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MR Diffusion Tensor Imaging: A Window into White Matter Integrity of the Working Brain

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Abstract

As Norman Geschwind asserted in 1965, syndromes resulting from white matter lesions could produce deficits in higher-order functions and “disconnexion” or the interruption of connection between gray matter regions could be as disruptive as trauma to those regions per se. The advent of in vivo diffusion tensor imaging, which allows quantitative characterization of white matter fiber integrity in health and disease, has served to strengthen Geschwind's proposal. Here we present an overview of the principles of diffusion tensor imaging (DTI) and its contribution to progress in our current understanding of normal and pathological brain function.

Keywords

Diffusion tensor imaging; White matter; Cognition; Psychiatric and neurological diseases

Introduction

In 1965, Norman Geschwind, an American neurologist, published ‘Disconnexion Syndromes in Animals and Man’ (Geschwind 1965a, b) in which he proposed a disconnectionnist theory that revolutionized clinical neurology and neurosciences research. He asserted that disconnection syndromes resulting from white matter lesions could underlie deficits in higher-order functions, thereby advancing the idea that disconnection of gray matter regions, by interrupting the communication between them, could be as disruptive as

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trauma to those regions per se. Advances in brain imaging methods now permit the exploration of such syndromes and their associated higher-order dysfunctions.

This review aims to provide an overview of the diffusion tensor imaging (DTI) modality of magnetic resonance imaging (MRI) and its contribution to progress in our current understanding of the brain. First presented is an introduction to DTI principles, followed by the role this MR modality has played in uncovering brain structure-function relationships. Highlighted is the concept that not only has DTI provided a means for in vivo exploration of normal white matter pathways and their role in cognition, but it has also enabled identification of systems' alterations or disruptions occurring in neurological and psychiatric diseases.

The central nervous system (CNS) is classically divided into two major components comprising gray and white matter. Gray matter consists predominately of nerve cell (neuron) bodies and their dendrites and glia, including astrocytes, oligodendrocytes, and microglia. White matter is composed of bundles of myelinated axons, the long, slender-projections of nerve cells that connect gray matter regions to one another and carry electrical impulses between neurons. Myelin encapsulates axons to create insulation and allow for rapid propagation of electrical signals. As lipids are the main constituents of myelin, they give white matter its color (Waxman et al. 1995).

Conventional imaging techniques, such as structural MRI, reveal anatomical features of the brain and can be used to characterize tissue quality and to quantify tissue macrostructure in terms of shape and size. DTI permits the interrogation of the brain's microstructure, allowing for a more refined characterization of white matter and the complex network of nerve fibers connecting different brain areas.

A Brief Description of Diffusion Tensor Imaging and Its Capabilities

A number of books and papers are available that provide extensive descriptions of the principles of DTI (Basser and Jones 2002; Chien et al. 1990; Goodlett et al. 2009; Jones 2008; Le Bihan 2003; Le Bihan et al. 2001; Pierpaoli et al. 1996; Poupon et al. 2001; Sullivan and Pfefferbaum 2010). Here, we provide a brief description of DTI, its metrics as used in human neuroimaging studies, and interpretation of those metrics.

DTI takes advantage of the fact that MR images of the brain are predominantly maps of water protons with contrast created by their immediate environment and their motility. In regions with few or no constraints imposed by physical boundaries, such as cerebral spinal fluid (CSF) in the ventricles, water movement is random and uniform in every direction and is therefore isotropic. In contrast to CSF, the path of a water molecule along a white matter fiber is constrained by physical boundaries such as the axon sheath causing movement to be greater along the long axis of the fiber than across it. This movement is called anisotropic; diffusion along the long axis of a fiber (axial or longitudinal diffusion) is greater than diffusion across the fiber (radial or transverse diffusion, (Song et al. 2002)).

The application of several magnetic gradients during image acquisition allows the detection of microscopic water movement. Freely diffusing particles will move more during image acquisition than those with physical restrictions. To characterize the orientation of the diffusion motion in three-dimensional space, observations are made by applying the diffusion gradients in at least six non-collinear orientations. For each voxel, the amount of diffusion is quantified by calculating the ratio of the signals with and without the diffusion gradients for each of the six or more gradient directions, resulting in at least six different diffusion weighted images, each comprising signal decrease due to the movement of water protons in the orientation of that particular gradient application.

DTI quantification requires computation of a tensor, which is a mathematical description of a three-dimensional ellipsoid depicting the magnitude and orientation of diffusion in individual voxels (Fig. 1). The tensor is associated with three corresponding orientational vectors (eigenvectors, λ_1, λ_2, λ_3), describing the diffusion ellipsoid by its major axes. The eigenvalue average, or trace, reflects the magnitude of diffusion, referred to as mean diffusivity (MD) or the apparent diffusion coefficient (ADC). The extent to which one eigenvalue, λ_1, dominates the other two, λ_2 and λ_3, determines the degree of anisotropy, that is, the degree of orientational preference within a voxel, typically measured as fractional anisotropy (FA), ranging between 0 and 1 on a normalized scale (Pierpaoli and Basser 1996). The largest eigenvalue, λ_1, is the axial (or longitudinal) diffusivity, λ_L, and reflects axonal integrity, whereas λ_2 and λ_3 quantify radial (or transverse) diffusivity, $\lambda_T = (\lambda_2 + \lambda_3)/2$, and reflect myelin integrity (Song et al. 2002;Sun et al. 2006) (Fig. 2). Thus, disruption of white matter microstructure detectable with DTI can reflect compromise of myelin, cytoskeletal structure, or axonal density (Basser 1995;Basser and Pierpaoli 1996;Spielman et al. 1996).

FA is the most commonly reported DTI metric, varying in magnitude with the characteristics of the tissue microstructure. For example, FA of the ventricular system, which contains mostly CSF, is near 0, whereas FA of the corpus callosum, where fibers are arranged in a regular and parallel fashion, can approach 0.8 to 0.9. Lower than expected FA (and the typically associated higher MD/ADC) in a region of fully volumed white matter can be an index of compromised white matter integrity. FA, however, is quite sensitive to tissue inhomogeneity from crossing fibers within a voxel (Pierpaoli et al. 2001) and partial voluming (Pfefferbaum and Sullivan 2003). Thus, if the fully volumed white matter voxels are in a region where multiple fiber tracts cross in different directions, such as adjacent to the corpus callosum, FA will be lower, not necessarily because of reduced fiber integrity but because no single orientation predominates within a voxel (Pierpaoli et al. 2001; Virta et al. 1999).

Approaches to Quantifying DTI

Several approaches have been used to quantify DTI metrics, including identification of regions on FA maps or voxel-by-voxel comparison with statistical parametric mapping (SPM; http://www.fil.ion.ucl.ac.uk/spm/) of brains normalized to a common space or template. One of the more desirable approaches is the use of quantitative fiber tracking to depict selective fiber tracts, commissures, and fasciculi.

