REVIEW ARTICLE

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Diffusion Tensor Imaging and Tractography in Clinical Neurosciences

Abstract: Rapidly evolving MR technology has allowed better understanding of structure and function of the human brain. Diffusion weighted MRI was developed two decades ago and it is now well established in diagnosis of acute ischaemia in patients with stroke. Diffusion tensor MRI uses the same principles but takes a step further allowing us to measure magnitude of the diffusion along different directions. This lead to the development of diffusion tensor tractography, a technique by which major neural pathways in the living brain can be visualized. There is a growing interest in exploring possible use of these techniques in clinical neurology and psychiatry. This article aims to review the principles of this technique and recent discoveries which may help us to better understand neurological and psychiatric disorders.

Keywords: Diffusion Magnetic Resonance Imaging, Neuroscience.

Introduction

MRI technology has made enormous contribution to the advancement of clinical neurosciences within the last two decades and continues to do so. Allocation of this year's Nobel Prize in Medicine and Physiology to Sir Peter Mansfield and Paul Lauterbur who discovered principles of MRI technology is evidence of the importance of this discovery. The impact of MRI technology in understanding the human brain extends from visualization of detailed brain structure to understanding the functions of different neural systems in the living brain. There are many types of MR contrast available for investigating brain structure and function; these include proton density, relaxation characteristics (e.g. T1, T2, etc), blood oxygen level-dependent (BOLD), perfusion and diffusion imaging. The latter has been focus of particular recent attention. One of the most recent advances is diffusion tensor imaging tractography by which visualisation of major neural tracts becomes possible. In this article we review principles of MRI-DTI and tractography and its possible applications in clinical neurosciences.

Physical Basis of Diffusion Tensor Imaging

Diffusion imaging is sensitive to the self-diffusion of water molecules in the brain. This can provide clinically useful information: diffusion-weighted imaging is routinely used clinically to detect acute stroke for example. In this case, the overall diffusivity of water is of interest, regardless of the direction of diffusion. However, there is also interesting information contained in the way in which diffusion differs along different directions. In white matter diffusion is greater along the axis of oriented fibres than against it [Henkelman et al 1994].

The degree to which diffusion differs in different directions is reflected in the measure of fractional anisotropy, and is sensitive to microstructural features of the underlying tissue. By obtaining a series of diffusion weighted images (DWI) with different diffusion-encoding gradients applied, and measuring the signal attenuation at each voxel for each gradient direction, it is possible to measure

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diffusion of water molecules separately along different directions [Basser et al, 1994]. This form of imaging can be described as diffusion tensor imaging (DTI). In DTI the dimentionality of diffusion is estimated as a diffiusion tensor, a type of 3-channel vector. [Basser et al 1994]. In order to provide sufficient information to calculate the six independent elements of the diffusion tensor, diffusion tensor gradients have to be applied in at least six non-collinear, non-coplanar directions [Basser et al 1994].

A geometric approach can be used to represent quantitative parameters provided by diffusion-tensor MRI (DT-MRI). In a geometrical context, the intrinsic quantities characterize different unique features like the size, shape and orientation of displacement profiles within each voxel. These can be displayed as diffusion ellipsoids. Scalar parameters, functionally related to the diagonal and off diagonal elements in the x, y and z planes, can also be displayed as an image, revealing ways in which the tensor field varies from place to place within the imaging volume [Pajevic et al 2002]. These quantities are independent of the orientation of the tissue structures within the MR magnet, the applied diffusion gradients, and the type of coordinate system [Basser et al 1992, 1994].

