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Review

# Advanced diffusion MRI fiber tracking in neurosurgical and neurodegenerative disorders and neuroanatomical studies: A review

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ABSTRACT

Diffusion MRI enabled *in vivo* microstructural imaging of the fiber tracts in the brain resulting in its application in a wide range of settings, including in neurological and neurosurgical disorders. Conventional approaches such as diffusion tensor imaging (DTI) have been shown to have limited applications due to the crossing fiber problem and the susceptibility of their quantitative indices to partial volume effects. To overcome these limitations, the recent focus has shifted to the advanced acquisition methods and their related analytical approaches. Advanced white matter imaging techniques provide superior qualitative data in terms of demonstration of multiple crossing fibers in their spatial orientation in a three dimensional manner in the brain. In this review paper, we discuss the advancements in diffusion MRI and introduce their roles. Using examples, we demonstrate the role of advanced diffusion MRI-based fiber tracking in neuroanatomical studies. Results from its preliminary application in the evaluation of intracranial space occupying lesions, including with respect to future directions for prognostication, are also presented. Building upon the previous DTI studies assessing white matter disease in Huntington's disease and Amyotrophic lateral sclerosis; we also discuss approaches which have led to encouraging preliminary results towards developing an imaging biomarker for these conditions.



## 1. Introduction

One of the great scientific challenges of the 21st century has been to advance our understanding of the structural–functional networks in the brain using non-invasive imaging techniques. A desire to understand these neural connections has been coupled with an eagerness to explore the nature of dysfunction occurring in these neurological, neurosurgical, and psychiatric disorders [1–3]. White matter imaging has never been more topical, particularly in light of the recent studies aimed at developing new imaging techniques towards mapping human brain connectivity [4–10]. Nonetheless, accurate imaging of structural connectivity *in vivo* is challenging with most techniques having a limited resolution at a scale of millimeters (mm). Reliable characterization of the connections at an axonal level requires better resolution, usually at a scale of micrometers (μm). Diffusion magnetic resonance imaging (MRI) detects microscopic changes in the diffusion pattern of water and reveals microstructural information regarding the human brain.

In this paper, we present an overview of the most popular diffusion MRI modeling method, diffusion tensor imaging (DTI) and discuss its limitations. We follow this with a discussion of the methods beyond DTI, based on our literature search. Finally, we illustrate the advantages of moving beyond DTI in clinical studies, in particular by highlighting our preliminary experience with the application of an advanced white matter imaging technique.

## 2. Diffusion tensor imaging

Diffusion MRI is an imaging modality, which utilizes diffusion of water to characterize the structural connections in the brain at a microscopic level. The earliest work, conducted by Stejskal and Tanner [11] applied diffusion MR-sensitizing gradients to measure diffusion coefficient and investigated structures at a microscopic level. This basic diffusion sequence then fuelled the development of diffusion MRI, further diffusion modeling methods and ultimately *in vivo* fiber tracking and tractography using DTI. DTI [12] is a diffusion MRI analysis method,

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which models diffusion pattern as a Gaussian distribution [13]. The tensor model requires at least six diffusion gradient samplings to calculate the diffusion tensor. The axonal direction can be determined by the principal direction of the tensor. Based on this principal direction, the trajectories of the axonal connections can be revealed by diffusion fiber tracking. This computational approach demonstrates the axonal connections between the cortical areas [14,15]. The tensor model however cannot demonstrate the crossing fibers, and therefore, DTI-based tractography may suffer from false connections or terminations. Although DTI has been widely used in multiple studies, its major limitations have been well described. These include its inability to represent the crossing of multiple fibers or to determine with precision their cortical and subcortical terminations [16–24].

