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Imaging white matter diffusion changes with development and recovery from brain injury

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Abstract
Purpose: This study reviews the application of diffusion tensor imaging (DTI) to the study of developmental and pathological changes in brain white matter. The ability to measure and monitor such changes *in vivo* would provide important opportunities for charting disease progression and monitoring response to therapeutic intervention. This study first reviews the use of DTI in studying normal human brain development. It goes on to illustrate how DTI has been used to provide insights into recovery from damage in selected brain disorders.
Conclusions: It is concluded that potential clinical applications of DTI include: (i) monitoring pathological change, (ii) providing markers that predict recovery and allow for individual targeting of therapy, (iii) providing outcome measures, (iv) providing measures of potentially compensatory structural changes and (v) improving understanding of normal brain anatomy to aid in interpretation of the consequences of localized damage.

Keywords: *Diffusion tensor imaging*, *tractography*, *anatomy*, *development*, *recovery*, *imaging*

Revisamos la aplicación de la imagen por tensión de difusión (DTI) en el estudio de los cambios del desarrollo y de los cambios patológicos en la sustancia blanca cerebral. La capacidad de medir y vigilar esos cambios en vivo proporcionará una oportunidad importante para seguir la progresión de la enfermedad y estudiar la respuesta a la intervención terapéutica. Nosotros revisamos inicialmente el uso de la DTI para estudiar el desarrollo del cerebro humano normal. Continuamos ilustrando como la DTI ha sido utilizada para brindar una visión acerca de la recuperación a partir del daño en alteraciones específicas del cerebro. Concluimos que las aplicaciones clínicas potenciales de la DTI incluyen: (i) Vigilar los cambios patológicos, (ii) Proporcionar los marcadores que permitan predecir la recuperación y orientar la terapia en forma individual, (iii) Proporcionar mediciones de resultados, (iv) Proporcionar mediciones de cambios estructurales potenciales para la compensación, (v) Mejorar nuestro entendimiento de la anatomía cerebral normal, con el propósito de ayudar en la interpretación de las consecuencias de un daño localizado.

Introduction

Pathological changes in white matter are important in a number of neurological and psychiatric disorders. The ability to measure and monitor such changes *in vivo* would provide important opportunities for charting disease progression and monitoring response to therapeutic intervention. Diffusion tensor imaging (DTI) provides measures that are related to the structural integrity of the brain white matter. This study explores ways in which such measures have been used to help to understand the processes of development and recovery from damage in selected brain disorders.

DTI is a non-invasive magnetic resonance imaging (MRI) technique. Images are acquired using the same scanner used for conventional MRI but the sequences are modified such that the signal is sensitive to the amount and direction of water diffusion in the brain. These are useful to measure because the amount and directionality of water diffusion depend on structural properties of the tissue that are altered in development or disease. DTI is therefore sensitive to the (typically static) structural integrity of the white matter. In this way, DTI is complementary to functional imaging techniques that provide dynamic measures of brain

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activity as reflected by electrical signals or their hemodynamic correlates. Indeed, many of the most promising applications of DTI in the clinical setting have used the technique in combination with functional imaging.

The usefulness of DTI depends on the fact that water diffusion within tissue with structured organization, such as brain white matter, is not random. Rather, diffusion in such structures displays directional dependence, or 'anisotropy', i.e. diffusion is greater along than across the axis of a bundle. This directional dependence is due to the presence of increased physical barriers to diffusion across the bundle, such as the axon membranes and myelin sheaths [1]. Any pathological process which affects the barriers to diffusion will lead to changes in the measured diffusion signal. Measures derived from DTI are therefore proposed to reflect white matter integrity.

Basic diffusion weighted imaging (DWI), in which diffusion is measured along three orthogonal directions, is used routinely in acute stroke, to quantify increases in diffusivity, as measured by apparent diffusion coefficient (ADC) maps at the site of an infarct. DTI provides additional information about the directional dependence of the diffusion signal. For DTI, imaging data are acquired while applying gradients that sensitize the signal to diffusion along a larger number of different directions (minimum of six). This allows for a mathematical model, known as the tensor model, to be fit to the measurements at each voxel (3-dimensional pixel) in the brain. The tensor model enables diffusion to be considered in 3D. The tensor is fully characterized by the length and direction of its three major axes. These lengths are referred to as the eigenvalues of the tensor, while the directions are its eigenvectors [2, 3]. The long axis of the tensor is the principal eigenvalue and corresponds to the direction along which diffusion is fastest, i.e. the principle diffusion direction or the path of least resistance. In a coherent fibre bundle, this direction typically corresponds to the long axis of an axon.