An important feature of DT-MRI is its ability to represent measures that reveal architectural features of anisotropic structures, such as nerve fibre tracts in the brain. In this context the directional pattern of diffusion ellipsoids within an imaging volume indicates the direction of the fibres. As suggested above, this is due to the fact that the eigenvector associated with the largest eigenvalue within a voxel (i.e., the estimated principal diffusion direction) is parallel to the orientation of the local major fibre bundles [Basser et al 1994]. Therefore, by using the diffusion tensor to estimate the principal diffusion direction at any point in the brain, we can infer the orientation of underlying major fibre bundles. This information can be conveniently visualised in the form of direction field mapping images (Figure 1). In this technique the direction of local fibre bundles is displayed as a vector in each voxel and colour coded according the direction of the vector [Jones et al 1997, Pierpaoli 1997, Pajevic and Pierpaoli 2000, Markis et al 1997, Basser et al 2000]. This display is typically also modulated by an image of fractional anisotropy that reflects the degree to which diffusion differs in different directions at each voxel. In this way, white matter regions, which have high anisotropy, will appear bright on the display. By following estimates of principal diffusion directions from voxel to voxel it is possible to reconstruct the trajectory of major fibre pathways and perform DT-MRI fibre 'tractography'.

Sources of Artefact in DT-MRI

Instrumental artefacts can arise from the MRI machine itself. They are usually due to large, rapidly switched magnetic field gradients which are produced by the gradient coils during the diffusion sequence and which in turn induce eddy currents in the electrically conductive structures of the MRI scanner.

This produces unwanted, rapid and slow decay of magnetic fields. Such artefacts result in changes in the field gradient as well as a slowly decaying field during readout of data which can result in geometrical distortion of the images. To reduce such artefacts use of bipolar diffusion-encoding gradients [Alexander et al 1997] and application of pre-emphasis to diffusion-encoding gradients [Papadakis et al 2000] have been suggested. Improper shimming of the MRI can increase the background gradient resulting in signal attenuation and ultimately inaccurate estimation of the tensor.

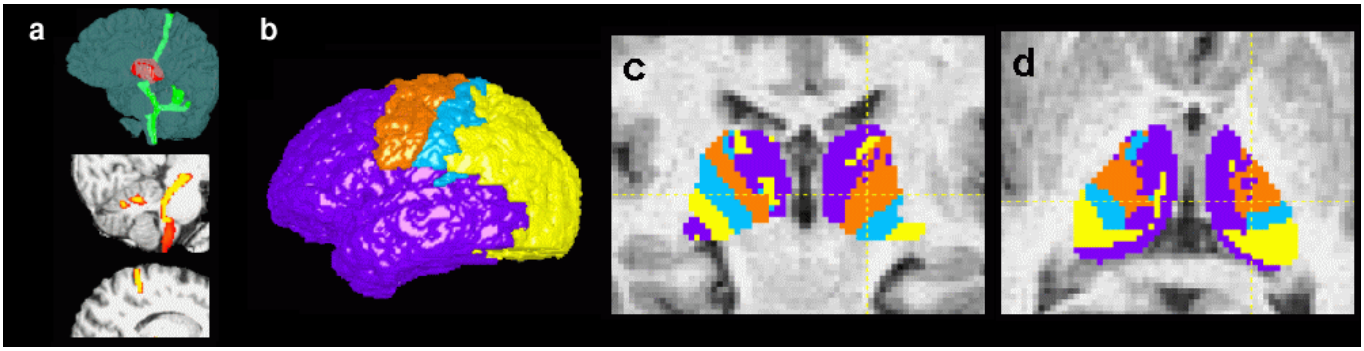

Figure 1: A: Example tract generated from seeding a single voxel in the motor nucleus of the thalamus. This generates ascending motor pathways up to the grey matter of the precentral gyrus and descending pathways down the brainstem and into the cerebellar cortex. B: Subdivision of the cortical surface used to define possible targets of thalamic tracts. C: coronal and D. axial slices through the thalamus. Voxels have been colour coded according to the cortical region with which they show the highest probability of connection. This results in commonly-connected clusters that correspond in size and location to major thalamic nuclear groups. Adapted from Behrens et al, 2003.

Magnetic susceptibility gradients at tissue–air interfaces are another source of image artefact. At this interface large discontinuities in bulk magnetic susceptibility occur which produce local magnetic field gradients that can severely attenuate signal and therefore distort DWIs. Regions adjacent to the sinuses are particularly susceptible to magnetic field distortion [Clark et al 2000]. This susceptibility is positively correlated with the strength of the magnetic field, B0.

Motion artefacts, caused both by the bulk motion of the subject and by pulsatile flow, can cause significant artefacts in diffusion data. Subject motion can be corrected for as part of the post-processing. Effects of pulsatile flow can be minimised by use of a cardiac gated acquisition scheme.

