Diffusion tensor imaging in the early phase of schizophrenia

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Clinical features of schizophrenia

Schizophrenia is the most severe disorder among adult psychiatric disorders, with a heterogeneous spectrum of disabling symptoms and signs, with a chronic course in the majority of the patients and with an overall unfavorable impact on quality of life. Schizophrenia is characterized by psychosis, with symptoms such as hallucinations, delusions and disorganized or bizarre thought, speech or behavior. Further characteristic symptoms and signs are negative symptoms that can be described as losses of normal functions (e.g. apathy, flat affect, lack of initiative, social withdrawal). Other features include depression, anxiety and cognitive impairments (executive functions, memory, psychomotor speed, attention, and social cognition). The onset of the illness is defined by the first psychosis and occurs generally in adolescence or early adulthood. Most often the first psychosis is preceded by a prodromal period characterized by affective and mood symptoms, negative symptoms, and a decline in social functioning. Although remission and recovery does occur in a minority of patients, the course is for the large majority of patients chronic, with psychotic relapses or even chronic psychosis and most often persistent negative symptoms. It is a debilitating disease and a relative minority of patients attain paid work, independent living or marriage. Many patients attempt suicide and about 5% of individuals with schizophrenia commit suicide. The prevalence in the general population is estimated at 2-10 patients per 1000 people. Despite a great effort in research there is no curative treatment and the available symptomatic treatments are mod-
estly effective. Medication is available for psychotic symptoms, but their antipsychotic effectiveness varies across patients (Tandon et al. 2008a, 2009).

Hypotheses on the causes of schizophrenia

In light of its clinical heterogeneity, schizophrenia may not be a unitary disorder but involve different disorders with different pathophysiology processes (Tandon et al. 2008b, Keshavan et al. 2008). However, attempts to demarcate homogeneous subtypes of schizophrenia have been inconclusive until now. Studies have revealed etiological and clinical risk factors for schizophrenia, and these have formed the basis for pathophysiological hypotheses. These risk factors and clinical characteristics include a strong heritability and genetic liability of schizophrenia from family, twin and adoption studies, several perinatal and pubertal environmental risk factors (e.g. obstetric complications, adolescent cannabis use), the onset of schizophrenia in adolescence or early adulthood, the neurochemical actions of antipsychotic medication (in particular dopamine antagonism), and the pharmacological properties of street drugs which mimic some features of schizophrenia (e.g. the glutamate antagonist ketamine).

In answer of when the brain abnormalities in schizophrenia occur, a prevailing hypothesis is the neurodevelopmental model. In this model genetic susceptibility factors interacting with environmental risk factors (e.g. prenatal and obstetric complications) would compromise brain development already in utero. This early developmental derailment then leads to an impaired development of functionally higher-order brain structures, in particular the temporal and frontal regions. These abnormalities can explain the premorbid precursors of schizophrenia. However, they fail to explain the absence of signs and symptoms before adolescence. In adolescence genetic factors may interact with environmental risk factors again, leading to late developmental structural brain changes (Keshavan et al. 1999). This process eventually culminates in the first psychotic episode. At least some structural abnormalities are present at onset, and there is evidence for further progressive change in the brain after onset of the first psychotic episode, probably based on neurotoxic events (Wyatt, 1991); more research is needed to further clarify when precisely which abnormalities occur.

Early and late developmental models have focused on what the patho-
logical substrate in the brain is. For instance, the substrate may be dysfunctional neurotransmission in the dopamine or glutamate systems, loss of brain gray matter as a result from excessive synaptic pruning in adolescence (Keshavan 1999), decreased levels of (poly)unsaturated fatty acid levels in cell membranes (Peet 2006). While most studies focused on gray matter, and indeed many gray matter abnormalities have been identified in schizophrenia, there has been increasing interest for white matter in schizophrenia, which is further discussed below.

Regardless of the pathological substrate, an important question focuses on the location of the brain abnormalities: is there a single brain structure implicated in schizophrenia, or are there a few distinct brain structures, or are widespread abnormalities (perhaps with varying regional penetration depending on the genetic and/or environmental risk factors) involved in individual patients? Another model proposes a lack of normal cerebral asymmetry and differentiation (Crow et al. 1989), while a more recent model suggests that disconnection in the network between brain areas is central to schizophrenia (Stephan et al. 2009).