In the tensor model, the degree to which diffusion is directionally dependent is measured by Fractional Anisotropy (FA), a parameter than can be calculated from the eigenvalues and takes values ranging from 0 (isotropic, i.e. diffusion is equal in all directions) to 1 (anisotropic) [3]. While changes in FA reflect changes in biologically meaningful tissue properties such as myelination, axon diameter or packing density [1], there is not a clear-cut relationship between FA changes and any pathological change and so findings should be interpreted with care. A decrease in FA could reflect a decrease in diffusivity in the principal diffusion direction, an increase in diffusivity in the orthogonal directions or a combination of these changes. To aid interpretation of FA changes, researchers therefore also sometimes report changes in diffusion along the principal diffusion direction, referred to as 'parallel diffusivity', or along the orthogonal directions, referred to as 'perpendicular diffusivity'. Although these measures provide additional information on what is driving observed FA changes, pathological interpretation of such measures is also ambiguous [4–13].

DTI is a relatively new technique that has rapidly been applied to a number of clinical populations. Although it offers exciting possibilities, it also suffers from some limitations. First, as explained above, there is not a one-to-one relationship between change in any DTI parameter and a particular neuropathological (or neurodevelopmental) change. For this reason, one should be cautious in biological interpretation of an observed change in a diffusion parameter. For example, alterations in FA could reflect differences in tract geometry as well as differences in tract integrity. As with any imaging technique, the power and interpretability of DTI depends on the quality of the acquired data and on the validity of the applied analysis techniques. For example, DTI data can be significantly affected by head motion, which impairs data quality and can induce artefacts in the images. Head motion tends to be greater in patient populations and in young subjects and so this issue should be closely monitored in studies of development or recovery. Data analysis steps, such as the amount of smoothing applied to the data [14], can significantly influence results and should be carefully considered [15].

In addition to deriving voxelwise estimates of diffusion parameters, DTI data can be used to perform tractography, in which estimates of the principle diffusion direction at each voxel are followed to reconstruct estimates of the path of the underlying fibre bundles [16–18]. This technique allows for so-called '*in vivo* dissection' of fibre bundles in the human brain [19] and has generated much excitement. Although applications of tractography in clinical populations are more limited to date, there is considerable potential. Again, however, the technique has limitations which should be carefully considered when planning or interpreting a study [20]. For example, the inability to trace a particular pathway in a clinical group does not necessarily mean that the pathway is not present. Multiple factors unrelated to the true presence or strength of the underlying pathway, such as head size, data quality, gross brain atrophy and the strength of crossing fibre populations, can influence the ease with which a tract is traced through diffusion data.

In spite of these limitations, DTI has enormous potential for use in studies of brain development or