1/ Whole Brain Analysis

One of the approaches to DTI quantification is voxel-based analysis of whole-brain DTI data, which is useful for identifying regions that differ with respect to diffusion metrics between groups when researchers do not have a-priori hypothesis regarding specific brain region. In voxel-by-voxel analysis, each subject's diffusion images are registered into standard space, and then voxel-wise statistics are carried out to detect regional differences between populations or to find areas that correlate with a covariate of interest. The voxel-based approach is less sensitive than other methods of DTI quantification because spatial normalization processes can be imperfect (see (Snook et al. 2007) for a further description of whole brain DTI quantification methodologies), and a certain amount of residual morphometric differences might remain. A new approach named TBSS, however, aims to remove such differences completely by using a “mean FA skeleton” (Smith et al. 2006) representing the center of fibers that is common to all subjects. Then, in the individual images, FA values can be assessed in the “heart” of the fiber of interest (Douaud et al. 2007).

2/ Region of Interest (ROI) Analysis

When a study is focused on a particular brain region, ROI analysis that involves operator-dependent manual outlining or automated parcellation routines is often employed. ROI analysis is time-consuming and requires practice to achieve adequate measurement reliability. Inaccurate ROI segmentation can result in different degrees of partial voluming. Another problem is the choice of images on which to draw the ROIs. One study overcame this problem by using a tissue segmentation procedure for distinguishing different brain tissue types in the tensor images and then applying ROIs based on anatomical images to the segmented DTI data (Pfefferbaum et al. 2000b). Overall, while manual ROI placement has its own challenges, it can provide complementary information and convergent validity to whole-brain analysis and furthermore allows relevant correlational analyses with cognitive measures.

3/ Quantitative Fiber Tracking and Tractography

The degree to which the diffusion orientation of a voxel is similar to its neighbors, that is, show orientational coherence between voxels (Jones et al. 1999; Pfefferbaum et al. 2000b), serves the conceptual basis for quantitative fiber tracking (e.g., (Fillard and Gerig 2003; Goodlett et al. 2009; Le Bihan 2007; Mori et al. 2005)) and provides exquisite visual modeling of fiber systems (Fig. 3). Analogous to following the linear trajectory of the longitudinal axis of bricks in a path, intervoxel coherence requires that neighboring eigenvectors do not vary by more than a set criterion and that intravoxel FA reaches a minimum value. An advantage of quantitative fiber tracking over other methods of DTI quantification is the ability to measure the diffusion properties of isolated fiber tracts along their full extent. A number of methods are now available for fiber identification and tracking quantification (e.g., (Goodlett et al. 2009; Le Bihan 2007; Mori et al. 2005)).

DTI Examination of Normal Development and Aging

1/ Brain Structure-Function Relationships

Compromise of white matter integrity contributes to age- and disease-related cognitive decline (Catani and ffytche 2005; Catani and Mesulam 2008a; Catani and Thiebaut de Schotten 2008). Indeed, the functional ramifications of DTI metrics have been regularly verified with observations of correlations between regionally-specific low FA or high diffusivity (i.e., MD/ADC) and poor cognitive (Bucur et al. 2008; Grieve et al. 2007; Madden et al. 2007; O'sullivan et al. 2001a; Schiavone et al. 2009; Shenkin et al. 2003), or motor (Sullivan et al. 2001; Sullivan et al. 2010a) test performance. Both whole brain (Turken et al. 2008) and tractography (Correia et al. 2008) analyses have confirmed that changes in normal appearing white matter are related to worse performance on tests that rely on processing speed and executive functioning (Malloy et al. 2007).

DTI has revealed radiological evidence for regional and sometimes widespread degradation of white matter systems that have been interpreted by some as “disconnection syndromes.” Perhaps a more measured consideration of the rather subtle microstructural derangement detectable with DTI is that the imaged white matter has compromised integrity suggestive of a “incomplete lesion” (see (Sullivan and Pfefferbaum 2005)). Nonetheless, examples of DTI-based “disconnection syndromes” include “functional” disorders such as schizophrenia (Okugawa et al. 2006; Wiser et al. 1998), autism (Frith 2001), and dyslexia (Demonet et al. 2004). In dyslexia, for example, both ROI and whole brain analyses have demonstrated reduced FA in left and right temporo-parietal white matter and in the left superior longitudinal fasciculi: FA values positively correlated with performance on a variety of reading tests (Carter et al. 2009; Klingberg et al. 1999). In another example, conventional MRI revealed little regarding the structural alterations underlying cognitive dysfunction in

ischemic leukoaraiosis. Yet, when FA was measured, significant differences in normal-appearing white matter emerged and correlated with executive dysfunctions as assessed by the Wisconsin Card Sorting Test in patients with ischemic leukoaraiosis compared with age-matched control subjects (O'sullivan et al. 2001b). In Asperger's syndrome, severity of social impairment, as measured by the Autistic Diagnostic Interview, negatively correlated with FA in fibers of the left superior cerebellar peduncle, suggesting a specific vulnerability of cerebellar neural pathways in individuals with Asperger's syndrome (Catani et al. 2008a).

Functional correlates of regional fiber tracking are also recognized, and a few examples are provided here (for review see (Sullivan et al. 2010a)). In alcoholics, for example, a recent study identified a double dissociation: higher diffusivity in sensory-motor and parietal bundles was associated with poor balance, whereas higher diffusivity in prefrontal and temporal bundles was associated with slowed psychomotor speed (Pfefferbaum et al. 2010). Also in alcoholics, the number of fibers per volume between the midbrain and pons, particularly low when compared to controls, correlated with an index of cognitive flexibility (Chanraud et al. 2009b) (Fig. 4). In normal aging, a large and multifactorial battery of neuropsychological tests reduced to three factor scores revealed that the Problem Solving and Working Memory factor scores correlated with indices of callosal genu and fornix integrity, whereas the Motor factor correlated with a widespread set of fiber systems, likely reflecting the multiple brain loci required to execute the motor tasks, which included measures of speed, dexterity, and choice reaction time (Zahr et al. 2009). Similarly, quantitative fiber tracking was used in young and older adults to measure FA in the genu and splenium (Pfefferbaum et al. 2010) of the corpus callosum and in the superior longitudinal fasciculi. In these subjects, components of decisional and non-decisional performance were also assessed from a task switching paradigm involving word categorization. FA in specific regions of the genu and splenium was found to mediate age-related differences in performance on the decisional component of the task (Madden et al. 2009). A combined DTI-based tractography and functional MRI (fMRI) study recently dissociated two distinct pathways involved in language processing (Saur et al. 2008). The dorsal pathway, usually thought to be the major language pathway, was restricted to sensory-motor mapping of sound to articulation (sublexical repetition of speech), whereas the ventral pathway was found to subserve higher-level language comprehension (linguistic processing of sound to meaning).

