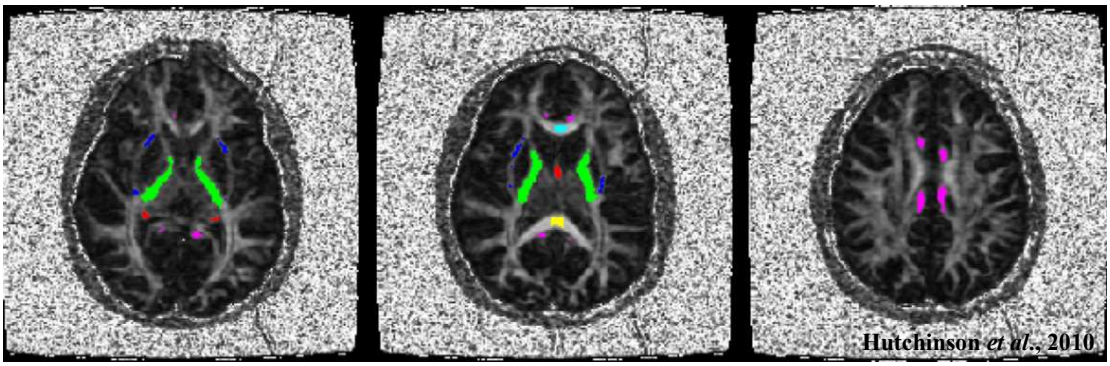
Maturation and abnormalities of white matter in children with epilepsy



Lisette Charbonnier

Acknowledgments

Suzanne M. Koudijs, MD

Kees P. Braun, MD, PhD

Abstract

Epilepsy is a disabling neurological disorder, affecting both children and adults. Up until the introduction of MRI, epilepsy has always been considered as a disease of gray matter. Consequently, white matter defects in epilepsy have received little attention. Especially the investigation of white matter in children with epilepsy is essential, as white matter maturation continuous until late adolescents and white matter damage could possibly disturb this maturation process. The aim of this thesis was to obtain a better insight into white matter maturation and disturbances of white matter in children and adolescents with partial epilepsy.

The majority of the studies discussed in this thesis reported a lack of white matter volume increase with age in children with partial epilepsy and decreased white matter volumes in adults with partial epilepsy. Furthermore in both children and adolescents decreased FA values, increased perpendicular diffusivity and increased mean diffusivity in a variety of white matter tracts, have been found. These diffusion abnormalities seem irreversible, as they persist after seizure control. The exact meaning of these diffusion disturbances are still unknown, however, myelin or axon abnormalities are being suggested.

1. Introduction

Epilepsy is a severe neurological disorder characterized by recurrent and unpredictable disruptions of normal brain function, known as epileptic seizures or fits (Fisher *et al.,* 2005). Epilepsy is diagnosed when two or more unprovoked seizures occur within one month separated by at least 24 hours (Shinnar and Pellock, 2002). The prevalence rate of active epilepsy in developed countries lies between the 4 and 10 per 1000 individuals (Sander *et al.,* 1996). In more than 60% of the cases the first epileptic seizure occurs in childhood or adolescence (Aicardi, 1994 *in* Neville, 1997). The annual incidence rates of epilepsy in developed countries ranges from 40-70 per 100000/year, with peak values in both children and adolescents, and elderly of 65 years and older (Sander *et al.,* 2003). In total, epilepsy is thought to effect 0.5-1% of all children, making it one of the most common neurological disorders in childhood (Shinnar and Pellock*.,* 2002).

Epilepsy can be classified into different syndromes based on different seizures, age of onset, abnormalities in the electroencephalogram (EEG), the presence of neurological defects, and family history (Carpay and Gijsen, 2004). Based on these characteristics, epilepsy can be divided into three syndromes, partial or focal epileptic syndromes, generalized epileptic syndromes, and epileptic syndromes which cannot be identified as partial or generalized (ILAE, 1989). In partial epilepsy, the most common epileptic syndrome in children (Berg, 1995 in Shinnar and Pellock, 2002), the seizures originate from a specific part of the brain in one of both hemispheres. However in generalized epilepsy both hemispheres are involved (Carpay and Gijsen, 2004). Based on the possible cause of epilepsy, both partial and generalized epileptic syndromes can be divided into three different categories, idiopathic, symptomatic, and cryptogenic (ILAE, 1989). In idiopathic epilepsy the cause is unknown, genetic factors are thought to be involved (Carpay and Gijsen, 2004). In symptomatic epilepsy, the epilepsy is a symptom of another disorder, whereas in cryptogenic epilepsy the seizures are presumed to be caused by another disorder which cannot be identified (Carpay and Gijsen, 2004). Especially developmental disabilities (mental retardation and/or cerebral palsy) are associated with an increased risk of acquiring epilepsy (for a review see Shinner and Pellock, 2002).

When treatment is desirable, several options are available. Depending on the syndrome, frequency of the seizures, and neurological findings, pharmacological therapies (antiepileptic drugs, AEDs), could be prescribed (Appleton and Cross, 2009). Fortunately 60-70% of the children eventually enter remission, with or without the use of AEDs (Camfield *et al.,* 1993a; Sillanpaa *et al.,* 1998). The rest of the patients continues to have seizures resulting in a poor

prognosis (Shinnar and Pellock, 2002). Ketogenic diets, vagal nerve stimulation or surgery are the only treatment options left for this group. Ketogenic diets contain high fats and low carbohydrates. These diets mimic several aspects of starvation, as the body is forced to burn fat instead of carbohydrates. The liver converts fat into fatty acid and ketone bodies. Ketone bodies function as alternative fuel for the brain, reducing the frequency of epileptic seizures in some patients. Another treatment option is a vagal nervestimulator, a device that is implanted under the skin and sends electric pulses to the left vagus nerve, which might result in seizure reduction. The last, but very effective treatment option is surgery (focal resection or disconnective hemispherectomy), when at least two different AEDs have proven to be ineffective. For example, functional hemispherectomy (i.e. removal of central portion of the cerebral hemisphere and subsequent disconnection of the anterior frontal and posterior parieto-occipital poles and corpus callosum) can be used in a highly selected group of young patients with hemispheric epilepsy and a catastrophic course (Duchowny, 2004).

In an attempt to acquire a better understanding of epileptogenesis, several studies have investigated brain abnormalities in epilepsy in children and adolescents (Lawson *et al.,* 1997, 1998; Martin *et al.,* 1999; Gaillard, 2000; Cormack *et al.,* 2005; Daley *et al.,* 2008; Herman *et al.,* 2010). The main focus of these studies was the morphology of gray matter (comprises a majority of the neurons) in epilepsy, as the origin of epileptic seizures is believed to lie within this cell layer. These studies reported abnormalities in overall cerebrum, cerebellum, frontal and temporal lobes, hippocampus, amygdala, and thalamus in children with partial epilepsy (Lawson *et al.,* 1997, 1998; Martin *et al.,* 1999; Gaillard, 2000; Cormack *et al.,* 2005; Daley *et al.,* 2008). A majority of these studies explored brain abnormalities in children suffering from partial temporal lobe epilepsy as this is the most common subtype of partial epilepsy in children (Berg, 1995 *in* Shinnar and Pellock, 2002). Furthermore, very recent studies have demonstrated abnormalities in frontal lobes, temporal lobes, thalamus and amygdala, even in children with idiopathic generalized epilepsy (Betting *et al.,* 2006; Pardoe *et al.,* 2008; Pulsipher *et al.,* 2009; Caplan *et al.,* 2009; Schreibman Cohen *et al.,* 2009).

Epilepsy has always been considered as a disease of the gray matter. Consequently, white matter defects in epilepsy have received little attention. With the development of new imaging techniques (e.g. DTI) the number of studies investigating white matter in epilepsy increases (Govindan *et al.,* 2008; Nilsson *et al.,* 2008; Herman *et al.,* 2010). White matter abnormalities are being reported and are perhaps more important than previously believed (Govindan *et al.,* 2008; Nilsson *et al.,* 2008; Herman *et al.,* 2010). Especially the investigation of white matter in children

with epilepsy is essential, as white matter maturation continuous until late adolescents and white matter damage could possibly disturb this maturation process.

To obtain a better understanding of white matter maturation and abnormalities in epilepsy, one should preferably focus on children with partial epilepsy. In idiopathic partial epilepsy, cognition is normal in most patients. In symptomatic and refractory forms of childhood partial epilepsy, however, mental delay is often reported, suggesting a more widespread disease of the brain, beyond the boundaries of the localized epileptogenic gray matter lesion. Generalized or distant disturbances in myelination, structural, or functional integrity of the brain white matter may be responsible for cognitive disturbances. These can either be caused by a more widespread underlying epileptogenic pathology (e.g. developmental malformations, or acquired vascular lesions), or may be a consequence of the frequent seizures themselves. The main objective of this literature study is to obtain a better insight into white matter maturation and disturbances of white matter in children and adolescents with partial epilepsy.

2. White matter

White matter is situated in the core of the brain. It comprises 40-50% of the adult human brain volume (Filley, 2005). White matter consist of billions of fibers (i.e. tracts) facilitating neuron communication in most often distant locations (Akers *et al.,* 2004). It predominantly contains densely packed axons wrapped in myelin.

Myelin functions as an electrical insulator, which drastically increases action potential conduction. In the central nervous system, myelination is executed by oligodendrocytes. Myelin consists of multiple layers of glial membrane made out of lipids (70%) and proteins (30%). Figure 2.1a, clearly shows these layers in a cross-section of a myelinated neuron. Along the axons, small regions (i.e gaps) are left unwrapped, these gaps are known as nodes of Ranvier (Figure 2.1b). Action potentials are only generated at these nodes, which greatly increases their conduction velocities (Purves *et al.,* 2004). Besides axons, oligodendrocytes, astrocytes, and ependymal cells, blood vessels are also present in white matter (Filley, 2005).

The major fiber tracts of the brain are known as the projection fibers, the association fibers, and the commissural fibers (Filley, 2005). The projection fibers (e.g. motor tract, part of internal capsule) connect the cerebral cortex to lower parts of the brain and spinal cord. The association fibers connect different parts of the brain within the same hemisphere (e.g.cingulum), while the commissural fibers connect the two hemispheres (e.g. corpus callosum). Figure 2.1c, shows the complexity of the major association and commissural fiber tracts. The corpus callosum is the

most prominent commissural fiber of the brain, containing approximately 200 million myelinated axons (Paus *et al*., 1999). It is essential for the integration of the activities of the right and left hemisphere (Lenroot and Giedd, 2006). These activities include memory storage and retrieval (Zaidel and Sperry, 1974 *in* Lenroot and Giedd, 2006), unification of sensory fields (Shanks *et al.,* 1975), attention and arousal (Levy, 1985 *in* Lenroot and Giedd, 2006), and language enhancement and auditory functions (Cook, 1986 *in* Lenroot and Giedd, 2006). The corpus callosum can be divided into three distinct regions, rostrum, genu, and splenium, shown in Figure 2.1d.

Up until the development of new imaging techniques (e.g. magnetic resonance imaging, MRI), gray matter has been the main focus of neuroscience (Filley, 2005). However with the introduction of MRI, a growing awareness of the importance of white matter has developed (Filley, 2005). White matter abnormalities are reported in a large variety of neurological disorders, from multiples scleroses to dementia, schizophrenia and epilepsy (Filley, 2005; Hermann *et al*., 2010).

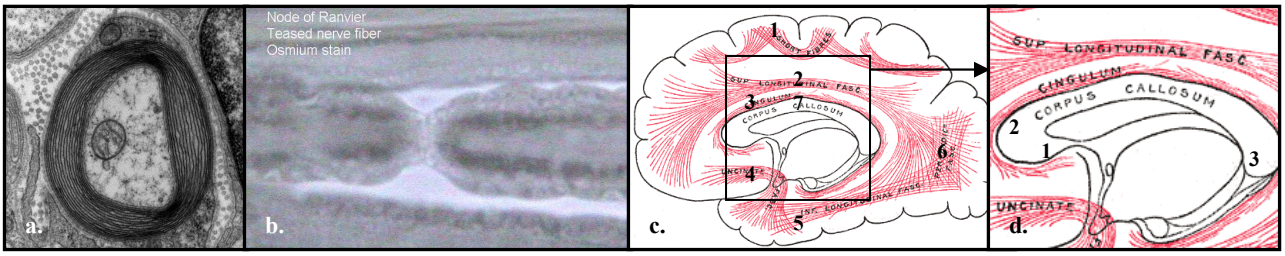


Figure 2.1 Cerebral white matter
a. Cross-section of a myelinated neuron; b. Node of Ranvier in the central nervous system; c. Major white matter tracts in the human brain, (Gray, 1918);1, short fibers; 2, superior longitudinal fasciculus; 3, cingulum; 4, uncinate fasciculus; 5, inferior longitudinal fasciculus; 6, perpendicular fasciculus; 7, corpus callosum; d. Corpus callosum; 1, rostrum ; 2, genu; 3, splenium.

3. Measuring white matter with MRI

Magnetic Resonance Imaging, is the most popular method to investigate white matter in the human brain, as it is both non-invasive and has a high spatial resolution (Hagmann *et al*., 2006). Several techniques are available to obtain white matter information with MRI. This chapter will only consider the techniques mostly used in the clinic.

3.1. Structural Magnetic Resonance Imaging (MRI)

The human body consists for 60%-80% of water. Water molecules contain hydrogen molecules with protons in their nuclei. Heat, generated by our body, energizes the protons causing the water molecules to spin, creating little magnetic fields which are randomly aligned (Figure 3.1a)

(Mackiewich., 1995). The static magnetic field (Bø) of a MRI scanner align the spinning protons, along the direction of the magnetic field (Figure 3.1b). Subsequently, a radio frequency (RF) pulse is applied, which causes the protons to tilt away from Bø. Protons, processing with the same frequency as the RF pulse, are able to absorb that energy. This causes differences in spinning movement (i.e. procession motion) frequencies. When the RF pulse is turned off, the protons return to their original orientation (i.e. equilibrium), parallel to Bø. The return to equilibrium is also known as relaxation. During this relaxation, the protons retransmit the absorbed energy, which produces a radio frequency signal. This signal is measured and processed to generate 3D MR images (Mackiewich., 1995).