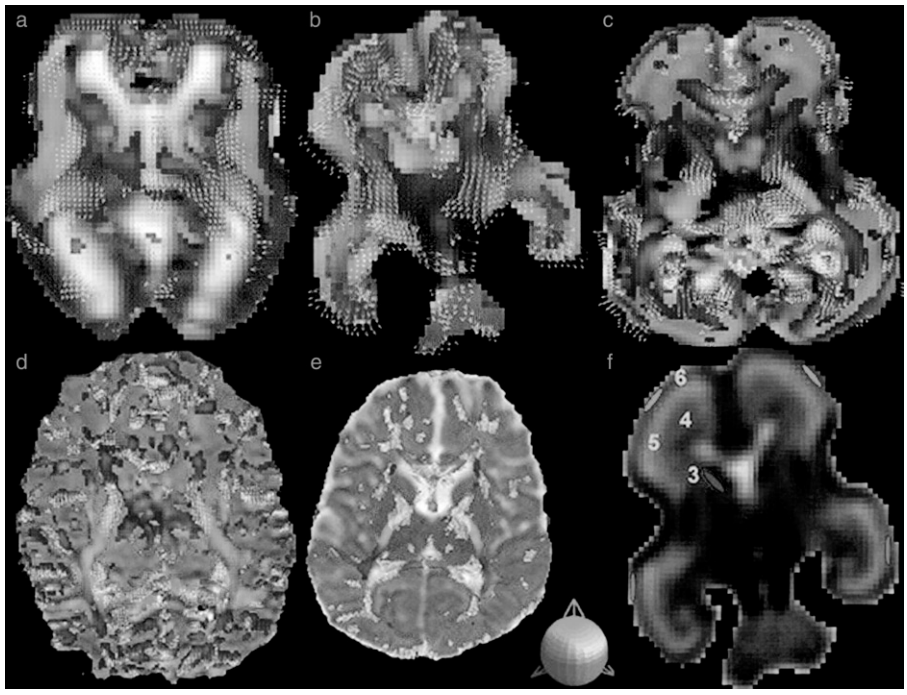

Figure 1. Representative FA maps modulated by the principal eigenvector showing changes in the cortical anisotropy at different gestational ages (GA). The small arrows (white and yellow) indicate the direction of the principal tensor eigenvector. Note the decrease in the radial orientation in the cerebral cortex from age 17 to age 27 weeks (a–c), corresponding to an increase of FA values, and its near disappearance at 37 weeks (d) and 133 days (e) of GA. The colour coding is shown in (e; lower right corner): red is right–left, green is anterior–posterior and blue is superior–inferior. (f) The figure displays the three eigenvalues along the three separate RGB channels. The numbers refer to the cortical plate (6), sub-plate zone (5), intermediate zone (4) and germinal matrix (3). From Gupta et al. 2005 [22]. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

recovery when carefully applied. It offers, for the first time, the ability to measure properties of white matter integrity across the whole brain in a relatively short time. Diffusion measurements are sensitive to any change in the structural barriers to diffusion in the white matter, through development, inflammation or degeneration. DTI-derived measures could therefore be used to monitor disease progression over time and potentially to enable identification of high-risk groups earlier in the course of disease who may benefit from specific intervention. Use of DTI measures to assess white matter integrity could increase understanding of many neurological diseases, not only those whose (primary) pathology directly affects white matter (e.g. multiple sclerosis, acute disseminated encephalomyelitis) but also those diseases which indirectly result in damage to white matter tracts (e.g. stroke, Alzheimer's disease, motor neuron diseases).

DTI changes during development

DTI studies in developing brains have provided important insights into the evolving structure of healthy cerebral cortex. DTI studies in embryonic mouse brains have shown that, during the very early stages of development, the cortical plate and the periventricular zone, both precursors of the cerebral cortex, exhibit a highly organized structure, similar to that observed in the white matter [21]. Human imaging studies of pre-term infants have shown that cerebral cortex exhibits increases of FA between 15–28 gestational weeks, consistent with the migration of neurons from the germinal matrix of the periventricular zone along the radial glia scaffolding [22] (Figure 1). FA values vary regionally in cortex, with a left predominance in the frontal cortex [22] and higher values in the superior occipital and frontal gyri compared to pre- and post-central gyri [23], possibly reflecting different maturational processes in different cortical areas. FA values in the human cerebral cortex reach a maximum at 26 gestational weeks, then constantly decrease until term [24]. During gestation, the principal diffusion direction within the cerebral cortex is oriented radially, consistent with a predominantly radial deployment of the cortical neurons [24]. After birth, studies in rats have demonstrated continuing decreases of cortical FA [25], especially in deep cortical layers [26], consistent with the transformation of the radial glia into the more complex astrocytic neuropil. However, these findings are in

contrast to a recent study demonstrating a localized increase of FA in the cingulate cortex of mice after birth, preferentially in the antero-posterior direction, and little or no change in other cortical areas [27].

The pattern of developmental change in deep grey matter structures is also unclear. Some studies report no DTI changes during the first days after birth in deep grey matter structures of rats [25] whereas others showed significant FA increases in the caudate-putamen of mice during the first 7 weeks after birth [27].

As for the white matter, different time-courses of FA changes for the maturation of different tracts (limbic, commissural, association and projections tracts) in the various phases of development have been identified [28]. The first increase of FA in white matter during development seems to take place during gestation, before the appearance of myelin [29], especially in the commissural fibres including the splenium and genu of corpus callosum [30].

After birth, different patterns of FA change over time seem to exist even within the same fibre system. For example, data from rats showed that FA values in the body of corpus callosum decrease significantly during the first 3 weeks after birth due to a decrease in parallel diffusivity and FA values increase thereafter due to a decrease in perpendicular diffusivity [25]. Studies in rabbits showed that these FA changes in the corpus callosum and also in the internal capsule coincide with the development of immature oligodendrocytes and with modifications in compound action potentials [31]. By contrast, studies in mouse revealed a steady FA increase in the genu of corpus callosum until 2 months after birth due to a decrease in perpendicular diffusivity, consistent with axon and myelin maturation [32]. It is not clear whether these different reported patterns reflect true differences in the maturation of different components of the corpus callosum or are due to methodological or species differences between these studies.