2/ DTI and White Matter Development

The interest in applying DTI to studies of normal development and aging has been fueled by the recognition of white matter's role in cognition and by evidence for significant changes in white matter over the course of the life span. The development of cognitive functions during childhood relies on several neuroanatomical maturation processes including myelination of fibers, which facilitates electrical conduction. DTI has allowed investigators to track age-related white matter changes and more particularly axonal growth and myelination during childhood and adolescence. Overall, DTI studies have revealed age-related decreases in diffusion magnitude (i.e., MD/ADC) and increases in anisotropy (i.e., FA) in a number of white matter regions, such as the arcuate fasciculus (Schmithorst et al. 2002; Snook et al. 2005). Such changes in DTI-derived measures may indicate ongoing maturation of the axon and its myelin sheath. Recently, FA and transverse diffusivity were demonstrated to be structural markers of functionally efficient myelination in childhood (Dubois et al. 2008). DTI can therefore track the course, timing and spatial distribution of functional development of the brain in children and adolescents (Giorgio et al. 2010; Goodlett et al. 2009; Mabbott et al. 2009; Rose et al. 2007; Westlye et al. in press).

The most dramatic changes in white matter occur during infancy. Rapid myelination during this period is reflected by changes in nearly all white matter measures including volume,

diffusivity, myelin water, and macromolecular metrics. In infancy, increased FA correlates with decreased grey matter density in cortical areas that may reflect synaptic pruning (Klingberg et al. 1999; Olesen et al. 2003). At adolescence, association and projection fibers, including those supporting cortical and brain stem integration become mature and may contribute to known enhancements in reaction time during this period. On the other hand, maturation of prefrontal-striatal connections, known to support top-down executive control of behavior (Liston et al. 2006) continues through adolescence. Tractography studies have also revealed that white matter of the corpus callosum, the corticospinal tract, and the uncinate fasciculus continues to mature in adulthood (Eluvathingal et al. 2007; Giorgio et al. 2008; Lebel et al. 2008). Together, these findings suggest that white matter connectivity supporting executive control of behavior is still immature in adolescence (Asato et al. in press) and thus may underlie the increased vulnerability to emergence of psychopathology (Luna et al. 2004; Paus et al. 2008), mortality due to risk-taking behavior (Spear 2000), and head trauma (Levin 1993) at this stage of development.

3/ DTI and White Matter Aging

Findings of age-related differences in white matter were first observed through post-mortem studies revealing specific alterations to anterior white matter systems (Kemper 1994; Peters and Sethares 2002) with a particular vulnerability of small fibers in the anterior corpus callosum (Marner et al. 2003). Degradation of myelin and microtubules and even axons deletion accompany normal aging (Aboitiz et al. 1996; Marner et al. 2003; Meier-Ruge et al. 1992). Quantitative in vivo studies using conventional MRI have provided consistent evidence for systematic age-related volume expansion of CSF-filled spaces, including sulci, fissures, and ventricles, that occur largely at the expense of cortical gray matter with little evidence for macroscopic volume change in white matter [e.g. (Blatter et al. 1995; Good et al. 2001; Pfefferbaum et al. 1994; Raz et al. 1997; Sullivan et al. 2001), but see, (Jernigan et al. 2001; Raz et al. 2005; Westlye et al. in press)]. By contrast, even in “normal appearing white matter” and in regions where volume declines were not detectable, DTI has provided evidence for microstructural degradation of white matter (O'sullivan et al. 2001a). Indeed, with advancing age and senescence, a consensus maintains a decrease in FA in brain white matter (Abe et al. 2002; Chepuri et al. 2002; Chun et al. 2000; Head et al. 2004; Helenius et al. 2002; Madden et al. 2004; Malloy et al. 2007; Nusbaum et al. 2001; O'sullivan et al. 2001a; Pfefferbaum et al. 2000b; Salat et al. 2005); that is similar in men and women (Hsu et al. 2008; Ota et al. 2006; Sullivan et al. 2001) and which is also characterized by an anterior-posterior gradient of decline (Ardekani et al. 2007; Bucur et al. 2008; Grieve et al. 2007; Madden et al. 2007; Pfefferbaum and Sullivan 2003; Salat et al. 2005; Sullivan et al. 2006; Takahashi et al. 2004; Yoon et al. 2008). Diffusivity measures increase but follow a similar but inverse (i.e., increase) pattern (Engelter et al. 2000; Head et al. 2004; Helenius et al. 2002; Naganawa et al. 2003; Pfefferbaum et al. 2005; Pfefferbaum and Sullivan 2003) and highlight an age effect on anterior white matter systems (Pfefferbaum et al. 2005). Quantitative fiber tracking confirms focal DTI measures of an anterior-to-posterior pattern of disruption of white matter integrity (Davis et al. 2009; Falangola et al. 2008) as, for example, the elderly have lower FA and higher diffusivity than the young in anterior but not posterior sectors of the fibers coursing through the corpus callosum (Hasan et al. 2008; Pfefferbaum et al. 2007; Sullivan et al. 2006). These cross-sectional studies have recently been confirmed with longitudinal analysis (Sullivan et al. 2010b). Recent work also supports a superior-inferior gradient of aging effects on white matter (Stadlbauer et al. 2008; Sullivan et al. 2010a; Zahr et al. 2009), whereas pontocerebellar and cerebellar hemisphere white matter tracts are relatively preserved (Stadlbauer et al. 2008; Sullivan et al. 2010a). Regarding relationships of DTI measures with neuropsychological performance, a longitudinal DTI study recently has revealed that global white matter diffusivity explained 10.8% of the variance in working memory across 2 years with no contributions to working

memory performance from white matter hyperintensities or volumes (Charlton et al. 2010). Thus, DTI seems to provide stronger markers of cognitive decline than classical MRI methods. To date, few whole-brain DTI analyses have been carried-out in samples spanning from children to elderly (Hasan et al. 2007; Westlye et al. in press); these studies diverged from volumetric ones in their findings, thus so far little is known about regional DTI changes across the life span.

DTI in Neurological and Psychiatric Conditions

This section is intended to provide examples, rather than an exhaustive review, of neurological and neuropsychiatric conditions that DTI has served to identify subtle white matter disruption that may contribute to—or in large part account for—functional impairment or at least compromised function. Where possible, we will provide references to recent reviews on specific diseases or conditions.

