by systematic data errors, can produce highly likely and reproducible fiber tracts. These tracts are erroneous, and have no correspondence to actual anatomy.

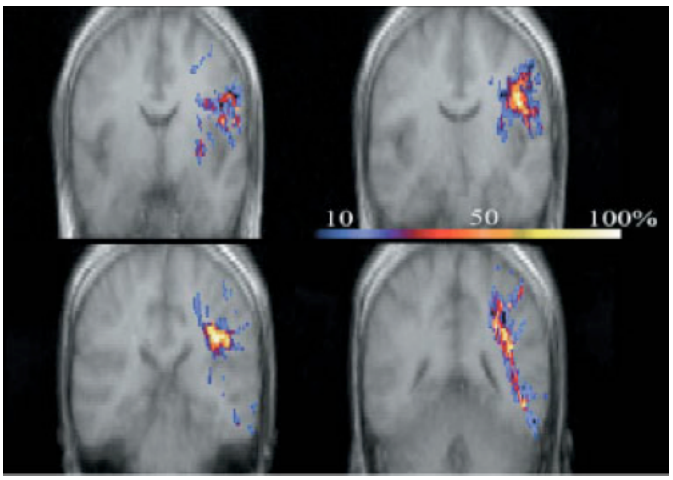

Figure 7. Probability tractography of the superior longitudinal fascicules in 10 subjects (Mori et al., 2002)

Schizophrenia and VBM

When researchers started using DTI to investigate schizophrenia they first used VBM method. Kubicki et al. (2007) and Kanaan et al. (2005) both wrote reviews of the VBM results between 1998 and 2004. We will start with a short recap of the results found in those reviews.

A total of 19 studies were conducted using DTI to investigate white matter changes in schizophrenia. VBM showed decreased FA in the prefrontal and temporal lobes, and in the fiber tracts connecting these areas. The connecting fiber bundles consisted of the uncinate fasciculus (UF), cingulum bundle and the arcuate fasciculus (AF). Two studies found an asymmetry associated with the corpus callosum (CC). Furthermore prefrontal white matter anisotropy seemed to be correlated with negative symptoms. These symptoms are rated as most disabling.

The first studies conducted showed overall DTI abnormalities, while 5 newer studies did not find any significant differences between patients and controls. Kubicki et al. (2007) and Kanaan et al. (2005) ascribe these inconsistent results to unstandardized imaging and analyzing methods. In addition small sample size, low signal to noise ratio, bad scanner gradient performance, partial volume effects due to low image resolution, methods of registration and anisotropic voxels will all reduce statistical power, which reduces the chance to find consistent results.

Another important result was that medication seemed to be related to left frontal and middle cerebellar peduncle white matter anisotropy. These results indicate the importance to report on medication usage and to include it as a covariate in the statistical analysis.

In addition to the studies discussed in the recap, this thesis looked at 8 more recent studies conducted using VBM in DTI (**Error! Reference source not found.**). Online searches were conducted using Google Scholar. Search terms included; schizophrenia, DTI and VBM.

Studies show improved image acquisition over the years, half of the studies now used 3 Tesla scanners, where 1.5 Tesla used to be the norm. The number of diffusion-weighted directions has increased, to a respectable 51 directions in one instance. Overall image resolution has increased with in one case slices of 1.13 mm thick. Unfortunately most studies still do not have isotropic voxels, and there were two cases with slice gaps. Isotropic voxels and no slice gapping are important ways to improve image quality and accurate tensor representation.

Researchers still have not agreed on a standard smoothing kernel. Within studies the full-width at half-maximum (FWHM) varied between 0 and 12 mm, a large variation as the study results are greatly influenced by the chosen size.

Most studies (n=6) used patient groups with a mean age around 40, and disorder duration of around 15 years. One study looked at adolescent schizophrenia and one study investigated first episode psychosis. All patients used antipsychotic medication.