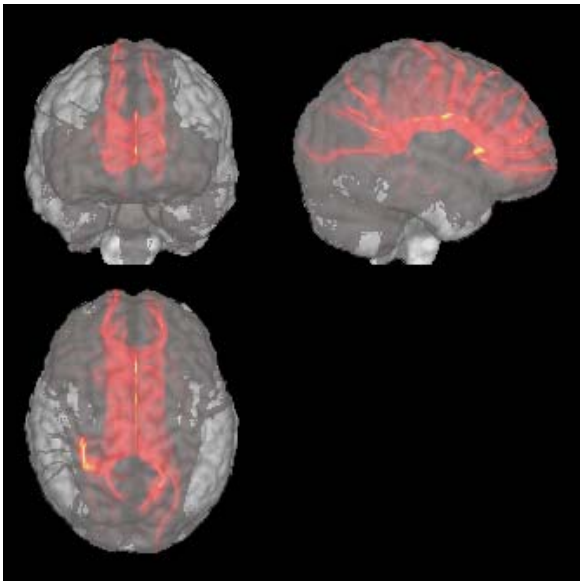

Figure 2: A. Example tract generated from seeding the entire corpus callosum. This generates all interhemispheric connections through the corpus callosum. Note that most anteriors interhemsipheric connection are from frontal lobe and particulay prefrontal cortex. Visual interhemsipheric connections are located posteriorly. These finding is consistent with our previous knowledge regarding the organization of fibers in corpus callosum which is obtained by postmortem histological examination.

This allows for image acquisition to be limited to the quiet phases of the cardiac cycle.

Data limitations can affect the accuracy of subsequence model fitting. Noisy, or too coarsely-sampled data or use of data from voxel-averaged direction fields are common sources of errors [Basser 1998]. In addition, incoherently organized pathways are difficult to follow correctly [Pierpaoli et al 1998, 2001] resulting in apperent connections which are not anatomically accurate present, require the researcher to be particularly vigilant [Basser et al 2000, Jones et al 1999]. This can be a particular problem with 'streamlining' approaches to tractography, in which there is no representation of the uncertainty associated with a particular pathway. Recently developed probabilistic approaches to diffusion tractography incorporate information on the uncertainty associated with estimates of fibre orientation, resulting in a representation of the estimated fibre pathway and also the confidence bounds associated with that estimate (Behrens et al, 2003a).

Studying Anatomy of Human Brain in Vivo Using DT-MRI

Diffusion tractography has been used to track major fibre pathways in the living human brain (Jones et al, 1999; Conturo et al, 1999; Mori et al, 1999). The larger reconstructed pathways are similar to what one would predict on the basis of traditional neuroanatomy (Stieltjes et al,2001; Catani et al, 2002) and are reproducible across individuals (Mori et al, 2002; Jones et al, 2002; Ciccarelli et al, 2003). For example, figure 2 shows interhemispheric connections through the corpus callosum which is consistent with our knowledge of anatomy regarding organization of fibers in the corpus callosum. In addition to confirming results from traditional neuroanatomy, DT-MRI has also been able to provide novel data in cases where existing neuroanatomical evidence is equivocal. For example, although traditional studies have suggested that the inferior longitudinal fasciculus provides a direct route from the occipital to temporal lobes, more recent studies have suggested that only indirect connections exist between these two regions (Tusa and Ungerlieder, 1985). Catani and colleagues used DT-MRI to support the existence of direct occipito-temporal connections from extrastriate to anterior temporal cortex in the human brain (Catani et al, 2003). However caution is still needed in using this young technology. Tracts can be artifactually present (or absent).

The majority of tractography applications have used traditional streamlining approaches to tractography, which can progress only when anisotropy is high. These approaches are unable to trace pathways all the way to their grey matter targets and are therefore limited to visualization of major fibre bundles. By using a probabilistic algorithm for tractography (Behrens et al, 2003a), it is possible to trace fibres into grey matter and this approach has proved successful at tracing thalamo-cortical connections (Behrens et al, 2003b). By classifying thalamic voxels according to the cortical target with which they show the highest probability of connection it is possible to parcellate the thalamus into subregions that correspond to nuclei or nuclear groups (Behrens

et al, 2003b; Figure 3). This parcellation approach could be applied to other grey matter structures. Probabilistic diffusion tractography provides a quantitative method for testing hypothesis concerning clinical groups in whom connectivity in a particular pathway is thought to be disrupted.