1/ Human Immunodeficiency Virus (HIV) Infection

HIV infection has a strong predilection for the brain (Masliah et al. 2000), with upwards of 90% of AIDS patients manifesting CNS lesions (Trillo-Pazos and Everall 1997). The first application of DTI to the study of HIV infection reported that DTI was capable of detecting toxoplasmosis and progressive multifocal leukoencephalitis (Chang and Ernst 1997). Even though DTI has not been helpful in identifying patients with early HIV infection (Thurnher et al. 2005), it has been able to reveal microstructural abnormalities in tissue appearing normal with conventional MRI including periventricular white matter and corpus callosum (Filippi et al. 2001; Pomara et al. 2001; Schaefer et al. 2001; Stebbins et al. 2007). Moreover, diffusion abnormalities in the splenium of the corpus callosum in patients infected with HIV was correlated with dementia severity and motor speed losses (Wu et al. 2006) and an interactive effect of age- and disease-related diffusivity changes have been observed in the genu of the corpus callosum (Chang et al. 2008). In several studies, DTI metrics quantified in the brains of HIV-infected subjects correlated with signs of disease severity, namely CD4 count and viral load (Filippi et al. 2001; Ulug et al. 2000). High diffusivity in selective regions of the HIV infected brain might reflect inflammatory responses to the infection. Examination with DTI may also serve to identify interactions with common comorbidities, most notably progressive multifocal leukoencephalopathy (Paul et al. 2002), alcohol use disorders (Pfefferbaum et al. 2002), and dementia (Chen et al. 2009; Pfefferbaum et al. 2009b) and to detect and track repair with positive pharmacological treatment. HIV associated dementia is the most advanced stage of central nervous system disease caused by HIV infection. Even though nondemented patients with HIV present diffusion metrics abnormalities, patients with associated dementia have higher diffusivity in the parietal white matter (Chen et al. 2009); in this study, both region of interest and voxel-based analyses revealed that radial diffusivity was affected to a much greater extent than longitudinal diffusivity by HIV infection suggesting that demyelination is the prominent alteration occurring in white matter. A quantitative fiber tracking study examined FA and MD in fibers from genu and splenium of the corpus callosum in HIV-infected men and women, with and without comorbidity for an alcohol use disorder. Compared with controls, the HIV group that was not comorbid for an alcohol use disorder had non-significantly lower FA and higher MD in both callosal regions. Two other concomitants of HIV infection, however, proved significant modifiers of callosal integrity: HIV-infection comorbid for alcoholism resulted in FA and MD values with .65 to 1.2 standard deviations from control values, and an AIDS-defining event occurring with alcoholism produced ~1.5 to 2 standard deviation abnormalities in both the anterior and posterior sectors of the corpus callosum (Pfefferbaum et al. 2007). Quantitative survey of brain fiber tract integrity carried-out in a recent study indicated that all HIV patients, regardless of presence or absence of dementia,

may have neuroradiological evidence for damage in association and commissural tracts (Pfefferbaum et al. 2009b).

2/ Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD)

DTI has been efficient in providing biomarkers helping in the identification of individuals at greatest risk of progressive decline such as those with MCI. For example, DTI has identified the left posterior cingulate gyrus as a region that can be used to distinguish individuals with MCI from cognitively normal individuals (Chua et al. 2009). In AD, DTI has demonstrated lower FA and higher diffusivity in a clinically significant region, i.e., the temporal lobe (Bokde et al. 2009). High MD has also been reported in patients with mild to moderate AD in other regions, including the temporal stem (Hanyu et al. 1998; Kantarci et al. 2001), anterior and posterior cingulate gyri (Kantarci et al. 2001; Rose et al. 2000; Takahashi et al. 2002; Zhang et al. 2007), and the corpus callosum (Duan et al. 2006; Sydykova et al. 2007; Teipel et al. 2007; Xie et al. 2006). Low FA in the left cingulate bundle, which connects the anterior thalamus, cingulate gyrus, prefrontal, and parietal cortices with the retrospenial cortex, parahippocampal gyrus, and presubiculum, correlated with impaired performance in a verbal recognition task and the Boston Naming test in AD patients (Fellgiebel et al. 2008). Also, a study based on histogram analysis of voxel-based distributions of diffusivity observed significant AD-related abnormalities in gray matter of the temporal but not parietal lobe, which correlated with scores on the mini-mental state examination (Bozzali et al. 2001). A follow-up study of FA and diffusivity in AD patients suggested that white matter FA and diffusivity abnormalities in these patients are due to Wallerian degeneration of fiber tracts secondary to neuronal loss in cortical regions (Bozzali et al. 2002). Taken together, these studies demonstrate the utility of DTI in detecting disruptions to regional white matter microstructure in AD and indicate that DTI could enable early detection of this disease, as well as pathological mechanisms underlying the disruptions. In this pathology, simultaneous quantification of a variety of DTI metrics has the potential of distinguishing different types of microstructural damage, e.g., a decrease in anisotropy along with an increase in diffusivity may indicate disruption to the microtubule system and to myelination, whereas decreases in both anisotropy and diffusivity may indicate a gliotic reaction to cell death (Pfefferbaum and Sullivan 2010).

3/ Multiple Sclerosis (MS)

Multiple sclerosis (MS) is characterized by perivenular inflammation with demyelination and incomplete remyelination (Hu et al. in press). In multiple sclerosis, abnormal DTI metrics have been reported within the lesions, and also in grey matter and normal appearing white matter (for review, see (Filippi and Rocca 2008)). Alterations in grey matter and normal appearing white matter are only partially related to focal lesions and thus not likely entirely due to retrograde degeneration of axons (Rovaris et al. 2005). Disease duration and neurological impairment seem to contribute to the severity of changes in DTI metrics. Furthermore, relationships between DTI metrics and the severity of language, attention, and memory deficits in these patients have been observed (Rovaris et al. 2002). There are only a few studies that used tractography in MS patients. All these studies focused on specific fiber tract, especially on the pyramidal tract; and found an alteration in the connections that was responsible for motor impairment (Lin et al. 2007; Pagani et al. 2005; Wilson et al. 2003). Then recently, Hu et coll., applied tractography method with seeds in both sides of the central semiovale in order to get more global fiber tracts, including cortical projection fibers, association fibers and cortical fibers. Lower fiber density was observed in MS patients compared to controls after fibers' reconstruction and fibers' density in patients was directly related to their clinical impairment (Hu et al. in press).

4/ Closed Head Injury

Head injury is the third leading cause of death in people younger than 45 in the United-States. Whereas conventional MRI has failed to correctly estimate the extent of damage following head injury, DTI provided information regarding injury severity as well as markers predictive of outcome and may therefore serve as a potential biomarker of recovery (Mayer et al. 2010). In animal studies, DTI has been used to detect early (0 to 4 h) pathophysiological consequences of cerebral ischemia in localized brain regions. In traumatic brain injury, high water diffusion indicative of bulk flow of extracellular fluid is likely indicative of vasogenic edema (Hanstock et al. 1994), whereas low water diffusion with no apparent orientation is likely indicative of cytotoxic edema. Indeed, diffusivity maps have been used to differentiate lesions with decreased or increased diffusion (Huisman et al. 2003). In a recent study, whole-brain analysis of head injury survivors at least 6 months after the injury revealed significant bilateral decreases in anisotropy in the major of white matter bundles evaluated and increases in diffusivity in most of the cortex, likely reflecting secondary damage. In the same cohort, impairment of learning and memory correlated with diffusivity in the left posterior cingulate, left hippocampal formation, and left temporal, frontal, and occipital cortices (Salmond et al. 2006).