The relaxation time can be measured in both longitudinal (T1) and transverse direction (T2).

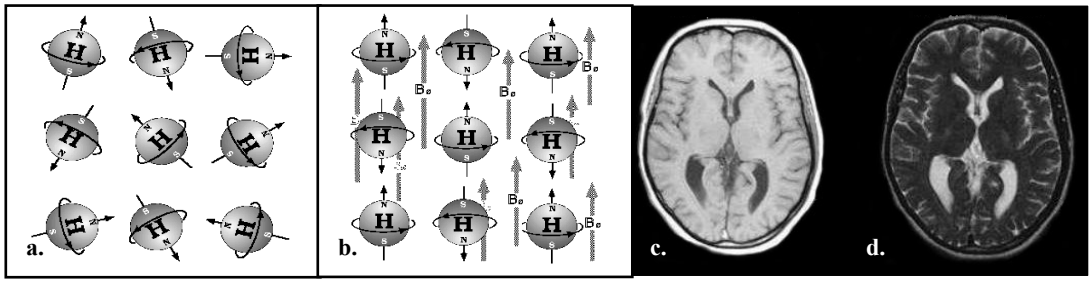


Figure 3.1. MRI T1 and T2
a: random proton movement; b: protons aligned along the direction of the magnetic field (Bø); c T1 weighted image; d T2-weighted image (Mackiewich., 1995)

T1-weighted images are obtained by measuring the time for the displaced proton to return to equilibrium (i.e. parallel with Bø). This relaxation time is dependant on the speed in which the majority of the protons in the different tissues give up their energy in the form of heat. The T2-weighted images are acquired by measuring the time in which the majority of the protons in the different tissues are dephased (Mackiewich, 1995). These different relaxation times enables the construction of T1- and T2- weighted image, shown in Figure 3.1c-d. These images give information about the macro anatomy of both gray and white matter. However, details in white matter tracts cannot be revealed.

Another technique, often used in the clinic, is called fluid attenuation inversion recovery (FLAIR). FLAIR uses a special inversion recovery sequence with long T1 to remove the effects of fluid from the obtained images. FLAIR is especially useful to detect lesions, which are normally covered by bright fluid signals in the images of the previously discussed T2 contrast (Kates *et al*., 1996).

3.2. Diffusion Weighted Magnetic Resonance Imaging (DWI)

The development of diffusion weighted magnetic resonance imaging, has provided a window into the details of white matter anatomy of the intact brain. Diffusion weighted magnetic resonance imaging (DWI) is a non-invasive technique to gain information about body tissues based on water movement (Moritani *et al.,* 2005). As previously mentioned, the majority of the human body consists of water. The protons in the nuclei of hydrogen molecules are energized by heat, generated by our body, causing the water molecules to move around randomly. This free random movement (i.e. isotropy) is influenced by the type of tissues the water molecules encounter and in which tissues the water molecules diffuse (spread out). The amount of this diffusion can be used as a measurement to obtain information about specific body tissues (e.g. the anatomy of the brain).

The first step of diffusion imaging is similar to the conventional MRI technique (Bø of an MR scanner, align the spinning protons, along its direction). Subsequently, the spinning protons (i.e. spins) are labeled by magnetic field gradients of certain duration, causing small differences in the frequency of spinning movement (precession movement) of the spins located within different tissues. At a later time, another gradient pulse is applied to measure the new location of the labeled spins (Moritani *et al.,* 2005). By means of this method information about the spread (diffusion) of the spins in a specific time-interval is obtained (Moritani *et al.,* 2005).

DWI is the simplest form of diffusion imaging, as it measures the diffusion in only one direction (Hagmann *et al.,* 2006). Figure 3.2a, shows a MR image constructed with this method (Hagmann *et al.,* 2006). Brain regions with high diffusion in the direction of the gradient (e.g. in ventricles), appear darker in the picture due to rapid decrease in signal intensity. However, areas with low diffusion show up in light colors. Although DWI provides limited information, it is an especially powerful tool to detect changes in lesions and changes caused by acute infarcts (Mosely *et al.,* 1990).

To obtain more accurate information about diffusion, the apparent diffusion coefficient (estimated diffusion coefficient) can be calculated. To acquire this information, the time and strength of the gradient pulses (i.e. weighting factor) need to be varied, so multiple diffusion weighted images can be generated (Figure 3.2 ; Boven *et al.,* 2009). As shown in Figure 3.2b, an increased weighting factor decreases the signal intensity in the pictures. The degree of signal intensity is influenced by the diffusion coefficient. In structures with high diffusion (e.g. ventricles), signal intensity decreases rapidly with weighting factor, whereas signal intensity in structures with low diffusion (e.g. white and gray matter) decreases slowly (Boven *et al.,* 2009). Subsequently the magnitude of the diffusion motion (i.e. Apparent Diffusion Coefficient, ADC)

can be calculated by fitting signal intensity decay against weighting factor (Figure3; Boven *et al.,* 2009). ADC values provide valuable and quantifiable information about the condition of the brain. Low ADC values are an indication for good organized white matter tracts, while high

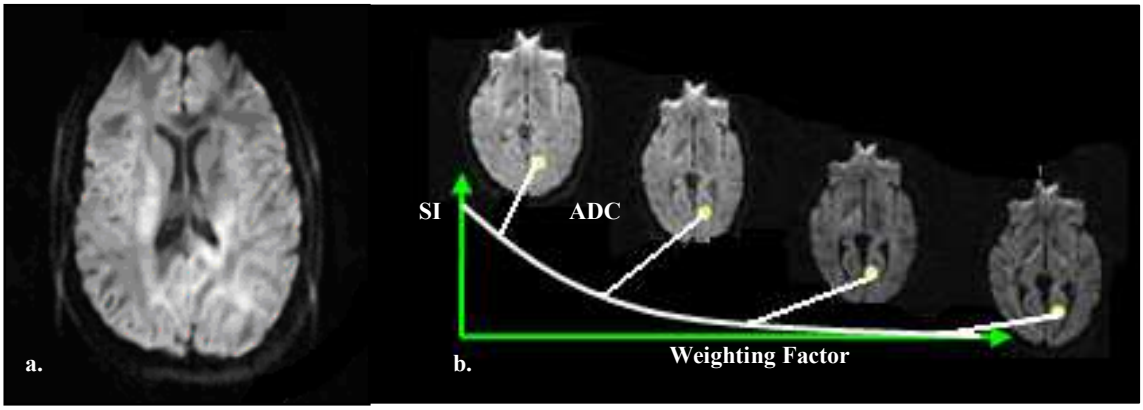


Figure 3.2 Diffusion Weighted Imaging and ADC
a. Diffusion weighted image (Hagmann *et al*., 2006); b. Apperent diffusion coefficient (ADC) graph ; SI, signal intensity (Boven *et al.,* 2009).

values indicate disorganized tracts (Boven *et al.,* 2009). The main limitation of this technique is that it is to simplistic, as it does not measure the diffusion differences in all its directions (Hagmann *et al.,* 2006).

3.3. Diffusion Tensor Imaging (DTI)

From the techniques previously discussed, DTI is the most elegant method to estimate brain fiber structures (white matter) and provides a measure of white matter microstructure or architecture in each individual voxel (1-5mm). DTI is able to calculate the directionality of diffusion, by using water diffusion properties (Mori and van Zijl, 2002). In contrast to gray matter, water diffusion in white matter is highly anisotropic (direction dependent) (Moseley et al., 1990). In anisotropic tissue water diffusion occurs more rapidly in the preferential direction aligned with the structure, whereas diffusion in the direction perpendicular to it, occurs more slowly (Mori, 2007). The two predominant factors that influence anisotropy of white matter are the thickness of the myelin sheets and of the axons (Wimberger *et al.,*1995). Furthermore it depends on the coherency and regularity of the myelinated axon distribution (Basser *et al.,* 1996), the relative permeability of the membrane to water, internal axonal structure, and tissue water content (Neil *et al*., 2002). Compared to water diffusion in anisotropic structures, water diffuses randomly in isotropic structures (e.g. gray matter). The differences in water diffusion between anisotropic and isotropic structures are depicted in Figure 3.3 (Hagmann *et al. ,*2006). Figure 3.3a, shows the random three dimensional (3D) diffusion in a voxels of an isotropic structure, whereas Figure 3.3b-c show the

3D diffusion patterns in anisotropic structures. Different patterns occur with different white matter tract organization, which provides important information about the structures (Hagmann *et al.,*2006).

The diffusion directionality, calculated with DTI, is based on Brownian motion (Brown, 1928). In Brownian motion, a group of water molecules reach the surface of an ellipsoid in an anisotropic structure. To characterize this diffusion ellipsoid, six parameters are needed (3 eigenvalues to define its shape, and 3 eigenvectors to define the orientation of the axis). The diffusion tensor (diffusivity) can be calculated with a minimum of six diffusion waited images (DWIs). However, usually at least 30 DWIs are recorded to increase the signal-to-noise ratio (SNR). Subsequently, the tensor (a mathematical model that can calculate the 3D diffusion) can be calculated. Fractional anisotropic (FA) values can be computed and range from 0, maximum isotropy, to 1, maximum anisotropy (Basser, 1996). High anisotropic values indicate coherent fiber organization, while low values indicate lack of coherence (Mori, 2007).

Although DTI can provide valuable information about white matter tracts, there are some general limitations that have to be mentioned. DTI cannot reveal information about axonal connectivity on a cellular-level and discrimination between afferent and efferent pathways of axonal tracts is impossible (Mori and van Zijl, 2002). In addition, DTI does not provide accurate maps of complex fiber structures, as fiber intersections result in ambiguous diffusion patterns, shown in Figure 3.3c (Hagmann *et al.,*2006).

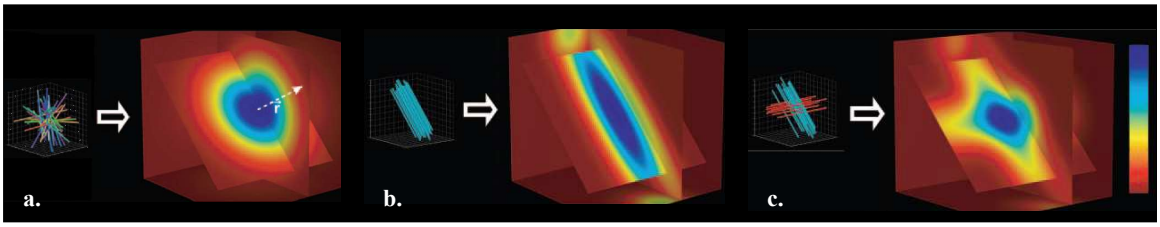


Figure 3.3. Diffusion in a single voxels (Hagmann *et al.*,2006)
3D diffusion propability density functions, lowest probability indicated by red while blue indicates highest probability. a. Random diffusion 3D displacement pattern in gray matter or in randomly distributed axons; b. Diffusion 3D displacement pattern when all the axons are aligned in the same direction; c. Diffusion 3D displacement pattern when two populations of axons intersecting at an angle of 90°.

Summary

Different MRI techniques are used to investigate white matter maturation (see Table 3.1 common DTI terms used in the literature). T1- and T2- weighted images give information about the macrostructure of white matter in the brain, FLAIR is used to detect lesions, while DWI and DTI, reveal more detailed information about tissue microstructure in general and white matter tracts in particular. DWI is the simplest form of diffusion imaging, as it measures diffusion in only one

direction. ADC estimates the magnitude of the diffusion of water molecules by applying multiple gradients with different weighting factors. The fractional anisotropy can be calculated from DTI, which shows the directional preference of the diffusion (Kimiwada *et al*., 2006). Although DTI has its limitations, it is the most favorable method as it sensitive to white matter anatomy (Klingberg *et al.,* 1999).

Table 3.1 DTI terms and definitions

DTI terms	***Definitions***
Apparent diffusion coefficient	***Estimation of diffusion magnitude***
Fractional anisotrophy, FA (diffusion anisotropy, A_σ)	***Directional preference of the diffusion, consist of linear, planar and spherical cases.***
Linear index, Cl	***Linear case of the diffusion anisotropy, sensitive to diffusion changes parallel to axons***
Mean diffusion, MD (i.e. trace, diffusion coefficient, $D\bar{}$)	***Total diffusion***
Parallel diffusivity, $\lambda \parallel$ (i.e. longitudinal diffusivity or axial diffusivity)	***Diffusivity parallel to the axons***
Perpendicular diffusion, $\lambda \perp$ (i.e. radial diffusivity, Drad)	***Diffusion perpendicular to the axons***
Planar index, Cp	***Planar case of the diffusion anisotropy***
Relative anisotropy, RA	***Relative degree of anisotropy***
Spherical index, Cs	***Spherical case of the diffusion anisotropy, sensitive for changes in water diffusion perpendicular to the axons***

4. Brain development and white matter in healthy children

The literature, on brain development in children, is dominated by studies examining gray matter development. Nevertheless, white matter maturation is an essential process of brain development. As previously mentioned, it contains myelinated axons which are important for both fast and distant neuron communication. White matter maturation is thought to continue throughout late adolescent or even early adulthood (for a review see Lenroot and Giedd, 2006; Steen *et al.,* 1997; Paus *et al.,*1999). Several studies, using both structural MRI and DTI, investigated white matter maturation in healthy children and adolescents (Yakovlev and Lecours, 1967; Benes *et al.,*1994; Caviness *et al*., 1996; Giedd *et al*., 1999*;* Lenroot and Gied, 2006;). The findings of these studies will be discussed throughout this chapter.