During early childhood (up to 5 years of age), three phases of FA change in white matter tracts have been observed in humans: rapid increases during the first year, slow modifications during the second year and relative stability thereafter [33]. However, these findings are not replicated by other studies on children with a wider age range (up to 16 years of age), in which age-related FA increase in white matter followed a mono- or bi-exponential course and continued in all deep white matter areas, in contrast to other brain areas, where adult values were reached during the third year [34]. In particular, FA increases in the splenium continued to a later age than those within the genu of corpus callosum, while the centrum semiovale showed the latest changes [35]. Regional FA differences were also demonstrated at the level of both the fronto-temporal segment, where a left predominance was reported, and the fronto-parietal segment of the arcuate fascicle, where lower FA values were found [36]. Eluvathingal et al. [36] summarized the process of white matter maturation during childhood by three patterns of diffusion change: increase of FA and decrease of all diffusivities in the left inferior longitudinal and fronto-occipital fascicles, decreases of all diffusivities with no FA changes in the left corticospinal tract and no age-related DTI changes along the somato-sensory pathways.

White matter structural changes during childhood are associated with developmental functional brain changes. In particular, FA increases in bilateral white matter association areas like the frontal and occipito-parietal areas were found to be positively correlated with IQ scores [37]. Moreover, FA values in the fronto-parietal white matter were significantly correlated with the magnitude of functional magnetic resonance imaging (fMRI) activations in closely located grey matter areas, such as the superior frontal sulcus and the inferior parietal lobe, during a working memory task [38].

Age-related FA increase in the white matter continues into adolescence [39–42]. In particular, ongoing increases in FA are prominent in the corona radiata [40, 42] and in the body [39, 40], genu and splenium [42] of corpus callosum. Increased FA in the body of corpus callosum has been linked to improved motor skills during adolescence [39, 41] and adulthood [43]. White matter FA changes in adolescents are driven by a decrease in perpendicular diffusivity, consistent with ongoing myelination of fibre pathways [40]. These white matter changes are not isolated but are associated with concurrent age-related decrease in grey matter density in the middle frontal and precentral gyri [40] (Figure 2), reflecting either increased cortical myelination [44] or synaptic pruning [45].

DTI studies of recovery

Quantitative and qualitative measures of white matter integrity and organization, as obtained from DTI, provide the clinician with novel means of investigating processes underlying recovery from brain injury *in vivo*. This additional information has important implications for clinician and patient, potentially aiding the development of targeted individualized therapy. The following section begins with a review of the use of DTI in investigating recovery in three selected contexts—stroke, multiple sclerosis (MS) and head injury. For a more thorough discussion of the use of DTI in neurological disorders, the reader is referred to

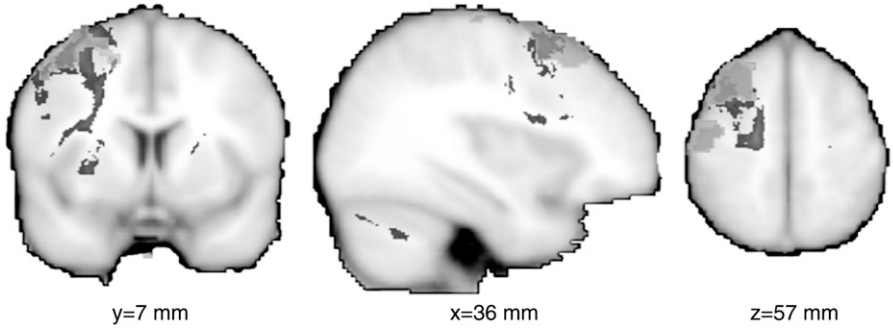

Figure 2. Relationship in adolescent subjects between tracts from white matter regions showing age-related FA increase (in red, tracts from superior region of the corona radiata) and the cortical regions showing age-related grey matter volume decrease (in blue, middle frontal and precentral gyri). From Giorgio et al. 2008 [40] with permission.

comprehensive recent reviews [46–53]. Next, the use of DTI in paediatric neurology is considered. To date, there have been a limited number of studies in this field; this study considers a few examples from periventricular leucomalacia (PVLM) and Krabbe's disease.