DT-MRI in Neurological and Psychiatric Disorders

Stroke

The application of diffusion-weighted imaging in detection of ischemic stroke in the brain is well established. Recent studies show that diffusion tensor imaging can also be useful [Sotak 2003]. For example, using DT-MRI, Werring et al [2000] demonstrated reduced anisotropy (thought to reflect reduced fiber coherence) associated with cerebral infarction in the corticospinal tract remote from the lesion, in five patients 2 to 6 months after ischaemic stroke. They suggested that DT-MRI could be used to detect and monitor the structural degeneration of fiber pathways, which may provide a better understanding of the pattern of clinical evolution after stroke.

In another study Gillard et al [2001] examined ten patients with stroke and showed that six had disruption of white matter tracts as determined by DT-MRI but one had distortion of white matter tracts around an infarct rather than actual disruption of the tracts themselves suggesting that the lack of tract destruction may imply a beneficial prognosis.

Because most strokes lead to disruption of neural pathways in the white matter, visualization of such pathways using DT-MRI tractography might be helpful in predicting disability.

Depression

Alexopoulos et al used DT-MRI to examine older patients with major depression who received open, but controlled, treatment with antidepressant citalopram for 12 weeks. They were interested in determining fractional anisotropy in preselected white matter regions in the frontal lobes. They found that lower fractional anisotropy of the right and the left frontal white matter regions 15 mm above the anterior commissure-posterior commissure plane was associated with a low remission rate. Remission was not significantly associated with fractional anisotropy of lower frontal regions or a temporal region. They concluded that microstructural white matter abnormalities lateral to the anterior cingulate may be associated with a low rate of remission of elderly depression.

Alzheimer's disease

A Japanese group pf researchers used DT-MRI to determine whether the diffusion abnormalities in brains of patients with Alzheimer's disease (AD) correlate with disease severity [Yoshiura et al 2002].

They measured mean diffusivity and fractional anisotropy (FA) as well as the three eigenvalues (lambda1, lambda2, and lambda3) of the diffusion tensor in the posterior cingulate white matter as well as the Mini-Mental State Examination (MMSE) score in 34 patients. Their result showed that mean diffusivity and the three eigenvalues, but not FA, significantly correlated with the MMSE score. They suggested that these measures could be used to monitor disease progression. In another study, Rose