In short, the question will be which pathophysiological process can be mapped on to which patients.

Dysconnection, white matter and schizophrenia

Schizophrenia is a heterogeneous complex of psychiatric symptoms and disturbances of cognitive, social and behavioral functions. As normal brain functions are served by macro-structural circuits of cortical and subcortical areas, disturbed communicating networks (‘dysconnectivity’) within and between brain regions may be the core pathology of schizophrenia. White matter alterations may form the basis for this dysconnectivity, as brain white matter consists of the axonal projections to other neurons and functional brain areas and is therefore key to neural communication. White matter is coloured white by the lipid-protein myelin, which is formed by oligodendrocytes and forms a sheath around the axons to increase their electrical conductivity. An important clue for a role of white matter in schizophrenia comes from metachromatic leukodystrophy, an illness characterized by demyelination and high rates of psychosis when onset occurs in adolescence (Hyde et al. 1992). The normal trajectory of white matter development includes formation of axonal projections prenatally, axonal ‘pruning’ postnatally (LaMantia and
Rakic 1994, Misgeld 2005) and myelination. Myelination is initiated prenatally and completed for most tracts within the first year after birth but continues during childhood, adolescence and adulthood (Benes 1994, Lenroot and Giedd 2006) and has a region-specific course where prefrontal regions myelinate the last (Lenroot and Giedd 2006). This development is paralleled by a gradual decrease in gray matter from early childhood, most likely reflecting synaptic ‘pruning’ (Keshavan 1999).

There is accumulating evidence as to what the causes of white matter pathology may be in schizophrenia. Several lines of evidence point to myelin dysfunction (Davis et al. 2003), reduced oligodendrocyte number or integrity (Segal et al. 2007), or possibly hyperglutamatergic states (Matute et al. 1999, Chang et al. 2007) particularly during exacerbation of psychosis (Christensen et al. 2004). Multiple studies support a genetic basis of these oligodendrocyte-myelin abnormalities (Tkachev et al. 2003, Konrad and Winterer 2008). However it is possible that these alterations are secondary to synaptic dysfunction, a secondary effect of phenomena associated with severe mental illness (e.g. substance abuse) (Konrad and Winterer 2008), while an effect of antipsychotic medication cannot be excluded either (Segal et al. 2007). Neurodevelopmental theories have suggested demyelination during adolescence and adulthood to occur in schizophrenia (Hyde et al. 1992), an arrest in the normal process of myelination during brain development in adolescence (‘hypomyelination’) (Bartzokis 2002), or the formation of dysplastic axonal projections in utero (Bullmore 1997).

Theories on which specific network in the brain is implicated in schizophrenia include aberrant inter-hemispheric connectivity through the corpus callosum (Crow et al. 2007), cortico-thalamo-cerebellar circuitry dysfunction (Andreasen 1999), and frontotemporal dysconnectivity (Friston and Frith 1995). Of special interest is the review by Innocenti and colleagues (2003), who concluded that although most evidence favors hypoconnectivity in schizophrenia, in some patients there may be hyperconnectivity between brain regions. Advances in available MRI techniques have led to further studies into which white matter tracts are specifically compromised in schizophrenia.