Stroke

DWI is a well-established method for monitoring pathological changes in acute stroke. Diffusion tensor measures, such as FA and ADC, can add useful additional information. Both FA and ADC show distinct changes with time after stroke. Most studies [54–56] have found that ADC values decrease immediately (within minutes to hours) after stroke, consistent with loss of tissue integrity, then increase slowly (within 7–10 days) towards normal values ('pseudonormalization') and finally become elevated, consistent with tissue necrosis. Generally, FA values decrease after stroke [57, 58], although some authors report an increase immediately after onset [59, 60] as a result of fluid shift from the extracellular to intracellular space (cytotoxic oedema). Overall, these conflicting results may be explained by differences in imaging methodology and by the heterogeneity of diffusion values within the lesion in the acute stage of a stroke. For extensive reviews see papers by Mukherjee [51] and Sotak [61].

Current research aims to use DTI measures to predict clinical outcome following stroke. Physiological studies have demonstrated that recovery from stroke in adults seems, in part, dependent on functional integrity of corticospinal tracts [62]. DTI has been used, both alone and in combination with transcranial magnetic stimulation (TMS) and fMRI, to gain more information on the importance of the structural integrity of the corticospinal tract to stroke recovery. Wallerian degeneration can be readily seen using DTI [63, 64] and with greater ease than conventional MRI [65]. The degree of corticospinal tract involvement within an infarct correlates with degree of recovery and stroke severity [66, 67]. Further, FA values within the corticospinal tract can be correlated with clinical outcome both acutely and sub-acutely, with lower FA values associated with worse outcome [68–70]. Decreases in FA are also found in the corpus callosum and in other normal appearing white matter tracts, although some recovery of FA values has been reported in the years following stroke [71, 72].

A combination of DTI and functional measures may provide even greater prognostic information. A recent study used multi-modal imaging and stimulation techniques to test whether a combination of structural and functional measures could accurately predict response to intervention in chronic stroke patients [73]. Patients in whom motor evoked potentials (MEPs) could be elicited by TMS to the affected hemisphere showed improved clinical outcome scores with intervention. By contrast, improvement in patients who had absent MEPs in the corticospinal tract was only possible if FA asymmetry of the corticospinal tract was higher than 0.25. Based on these results, the authors propose a decision pipeline for determining individualized therapeutic approaches. This paper emphasizes the important role DTI could play in the clinical setting of recovery post-stroke as a predictive tool, enabling rationalization of therapy in combination with other techniques.

When combined with functional imaging approaches, DTI can be used not only to predict outcome but also to determine the type of structural change that results in functional plasticity. There is now substantial information regarding the role of compensatory functional plasticity in stroke recovery from fMRI research. For example, bilateral activation is seen when patients perform a motor task with their dominant, affected hand

[74, 75]. However, the importance of the activation in the contralesional hemisphere is still unknown; indeed some authors feel persistent activation in the contralesional hemisphere has a negative effect on recovery [76]. DTI allows one to combine imaging modalities to determine the circumstances that evoke such contralesional activation. A small case series by Newton et al. [77] showed that enhanced ipsilesional functional MRI activation for a motor task was associated with greater damage to the cortico-fugal tracts (as defined using diffusion tractography in a group of healthy subjects). By acquiring DTI and fMRI data in the same individuals, Schaechter et al. [78] demonstrated that greater corticospinal tract damage (as detected through decreased fibre count using streamline tractography) correlated with increased fMRI activation during affected hand movement in contralesional primary sensorimotor cortex (M1/S1). In other words, the greater the structural damage to the corticospinal tract the greater the potential compensatory functional response, consistent with electrophysiological studies in monkey models of stroke showing, for example, greater functional remapping of ventral premotor cortex with increasing damage to primary motor cortex [79]. These correlations cannot establish the functional significance of this contralesional activity, but studies using TMS have suggested that, at least in some poorly recovered patients, the undamaged hemisphere is playing a functionally relevant role in movement of an affected limb [80, 81].

Another important role for DTI in understanding recovery from localized brain damage such as stroke comes through the use of tractography to increase knowledge of human brain anatomy. Much of the knowledge of white matter anatomy comes from early pathological and gross dissection work and more recent tracer studies in animals [82]. Tractography can provide important additional anatomical information in living human brain and studies have provided novel information on normal human brain anatomy [83] and can also provide insight into the consequences of damage [20, 84]. For example, Catani et al. [19] use tractography to delineate pathways underlying language processing in the human brain. They find that in addition to the classical arcuate fascicle route, travelling directly between Broca's and Wernicke's areas, there is an indirect pathway connecting Broca's and Wernicke's area via the inferior parietal lobe. The presence of this indirect tract helps to explain the many different types of aphasias that can arise from lesions within this area. It suggests that there is a degree of redundancy in the system that might be important in recovery.