Results of the new studies are in agreement with the studies of the two reviews. Four out of 8 studies showed white matter changes in the frontal lobe (Buchsbaum et al., 2006; Mori et al., 2007; Miyata et al., 2009; Pomarol-Clotet et al.,

2010), two showed reduces FA in temporal lobe (Mori et al., 2007; Miyata et al., 2009), and two studies found abnormalities in the UF (Mori et al., 2007; Sussmann et al., 2009). In addition reduced hemispheric asymmetry was observed in schizophrenia patients, while this asymmetry is normally observed in healthy subjects (Park et al., 2004).

Abnormalities were already observed in first episode patients, where reduced white matter integrity in the right inferior longitudinal fasciculus (ILF) was found (Chan et al., 2010). In addition child and adolescent patients (mean age 15 years) showed abnormalities in the left posterior hippocampus, an important area for encoding and retrieving of sensory information (White et al., 2007).

Schizophrenia and Tractography

DTI research in schizophrenia was focused on VBM for a long time period, only recently did researchers start to use fiber tractography to research schizophrenia. A search of researchers using this method produced 12 studies (**Error! Reference source not found.**). Search criteria included: schizophrenia, DTI and tractography. Six studies used chronic schizophrenia patients, 2 studies used first episode psychosis patients and 1 study used both, the other studies did not define the specific disease of their patients beyond schizophrenia as defined by DSM.

Regions of interest that were used in the studies included corpus callosum (CC), cingulum, uncinate fasciculus (UF), superior longitudinal fasciculus (SLF), inferior frontal-orbital fasciculus (IFOF), anterior thalamic radiation (ATR), fornix and arcuate fasciculus (AF).

Increased quality of image acquisition protocol also occurred in the tractography studies, only 4 studies used as little as 6 diffusion directions, all other studies used between 12 and 64 directions. Only one 3 Tesla scanner was used, though in diffusion imaging increased magnetic field does not necessarily improve image quality. Increased magnetic field also increases the image distortion (Alexander et al., 2006). Average voxel size in these studies varied around 2.5 mm. Slice gapping now only occurs in 3 out of 12 studies.

The majority of studies (n=9) used patient groups with a mean age around 35 years. Three studies investigated first episode psychosis. And one study compared older chronic patients to patients of average age. A majority of patients used antipsychotic medication.

The results of the 12 studies reviewed here show similar inconsistencies as found in the VBM studies. Three studies found reduced FA in the uncinate fasciculus while 3 other studies did not. One study showed that there was an altered distribution of FA values in the UF tract. It showed a skewed distribution with a reduced number of high FA values. While the mean FA did not differ between patients and control subjects. A possible explanation for this result could be reduction in deep internal track integrity (Price et al., 2008).

The effect of aging and medication on white matter in schizophrenia patients still remains illusive. Two studies indicated no effect of aging (McIntosh et al., 2008; Voineskos et al., 2010), and two find no effect of illness duration or medication on white matter structure (McIntosh et al., 2008; Rosenberger et al., 2008). While one found age related decline of cingulum and UF, but not IFOF (Rosenberger et al., 2008). The UF effect was replicated for the left side in one study (Voineskos et al., 2010), and was shown to increase with age (Mandl et al., 2008). This UF effect was not found in 3 other studies (Jones et al., 2006; Nestor et al., 2008; Phillips et al., 2009)

One study found modest wide spread FA reductions in chronic patients but not in first episode patients (Friedman et al., 2008). One study even found reduced FA in left SLF in younger patients but not in older patients, though this study had a fairly low n of 14 (Jones et al., 2006).

One result that seems consistent in schizophrenia research is abnormality in inter-hemispheric connectivity. Tractography studies revealed at least three studies with reduced FA in the corpus callosum in schizophrenia patients (Kanaan et al., 2006; Price et al., 2007; Kubicki et al., 2008).

Discussion

This thesis set out to explore the current development of white matter connectivity research in schizophrenia. Investigation of the etiology of schizophrenia started with a multitude of MRI studies. None could give a definitive answer on the etiology of the disorder; the only results that showed up consistently were the clearly increased lateral ventricles and a slightly decreased gross brain volume.