Diffusion tensor imaging in schizophrenia

Magnetic resonance imaging (MRI) offers the opportunity to study brain structure in vivo. Results of structural MRI studies have provided sup-
port for white matter abnormalities in schizophrenia (e.g. Sigmundsson et al. 2001, Spalletta et al. 2003, Arnone et al. 2008). These MRI studies indicate macro-structural volume reductions, but are limited in determining the precise location of the white matter abnormalities, that is, which matter tracts are affected. Diffusion tensor imaging (DTI) makes it possible to assess microstructural abnormalities of brain white matter, and the probable trajectories of fiber tracts can be calculated and visualized, allowing tract-specific measurements. Structures too small to be measured through conventional MRI can be imaged indirectly through their interaction with free water molecules. Free water diffuses throughout the brain in three dimensions. Locally, the diffusion is affected by the microstructure of the axonal fiber bundles. Water diffusion is restricted in the directions perpendicular to axons, as the water molecules bump into the elongated bundles. DTI uses a specifically designed diffusion-sensitive MR imaging sequence to determine the distribution of the three-dimensional diffusion directions at each point in the brain (the points composing the DTI image are called voxels and their size depends on the acquired resolution). The diffusion tensor consists of six values, describing the diffusion along the three main axes as well as the diffusion in the X-Y, Y-Z and Z-X planes. The tensor can be thought of as an ellipsoidal shape that matches the distribution that water molecules placed at its center will form after diffusing. The longest axis of the ellipsoid corresponds to the direction in which the diffusion is the strongest, which is called axial diffusion. The size of the ellipsoid along the other two axes corresponds to the diffusion perpendicular to the main diffusion direction, and is called radial diffusion. In this way, the diffusion tensor provides a three-dimensional direction in which the diffusion is the greatest and thereby, the most-likely axonal fibre orientation at each voxel. The ratio between the amount of diffusion along the axonal fibre and the amount of diffusion perpendicular to it is called diffusion anisotropy. If the anisotropy is high, then most of the diffusion occurs in the axonal direction, indicating a high level of orientation in the underlying structure. Different metrics can be used to define the amount of anisotropy. A DTI index called fractional anisotropy (FA) is thought to be a marker of the structural integrity of fibers (Beaulieu 2002), the degree of myelination (Gulani et al. 2001), coherence of fiber tracts (Ono et al. 1995), and fiber diameter and packing density (Beaulieu 2002); changes in this index could indicate changes in any of these characteristics or a combination of them. Reduced FA is found in several neurological white matter diseases (Horsfield et al. 2002).

DTI studies in chronic schizophrenia indicate microstructural abnor-
malities of the corpus callosum, anterior limbs of the internal capsule, superior longitudinal fasciculus and cingulum, but conflicting results exist regarding which tracts are affected (Konrad and Winterer 2008). There may be widespread white matter abnormalities with variability in the affected fiber tracts depending on the different causative factors in individual patients, in contrast with specific tracts in distinct networks being affected. Regarding this, an interesting study by White and colleagues (2009) showed that there were more and larger non-spatially overlapping ‘potholes’ of lower FA in adolescent schizophrenia patients than in healthy adolescents. These potholes did tend to cluster in certain fiber tracts, such as the corpus callosum. Another important issue is the timing and course of DTI abnormalities in schizophrenia. In healthy individuals, there is a general increase of FA during adolescence (Schmithorst and Yuan 2010) followed by a linear decline from about age 20 years onwards (Sullivan and Pfefferbaum 2006) with a regional anterior-posterior gradient starting at the cingulum (Yoon et al. 2008). Combined volumetric MRI and DTI analyses suggest that FA decline sometimes precedes white matter volume loss and can therefore be considered a more sensitive marker of aging (Hugenschmidt et al. 2008).

The relevance of DTI abnormalities in schizophrenia is further supported by associations between DTI measures and clinical features of the illness. Negative symptoms correlated with low FA in inferior frontal white matter (Wolkin 2003), and auditory hallucinations were positively related to FA in the anterior corpus callosum, cingulum and superior longitudinal fasciculus (Hubl et al. 2004, Shergill et al. 2007, Seok et al. 2007). Neuropsychological dysfunction of (working) memory and executive functions correlated with reduced FA in the uncinate and arcuate, and cingulate fasciculi respectively (Nestor et al. 2008, Szeszko et al. 2008, Karlsgodt et al. 2008). Patients with poor outcome compared to good-outcome patients showed more pronounced FA reductions in the posterior corpus callosum and fronto-occipital fasciculus (Mitelman et al. 2007). Reduced FA in the inferior longitudinal fasciculus predicted social functioning at follow-up in ultra-high-risk subjects (Karlsgodt et al. 2009).

This thesis

In the studies involved in this thesis we employed the first-episode strategy to study the neurobiology of schizophrenia. First-episode patients of-
fer the opportunity to study schizophrenia without confounding effects of illness and pharmacotherapy chronicity. We focused on brain white matter abnormalities as measured with diffusion tensor imaging in the context of the dysconnecction 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). Post-mortem 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 postnataally and as myelination progresses OA increases significantly (Martinez 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.

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