Multiple sclerosis

DTI has provided useful measures in MS, both within and outside lesions. When used to monitor pathological change, DTI findings in MS lesions appear to relate to different pathological features of tissue damage (oedema, demyelination, axonal loss, gliosis). However, conflicting results have been achieved when comparing DTI values in acute vs. chronic MS lesions. In general, lowest FA in acute (gadolinium-enhancing) lesions [85–87] and highest ADC in chronic destructive (T1 hypointense) lesions [85, 87–90] have been reported. Longitudinal studies have demonstrated that DTI is sensitive to the evolution of tissue damage within MS lesions over relatively short periods of time, with diffusion changes reported in T2 lesions in patients with primary and secondary progressive [91] and relapsing-remitting [92] MS after 15 and 18 months, respectively. However, there is still the need of further longitudinal studies to address the issue of how much tissue disorganization in acute lesions is permanent (i.e. due to axonal loss) and how much is transient (i.e. due to oedema, demyelination).

Unlike conventional MRI, DTI is able to detect abnormalities in the so-called normal appearing white matter (NAWM) of MS patients. Altered diffusion properties in the total NAWM have been found not only in established MS [85, 87–89, 93–95] but also in early-onset MS (i.e. within 5 years of symptoms) [96], in clinically isolated syndromes suggestive of MS [97] and, to some extent, in early relapsing-remitting MS patients (i.e. within 3 years of symptoms onset and with low disability) [98]. NAWM damage has been localized to specific areas such as subcortical white matter [94] and well-defined white matter tracts such as the internal capsule [85, 99], frontal white matter [85], centrum semiovale [85], whole corpus callosum [99–103], body of corpus callosum [100, 104, 105] and pyramidal tracts [102, 106, 107] in relapsing-remitting MS patients, to the corpus callosum and internal capsule in primary progressive MS patients [86] and to the whole corpus callosum in a MS population with different phenotypes of the disease [108]. In early MS (onset before 16 years of age), only a slight increase of ADC in the NAWM of patients compared to white matter of healthy controls has been shown [109], probably explaining why these patients typically have a more favourable clinical course than adult-onset MS.

DTI studies have also tried to gain insight into the pathogenic mechanism of damage in NAWM of MS brains. Reported correlations between DTI metrics and lesion volume measures support the hypothesis that Wallerian degeneration of axons transected by

remote but connected focal lesions is an important feature in a number of disease sub-types [100, 106, 108], although others find no such correlations [88, 97, 110]. The latter findings are consistent with a recent study in which DTI measures were associated with decreased blood perfusion in the normal appearing corpus callosum of MS patients, consistent more with a primary ischemia than a secondary hypometabolism from Wallerian degeneration [111].

The use of DTI in longitudinal studies has increased understanding of pathogenic mechanisms of reversible and persistent disability. For example, DTI has demonstrated short-term accrual of grey matter damage in patients with progressive [91] and relapsing-remitting [92] MS. An increase of DTI abnormalities in NAWM have been shown over 1 year in MS patients with clinically isolated syndromes [112] and primary progressive MS [113]. By contrast, in a recent study in early relapsing-remitting patients [114] no significant DTI differences in longitudinal rates of change between patients and controls over 2 years were seen, suggesting a limited role for global DTI assessment of NAWM in following the early disease course.

In some cases, DTI has also been able to predict temporal dynamics of tissue damage in MS. More severe grey matter damage measured by DTI identified those primary progressive MS patients with an increased risk of disease progression over the following 5 years [115]. Importantly, ADC was shown to be higher in NAWM that would go on to become visible acute lesions 6 weeks [116] and 6 months later [117]. By contrast, in patients with clinically isolated syndromes suggestive of MS, the severity of NAWM damage did not predict new lesion formation in the short-term (1 year) [97].