More recently, the same pattern of results was described in 35 patients suffering of a traumatic brain injury. These patients were evaluated in two follow-up visits, 2 months and 1 year after brain injury, with DTI and morphometric scans and whole brain analysis and with neuropsychological assessment (Bendlin et al. 2008). Both cross-sectional and longitudinal analyses revealed FA and diffusivity abnormalities in all the major white matter bundles examined: corpus callosum, cingulum, superior and inferior longitudinal fasciculi, uncinate fasciculus, and brain stem fiber tracts. Despite persistent white matter compromise, neuropsychological performance at the second visit was globally better than for the first visit. Thus, memory function and executive function were only minimally related to brain measures, suggesting that functional compensatory mechanisms could take place over time even without radiologically-detectable evidence for recovery. Thereafter, a region of interest analysis using parcellation methods focused on the exploration of the thalamus, because this structure is highly involved in sensory and motor gating and thus a majority of cognitive processes. FA was extracted from seven regions of the thalamus and used as seeds for fiber tracking reconstruction. Relative to controls, the 24 patients with a history of brain injury showed FA deficits in fibers identified from seed voxels in the anterior and ventral anterior thalamic nuclei with functional ramifications. Specifically, links emerged between FA in fibers reconstructed from the thalamic seed voxels and executive function, attention, and memory (Little et al. 2010). Even in children, DTI has proved sensitive to white matter injury at 3 months following moderate to severe head injury, even in brain regions appearing normal on conventional MRI. Thus, DTI measures, especially those derived from fiber tracking analysis, can be good markers of outcome as they were related, in the same patients, to global outcome and cognitive processing speed (Levin et al. 2008).

5/ Alcoholism

Recent work in alcoholism has focused on “uncomplicated alcoholics,” that is, individuals that meet objective criteria for alcohol dependence but do not present complicating conditions that are frequent concomitants of alcoholism, such as clinically detectable nutritional deficiency, head injury, severe hepatic disease, cancer, or significant cardiovascular problems. In chronic uncomplicated alcoholism, postmortem neuropathological studies have demonstrated a particular vulnerability of brain white matter (Badsberg-Jensen and Pakkenberg 1993; De la Monte 1988; Harper 1998; Harper et al. 1985). Alterations include regional white matter volume deficits, demyelination, loss of myelinated fibers, and axonal deletion (Alling and Bostrom 1980; Harper and Kril 1989;

Harper et al. 1987; Kril et al. 1997). Conventional MRI studies are consistent with postmortem studies revealing white matter volume shrinkage in the cerebrum (Hommer et al. 2001; Pfefferbaum et al. 1992; Pfefferbaum et al. 1997) and corpus callosum (Estruch et al. 1997; Pfefferbaum et al. 1996). In vivo DTI has proved to be sensitive to the detection of white matter degradation indicated in postmortem study. The brains of alcoholic men demonstrate lower FA in the corpus callosum and centrum semiovale than age- and sex-matched controls (Pfefferbaum et al. 2000a). In addition, alcoholics illustrate an age-alcoholism interaction, where older alcoholics had higher diffusivity in callosal genu and splenium than would be expected with respect to their age (Pfefferbaum et al. 2006). Quantitative fiber tracking has also demonstrated in alcoholics compared with controls greater FA deficits in anterior than in posterior fibers of supratentorial and infratentorial white matter bundles; also, an increase in diffusivity was observed which may indicate myelin degradation; a specificity to alcoholic women was also revealed in this study as white matter degradation was more severe than in alcoholic men in several fiber bundles despite having a similar magnitude of alcohol exposure (Pfefferbaum et al. 2007). The finding of a particular sensitivity of radial diffusivity was replicated in a more recent study revealing effects on all fiber tracks assessed with the exception of the sensory-motor bundle (Pfefferbaum et al. 2010). Even infrequent consumption of large doses of alcohol can cause widespread reductions in FA in adolescents as revealed by TBSS (McQueeny et al. 2009). Regarding to DTI-function relationships in alcoholism, frontal fibers connecting left and right hemispheres predict performance by alcoholics on a coordinated psychomotor task (Rosenbloom et al. 2008), and number of reconstructed fibers running between the pons and the midbrain is related to cognitive flexibility performance of alcoholics (Chanraud et al. 2009b). Also, diffusivity values in the hippocampus grey matter, which is lower in alcoholics than in controls, is related to episodic memory impairment (Chanraud et al. 2009a). A survey of multiple supratentorial and infratentorial fiber systems in alcoholics indicated that DTI changes were correlated with impairment in speeded performance and postural stability (Pfefferbaum et al. 2009a).

6/ Schizophrenia

Schizophrenia generally strikes in late adolescence and affects ~1% of the population (Regier et al. 1993). While some DTI studies observe widespread changes to FA, e.g., in a mixed group of schizophrenic and schizoaffective patients compared with age-matched controls (Nierenberg et al. 2003), other studies have revealed regionally restricted changes such as lower FA in prefrontal white matter tracts, especially of the right hemisphere (Buchsbaum et al. 1998). Even in studies with no evidence of diffusion metrics differences between schizophrenic patients and controls, complementary analyses, either tractography or correlational analyses between diffusion metrics and behavioral data, have exposed different patterns of results between the two groups (Carbon et al. 2003; Kubicki et al. 2002). For example, lower FA is a significant predictor of higher motor impulsivity (Hoptman et al. 2002) and severity of negative symptoms (Shergill et al. 2007; Wolkin et al. 2003), and higher diffusivity is a predictor of greater aggression (Hoptman et al. 2002). For a more complete review, see (Pfefferbaum et al. 2010). Even though not all schizophrenic patients present cognitive impairment, it is a core feature of schizophrenia. Diffusion abnormalities correlates of working memory impairment in schizophrenic patients have been found in thalami and hippocampi bilaterally and left accumbens in a schizophrenic group (Spoletini et al. in press). FA reduction within the right inferior longitudinal fasciculi has been specifically shown to negatively correlate with measures of thinking disorder (Phillips et al. 2009). Interestingly, DTI has enabled differentiating patients with and without cognitive impairment (Perez-Iglesias et al. 2010); in this study several neuropsychological tests were used and for each test, the patient sample was subdivided according to performance (impaired or non impaired); then, white matter FA in impaired and non-impaired subgroups

was compared using a voxel-based analysis. Impairment in cognitive flexibility was associated with reduced FA in the anterior thalamic projections bilaterally and inferior fronto-occipital fasciculus, forceps minor, and left superior and inferior longitudinal fasciculi. Patients exhibiting upper motor impairment showed reduced FA in the forceps minor, inferior fronto-occipital fasciculus, anterior thalamic radiation, and corticospinal and corticopontine tracts.