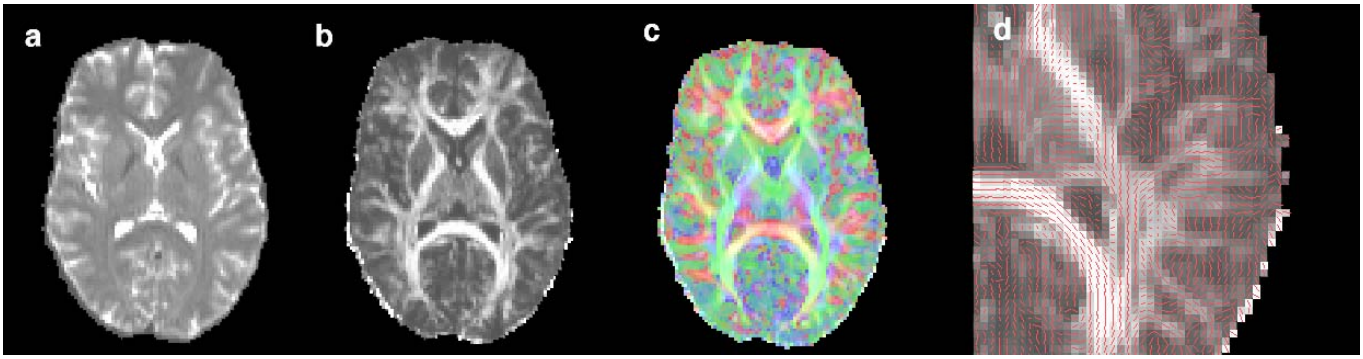

Figure 3: A: T2_weighted axial image. B: Image showing fractional anisotropy at same slice. Note that anisotropy is high in the white matter and low in the grey matter. C. Diffusion tensor information overlaid in colour. Red indicates diffusion principally in the x-direction, green in the y-direction and blue in the z-direction. Therefore the splenium of the corpus callosum shows up red whereas the corticospinal tract traveling through the internal capsule shows up blue. D: Zoomed up image of the corpus callosum with estimates of principal diffusion direction shown by red vectors at each voxel overlaid on a background map of fractional anisotropy. In areas of high anisotropy, such as the corpus callosum, vectors line up with one another.

and colleagues [2000] used diffusion tensor imaging to compare the integrity of several white matter fibre tracts in patients with probable Alzheimer's disease in comparison to normal controls. They showed that patients with probable Alzheimer's disease showed a highly significant reduction in the integrity of the association white matter fibre tracts, such as the splenium of the corpus callosum, superior longitudinal fasciculus, and cingulum but no changes in pyramidal tract.

Schizophrenia

Buchsbaum et al reported the first use of DT-MRI in a study of five patients with chronic schizophrenia and six controls. DT-MRI showed lower diffusion anisotropy in prefrontal white matter. In another study Lim et al showed wide spread white matter decreases in anisotropy, particularly in frontal and occipital regions. Similarly Foong et al found a significant reduction of anisotropy in the splenium of the corpus callosum and adjacent occipital white matter of schizophrenic patients. A follow-up analysis showed that the fractional anisotropy abnormality was not related to T2 prolongation in white matter; such a correlation would have been indicative of greater presence of interstitial water in the schizophrenics [Pfefferbaum et al 1999]. Other studies investigated regional microstructural integrity of the corpus callosum and reported greater diffusivity or lower FA in the splenium but not the genu [Agartz et al 2001]. Kubicki and colleagues used DT-MRI to examine fiber tracts forming temporal-frontal connections. They showed that patients with schizophrenia showed a lack of normal left-greater-than-right asymmetry seen in the comparison subjects.

Neurodevelopmental disorders

Conventional T1 and T2 weighted MR imaging is used for detection of structural brain malformations in children, particularly for abnormal myelination maturation within the first 2 years [Dietrich et al 1988, Martin et al 1988, Martin et al 1991, Brody et al 1987; Barkovich et al 1988; van der Knapp and Valk 1990, Christophe et al 1990, Bird et al 1988, Lee et al 1985, McArdle et al 1987, Dietrich et al 1988, Holland 1986, Barkovich 2000]. More recent studies used diffusion-tensor MR imaging to examine normal myelination patterns in healthy children, measuring anisotropy as a quantitative marker of myelination [Huppi et al 1998, Neil et al 1998, Inder and Huppi 2000]. Miller and colleagues [2003] provided a useful pictorial representation of the changes in brain water diffusion in children from 26 weeks' estimated gestational age to 16 years old (postnatal age) and compared them with the well-known changes of brain maturation found on T1- and T2-weighted MR imaging. They showed that because anisotropy increases with myelination during early brain development of newborns, the anisotropy index also increases. They suggested that anisotropy could be used as an index of brain development.

Many neurodevelopmental disorders are associated with gross or subtle anatomical abnormalities of neural pathways. Since anisotropy is sensitive to micro structural features of tissue such as fibre orientation and myelination, it can be useful in assessing developmental abnormalities during early childhood. In a retrospective study, Mukherjee and colleagues [2001] looked at DT-MRI scans of 153 children (age 1 day to 11 years) with normal T1W- and T2W-MRI. They found a steep nonlinear increase of anisotropy in white matter tracts that paralleled the time course of the decline in diffusion coefficient and correlated with the subject's age. A lesser degree of similar changes were found in the basal ganglia and thalamus. They suggested that diffusion-tensor MR imaging could be used as a surrogate marker for brain maturity in children. In another study Filippi and colleagues [2003] used diffusion-tensor MR imaging to study 20 children with developmental delay and compared them with 10 age-matched healthy children. Both groups of children had normal MRI scans using conventional MR imaging. They measured anisotropy in regions of interest in the centrum semiovale, corona radiata, internal capsule, corpus callosum, and subcortical white matter of the frontal and parieto-occipital lobes. They showed that, compared to healthy controls, children with developmental delay have significantly decreased anisotropy in all white matter fibre tracts studied except the posterior limb of the internal capsule [Filippi et al 2003].