Associations between DTI measures in MS brains and clinical disability, usually measured by Expanded Disability Status Scale (EDSS) score, have also been investigated, although conflicting results have been found. EDSS score did not correlate with FA in regions of interest of NAWM in early MS [98], relapsing-remitting [86, 104], secondary and primary progressive MS [86]. By contrast, in relapsing-remitting MS patients DTI metrics of pyramidal tracts were significantly correlated with EDSS score [107] and with pyramidal functional score [102, 107]. EDSS score in a mixed population of MS patients was significantly correlated to DTI metrics in the cerebral peduncles [93]. In the same study, in a sub-set of relapsing-remitting MS patients, EDSS score significantly correlated with DTI metrics within the whole NAWM (both supratentorial and infratentorial). Moreover, by using a recent voxelwise analysis of DTI data [15], decreased FA in the normal appearing corpus callosum was significantly correlated with increasing disability in clinically definite MS (mostly relapsing-remitting) [118]. A significant relationship between clinical disability and DTI measures has been also demonstrated in the cortical grey matter of MS patients with different phenotypes of the disease [95, 119]. Finally, the ADC of corpus callosum significantly correlated with a measure of cognitive performance (Paced Auditory Serial Addition Test) in relapsing-remitting MS patients [101, 102], suggesting a role for DTI also in charting cognitive performance in MS patients. Moreover, callosal damage in MS, as measured by FA and perpendicular diffusivity, was associated with alterations in a behavioural task (redundancy gain effect) that relies on interhemispheric communication efficiency [103].

As well as relating DTI findings to behaviour in MS, the relationship between structural and functional changes has been explored by combining DTI and fMRI results. A correlation between anatomical connectivity of transcallosal motor pathways, assessed by DTI measures (FA and perpendicular diffusivity), and functional connectivity of the primary sensorimotor cortices, measured by low-frequency hemodynamic fluctuations in the resting state, was recently reported [120].

Diffusion tractography has been applied to the study of MS, allowing for study of specific important functional pathways such as the corpus callosum [101, 102, 118, 121], motor pathways [107, 122, 123], white matter bundles involved in cognitive performance [124, 125]. The use of tractography has also allowed for demonstration of the presence of structural and functional plasticity in MS brains. In particular, an apparent increase in the number of tractography-derived connections between the left and right thalami was shown in early relapsing-remitting MS patients, potentially suggesting a compensatory structural plasticity of the white matter in MS [124]. Furthermore, in benign MS abnormal DTI measures in white matter fibre bundles involved in frontal lobe executive functions (Stroop task) were accompanied by increased bilateral cortical activations of connected areas [125]. In relapsing-remitting MS patients a significant correlation was found between measures of functional connectivity (above all between supplementary motor cortex and cerebellum) and DTI measures of some of the major motor white matter tracts [123]. Both these studies seem to suggest an adaptive role of functional connectivity in limiting the clinical consequences of structural damage in MS patients.

Overall, DTI appears to be a promising tool for testing the integrity of brain structure in MS, even

though further investigations are warranted to better elucidate the pathological correlates of tissue damage in MS.

Head injury

Diffuse axonal brain injury is a consequence of severe head injury. Again, DTI measures have been used to monitor pathological changes, although studies on head injured patients are far fewer than those in stroke and MS. Decreases in FA have been shown acutely and chronically [126–128] in the white matter of patients with diffuse axonal injury. By 9–15 months post-injury, however, there is some recovery of FA values [129]. DTI measures also predict clinical outcome in this patient group; FA values within the cerebral peduncle 5–11 weeks after severe brain injury, in combination with a functional independence score at this timepoint, predict Glasgow outcome scale at 1 year with 100% accuracy [129]. This study again shows the potential importance of DTI in predicting recovery. However, it must be stressed that this group of patients was at the severe end of a wide spectrum of possible clinical outcomes post-head injury.

Paediatric neurology

To date, there have been few studies using DTI in paediatric neurological disorders. This study reviews a few examples from the study of periventricular leucomalacia (PVLM) and Krabbe's disease. Corticospinal tract damage is thought to be the underlying basis for the motor deficit observed in PVLM [130]. Use of DTI to monitor pathological changes has demonstrated reduced FA in a number of fibre systems. Following identification of qualitative differences in anterior thalamocortical fibres in two children with PVLM compared to age-matched children [131], Nagae et al. [132] studied 24 children with cerebral palsy associated with PVLM. They found a total of 19 white matter tracts affected, including sensory tracts of the posterior thalamic radiations. However, these tracts were only qualitatively assessed and there was marked clinical phenotype heterogeneity. This information, combined with quantitative diffusion measures, could aid classification of these clinical phenotypes and begin to form the basis for providing more targeted therapy.