4.1. Pre-natal brain development and white matter

The development of the nervous system starts in the uterus within the first weeks of pregnancy. It all begins with the formation of the neural tube which will eventually progress into the spinal cord at one end and brain at the other end. Between week 3-4 of pregnancy, the formation of the neural tube is completed. In the following 8 weeks, the upper part of the neural tube will develop

into a premature brain, whereas the lower part will give rise to the spinal cord. In the first stage of brain development, three distinct areas will form. These primary brain vesicles are known as, prosencephalon (forebrain), mesencepalon (midbrain) and rhombencephalon (hindbrain). After the 7th week of development, these areas will split and further develop into secondary brain vesicles. From these secondary vesicles, neurons migrate, with the help of glial cells, to their final location, forming the structures present at birth (for more details on neuron migration see Wolpert *et al.,* 2002). The gray matter comprises cell bodies of the neuron, while the white matter consists of their myelinated axons.

Myelination in an essential process of neural development as it dramatically speeds up neuronal communication. It begins at approximately 16 weeks of pregnancy and first starts in the spinal cord (column of Burdach) and proceeds from caudal to cranial, from the afferent to the efferent areas (Knaap and Valk.,1995). At 29 weeks the myelination process starts in the auditory pathway of the brainstem (Inder and Hüppi, 2000). Figure 4.1 shows myelin (visualized with black stain) in the brainstem of a premature born human fetus of 29 weeks (Yakovlev and Lecours, 1967). In this picture, myelin is present in the inferior colliculus (ICol), Lateral lemniscus (LLm), medial longitudinal fasciculus (MLF), and medial lemniscus (MLm) of the brain stem (Yakovlev and Lecours, 1967). In the brain myelination further proceeds centrifugally (i.e. moving away from the centre) (Knaap and Valk, 1995). At 37-40 weeks, myelin is present in the posterior limb of the capsula interna (a dense white matter region which connects the thalamus to the frontal lobe) and lateral cerebellum. Myelin in frontal and posterior frontal white matter, is not present until 47-50 weeks of pregnancy (Inder and Hüppi, 2000). The maturation duration of myelin varies tremendously for different tissues. White matter maturation in the posterior limb of the capsula interna can be completed within 6 weeks, whereas other regions (e.g. axons within the cortex), the myelination process continues into late adolescents and early adulthood (Yakovlev and Lecours, 1967 in Lenroot and Gied, 2006; Benes *et al.,*1994).

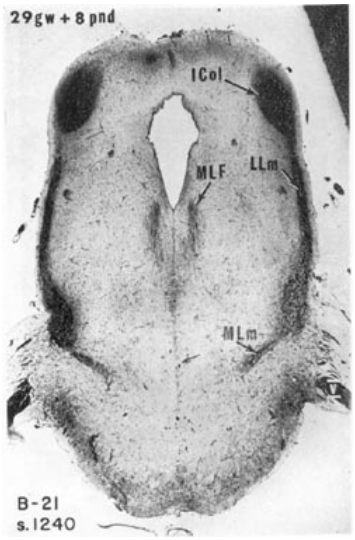


Figure 4.1 Brainstem auditory pathway human fetus of 29 weeks
Yakovlev & Lecours, 1967

4.2 White matter development in children and adolescents

Structural MRI

The first studies using structural MRI to investigate brain structure in the first two years of development, originate from the 1980s (For a review see Lenroot and Giedd, 2006). These studies used qualitative descriptions of both gray and white matter. In the 1990s quantitative MRI studies in brain development of young children were first reported. These studies give an indication of differences in brain volumes between children at differences ages.

Allen *et al.* (1991) examined the surface area of the corpus callosum in 24 children (age range 2-15 years; mean age girls 9.25 years, Standard Error of the Mean (SEM) 3.8; mean age boys 8.9 years, SEM 3.8; girls/boys 12:12). They found significant increases in corpus callosum surface area with age. Gender differences in surface are of the corpus callosum were not observed (Allen *et al.,* 1991).

Caviness *et al*., (1996) conducted a volumetric analysis using MRI to investigate both gray and white matter volumes in thirty children (age range 7-11 years; mean age girls 9.3; mean age boys 9.1; girls/boys 15:15). In this cross-sectional study (i.e. one time of measurement per subject; Kraemer *et al., 2000*), overall volumetric differences in relation to age of the children were not found. However gender comparison revealed differences in both gray and white matter in children of the same age. Female brains were smaller than male brains (93% of the volume of a boy). The central white matter volume of the girls varied from 92-95% compared to the white matter volume of the boys.

The National Institute of Mental Health (NIMH) started one of the first large pediatric longitudinal studies in 1989 (Lenroot and Giedd, 2006). In a period of 15 years they collected data of 1000 healthy children, scanned at different time-intervals (Lenroot and Giedd, 2006). Not all participants are included in each analysis, as this is very time

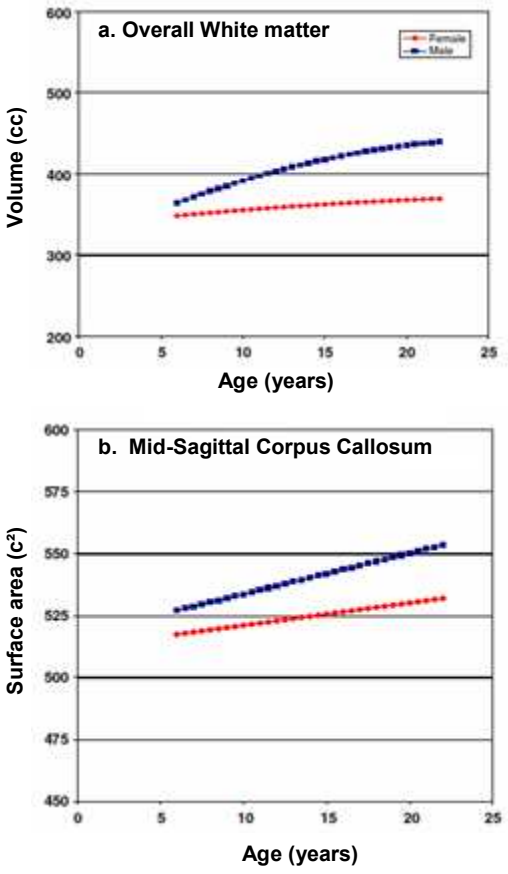


Figure 4.2 White matter
(Lenroot and Giedd, 2006)
224 females (375 scans) in red and 287 Males (532 scans) in blue; a. Overall white matter volume increase with age; b. Mid-sagittal corpus callosum surface area increase with age

consuming. Giedd *et al.* (1999) from NIMH, investigated white matter volume in 145 healthy children (age range 4.2-21.6 years; girls/boys 56:89) and reported a linear increase with age (net increase across age 12,4%). Furthermore white matter development did not differ significantly in different lobes (Giedd *et al.,*1999). In addition they observed less increase in white matter volume of girls compared to boys (Giedd *et al.,*1999). In a larger sample of NIMH, including 511 children (age range 6-21.6 years; girls/boys 224:287), the same results (shown in Figure 4.2a) were obtained (Lenroot and Giedd, 2006). Additionally, the surface area of the mid-sagittal corpus callosum was calculated. Figure 4.2b shows the gradual increase in surface area with age for both girls and boys. Gender differences in corpus callosum surface area were not significant.

In addition Knickmeyer *et al.* (2008) investigated total hemispheric white matter in 98 healthy children from birth to two years of age (age range 2 weeks- 2 years; girls/boys 49:49). They found an increase in total white matter volume of 11% in the first year and 19% in the second year.

DWI and DTI

Hüppi *et al.* (1998) investigated RA (relative anisotropy) and ADC values in white matter of the posterior limb of the internal capsule and central white matter in 17 preterm infants (mean gestational age 30.9±2.3wk, range 25-35wk) and 7 full-term infants (mean gestational age 39.4±0.8wk, range 38-40wk). In ten preterm infants, a second scan was obtained at term. In both the posterior limb of the internal capsule and central white matter regions, ADC values decreased with age, whereas the degree of anisotropy increased (Figure 4.3a).

Mukherjee *et al*., 2001 examined the isotropic diffusion coefficient ($\bar{D}$) and diffusion anisotropy (A_σ) of white matter in a larger sample from a clinical population of children (N=153;

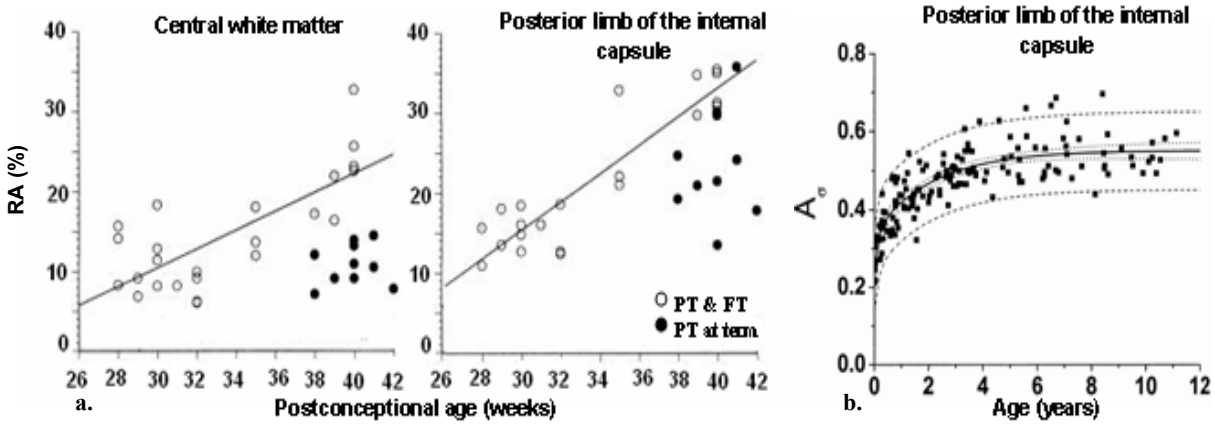


Figure 4.3
a. Relative anisotropy (RA) values for central white matter and posterior limb of the internal capsula in preterm (PT) infants, full-term (FT) infants and preterm infants at term, (Hüppi *et al.* 1998); b. Diffusion anisotropy (A_σ) values in the posterior limb of the internal capsule in children of different age (Mukherjee *et al*., 2001).

mean age 3.5 years, range 1 day-11 years; girls/boys 58:95). In this cross-sectional study the anterior and posterior limbs of the internal capsule and the genu and splenium of the corpus callosum were selected as volume of interest (Mukherjee *et al*., 2001). In all four brain regions A_σ increased with age, whereas $\bar{D}$ decreased. In Figure 4.3b the non-linear increase of anisotropy with age in the posterior limb of the internal capsule is shown.

In line with these results, Schmithorst and collegues (2002) reported significant positive correlation between FA and age in the internal capsule, corticospinal tract, left arcuate fasciculus, and right inferior longitudinal fasciculus (N 33; mean age 10.8 years, SD 3.7, range 5-18; girls/boys 17:16). In addition, negative correlations were found between ADC values and age throughout the white matter.

In addition, Gilmore *et al*. (2004) conducted a cross-sectional study and obtained 13 usable DTI scans of newborns (age range 17 ± 8 days; girls/boys 7:6). Although a small sample size was used, they found a significant increase in fraction of anisotropy (FA) with age in the genu and splenium of the corpus callosum, while FA values in other white matter tracts did not increase.

In a follow-up study Gilmore *et al*. (2007) combined T1-weighted (T1W) MRI, T2-weighted (T2W) MRI, and DTI, to further investigate the corpus callosum and corticospinal white matter in 47 healthy newborns (mean gestational age girls 42.6 ± 1.6wk; mean gestational age boys 43.1 ± 1.7 wk; girls/boys 19:28). They observed lower MD, higher FA, higher T1W, and lower T2W intensity in central regions compared to peripheral cortical regions. Furthermore, in the genu and corticospinam tract MD decreased, FA increased, and T2W signal intensity decreased with age. In contrast to Gilmore *et al*. (2004), MD, FA, TW2, and TW1 values did not change with age in the splenium. This difference could be the result of the small age-range that was examined.

Lebel *et al*. (2008) studied a large group of 202 children, adolescents and adults (mean age 15.2, SD 6.1, range 5.6-29.2; females/males 98:104; handedness, 187R, 13L, 2RL). They examined ten distinct white matter tracts (shown in Figure 4.5, genu and splenium of the corpus callosum, the inferior and superior longitudinal fasciculi, the inferior and superior fronto-occipital fasciculi, fornix, cingulum, uncinate fasciculus, and corticospinal tract) using tractography and subsequently conducted ROI analyses in 6 white matter regions (anterior and posterior limbs of the internal capsule, external capsule, corona radiata, centrum semiovale, subcortical white matter in gyri). FA values increased significantly with age in all structures, shown in Figure 4.5, with exception of the fornix, coronal radiate, and centrum semiovale. Furthermore, FA values in the corpus callosum and the inferior longitudinal fasciculus, increased faster and earlier compared to the other tracts. Perpendicular diffusivity decreased in all tracts, whereas parallel diffusivity remained constant or decreased slightly. Additionally, mean diffusivity decreased in all

structures. The changes in FA and mean diffusivity occurred most rapidly in childhood, slowed in adolescents and most often, reached a plateau in late adolescent or early adulthood. Furthermore gender differences in FA changes were not significant, while MD patterns did show gender differences in five structures, not further specified by the authors.