7/ Autism and Asperger's Syndrome

Autism is a neurodevelopmental disorder with a range of clinical presentations, from mild to severe, referred to as autism spectrum disorders (ASD). Its symptoms include differences from normal development and disabilities in many functional areas, notably social communication skills, fine and gross motor skills, and sometimes intellectual skills. The most common clinical sign is social-interaction impairment, which is associated with verbal and nonverbal communication deficits and stereotypies and compulsive behaviors (Zilbovicius et al. 2006). Asperger's syndrome is an autism spectrum disorder, which differs from other ASD by its relative preservation of linguistic and cognitive development. The first published study examining DTI in autistic children showed lower FA values in the genu and rostral body of the corpus callosum in high functioning autistic male children and adolescents compared with controls (Barnea-Goraly et al. 2004). Such callosal abnormalities have been interpreted as evidence for poor information integration dependent on interhemispheric communication (Melillo and Leisman 2009). This pattern of results was confirmed in another study of high functioning subjects with autism compared with controls matched for age, handedness, IQ, and head size. Three subregions (genu, body and splenium) of the corpus callosum showed significant differences in volume, FA, mean diffusivity, and radial diffusivity between groups. In genu and splenium of the autistic group, FA was positively correlated and radial diffusivity was negatively correlated with performance IQ assessed with Weschler scales (children or adults), whereas IQ was negatively correlated with MD in the total corpus callosum and within each subregion for the autistic participant group (Alexander et al. 2007). A whole brain exploration using TBSS later indicated that adolescents with autism had significantly lower FA in the right posterior limb of internal capsule with complementary higher radial diffusivity distally and longitudinal diffusivity centrally. Also, relative to unaffected controls, the autistic group had significantly greater FA in the frontal lobe (with lower radial diffusivity), right cingulate gyrus (reduced radial diffusivity), bilateral insula (reduced radial diffusivity and increased longitudinal diffusivity), right superior temporal gyrus (reduced radial diffusivity), and bilateral middle cerebellar peduncle (reduced radial diffusivity). Notably, aberrant white matter changes during this stage of development appeared in the 25 adolescents tested, expressed by opposite pattern of age-related FA changes compared to the one in controls (Cheng et al. 2010).

A novel method using a new DTI segmentation algorithm (Fletcher et al. 2007) was used for the specific exploration of the arcuate fasciculus microstructure in subjects with autism. Impairments in language development and functioning have great relevance to autism (Zilbovicius et al. 2006), highlighting the importance of the arcuate fasciculus, a white matter fiber tract highly involved in language (Catani and Mesulam 2008b). DTI was used to infer white matter integrity in the arcuate fasciculi, which was automatically extracted from the imaging data using the new volumetric method. The results showed significantly higher MD in the autism than control group, due mostly to high radial diffusivity, again implicating myelin disruption. A test of the lateralization of DTI measurements showed that both MD and FA were less lateralized in autistic than unaffected individuals. This pattern of results likely represents the manifestation of complex microstructural changes and suggests that the language specialization occurring in the left arcuate during adolescence of healthy subjects

is not as evident in autism, which may be related to poorer language functioning (Fletcher et al. in press).

Focusing on specific tracts, two studies revealed white matter abnormalities in subjects with autistic disorder (Kumar et al. in press; Pugliese et al. 2009). The first one investigated limbic circuits that underlie social behavior and emotions in healthy subjects. In this study, microstructural integrity and age-related differences in the extended limbic pathways were examined in Asperger's syndrome and controls. Tractography quantified limbic tract-specific diffusion metrics and volumes, estimated from the number of streamlines derived from the DTI analysis. The parcellated limbic circuits included the inferior longitudinal fasciculus, inferior frontal-occipital fasciculus, uncinate fasciculus, cingulum, and fornix. There were no significant between-group differences in FA and MD. Compared with controls, however, subjects with Asperger's syndrome had significantly more streamlines bilaterally in the cingulum and inferior longitudinal fasciculus but fewer streamlines in the right uncinate fasciculus. An age-related between-group difference was described in mean diffusivity of the left uncinate fasciculus indicating differences in the maturation of this limbic tract. Even though correlations of DTI metrics with neuropsychological measures was not investigated, these findings converge on previous reports on anatomical, metabolic, and functional differences in the limbic regions of people with ASD (Haznedar et al. 2000; Siegel et al. 1992).

The cingulate cortex is part of a network that participates in tasks associated with empathic cognition, social behavior and pain perception. This region has been reported to be significantly less activated during social tasks in people with ASD than controls (Di Martino et al. 2009). The right uncinate fasciculus participates in a network underpinning episodic memory and autonoetic awareness (Levine et al. 1998); and the inferior longitudinal fasciculus plays an important role in social tasks requiring recognition of face emotion expression (Kleinhans et al. 2008). Therefore, brain regions highlighted in this study as being anatomically different in subjects with autism than in controls, seem to be organized in a network connecting the cingulum to other tracts and involved in social cognition and emotions (Pugliese et al. 2009). The other study focused on major frontal lobe tracts (uncinate fasciculus, inferior fronto-occipital fasciculus, arcuate fasciculus, cingulum and corticospinal tract) and corpus callosum exploration in children with autism, nonautistic developmentally impaired children, and typically developing children, using tractography and TBSS methods. Lower FA in the right uncinate fasciculus, cingulum, and corpus callosum was observed in children with autism and those with developmental impairment; bilateral inferior fronto-occipital fasciculus in developmentally impaired children was also compromised. Diffusivity was high in right arcuate fasciculus in both groups of impaired children. Interestingly, higher fiber volume of bilateral uncinate fasciculus and right arcuate fasciculus were found to be positively associated with severity of symptoms (stereotypic behavior, social isolation, and overall autistic triad symptoms evaluated with the Gilliam Autism Rating Scale-2nd Edition (Gilliam 1995)). Also, the alteration found in the arcuate fasciculus is consistent with language impairment characteristic of autism. Again, tracts showing alterations in the autistic group are those known to be involved in socio-emotional and language functions.

Conclusions

DTI is a quantitative, noninvasive imaging method that provides insight into properties of brain microstructure. It is especially used for tracking white matter fibers and to address anatomical connectivity in the human brain. DTI has added substantially to our understanding of the human brain and of the relationships between disturbance of white matter integrity and neuropsychological functioning and its vulnerability to disease, trauma,

and aging. Its application in the study of psychiatric and neurological disorders has successfully identified subtle connection abnormalities and is quickly becoming part of many routine clinical protocols. The noninvasive properties of DTI enable evaluation of both normal and pathological changes in white matter and brain connectivity during the course of a disease and across the entire human life span. All studies described in this chapter highlight the consequences of disorder of cerebral networks on cognitive functions and dependent on white matter connectivity. Although a cortical abnormality may result in functional impairment specific to that region, abnormal cerebral connectivity described as "disconnection syndromes," would result in the impairment in integrating or binding the functions of multiple affected cortical regions. From this perspective, investigation of cognitive deficits require consideration of the relevance of the health of white matter's microstructure and quantification and depiction of connectivity enabled by MR diffusion imaging in assessing syndromes involving multiple, often distant loci and forming the basis of "disconnection syndromes" (Geschwind 1965a, b).