Again, DTI measures have been used not only to monitor pathological changes but also to detect potentially compensatory changes. For example, streamline fibre counts within the corticospinal tract are significantly decreased in the lesioned hemisphere, consistent with widespread reduced FA, but are significantly increased in the contralesional hemisphere [133] (Figure 3). As the initial pathological damage in PVLM is in the perinatal period, i.e. before white matter maturation, the authors hypothesize that in these adolescent patients the increase in the contralesional hemisphere could represent attempts at compensatory white matter reorganization.

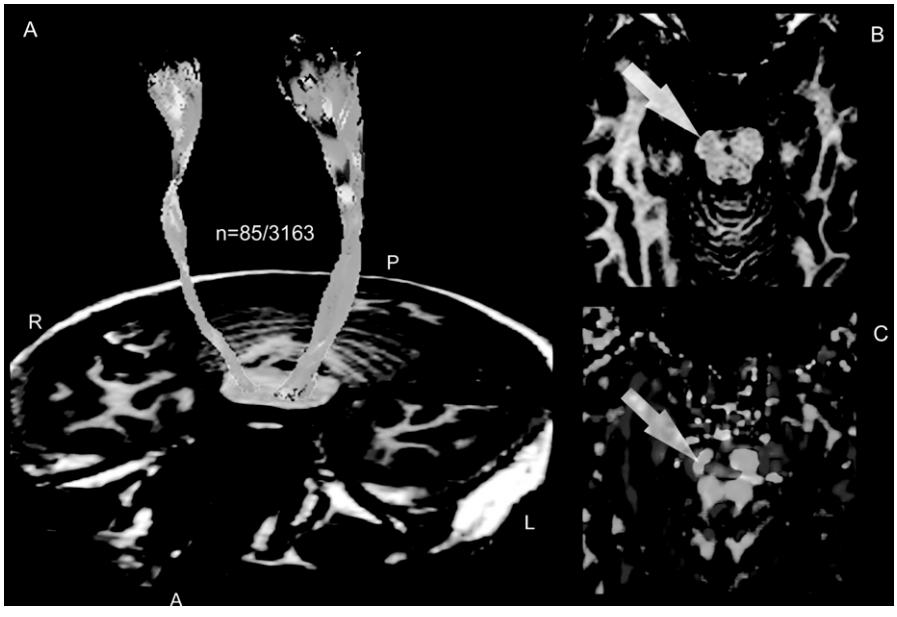

Figure 3. In (a) the corticospinal tract of a patient with periventricular leucomalacia (PVLM) shows a significantly reduced number of fibres on the affected right side. In (b) axial anatomy section through the midbrain shows atrophy of the right cerebral peduncle (arrow) due to Wallerian degeneration of corticospinal tract, which is better demonstrated on DTI colour map (c). Note the marked rarefaction of the corticospinal tract (blue) on the affected side (arrow). $n =$ DTI fibre count. From Thomas et al. 2005 [133] with permission.

A promising example of the use of DTI in monitoring response to treatment is provided in a study of Krabbe's disease [134], a neurodegenerative metabolic disorder caused by a deficiency of beta-galactocerebrosidase [135]. One potential therapy for this disorder is stem cell transplantation [136]. Evidence suggests that early transplantation is associated with longer life expectancy. In a small series of cases, Provenzale et al. [134] compared alteration in DTI measurements in different white matter regions of interest between patients transplanted early (within a few weeks of birth) or later (5–8 months old). Subjects were scanned serially at different time intervals up to 4 years post-transplant. FA ratios (ratio of FA values within a specific white matter region in a Krabbe patient to FA values within the same structure in a group of normal control subjects) were similar at the time of transplantation for the two groups. However, following transplantation FA ratios remained high or slightly decreased for early transplantation infants, whereas the ratios markedly decreased for the late transplantation infants. Furthermore, FA values showed good correlations with neurodevelopmental scores. This study therefore provides further evidence for the benefit of early stem cell transplantation in Krabbe patients. In addition, it demonstrates the usefulness of DTI for monitoring response to specific treatment regimes and may serve as a model for application of DTI to other therapies in various white matter disorders such as multiple sclerosis and dysmyelinating disorders of childhood.

Conclusions

DTI provides measures of white matter integrity that can be used to study structural changes occurring both with normal development and as a result of damage. There are indications that DTI measures may provide complementary information to conventional MRI in monitoring pathological changes. The clinical utility of DTI has so far been limited to demonstrations that early measures often predict later clinical outcomes. Future studies should aim to take the technique beyond simple observations of change and push towards use of DTI to aid clinical decision-making. There are emerging demonstrations that early measures of structural tract integrity could be used, particularly in combination with functional measures, to tailor individualized therapeutic interventions.

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