Summary

The results of the studies previously discussed are summarized in Table 4.1. The majority of the literature conducted cross-sectional studies with most often small sample sizes to investigate brain development in children and adolescents (Yakovlev and Lecours, 1967; Caviness *et al*., 1996; Hüppi *et al.* 1998; Mukherjee *et al*., 2001; Schmithorst *et al.,* 2002; Gilmore *et al*. 2004; Gilmore *et al*., 2007; Lebel *et al*., 2008). From these studies Lebel *et al*. (2008) examined the largest group. Several studies examined white matter development in children in a longitudinal design (Giedd *et al*., 1999; Lenroot and Giedd, 2006; Knickmeyer *et al.*, 2008). Based on these studies we can conclude that the total cerebral white matter volume, total central white matter volume and total corpus callosum volume significantly increases with age (Yakovlev and Lecours, 1967; Caviness *et al*., 1996; Giedd *et al.,* 1999; Lenroot and Giedd, 2006; Knickmeyer *et al.*, 2008). Furthermore, FA values increases with age as well, while ADC values tend to decrease (Hüppi *et al.* 1998; Mukherjee *et al*., 2001; Gilmore *et al*. 2004; Schmithorst *et al.,* 2002; Gilmore *et al*., 2007; Lebel *et al*., 2008). Although DTI studies investigating infants from 0 to 2 years old are limited, FA values seem to increase more rapidly in this age group (Mukherjee *et al*., 2001). In addition, some studies report gender differences in white matter development, were white matter volumes in girls seem to increase more slowly compared to boys (Caviness *et al*., 1996; Giedd *et al*., 1999). However gender differences in FA changes with age were not significant, while MD patterns did show gender differences in several structures (Lebel *et al.,* 2008).

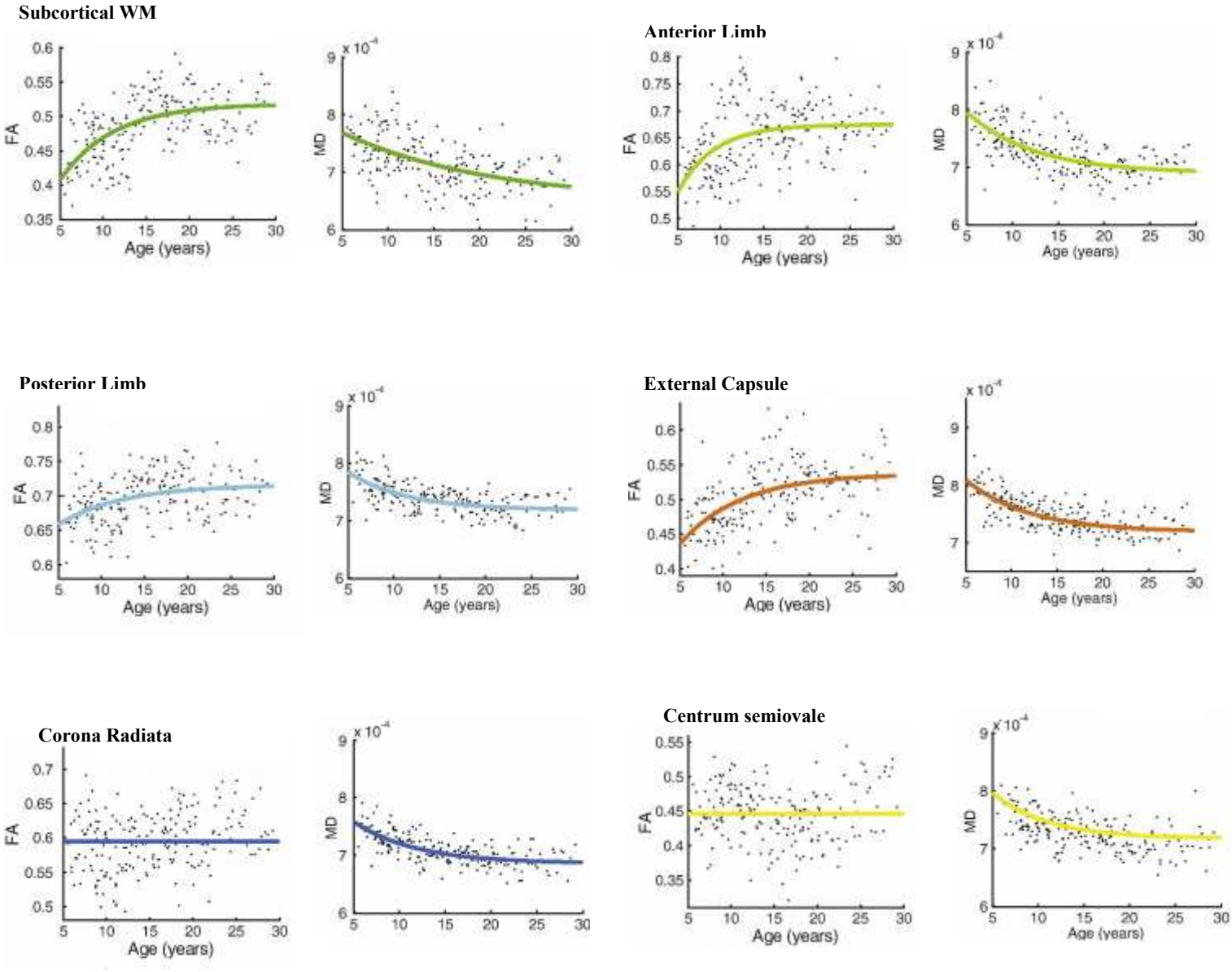


Figure 4.5a Label *et al.,* 2008

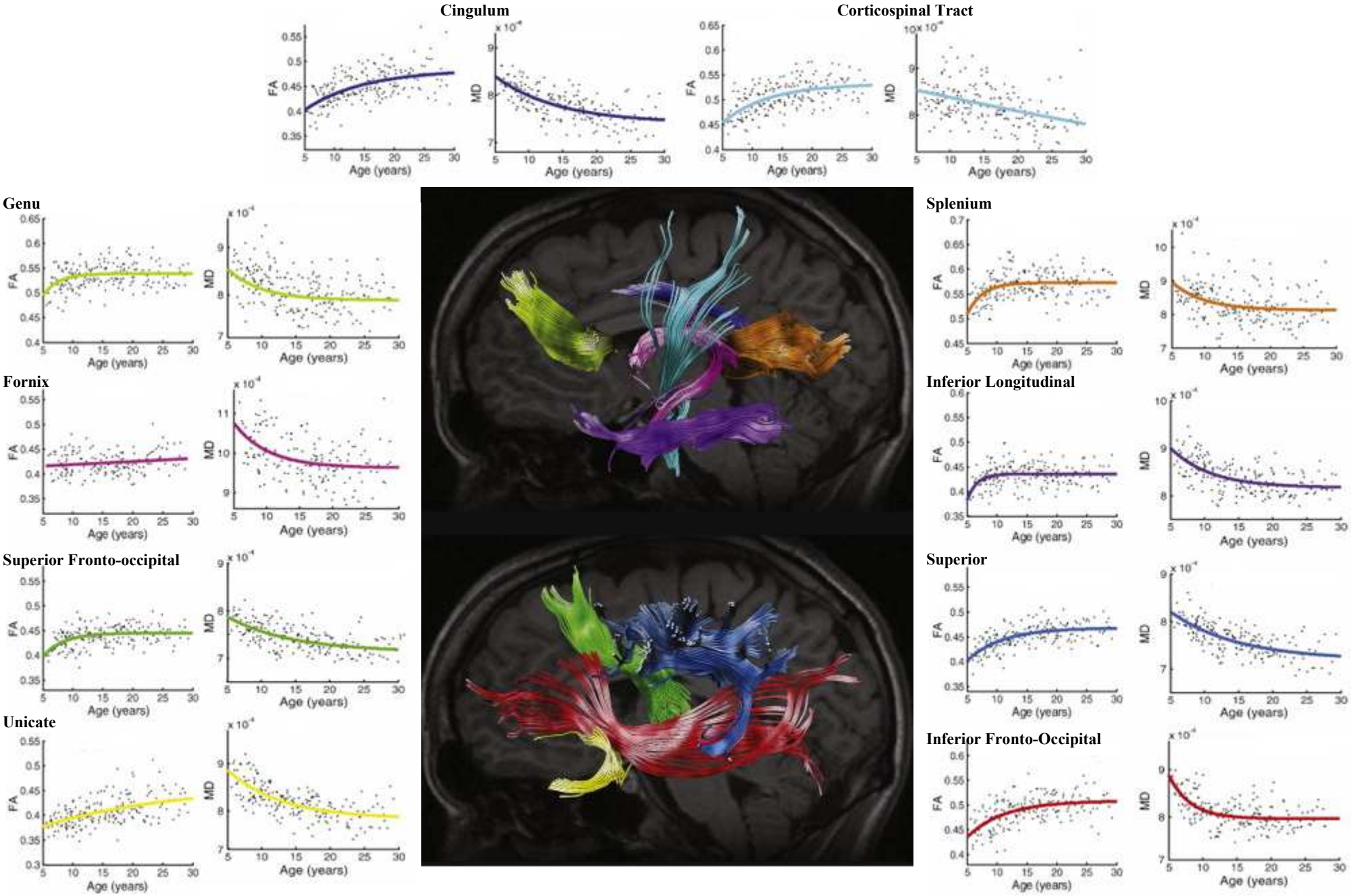


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Table 4.1 Studies on white matter development in healthy children

Study	N	Mean age (yrs)	♀/♂	Time interval between scans (yrs)	Number of scans per subject	White matter
			Healthy children			
Structural MRI						
Allen *et al.,*1991	24	♀ 9.25 SEM 3.8 range 2-15 ♂ 8.9 SEM 3.8 range 2-14	12:12	-	1	↑corpus callosum surface area with age No gender differences observed
Caviness *et al*.,1996	30	♀ 9.3 ♂ 9.1 range 7-11	15:15	-	1	No volumetric differences in age WM volume lower in girls *Comment:16 children evaluation headaches*
Giedd *et al.,* 1999	145	range 4.2-21.6	56:89	± 2	1-5	Linear ↑ in WM volume with age Not differences in WM volume ↑ between different lobes Less WM volume↑ in girls
Lenroot and Giedd, 2006	511	range 6-21.6	224:287	± 2	1-5	Linear ↑ in WM volume with age Not differences in WM volume ↑ between different lobes Less WM volume↑ in girls ↑corpus callosum surface area with age Gender differences not significant
Knickmeyer *et al.,*2008	98	range 2wk - 2	49:49	1-2	1-3	↑ total WM volume with age
DTI						
Hüppi *et al.,*1998	17 PT	Gestational age 30.9±2.3wk range 25-35wk	-	± 11 wk	1-2	ADC values ↓ and RA values ↑ with age in: • Posterior limb of the internal capsule and • Central white matter
	7 FT	39.4 ± 0.8wk 38-40wk	-	-	1	
Mukherjee *et al.,*2001	153	3.5 range 1 day-11 yrs	58:95	-	1	A_σ↑ and $\bar{D}$↓ with age in: • Anterior and posterior limbs of the internal capsule and • Genu and splenium of the corpus callosum: *Comment: clinical MRI scans*
Schmithorst *et al.,*2002	33	10.8 SD 3.7 range 5-18	17:16	-	1	Positive correlations between FA values and age in: • Internal capsule, • Corticospinal tract, • Left arcuate fasciculus • Right inferior longitudinal fasciculus
Gilmore *et al.*,2004	13	17 ± 8 days	7:6	-	1	FA values ↑ with age in genu and splenium
Gilmore *et al.,*2007	47	Gestational age ♀ 42.6 ± 1.6wk ♂ 43.1 ± 1.7 wk	19:28	-	1	MD and FA were different in the genu, splenium, and left corticospinal tract central and peripheral cortical portions of the genu and the left corticospinal tract, FA ↑ and MD ↓ with age
Lebel *et al.,* 2008	202	15.2 SD 6.1 range 5.6-29.2	98:104	-	1	↑ FA with age in 13WM regions ↓ MD with age in 16WM regions

WM white matter; ADC; FA= Fractional anisotrophy; A_σ = diffusion anisotropy $\bar{D}$= diffusion coefficient; FT full-term infants; PT, preterm infants.

5. White matter abnormalities in children with epilepsy

The vast majority of studies on epilepsy focuses on gray matter abnormalities in most often adult patients. Unfortunately, white matter studies in children with epilepsy are scarce. However, the awareness of white matter importance in children with epilepsy is rapidly increasing. DTI is increasingly being incorporated in the standard clinical MRI protocol and within a few years, studies on white matter in children with epilepsy will most probably have doubled or tripled. Several studies, examining white matter in children with epilepsy using structural MRI or DTI, will be discussed in this chapter (Kimiwada *et al*., 2006; Caplan et al., 2008; Govindan *et al.*, 2008; Nilsson *et al*., 2008; Hermann *et al.* 2010; Hutchinson *et al*., 2010; Widjaja *et al.,* 2010).

5.1 Volumetric white matter studies

Caplan *et al.* (2008) investigated 42 children with cryptogenic epilepsy with complex partial seizures (mean age 6.6, range 5–16 years; girls/boys 21:21) and 41 age and gender matched healthy controls (mean age 10.7; girls/boys 23:18). The epileptic foci of the complex partial seizures differed widely (e.g. left, right, bilateral, temporal, frontal). They found smaller inferior frontal white matter, superior temporal white matter and "Heschl's gyrus white matter" in children with complex partial seizures compared to controls (differences ranging from 0.13 mm^3 heschl's gyrus- 1.26 mm^3 superior temporal). However, total white matter volumes, orbital frontal white matter, "dorsolateral prefrontal gyrus (DLPFC) white matter", and temporal lobe white matter volumes were increased in the epileptic group compared to controls (differences ranging from 0.04 dorsolateral prefrontal gyrus white matter - 4.6 significant increase in temporal lobe white matter). In addition, higher former thought disorder scores were significantly associated with smaller DLPFC white matter volumes, and STG white matter volumes. From previous studies on white matter maturation we know that white matter volume in healthy children significantly increases with age (Yakovlev and Lecours, 1967; Caviness *et al*., 1996; Giedd *et al.,* 1999; Lenroot and Giedd, 2006; Knickmeyer *et al.*, 2008). Although Caplan *et al.,* (2008) included children from 6 to 16 years old in their study, they did not correct for age. In addition the foci of the seizures varied widely between the participants. Further research is needed to investigate possible differences in white matter volume in different seizure foci.