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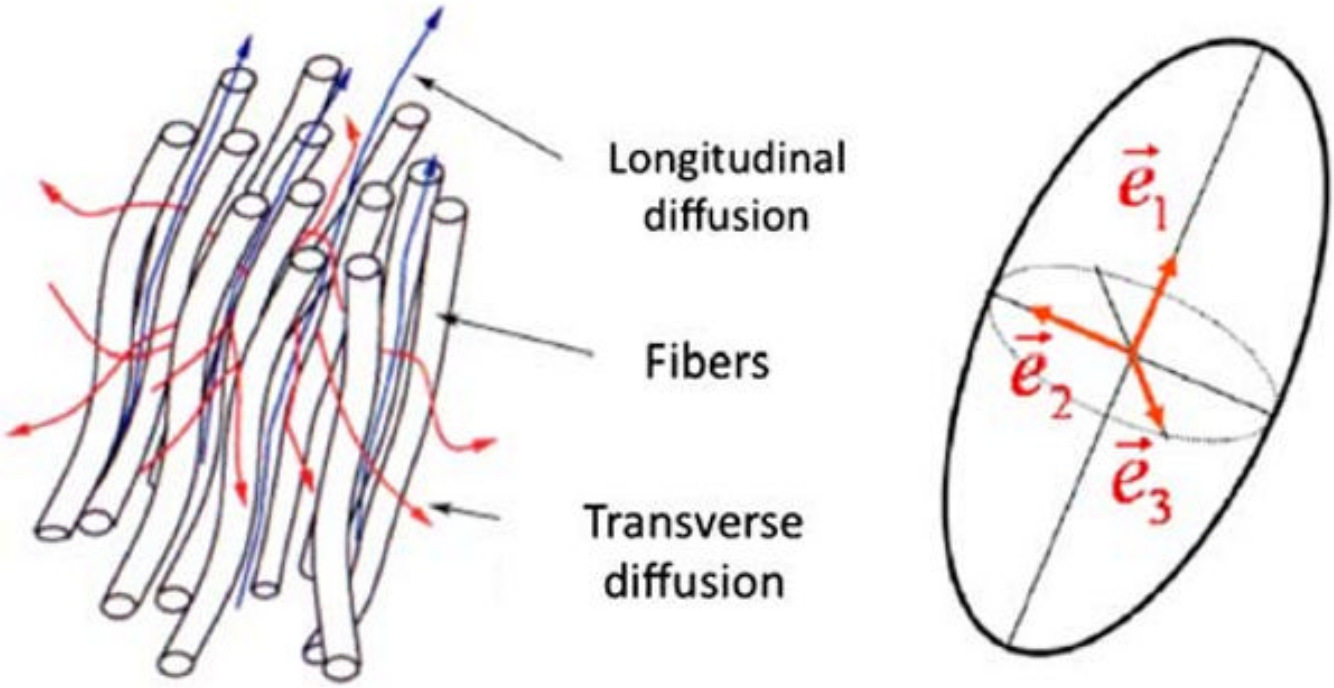

Fig. 1. Model of diffusion of water molecules and its representation by a tensor

Left: Diffusion in anisotropic tissue. Water molecules (movement represented in the *blue* and *red* arrows) preferentially diffuse parallel to fibers. *Right*: Representation of diffusion tensor; ellipsoid with principal axis $\vec{e}_1$ reflecting the preferential orientation of diffusion (longitudinal or axial diffusivity, λ_L); $\vec{e}_2$ and $\vec{e}_3$ are the short axes of the ellipsoid and their mean equals transverse or radial diffusivity, λ_T

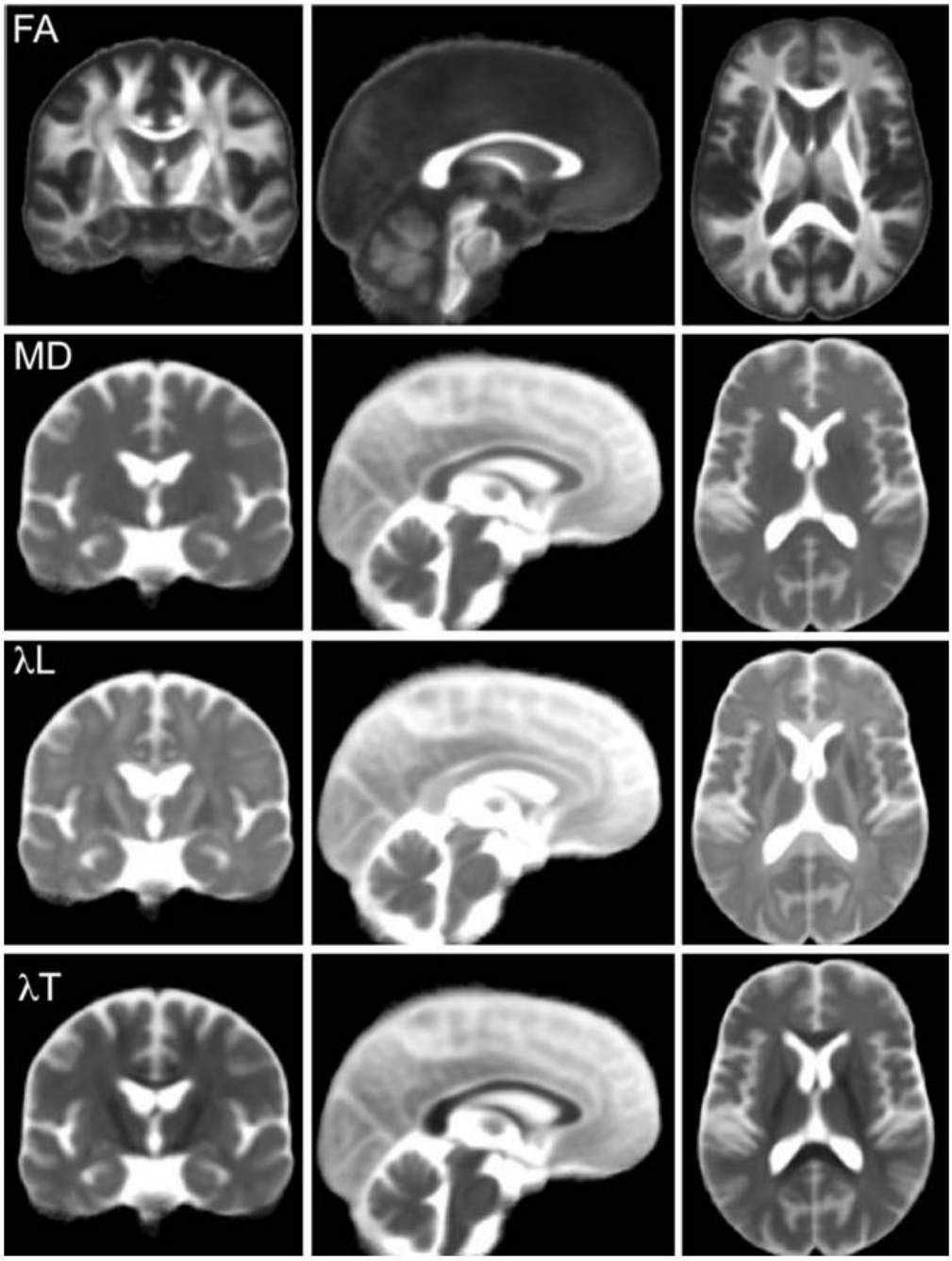

Fig. 2. Diffusion-tensor images

Group average images of FA, MD, λ_L, and λ_T in three views (coronal, sagittal, and axial) generated from 31 men with a mean age of 51 years old. The FA images display white matter as bright white, indicating high linearity and organization of fiber tracts. The MD images display CSF as bright and white and gray matter as dark (for example, note the corpus callosum in the sagittal view). λ_L provides greater visual distinction and regional variability of white matter tracts, with regions of high FA having relatively high λ_L. Conversely, λ_T depicts these white matter tracts as dark (low intensity), indicating low local radial diffusivity