Sommer and colleagues [2002] used DT-MRI to test whether disconnection between speech-related cortical areas was the structural basis of persistent developmental stuttering. They examined 15 people with stutter and 15 closely matched healthy volunteers. They found that the diffusion characteristics of the group with persistent developmental stuttering and controls differed significantly in the region immediately below the laryngeal and tongue representation in the left sensorimotor cortex. There has been far less work on use of DT-MRI-tractography in neurodevelopmental disorders but reports are emerging. For example Hoon and colleagues [2002] examined two patients with cerebral palsy and showed that DT-MRI-tractography might be useful in understanding

clinico-pathological correlations in this heterogenous group of disorders.

Developmental Dyslexia

In a study of developmental dyslexia, Klingberg and colleagues [2000] used DT-MRI and analyzed data using statistical parametric mapping. They showed abnormally low fractional anisotropy selective to the left temporo-parietal region in dyslexia. The reduction in anisotropy in this region correlated with the quantitative measure of reading skill.

Motor Neuron Disease

In a study of 21 patients with MND fractional anisotropy and mean diffusivity along the pyramidal tracts from the internal capsules down to the pyramids was compared with that of 14 normal controls [Toosy et al 2003]. Although changes in both parameters were found along the corticospinal tract, these changes had no correlation with patients' degree of disability.

White Matter Disease

DT-MRI could be particularly useful in study of disorders of white matter like multiple sclerosis and small vessel disease in which major neural bundles are disrupted or demyelinated. For example, Rovaris et al. [2002] performed DT-MRI to assess the magnitude of the correlation between DTI measures (mean apparent diffusion coefficient and fractional anisotropy) and correlated with measures of cognitive impairment in patients with relapsing-remitting multiple sclerosis. They found moderate correlations between symbol digit modalities test, verbal fluency test and 10/36 spatial recall test scores and the DTI measures. In another study O'Sullivan et. al. [2001a] observed fractional anisotropy changes in ischemic leukoaraiosis as a consistent concomitant of vascular dementia. Conventional MRI provides little information about underlying white matter tract disruption and correlates poorly with cognitive dysfunction. However, they found significant changes in fractional anisotropy in the normal-appearing white matter in 30 patients with ischemic leukoaraiosis compared with 17 age-matched control subjects. These changes correlated with executive dysfunction assessed by the Wisconsin Card Sorting Test. This same group also looked at the effects of normal aging with DTI, correlating measured executive skills (the Trail Making Test) with DTI [O'Sullivan et al., 2001b]. While it has been suggested that cortical "disconnection "due to the loss of white matter fibers may play an important role, there has been no direct demonstration of structural disconnection in humans in vivo. They found that diffusion anisotropy was reduced in the white matter of older subjects and fell linearly with increasing age in the older group. Mean diffusivity was higher in the older group and increased with age. In the older group, anterior mean diffusivity correlated with executive function assessed by the Trail Making Test. They conclude that these findings provide direct evidence that white matter tract disruption occurs in normal aging and would be consistent with the cortical disconnection hypothesis of age-related cognitive decline. Maximal changes in anterior WM provide plausible structural basis for selective loss of executive functions.

Conclusion

Although there are only a handful of studies on the application of diffusion tensor imaging and tractography in clinical neurosciences, there is increasing evidence that these techniques may be useful in differential diagnosis of diseases or monitoring disease progress. This is particularly important in disorders involving major myelinating pathways like multiple sclerosis, vascular disorders and neurodevelopmental anomalies.

Acknowledgments

H.J-B is supported by U.K. Wellcome Trust Training Fellowship and M.Z. is supported by U.K. Department of Health Clinician-Scientist Fellowship Award and PMM is the Director of FMRIB Centre and is supported by Research Professorship from MRC, UK.

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