Hermann *et al.* (2010) conducted a longitudinal volumetric MRI study, in two years period, on 38 children with epilepsy (21 localization-related epilepsy; 17 idiopathic generalized epilepsy; mean age 12.97; girls/boys 19:15), and 34 healthy first-degree cousins controls (mean age 12.94; girls/boys 18:20). The prospective changes of total white matter increases are shown in Figure

5.1. Compared to baseline volumetric measurements, the control group experienced significant increases in total cerebral, frontal, parietal and temporal white matter volumes. However, the children with epilepsy did not show significant white matter increases in these areas. In addition, differences between both cerebral and frontal white matter volumes of controls and epileptic children were significant. Older children experienced less increase in white matter volume compared to younger children. Furthermore differences in white matter volume between localization-related epilepsy and idiopathic generalized epilepsy were not significant.

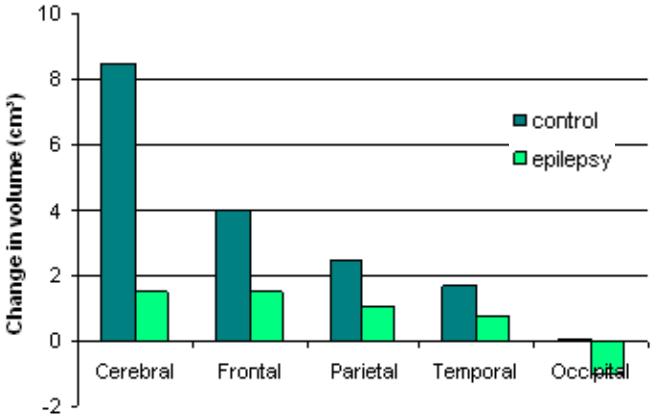


Figure 5.1 Change in white matter volume Hermann *et al.* (2010)

Widjaja *et al.,* 2010 examined white matter volumes in 20 children (mean age 13, range 1-16 years; girls/boys 6:14) with intractable partial epilepsy. The seizure-origin varied between frontal lobe, temporal lobe, rolandic and more than one lobe. Ten patients suffered from cortical dysplasia and three had mesial temporal sclerosis, visible on the MRI scans. The children were scanned on two different occasions, with a time interval between 1-7 years. Total white matter volume did not increase with age in any of the children.

5.2 DTI white matter studies

The study of Kimiwada *et al*., 2006 is one of the first to investigate alterations in anisotropy and apparent diffusion values in children with partial temporal lobe epilepsy. They examined 14 children (age 1-16 years; girls/boys 10:4), 7 with partial seizures and 7 with partial seizures followed by generalized seizures. Three regions of interest (ROIs) were defined (thalamus, hippocampus, and lentiform nucleus). Compared to controls (healthy children of approximately the same age), the children with epilepsy showed decreased FA values in the bilateral hippocampus. In addition, ADC values were increased for the hippocampus ipsilateral to the epileptic focus. Differences between the two patient groups (partial epilepsy and partial epilepsy with generalized seizures) were not significant. Unfortunately, white matter was not investigated.
Govindan *et al.* (2008), did use DTI to study white matter development in 13 children suffering from refractory left TLE (mean age 10.9±6.3, range 11 months-19 years; girls/boys 8:5; mean

duration of illness 5 -175 months) and 12 healthy controls (mean age 13.2±3.4, range 7-18; girls/boys 7:5). In addition to FA values, C_l (linear index, sensitive to diffusion changes parallel to axons), C_p (planar index) and Cs (spherical index, sensitive for changes in water diffusion perpendicular to the axons) values were calculated, to provide additional information about the diffusion directionality. The patients had decreased FA, C_l and C_p values in the unicate fasciculus (UNF), arcuate fasciculus (ARF), inferior longitudinal fascilicus (ILF) and corticospinal tract (CST) of the left hemisphere. Nevertheless, Cs values in these white matter tracks, were increased. Additionally, FA values in UNF, ARF ILF and CST, C_p in the UNF, ILF and CST, and C_l values in the UNF and CST, were decreased in the right hemisphere of the epileptic patients. In line with the results for the left hemisphere, the Cs values in UNF, ILF and CST in the right hemisphere, were also increased in the patients.

Furthermore, Nilsson *et al*.(2008), studied diffusion anisotropy in temporal lobe white matter (TLWM) and cingulate gyrus white matter (CGWM) of children with temporal lobe epilepsy. The sample used in this study was small, the epileptic group consisted of eight children (mean age 12.8; girls/boys 3:5; mean age at onset 7.9) and the control group of ten (mean age 12.9; girls/boys 7:3). In addition the sample was rather heterogeneous, as unequal number of boys and girls of different ages were included. Furthermore, although the majority of the children suffered from complex partial epilepsy only, three also experienced infrequent secondary generalized seizures. In addition, several children had undergone temporal lobe resection. Six children showed abnormalities on the MRI scan, varying from subtle lesions to mesial temporal sclerosis and gliosis. Nilsson *et al.*(2008) found no significant differences between FA in TLWM and CGWM of patients and controls. However, they demonstrated a significant increase in trace (diffusivity), parallel ($\lambda_{\|}$) and perpendicular ($\lambda\perp$) diffusivity in TLWM and CGWM of patients.

Hutchinson *et al*. (2010) studied 19 children suffering from recent onset epilepsy with localization related (N=11; mean age 10.5, SD 1.8; girls/boys 4:7) or idiopathic generalized epilepsy (N=8; mean age 15.2, SD 3.2; girls/boys 4:4) and 11 healthy controls (mean age 13.8, SD 3.4; girls/boys 6:5). As depicted in Figure 5.2, they found significantly decreased FA values in the posterior corpus callosum and cingulum of the patients compared to controls. Furthermore, mean diffusion (MD) values were increased in the posterior corpus callosum of the patients and radial diffusivity (D_{rad}) was increased in both posterior corpus callosum and cingulum of the patients compared to controls. However, these results became non significant trends when the epileptic group was divided into a localization related (LRE) and an idiopathic generalized (IGE) group. Additionally, the MD and D_{rad} in the fornix of the LRE group were significantly

increased, compared to controls. Differences in gray and white matter volumes were not observed and the axial diffusivity did not differ between the patients and controls.

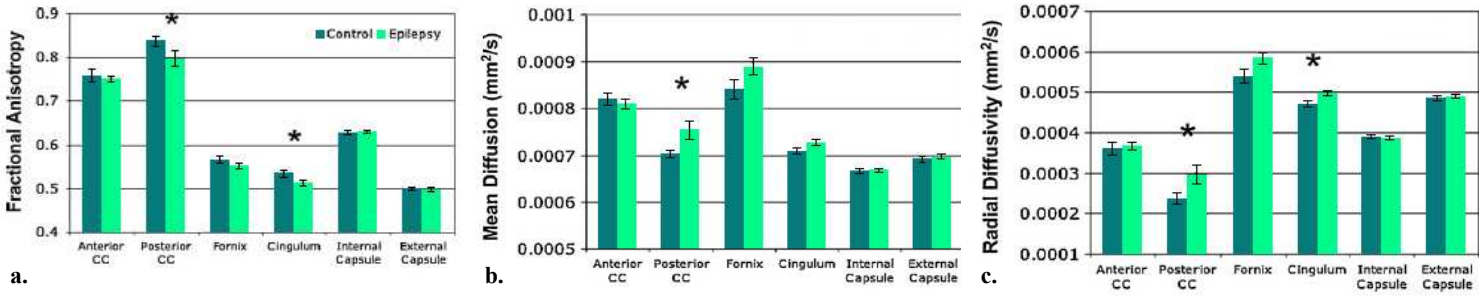


Figure 5.2 Diffusion in white matter of epileptic patients and controls (Hutchinson *et al*., 2009)
a. FA values; b. MD values; c. Drad values in the anterior corpus callosum, posterior corpus callosum, fornix, cingulum, internal capsule and external capsule of epileptic patients and controls.

Summary

Cross-sectional and longitudinal designs using structural MRI and DTI were used to study white matter abnormalities in children with epilepsy (for a summary see Table 5.1). These studies showed that children with parietal epilepsy seem to have disturbances in white matter volume, FA values, and ADC values in different brain regions (Caplan *et al*., 2008; Govindan *et al.*, 2008; Nilsson *et al*., 2008; Hermann *et al.,*2010; Hutchinson *et al*., 2010; Widjaja *et al*., 2010). Nevertheless, these result have to be interpreted with great caution as relatively small heterogeneous groups were used, in most often cross-sectional designs (Kimiwada *et al*., 2006; Caplan *et al*., 2008; Govindan *et al.*, 2008; Nilsson *et al*., 2008; Hutchinson *et al*., 2010). The longitudinal structural MRI studies revealed no significant changes with age in WM volume of children with partial epilepsy (Widjaja *et al*., 2010) and a mixed group of children with partial and generalized epilepsy (Hermann *et al.,* 2010). Caplan *et al*., 2008 conducted the largest cross-sectional study and found both increases and decreases in WM volumes of patients with partial epilepsy, but did not control for age. From these structural studies, especially the findings of Hermann *et al. (*2010), no significant increase in frontal and total cerebral WM volume with age, could be relevant as they used a longitudinal design and age-matched controls. In addition, the DTI studies reported decreased FA values in several white matter tracks (CC, Cingulum, UNF, ARF ILF and CST) (Govindan *et al.*, 2008 ; Hutchinson *et al*., 2010). Furthermore, ADC (Nilsson *et al*., 2008), MD, Drad (Hutchinson *et al*., 2010), and Cs values (Govindan *et al.*, 2008), were increased.

Clearly diffusion abnormalities in children with partial epilepsy are present. However, the exact meaning of these disturbances is still unknown. Govindan *et al.* (2008) showed that the loss of white matter anisotropy could predominately be the result of increased Cs values, most sensitive for changes in diffusivity perpendicular to the axons. They speculate that axonal swelling could be a possible explanation for the increased perpendicular diffusivity without decreased parallel diffusivity. Furthermore, they state that diffusion changes could also be caused by progressive degeneration in white matter due to seizures. Nilsson *et al*.(2008) reported increased trace (diffusivity), parallel ($\lambda_{\|}$) and perpendicular ($\lambda\perp$) diffusivity, while no differences between FA values of patients and controls were found. Nilsson *et al*.(2008) speculate that the increase in $\lambda_{\|}$ and $\lambda\perp$ could be explained by an increase in the extracellular fluid space due to degeneration of fibers or edema. Hutchinson *et al*. (2010) decreased FA and increased MD and Drad of the corpus callosum and cingulum, in recent onset epilepsy independent of volumetric differences in gray and white matter. Normal white matter development is suppose to show reduced Drad values which is thought to correspond to compacting fibers and myelination (Snook *et al.,* 2005; Hasan *et al.,* 2009), while alterations in Drad values are believed to be related to myelin abnormalities (Budde et al.,2007; Song et al., 2005). Therefore Hutchinson *et al.* (2010) speculate that increased diffusivity could reflect disrupted axon myelination slowed by epileptogenesis, in children with recent onset epilepsy. However, they state that these increased in diffusivity could also reflect seizure-related damage to the corpus callosum.

Table 5.1 Studies on white matter in children with epilepsy

		Epileptic group							Control group			White matter abnormalities
Study	Syndrome	N	Age (yrs)	♀/♂	Age onset (yrs)	Duration of illness (yr)	Seizure free (hr)	Time between scans (yrs)	N	Age (yrs)	♀/♂	
Structural MRI												
Caplan *et al.,* 2008	*Cryptogenic epilepsy with CPS with different foci*	42	10.2 SD 2.55 range 5–16	21:21	6.6 SD 3.10	3.6 SD 2.51	-	-	41	10.7 SD 2.41	23:18	CPS ↓ WM volumes (range 0.13-1.26 mm³): • inferior frontal WM • superior temporal WM • heschl's gyrus WM CPS ↑ WM volumes (rang 0.04-4.6 mm³): • total cerebral WM • orbital frontal WM • dorsolateral prefrontal gyrus WM • temporal lobe WM
Hermann *et al., 2010*	*Epilepsy* localization-related (21) idiopathic generalized (17)	38	12.97 SD 3.3	19:15	12.3 SD 3.6	8.9 months SD 4.3	-	2	34	12.94 SD 3.2	18:20	Contols ↑ WM volumes with age: • total cerebral • frontal area • parietal area • temporal area
Widjaja *et al., 2010*	*Intractable partial epilepsy* with different foci	20	13 range 1-16	6:14	3 range 2w-9yrs	7	-	3 range 1-7	-	-	-	Epileptic group, no significant ↑ WM volumes with age No ↑ or ↓ in WM volume with age
DTI												
Govindan *et al., 2008*	Refractory left TLE	13	10.9±6.3 range 11months-19yrs	8 :5		5 -175 months	-	-	12	13.2±3.4 range 7-18	7 :5	TLE ↓ FA, *C*l, and *C*p values and↑ Cs, in left hemispheric: • UNF, ARF ILF and CST In right hemispheric: • ↓ FA in UNF, ARF ILF and CST • ↓ Cp in UNF, ILF and CST • ↓ Cl in UNF and CST • ↑ Cs in UNF, ILF and CST
Nilsson *et al*., 2008	*CPS* SGS (3)	8	12.8 range 5.9-17.4	3 :5	7.9 1-16	5.2 range 0.6-15.1	24h	-	10	12.9 range 9.5-17.2	7 :3	CPS ↑ trace, $\lambda_{\parallel}$ and $\lambda^{\perp}$ diffusivity temporal lobe and cingulum WM
Hutchinson *et al*., 2010	Recent onset LRE	11	10.5 SD1.8	4:7	-	max.12 months	-	-	11	13.8 SD3.4	6:5	Epilepsy: ↓FA values posterior CC ↓FA values cingulum ↑ MD posterior CC ↑ Drad posterior CC and cingulum LRE ↑ MD and Drad fornix
	IGE	8	15.2 SD3.2	4:4	-	max.12 months	1	-				

CPS=complex partial seizures; TLE= temporal lobe epilepsy; SGS= secondary generalized seizures; WM white matter; CC, corpus callosum; MD, mean diffusion; D rad, radial diffusivity; LRE, localization related epilepsy; IGE, idiopathic generalized epilepsy; trace, total diffusivity; $\lambda_{\parallel}$, parallel diffusivity; $\lambda^{\perp}$, perpendicular diffusivity

6. White matter abnormalities in adults with epilepsy

In this chapter studies examining white matter in adults with both late and early onset epilepsy, using structural MRI and DTI will be discussed.