Research continued with post-mortem, gene and electron microscopy studies, of which many indicated that the origin of the disorder could possibly lie in a disrupted communication between brain areas stemming from reduced oligodendrocyte numbers and abnormalities in myelin sheaths.

As imaging methods progressed possibilities arose to further investigate the disrupted communication hypothesis of schizophrenia. Diffusion tensor imaging was especially suited for this issue. In this thesis a total of 40 studies were discussed that used DTI to investigate schizophrenia.

Between all studies a total of 8 fiber tracks were connected to the disorder, the tracks included the UF, CC, cingulum, AF, ATR, ILF, IFOF and fornix. The UF and CC showed overall the most robust results. In addition decreased FA in the prefrontal and temporal lobes was consistently shown in schizophrenia.

While the uncinate fasciculus showed significant abnormalities in 7 studies, there were 3 studies that looked at that specific region and did not find any differences in the disorder. Although one might consider this a clear indication that the UF plays a role in the etiology of schizophrenia the review of Kanaan et al (2005) did not consider the UF an important fiber track in this disorder.

A similar issue arose with the corpus callosum. The review of Kanaan et al. (2005) stated; "(…) the balance is against a difference in the corpus callosum.". After reviewing the new studies in this thesis, which showed 4 studies in favor of an abnormality in the corpus callosum in schizophrenia and none against it, it seems this statement has to be refuted.

Although the review of Kubicki et al. (2007) indicated that medication influences white matter, these results were not replicated in the tractography studies. Two studies indicated no effect of medication.

Voxel based morphometry and fiber tractography are two methods using a fairly different approach. In VBM the whole brain is investigated, but the method relies heavily on effective registration between subjects. When regions of abnormal FA values do not map onto each other correctly this will greatly reduce the chance to find significant results. Only two of the here reviewed studies used track based spatial statistics (TBSS) to guide the alignment. Which is a good method to increase the reliability of registration (Smith et al., 2006).

In tract-based analysis specific a priori regions of interest or specific tracks are selected to be compared. Theoretically this method should help the hypothesis testing and accepting or refuting process. Unfortunately practice did not show this, when 3 studies showed an UF change and 3 studies did not.

It seems that it is impossible to provide one clear reason for the contrasting study results. Possible issues to consider are that with duration of the disorder the

differences between groups seem to increase; as chronic patients show more widespread brain abnormalities compared to first episode schizophrenics (Friedman et al., 2008), adolescents with schizophrenia only show abnormalities in their left posterior hippocampus (White et al., 2007), and first episode patients do show abnormal distribution of FA in the UF, but no significant FA differences of the entire tract (Price et al., 2008). Another reasons for contradicting research results could originate in small sample sizes. Jones et al. (2006) and Price at al. (2008) both have patient groups of respectively 14 and 19 subjects.

Deterministic versus probabilistic fiber tracking do not seem to make the difference in study results. Since both a probabilistic and a deterministic study find no effect in the UF (Price et al., 2008; Nestor et al., 2008), while another probabilistic study did find an effect in the UF (McIntosh et al., 2008). Voxel size does not seem to influence the study results, both small and large voxels show positive and negative results in the UF. The same is true for isotropic versus non-isotropic voxels.

Future studies using DTI should try to use imaging protocols with isotropic, high-resolution voxels, more than 6 gradient directions and no slice gapping. In addition it might be effective to include cut-off values for FA and angle values during fiber tracking. When using VBM methods, TBSS can be a useful way to optimize subject registration (Smith et al., 2006), as well as T-SPOON (Lee et al., 2009). All these methods should ensure to increase power and reliability.

Future research might be able to use magnetization transfer ratio (MTR) imaging, a method that is able to image the density of macromolecules, like myelin cells. Abnormalities in the temporal regions in schizophrenia have been shown in research by Foong et al. (2000) and Mandl et al. (2008).

In conclusion it can be said that, although DTI is a new and promising method, the results acquired still show important inconsistencies. Even after at least 40 DTI studies a clear answer regarding the etiology of schizophrenia is still far away.

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