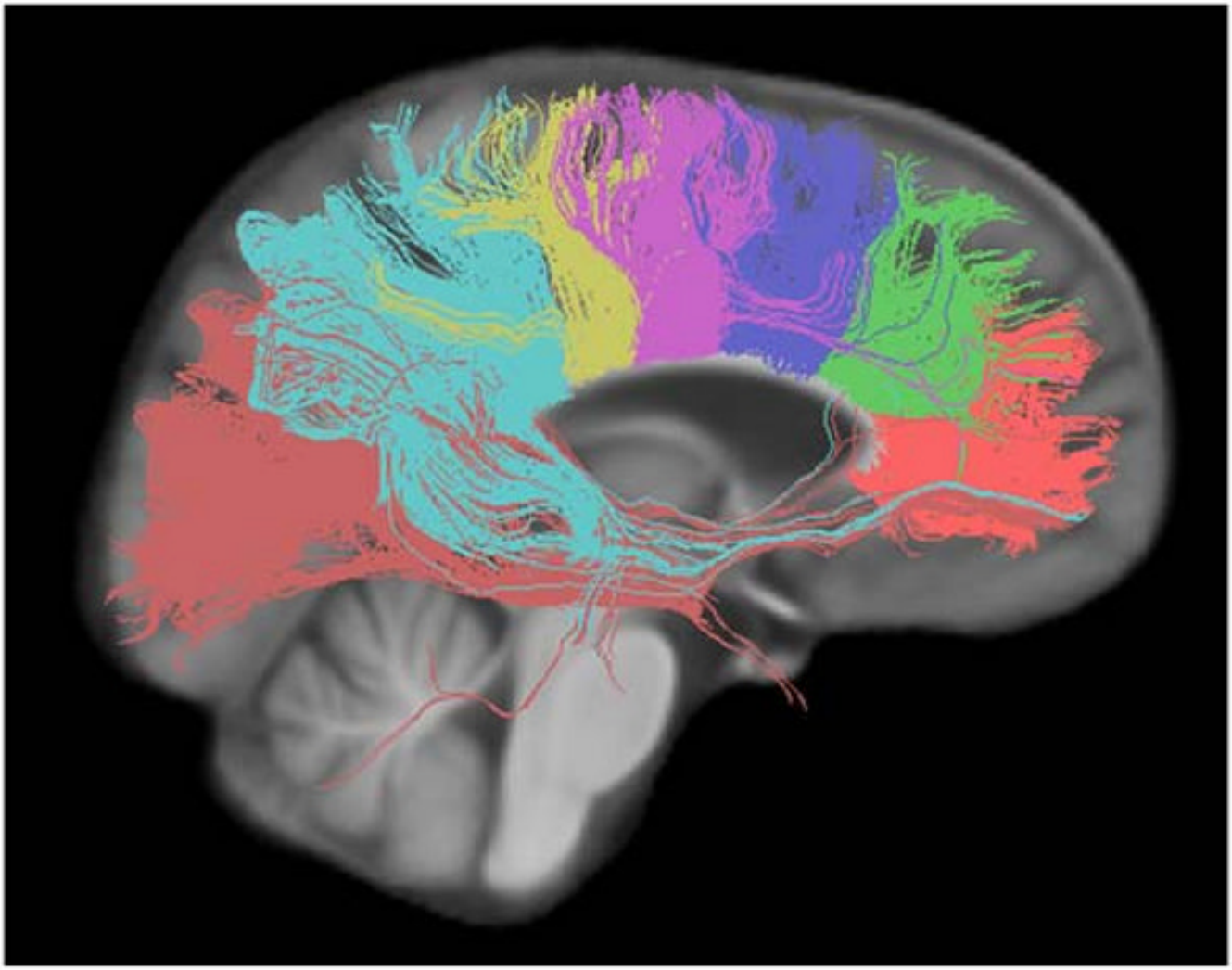

Fig. 3. Illustration of a DTI-based fiber tracking

Fibers reconstructed with the tracking system distributed by G. Gerig (http://www.cs.unc.edu), using 7 geometrically defined sectors of the human corpus callosum, from the genu (*right, anterior fibers*) to the splenium (*left, posterior fibers*). The fiber tracks are displayed on an average mid-sagittal anatomical MRI. Colors are used for differentiating fibers reconstructed from each sources

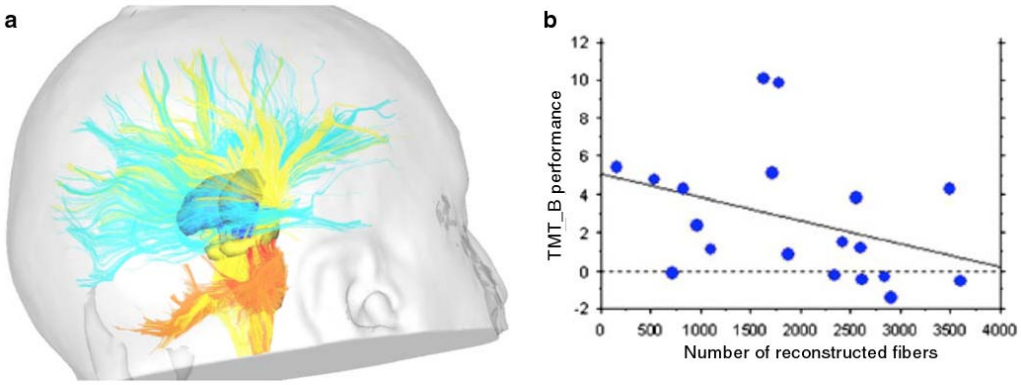

Fig. 4. Tractography results in one healthy subject and correlation between reconstructed fibers and neuropsychological performance in an alcoholic group

a/ 3D view of tractography results in an healthy subject using the pons and the thalamus as sources. *Orange*: Pons and reconstructed fiber bundles connecting the pons and the cerebellum. *Yellow*: Midbrain and reconstructed fiber bundles passing through the midbrain. *Light blue*: Thalamus and reconstructed fiber bundles passing through the thalamus. *Dark blue*: Reconstructed fiber bundles connecting the midbrain to the thalamus. *Red*: Reconstructed fiber bundles connecting the midbrain to the pons. b/ The relationship between number of tracked midbrain–pons fibers per unit of volume and corrected z-scores obtained in the Trail-Making Test part-B (TMT-B) by alcohol-dependent subjects (r^2=-0.154). Lower z-scores reflect better performance