6.1. Structural MRI white matter studies in adults with epilepsy

Hermann *et al.*(2003a) conducted a volumetric MRI study, examining 58 patients with complex partial seizures of temporal lobe origin (mean age, 34.1, SD, 11.3; females/males, 40:18; mean age at onset, 12.5, SD 8.7) and 62 age-matched healthy controls (mean age, 33.4, SD, 12.6; females/males, 37:25). The epileptic group showed significantly reduced overall cerebral white matter volumes, compared to controls (-9.8% reduction). This white matter reduction concerned the frontal, temporal, and parietal lobes, but not in the occipital lobe. White matter reduction was most prominent in the ipsilateral side of seizure onset (-9.3% reduction). Although the contralateral hemisphere was affected as well (-7,8% reduction).

In a follow-up study, Hermann *et al.* (2003b) investigated total corpus callosum volume in 16 patients with early onset TLE (mean age, 26.8, SD 11.1; female/males, 11:5; age at onset, 6.3, SD 3.8), 16 with late onset TLE (mean age 39.2, SD 9.9; female/males, 11:5; age at onset, 20.7, SD 6.2) and 15 healthy controls (mean age, 29.1, SD 10.9; females/males, 9:6). The patients were matched for duration of the epilepsy and all groups were matched for gender and handedness (for more details see Hermann *et al.* 2003b). In Figure 7, the striking results of this study are shown. Corpus callosum volume was significantly decreased in patients with early onset epilepsy compared to both controls and late onset epileptic patients. Furthermore, Hermann *et al.* (2003b) reported regional differences in volume decrease. The posterior side of the corpus callosum was most affected, followed by the anterior side. Moreover, volume decrease was associated with poorer neuropsychological performance (nonverbal problem solving, immediate memory, complex speeded psychomotor processing and speeded motor dexterity) (Hermann *et al.,* 2003b).

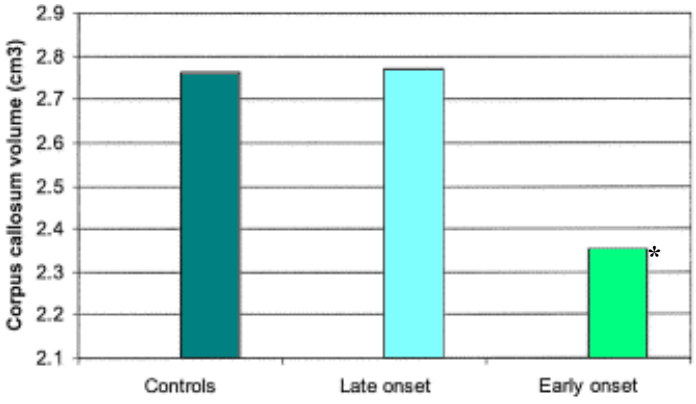


Figure 6.1 Total corpus callosum volume (cm^3)
ICV and age as covariates; *, differences between groups was significant Hermann *et al.,* 2003b

In addition McMillan *et al.* (2004) used voxel-based morphometry to investigate white matter abnormalities in 25 patients suffering from childhood onset complex partial seizures of unilateral temporal lobe origin (mean age 32, SD 11; left/right TLE, 13:12; males/females not reported; mean age at onset 12 years) and 61 healthy controls (mean age 32, SD 12; males/females not reported). Figure 6.2 shows the areas of decreased white matter volume in patients with left (6.2a) and right (6.2b) TLE. In both left and right TLE, the white matter decreases are most prominent in the ipsilateral temporal lobe. In addition, both groups experienced volume losses in the corpus callosum, whereas the fornix was only affected in the right TLE group and bilateral prefrontal white matter losses only affected the left TLE group.

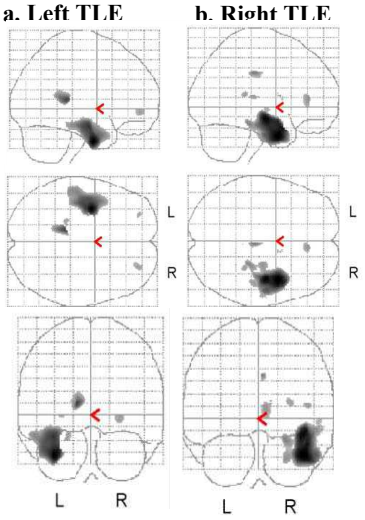


Figure 6.2 Decreased WM voulumes TLE McMillan *et al.* (2004)

6.2 DTI white matter studies in adults with epilepsy

Rugg-Gunn *et al*. (2001) compared DTI maps of patients with partial epilepsy and MRI visible lesions (N 10; median age 36 years, range 20-53; females/males 1:10), to patients with cryptogenic partial epilepsy without MRI abnormalities (MRI-negative; N 30; median age 36 years, range 18-55 years; females/males 13:17) and healthy controls (N 30; median 30, range 20-50; females/males 20:10). All patients (with one exception) were seizure free 24 hours prior to the MRI scans. The patients with cerebral injury had significantly reduced FA values, while diffusivity was increased. In a vast majority of the patients the regions of increases in FA and decreases in diffusivity, corresponded to the MRI abnormalities detected during the visual inspection of the scans. In contrast to the cerebral injury epileptic group, only two MRI-negative patients revealed decreases in FA and eight patients had regions of increased diffusivity. Group analysis on patients with EEG evidence of left (N 9) or right (N 6) TLE, showed a significant decrease in FA and increase in diffusivity in left temporal lobe white matter, in the left TLE group compared to controls (Figure 6.3). Nevertheless, in the right TLE group the FA reduction did not

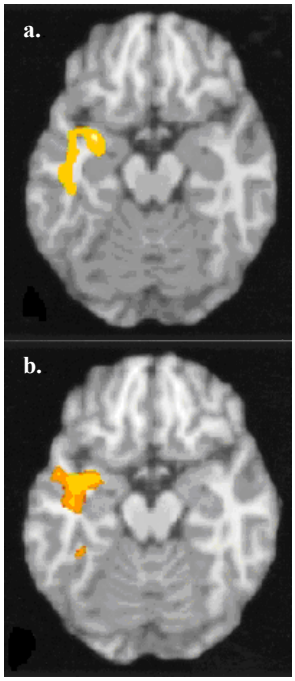


Figure 6.3 FA and diffusivity in LTLE (Rugg-Gunn *et al*. 2001) a. decreased FA in LTLE; b. Increased diffusivity in LTLE

reach significance.

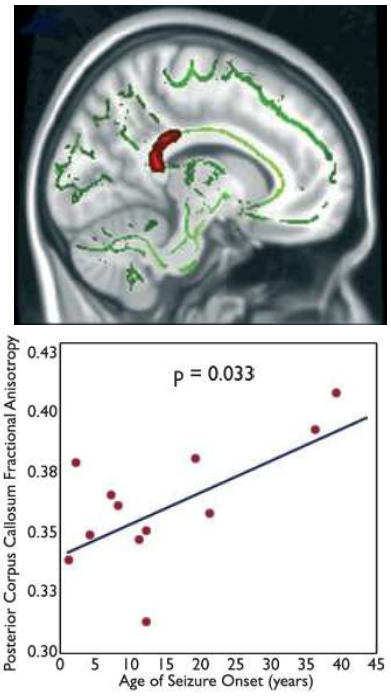
Furthermore, Arfanakis *et* al. (2002) investigated fifteen patients (mean age 31.6 ± 8.9 years) suffering from complex partial seizures with temporal lobe origin and fifteen age-matched controls (mean age 29.7 ± 11.2 years). Voxels in the bilateral external capsule, posterior corpus callosum, anterior corpus callosum, posterior limb of the internal capsule and anterior limb of the internal capsule, were selected as regions of interest. They reported significantly increased λ2 and λ3 values (second and third eigenvalues, diffusivities along directions that are perpendicular to the primary diffusion direction) in the external capsule, and increased mean λ2 in the posterior and anterior corpus callosum. Furthermore, significantly decreased mean FA values were found in the external capsule and the posterior corpus callosum of the patients compared to controls. In the other white matter structures FA values of white matter were also reduced, although these results were not significant. There was a significant negative correlation between FA and the age of the subjects in the anterior corpus callosum and the posterior limb of the internal capsule (Arfanakis *et* al. 2002).

In line with these findings, Gross *et al.* (2006) also reported significant decreased FA values in the genu of the corpus callosum and external capsule in patients with TLE (N 11; mean age 38; females/males 8:3; mean age ad onset 10) compared to healthy controls (N 14; mean age 32). Furthermore they found elevated perpendicular ADC values ($ADC^{\perp}$) in the genu, splenium, and the external capsule, in TLE.

In addition, Concha *et al*.(2007) investigated whether diffusion abnormalities could be reversed after epilepsy surgery. Therefore 11 patients with TLE and unilateral MTS were scanned before epilepsy surgery, 8 patients (age range 22-61 years; females/males 6:2; TLE duration range 12-47 years) became seizure free after surgery and were scanned a second time, approximately one year after surgery. Furthermore, 22 healthy controls (mean age 31, range 19-54 years; females/males 8:16) were included in this study. Before surgery, the fornix, cingulum, external capsule and genu of the corpus callosum in both ipsilateral and contralateral hemisphere of MTS, showed increased perpendicular diffusivity ($\lambda^{\perp}$) and normal parallel diffusivity ($\lambda\|$). This change in $\lambda^{\perp}$, caused increased mean diffusivity and decreased fractional anisotropy. One year after surgery, these diffusion abnormalities became more prominent in the ipsilateral hemisphere of MTS most probably due to downstream wallerian degeneration of the fornix, cingulum, external capsule and genu of the corpus callosum. The diffusion parameters of the white matter bundles in the contralateral hemisphere also failed to normalize, while these tracts were not directly affected by the surgery (Concha *et al*.2007).

In addition, Ahmadi *et al*. (2009**)** studied eight large fiber tracts in 21 patients with TLE (mean age, 37.3, SD 19; females/males, 11:10; left/right TLE, 10:11; mean age at onset 14.3, SD 11.5) and 21 age and gender matched healthy controls (mean age, 33.0, SD 10.2; females/males, 11:10). These fiber tracts included, the cigulum fibers (CG), parahippocampal fibers (PH), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), uncinate fasciculus (UF), fornix (FORX), anterior thalamic radiations (ATR), and inferior fronto-occipital fasciculus (IFOF). They reported significant decreased FA values in ipsilateral CG, PH, ILF, IFOF and SLF, in patients with TLE compared to controls. Moreover, FA values in ipsilateral IFOF, SLF, FORX, ATR, and contralateral CG, ATR, and IFOF were significantly decreased in left TLE, while FA values in right TLE were only significantly decreased in ipsilateral ILF.

Riley *et al.*(2010) examined 12 unilateral temporal lope epilepsy patients (mean age 37.9; females/males 9:3; range age at onset 1-39 years) and 10 age-matched healthy controls (mean age 42.1; female/male 4:6). Of the epilepsy patients, four had undergone epilepsy surgery. The TLE patients had reduced FA values, predominately in the affected hemisphere, compared to the controls. Four distinct cluster showed decreased FA values in the anterior temporal lobe (uncinate fasciculus), posterior mesial temporal lobe (fornix), cerebellum, ipsilateral to the seizure focus and frontoparietal lobe (the arcuate fasciculus), contralateral to the affected hemisphere. Additionally, mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were examined and showed increased MD, RD, and no change in AD in the anterior temporal lobe. In addition FA values of the anterior lobe, mesial temporal lobe and cerebellum were associated with cognitive performances. Furthermore correlations between corpus callosum FA values and age of seizure onset were investigated. As shown in Figure 6.4 early childhood onset was correlated with decreased posterior corpus callosum FA values. The small sample size and heterogeneity of the group are the main limitations of this study.



6.4 Correlations posterior callosal FA values and with age of seizure onset

Shon *et al.* (2010) studied 19 patients with temporal lobe epilepsy suffering from hippocampal sclerosis (TLE-HS; mean age, 34.1 ± 10.3 years; left/right TLE, 12:7; female/male patients,13:6), and 18 patients with TLE without hippocampal sclerosis (TLE-NS; mean age, 30.2

± 7.4 years; left /right TLE, 10:8; female/male patients, 10:8). The control group consisted of 20 healthy males and females (mean age 30.6 ± 7.9; female/male 10:10). Patients with left TLE-HS showed increased mean diffusivity in the ipsilateral posterior cingulum, isthmus of corpus callosum, and contralateral occipital and temporal regions, compared to patients with right TLE-HS. Furthermore patients with left TLE-NH showed increased mean diffusion in the ipsilateral posterior fornix and posterior cingulum.

Summary

For a summary of the studies previously discussed, see Table 6.1. The vast majority of the studies on partial epilepsy in adults, investigated patients with temporal lope epilepsy (Hermann *et al.,* 2003a, 2003b; McMillan *et al.,*2004; Arfanakis *et al.,*2002; Gross *et al.,*2006; Ahmadi *et al*.,2009; Riley *et al.,*2010; Shon *et al.,*2010). As in children with partial epilepsy, alterations of WM in adults with partial epilepsy have been found in both structural and DTI studies (Rugg-Gunn *et al*., 2001; Hermann *et al.,* 2003a, 2003b; McMillan *et al.,*2004; Arfanakis *et al.,*2002; Gross *et al.,*2006; Ahmadi *et al*.,2009; Riley *et al.,*2010; Shon *et al.,*2010). In patients with TLE decreased WM volumes have been reported (Hermann *et al.,* 2003a, 2003b; McMillan *et al.,*2004). Hermann *et al*. (2003b), was the only study that investigated the differences between early and late onset TLE. They clearly showed that corpus callosum volume was decreased in patients with early onset TLE, compared to late onset TLE and controls. Furthermore, DTI revealed decreased FA values (Riley *et al.,*2010) and increased MD and ADC, in several white matter regions (Rugg-Gunn *et al*., 2001; Arfanakis *et al.,*2002; Gross *et al.,*2006; Shon *et al.,*2010). The studies that investigated white matter ipsilateral versus contralateral to the epileptic foci, reported predominantly disturbances in ipsilateral white matter (Ahmadi *et al*.,2009; Riley *et al.,*2010; Shon *et al.,*2010).

Although interesting findings, it is still unclear what these changes in diffusivity exactly mean. Rugg-Gunn *et al*. (2001) suggests that the regions of significantly increased diffusivity in patients without MRI abnormalities and the reduced FA and increased diffusivity in the TLE group, could be the result of a disturbed microstructural environment due to, for example, recurrent seizures. Arfanakis *et al.* (2002) showed significant reduction in FA in the external capsule and posterior corpus callosum, most probably due to an increase in diffusivity in the direction perpendicular to the axons. They state that this might be caused by myelin disturbances, increased permeability of the axon membranes, or a less tightly packed neuronal network. Gross *et al.,*2006 found similar results and claim that the reduced FA and increased $ADC^{\perp}$ values in the genu of the corpus callosum and external capsule, reflect myelin degradation in these areas.

Concha *et al*.(2007) speculate that the diffusion abnormalities, decreased FA due to increase $\lambda\perp$, in both before and after surgery, could reflect irreversible myelin abnormalities or disturbances in axon density. Furthermore, Ahmadi *et al*.(2009) do not make assumptions about the possible meaning of decreased FA values they found in WM tract in TLE, left TLE and right TLE group. Ahmadi *et al*.(2009) speculate that the diffusion abnormalities found in both ipsilateral and contralateral hemisphere of left TLE, could indicate that neuronal connection in the left hemisphere could be more prone to support seizure propagation to the contralateral hemisphere. Riley *et al*.(2010) state that the diffusivity pattern in the anterior temporal lobe (decreased FA, increased MD, increased RD and no changes in AD) has been associated to both chronic WM degeneration and chronic changes related to ischemic stroke. This could be the result of a combination of myelin and axonal loss, resulting in a reduced membrane density and increased extra cellular volume. In addition, the other regions only showed decreased FA values, which may reflect more subtle WM incoherencies (Riley *et al.*, 2010). Additionally, according to Shon *et al.*(2010), the extensive diffusion abnormalities found in left TLE in patients with and without HS, indicate "a lesion side-specific distribution of the pathology".

Table 6.1 Studies on white matter in adults with epilepsy

		Epileptic group						Control group			
Study	syndrome	N	Age (yrs)	♀/♂	Age onset (yrs)	Duration of illness (yrs)	Seizure free (hr)	N	Age (yrs)	♀/♂	White matter abnormalities
Structural											
Hermann *et al.,* 2003a	TLE	58	34.1 SD 11.3	40:18	12.5 SD 8.7	21.4 SD 12.2	-	61	33.4 SD 12.6	37: 25	TLE ↓total cerebral WM volume
Hermann *et al.,*2003b	Early onset TLE	16	26.8 SD 11.1	11:5	6.3 SD 3.8	20.5 SD 13.8	-	15	29.1 SD 10.9	9:6	Early onset TLE ↓ Corpus callosum volume
	Late onset TLE	16	39.2 SD 9.9	11:5	20.7 SD 6.2	18.5 SD 9.3	-				*Note: groups were matched on both gender and handedness*
McMillan *et al.,*2004	Unilateral TLE (left/right 13:12)	25	32.23 SD 11.2	-	11.95 SD 9.07	19.09 SD 12.34	-	61	32.42 SD 12.18	-	TLE ↓ WM ipsilateral temporal lobe TLE ↓ volume corpus callosum right TLE ↓ WM fornix left TLE ↓ WM bilateral prefrontal area
DTI											
Rugg-Gunn *et al*., 2001	Partial epilepsy with cerebral injury	10	Median 36 range 20-53	1:10	-	21 range 2-48	≥24 h Except 1	30	Median 30 Range 20-50	20:10	PTs cerebral injury: ↓FA, ↑diffusivity PTs no cerebral injury: 2PTs↓FA, 8PTs↑diffusivity LTLE:↓FA, ↑diffusivity left TL WM
	Partial epilepsy without cerebral injury	30	Median 36 range 18-55	13:17							
Arfanakis *et al.,*2002	TLE	15	31.6 ± 8.9	-	-	-	-	15	29.7±11 .2	-	TLE : ↑ mean λ2 posterior and anterior CC ↑ mean λ2 & λ 3 EC ↓ FA values EC and posterior CC
Gross *et al.,*2006	Unilateral TLE with MTS (left/right 7:4)	11	38 range 24-54	8:3	9.81 range 1-39	27.72 range 12-47	-	14	32 range 24-54	-	TLE: ↓ FA values in genu of CC and EC ↑ ADC⊥ values in genu, splenium and EC
Concha *et al*., 2007	TLE and unilateral MTS Seizure-free 1 year after surgery	8	range 22-61	6:2	-	range 12-47		22	31 range 19-54	8:16	Before & after surgery ↑λ⊥, ↑MD and ↓FA in: • fornix • cingulum • external capsule • genu of the corpus callosum
Ahmadi *et al.,*2009	TLE (left/right 10:11)	21	37.3 SD 19	11:10	14.3 SD 11.5	23.0 SD14.6	-	21	33.0 SD 10.2	11:10	TLE ↓ FA values in ipsilateral: • CG • PH • ILF • IFOF • SLF
Riley *et al.,*2010	Unilateral TLE (left/right 9:2) 1Left >>Right interictal	12	37.9, SEM 3.2 range 20–52	9:3	14.33 range 1-39	22.75 range 9-51	-	10	42.1 SEM 3.1 range 33–55	4:6	LTLE ↓ FA ipsil. IFOF, SLF, FORX, and ATR and contral. CG,ATR, and IFOF RTLE ↓ FA ipsilateral ILF TLE ↓ FA values ipsilateral to seizure focus: • anterior TL (UF) • posterior MTL (fornix) • cerebellum TLE ↑ FA values contraletral to seizure focus: • frontoparietal lobe (AF)
Shon *et al.,*2010	Unilateral TLE-HS (left/right 12:7)	19	34.1 ± 10.3	13:6	17.1±10.7	17.0±10.4	≥24 h	20	30.6 ± 7.9 range 15–46	10:10	Left TLE-HS ↑ MD ipsilateral posterior cingulum, isthmus of corpus callosum, and contralateral occipital and temporal regions
	TLE-NH (left/right 10:8)	18	30.2 ± 7.4	10:8	19.1±7.7	11.1±7.8	≥24 h				Left TLE-NH ↑ MD ipsilateral posterior fornix and posterior cingulum

λ2, λ 3, second and third eigenvalues, diffusivities along directions that are perpendicular to the primary diffusion direction, and to each other; CC, corpus callosum; EC, external capsule; CG, cingulum fibers; PH, parahippocampal fibers; ILF, Inferior longitudinal fasciculus; IFOF, inferior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus; FORX, fornix ; ATR, anterior thalamic radiations; TL, temporal lobe; UF, uncinate fasciculus; MTL, mesial temporal lobe; AF, arcuate fasciculus; PT, patient

7. White matter changes in animal models of epilepsy

The previous chapters clearly show that studying epilepsy, especially in children, is a huge challenge. Small sample sizes and the heterogeneity of the groups (e.g. different epileptic syndromes, gender, age, duration of illness, age of onset) result in large limitations, which are hard to overcome. Therefore animal models for epilepsy can provide good alternatives to obtain a better insight in epileptogenesis and in the consequences of seizures for white matter integrity. Although a large variety of animal models are available for different syndromes, the main focus of this chapter will be animal models for partial epilepsy.

7.1. Animal models for partial epilepsy

Animal models for partial epilepsy should meet several of the following criteria to be reliable. These criteria include, similar EEG activity patterns compared to the human epileptic syndrome, similar etiologies, similar age of onset, similar pathological changes, similar response to AEDs with similar mechanisms, and similar behavioral characteristics.

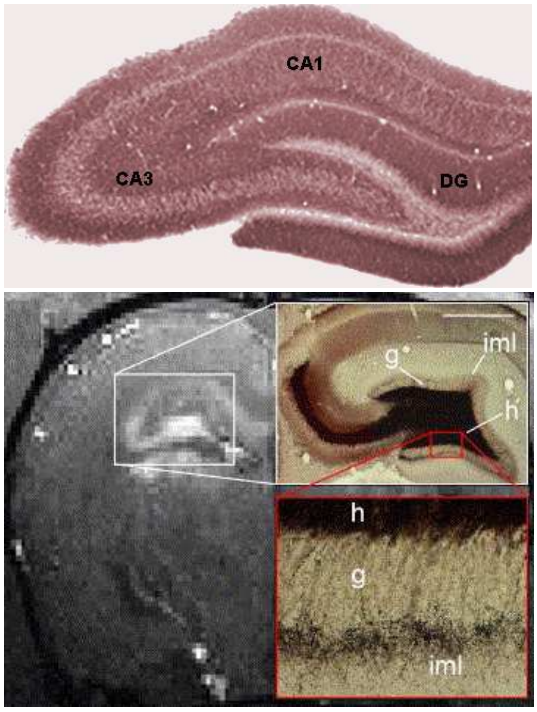
Partial epilepsy models induce seizures by several different techniques. Simple partial seizure can be caused by focal application of inhibitory amino acid blockers (e.g. penicillin), cortically implanted metals (e.g. aluminum), acute focal electrical stimulation, focal application of excitatory agents (e.g. glutamate agonists), GABA withdrawal, and freeze lesions to skull surface (Sarkisian, 2001). Complex partial seizures can be induced by tetanus toxin, systemically injected acids (e.g. kainic acid), administration of pilocarpine or soman, area tempesta injections, and Kindling (Sarkisian, 2001).

In TLE models, the kainic (KA, a glutamate analogue) and pilocarpine (PILO, a cholinergic agonist) seizure induction methods are most commonly used (Sarkisian, 2001). After injecting an animal (most often rodents) with one of these substances, acute seizures are induced with subsequent status epilepticus. After a quiescent period of several weeks, the rodent develops spontaneous recurrent seizures. In addition, the injection of KA or PILO causes behavioral characteristics in the rodent, similar to human epileptic patients. Furthermore, the rodents develop lesions, similar to patients with mesial temporal sclerosis. The major downside of this model is that it does not work in rodents younger than P20 (Sarkisian, 2001). In young rodents, KA or PILO injections induce a first seizure but they do not develop status epilepticus with spontaneous seizures. The only available juvenile TLE model for rats is the lithium-pilocarpine induced status epilepticus model (Wu *et al.,*2001). However, white matter abnormalities have not yet been examined with this model.

7.2. White matter in TLE animal models

The vast majority of studies examining TLE in animal models using MRI and DTI, focus on gray matter pathology. Righini *et al*. (1994) showed decreased ADC values in the amygdala and periform cortex of rats, 24 hours after KA SE induction. Subsequently the ADC values in these areas increased. Zhong et al. (1995) also reported temporally depressed ADC values after seizure discharge in flurothyl-induced status epilepticus in rats. Wang et al. (1996) showed decreased postictal ADC values, in the pyriform cortex, amygdala, and hippocampus, in KA induced epileptic rats. However, seven days later the ADC values returned to normal. These studies show that diffusion is not static but dynamic and that it can be influenced by epileptic state. Unfortunately, they did not examine ADC values of white matter tracts.

Nairismagi *et al.*(2006) investigated mossy fiber plasticity in the KA TLE animal model. Mossy fibers are white matter tracts of unmyelinated axons, which originate from the granule cells of the dentate gyrus (DG) of the hippocampus and project to the cornu ammonis 3 (CA3) region (Nairismagi *et al.,* 2006). Mossy fibers are thought to be involved in the epileptogenesis of TLE after suffering from a first seizure or status. Nairismagi *et al.*(2006), examined mossy fiber sprouting in 20 adult male Wistar rats (14 KA-treated; 6 controls; weight 303 ± 24 g). Manganese-enhanced magnetic resonance imaging (MEMRI) was used to investigate the mossy fibers. Mn2+ solution is injected in the rodents and subsequently enters cells through voltage gated Ca2+ channels. Mn2+ is a paramagnetic MRI contrast agent, which is used in MEMRI to enhance the signal to improve the T1-weighted images (Nairismagi *et al.,* 2006).



7.1. Rat hippocampus
a. cross-section rat hippocampus; b. Mn enhancement in T_1-weighted MRI of rat hippocampus, most pronounced signal in the same area that appears dark in Timm staining (c); c. sprouting mossy fibers in Timm staining; d. inner molecular layer (iml) showing sprouted mossy fibers in greater detail; CA, cornu ammonis; DG, dentate gyrus; g, granule cell layer; h, hilus; b-d Nairismägi *et al.,* 2006

By using this technique, Nairismagi *et al.*(2006) found experienced increased mossy fiber sprouting in both the supragranular region and inner molecular layer of the dentate gyrus of KA-treated animals (Figure 7.1).

Parekh and colleagues (2010) investigated changes in the parahippocampal gyrus in an animal model of chronic limbic epilepsy. They induced self-sustaining status epilepticus (SE) by hippocampal electrical stimulation in 14 males Sprague-Dawley rats (mean weight 302±66 g). Twelve rats underwent surgery for electrode implantation in the right ventral hippocampus. The two remaining rats did not undergo surgery, as they served as age-matched controls. After 7-14 days post-surgery the rats were stimulated to induce a self-sustaining SE. MRI scans were made prior to the electrode implantation, post-electrode implantation, and at day 3, 5, 7, 10, 20, 40, and 60 post-SE (Parekh *et al.,* 2010). Subsequently the animals were divided into three separate groups namely a control group (n=3), a spontaneous seizure (SS) group (n=8) and a non-spontaneous seizure group (NS) group (n=3). The SS group was examined for differences in three different phases, the acute phase (MRI session at day 3-5 post SE), the latent phase (MRI sessions between 5 days post-SE and before onset of SS), and the chronic phase (MRI sessions after onset of SS to 60 days post-SE). Compared to the control rats, reduced fimbria (white matter tract of the hippocampus) thickness was observed in all SS rats (Figure 7.2a black arrow). In addition, FA values in the fimbra/fornix in the SS group was also reduced for all time points in vivo and in excised imaging (Figure 7.2b) Furthermore, FA values in the region of mossy fibers were significantly increased in the SS group compared to the controls. Additionally, reduced myelin staining was observed in the contralateral piriform cortex of the SS group (Figure 7.2c).

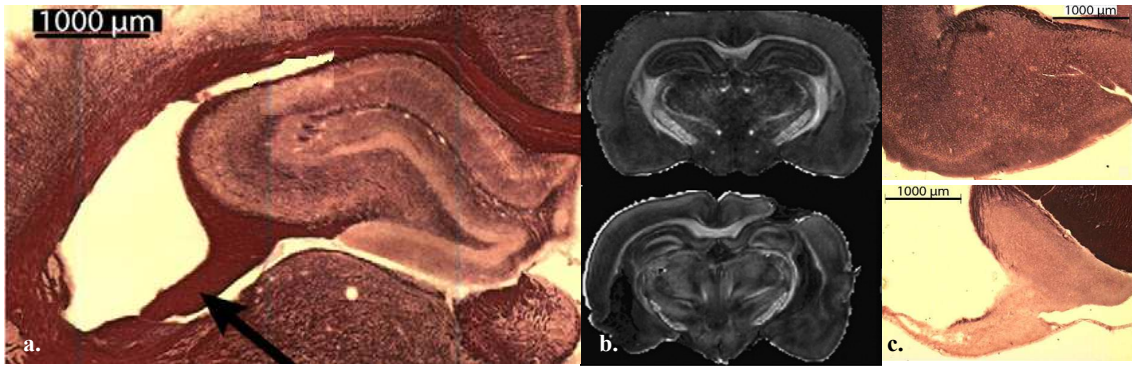


Figure 7.2.**White matter abnormalities in epileptic rats (Parekh *et al.*, 2010)**
a. Black Gold staining in the contralateral hippocampus of SS rat, black arrow reduced fimbria thickness; b. FA excised brain, upper image control rat, lower image SS rat; c. black gold II myelin staining, upper image controls, lower image reduced myelin piriform cortex and amygdala SS rats.

Summary

Although a limited number of studies using animal models of partial epilepsy investigated white matter, abnormalities seem to be present in animals with induced partial epilepsy (Nairismagi *et al.*2006; Parekh *et al*., 2010). Nairismagi *et al.* (2006) reported increased hippocampal mossy fiber sprouting, in rats treated with KA injections. Parekh *et al*. (2010) found decreased fimbria thickness and reduced myelin in the periform cortex in rats with self sustaining status epilepticus. In addition, FA values were decreased in the fimbra/fornix at all time points. Large longitudinal studies investigating white matter in partial epilepsy combing both structural MRI and DTI are lacking from the literature.

8. Discussion

In this thesis the literature on white matter abnormalities and development in children with partial epilepsy was reviewed. The aim of this study was to provide an overview of the current knowledge of white matter in children suffering from parietal epilepsy. Therefore, studies of healthy WM development, WM in children with parietal epilepsy, adults with parietal epilepsy, and animal models of parietal epilepsy have been discussed.

8.1 WM development in healthy children

In healthy children, white matter development starts in the second trimester of pregnancy and continues into late adolescents and early adulthood (Yakovlev and Lecours, 1967 in Lenroot and Gied, 2006; Benes *et al.,*1994; Knaap and Valk, 1995). Volumes of total cerebral WM, total central WM and total corpus callosum WM, increase with age (Yakovlev and Lecours, 1967; Caviness *et al*., 1996; Giedd *et al.,* 1999; Lenroot and Giedd, 2006; Knickmeyer *et al.*, 2008). In addition, DTI studies revealed increased in FA values with age, while ADC values decreased (Hüppi *et al.* 1998; Mukherjee *et al*., 2001; Gilmore *et al*. 2004; Schmithorst *et al.,* 2002; Gilmore *et al*., 2007; Lebel *et al*., 2008). Young children ranging from 0-2 years showed the most rapid increase in FA values, compared to older children (Mukherjee *et al*., 2001). In addition, Lebel *et al*.(2008) examined 16 white matter tracts in children, adolescents and adults between 5-29 years old and showed that FA values most rapidly increase and MD values rapidly decrease in children. Several studies reported differences in WM development between boys and girls (Caviness *et al*., 1996; Giedd *et al*., 1999), while others did not (Lenroot and Giedd, 2006; Allen *et al*., 1991).

From these studies we can conclude that major changes in white matter seem to occur during childhood. It is however hard to make any statements about the exact time course of WM development in the different brain regions, as the majority of these studies used both small samples sizes and cross-sectional designs (Allen *et al*., 1991; Caviness *et al.,* 1996; Schmithorst *et al*., 2002; Gilmore *et al*., 2004, 2007) . The largest longitudinal study (n=511) was provided by the National Institute of Mental Health (NIMH), Lenroot and Giedd (2006). However, they only used volumetric analyses of WM and did not examine young children between 0-6 years old, while drastic WM changes seem to occur during this age range (Mukherjee *et al*., 2001). In contrast to the previous study, Mukherjee *et al*. (2001) conducted a large DTI study on younger infants, but used a clinical population of children with an unequal number of boys and girls in a cross-sectional design (n=153; mean age 3.5; girls/boys 58:95). In addition, Gilmore *et al*., investigated WM using DTI in the youngest infants of 43 weeks, gestational age but examined a rather small time span in a cross-sectional design. The largest DTI study was conducted by Lebel *et al*. (2008) but unfortunately they used a cross-sectional design and did not examine children under the age of five.

Large longitudinal MRI studies, combing structural MRI with DTI in newborns, children and adolescents are lacking from the literature. The National Institute of Mental Health, is one of the few institutes who conducted a large longitudinal study on brain development in healthy children and adolescents (Lenroot and Giedd, 2006). Unfortunately only volumetric data of both gray and white matter from children between 4-18 years old have been published so far. However, this longitudinal study is ongoing, data is still being collected, newborns are included and DTI scans have been added to the protocol (Almli et al., 2007). Hopefully in the future the results of these longitudinal studies will provide us with more detailed information on white matter development in newborns, children and adolescents.

8.2 WM in children with partial epilepsy

The fast majority of the studies on children with partial epilepsy investigated gray matter abnormalities. Based on the few studies examining white matter in children with partial epilepsy, we can conclude that these children seem to have disturbances in white matter volume and several diffusion parameters (Kimiwada *et al*., 2006; Caplan *et al*., 2008; Govindan *et al.*, 2008; Nilsson *et al*., 2008; Hermann *et al.,*2010; Hutchinson *et al*., 2010; Widjaja *et al*., 2010). The majority of these studies used cross-sectional designs and small heterogeneous groups (Kimiwada *et al*., 2006; Caplan *et al*., 2008; Govindan *et al.*, 2008; Nilsson *et al*., 2008; Hutchinson *et al*.,

2010). However, two structural MRI studies used a longitudinal design and reported no significant changes in WM volume with age (Hermann *et al.,* 2010; Widjaja *et al*., 2010). In addition, Hermann *et al*. (2010) showed that total WM, temporal, frontal and parietal WM, significantly increased with age in the healthy control group. Although the majority of the sample from this study included children with localization related epilepsy, children with generalized epilepsy have also been included. In addition, adults with early onset TLE showed a significant decreased corpus callosum volume, compared to patients with late onset TLE and controls (Hermann *et al*., 2003b).

The DTI studies used cross-sectional designs (Kimiwada *et al*., 2006; Govindan *et al.*, 2008; Nilsson *et al*., 2008; Hutchinson *et al*., 2010). Although most studies investigated different white matter tracts, overall FA values were decreased, wile ADC, MD, diffusivity and perpendicular diffusivity values were increased in the children with partial epilepsy (Govindan *et al.*, 2008; Nilsson *et al*., 2008; Hutchinson *et al*., 2010).Nevertheless, the samples were small (ranging from 8-19children), included both girls and boys, children with both partial seizures with different foci and generalized seizures, with different ages at onset, and durations of illness.

Additionally, with the exception of Nillson *et al.*(2008), all studies failed to mention whether the children were seizure free 24 hours prior to the MRI scan (Kimiwada *et al*., 2006; Caplan *et al*., 2008; Hermann *et al.,* 2010; Widjaja *et al*., 2010). This is a major confounding factor, because the alterations found in these studies could reflect changes of both the periictal state (the period during and directly after a seizure) and interictal state (period between seizures). It is important to discriminate between these states, as periictal MRI abnormalities are thought to be the direct consequence of the seizures, whereas abnormalities found in the interictal state are believed to reflect the possible cause of the seizures or the chronic consequences of frequent seizures for the structural integrity of white matter (Raghavendra, 2007; Yogarajah *et al.,* 2009). In both human and animal studies, ADC values tend to decrease in the periictal state (Righini *et al*., 1994; Yogarajah *et al.,* 2009). However, in the interictal state, ADC values are increased, while FA values are decreased (Kimiwada *et al*., 2006).

It is clear that the field of childhood epilepsy research would greatly benefit from large longitudinal MRI and DTI studies, in which children undergo an MRI scan after a first seizure and subsequently are scanned multiple times during their development (even after remission). By using such a design, a clear overview can be obtained of the WM development of each child.

8.3 Similar DTI abnormalities in children and adults with partial epilepsy

In the majority of the DTI studies on partial epilepsy in both children (Govindan *et al.,* 2008; Hutchinson *et al*. 2010) and adults (Arfanakis *et al.,* 2002; Gross *et al.,* 2006; Concha *et al*., 2007; Riley *et al.*, 2010), discussed in this thesis, the decreased FA values in several white matter tracts were most probably the result of increased perpendicular diffusivity. Furthermore these abnormalities seem to persist after seizure control (Concha *et al.,* 2007). Although it is still unknown what these diffusion abnormalities exactly mean several explanations, concerning both axons or myelin have been proposed. The explanations include axonal swelling due to recurrent seizures (Govindan *et al.* 2008), disrupted axon myelination (Hutchinson *et al.* 2010), myelin abnormalities (Arfanakis *et al.* 2002; Concha *et al*.2007), myelin degeneration (Gross *et al.,* 2006), disturbances in axon density (Concha *et al*.2007), increased permeability of the axon membranes, and less tightly packed neuronal network (Arfanakis *et al.* 2002).

Rugg-Gunn *et al*. (2001) also found decreased FA and increased diffusivity, without measuring the parallel and perpendicular diffusivity. They speculate that it could be caused by disturbed microstructural environment due to, for example, recurrent seizures. In addition Ahmadi *et al*.(2009), also found decreased FA values in several WM tract without examining other diffusion parameters, while Shon *et al*., (2010) found increased MD without examining FA. Nilsson *et al*.(2008) is the only study that reported increased trace (total diffusivity), parallel ($\lambda_{\parallel}$) and perpendicular ($\lambda \perp$) diffusivity, while no differences between FA values of patients and controls were found. They speculate that their results "may reflect an increase in the extracellular fluid space due to degeneration of fibers or edema".

Conclusions

White matter disturbances, in both volume and diffusion parameters, are present in a variety of structures in children with partial epilepsy (Caplan *et al*., 2008; Govindan *et al.*, 2008; Nilsson *et al*., 2008; Hermann *et al.,*2010; Hutchinson *et al*., 2010; Widjaja *et al*., 2010). However, the small sample sizes, heterogeneous groups and most often cross-sectional designs used in these studies, make it hard to draw conclusions. Volumetric studies showed disturbed white matter increases with age in children wit partial epilepsy, and in adults decreased WM volumes were present (Hermann *et al.* 2003a, 2003b,2010; McMillan *et al.,*2004; Widjaja *et al*., 2010). In both children and adults with partial epilepsy, the majority of the studies show decreased FA values, increased perpendicular diffusivity and mean diffusivity in several white matter tracts (Arfanakis *et al.,* 2002; Gross *et al.,* 2006; Concha *et al*., 2007; Govindan *et al.,* 2008; Hutchinson *et al.*

2010; Riley *et al.*, 2010). These diffusivity disturbances seem to be irreversible, as they persist after seizure control (Concha *et al.,*2007). The exact meaning of these diffusion abnormalities are unknown, but myelin or axon abnormalities have been suggested (Arfanakis *et al.,* 2002; Gross *et al.,* 2006; Concha *et al*., 2007; Govindan *et al.,* 2008; Hutchinson *et al*. 2010; Riley *et al.*, 2010). Further research is needed to unravel the meaning of these abnormal diffusion patterns. Additionally, it is unclear whether these diffusion abnormalities are present before seizure onset or whether they are caused by recurrent seizures. Large longitudinal studies, combining both structural MRI and DIT in animals, healthy children (adolescents and adults) and children (adolescents and adults) with partial epilepsy are needed to provide a better understanding of these white matter abnormalities.

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