In addition to demonstrating axonal connections and qualitative tractography data, DTI also offers several quantitative indices to characterize the axonal integrity. These include fractional anisotropy (FA) and diffusivities [25,26], both of which have been applied in clinical studies. FA is one of the most commonly used DTI-based quantitative measure of anisotropy [27,28] and has been applied in the evaluation of white matter integrity in multiple disease states including multiple sclerosis [29], stroke [30], amyotrophic lateral sclerosis (ALS) [31–33], cavernous malformations (CMs) [34] and brain tumors [35,36]. It has been suggested that the changes in FA may reflect changes in the organization of fibers [37] with a reduction reflecting axonal fiber degeneration and myelin breakdown in the central and peripheral nervous systems [38,39]. Studies have shown that the indices derived from DTI can be affected by field strength [40]; b-value [41]; number of gradient directions; spatial resolution [28]; partial volume effect [18,20,42,43]; head motion [44]; and the crossing fiber configuration [16,17]. This can lead to the underestimation of the anisotropic values in areas with multiple crossing fibers [18,28]. Such limitations associated with DTI are accentuated in cases of clinical applications. A cerebral tumor, for example may be present with surrounding edema and mass effect [18, 36,45] with associated potential thinning of the tracts, all of which may contribute further to the partial volume effects and misinterpretation of the data. Other DTI-derived measures include radial diffusivity, which has been shown to increase with demyelination [46]. A decrease in apparent diffusion coefficient (ADC) is correlated with the increased cellularity of brain tumors [47,48]. ADC derived from DTI, however cannot differentiate vasogenic edema or define tumor infiltration [49,50]. Although DTI can reveal some characteristics of the white matter pathways and provide qualitative tractography data, its use as a *gold standard* diagnostic tool has been limited. One problem with DTI relates to the diffusivity being overestimated or underestimated, when axonal injury occurs with cell infiltration [51]. This therefore, limits its application in neurological conditions. To overcome the limitations of DTI-based fiber tractography and its derived indices, studies have used more complex models to resolve the crossing fibers and quantify diffusion characteristics. These endeavors have led to the development of methods beyond DTI.

## 3. Advanced white matter imaging techniques beyond diffusion tensor imaging

### 3.1. Literature search criteria

We searched PubMed (May 2014) using keywords such as "tractography" or "fiber tracking" and limited the search criteria to the recent papers (restricted to the last five years). A total of 1838 papers were identified, of which we excluded studies using conventional DTI-based fiber tracking approach, resulting in 735 papers. The abstract of these papers were then scrutinized to select publications demonstrating clinical application. Methodology, engineering, and review papers were excluded. These further criteria resulted in the inclusion of 84 clinical research publications. These papers were then extensively reviewed to document their fiber resolving methods, tracking algorithms, and analytical approaches (Supplementary Table 1). In summary, the ball-and-stick model was the most popular method for resolving crossing fibers (57%). Diffusion spectrum imaging (DSI) was the next most popular method (15%) followed by constrained spherical deconvolution (CSD) (11%). For fiber tracking, 64% of the studies used probabilistic fiber tracking, whereas 36% used deterministic fiber tracking. The analysis was done in the majority using tract-specific analysis (58%) followed by connectivity approach (31%) and pathway visualization (14%). In the following sections, we introduce these methods in detail.

### 3.2. Fiber resolving methods

The fiber resolving methods can be categorized into the model-based and model-free methods. The analytical approaches can be categorized into voxel-based analysis (VBA); tract-specific analysis; connectivity analysis; pathway visualization; and tract morphology analysis. It is noteworthy that a particular study may use different combinations of fiber resolving methods tracking algorithms, and analytical approaches. In the following sections, we introduce majority of these methods which have been widely used in clinical studies.

#### 3.2.1. Model-based methods

Several new diffusion methods (model-based and model-free) have been proposed to overcome the limitations of DTI. The model-based approaches use a model to describe the diffusion pattern. The parameters for these models are calculated using numerical optimization. For example, the most popular method beyond DTI, according to our literature review is the ball-and-stick model [52], which is included in the FSL bedpostx routine. The ball-and-stick model is a specific form of multiple tensors that models free diffusion (ball) and axons (sticks). The CHARM model [53] describes the diffusion pattern using a composite diffusion model [54]. Diffusion kurtosis imaging [55] models the non-Gaussian characteristics of diffusion and provides information on the pathological conditions [56–59]. Diffusion basis spectrum imaging [51] separates the effects of vasogenic edema, cell infiltration, and axonal injury. It further provides information about the cell and fiber ratios; local edema; and density distribution of the axonal fibers. Spherical deconvolution [60] obtains fiber orientation distribution by calibrating the signal profile of a single fiber as the model and deconvoluting the MR signals to obtain the orientation distribution. Further improvements can be achieved by CSD [61]; deconvolution with reduced background effect [62]; diffusion deconvolution [63]; and compressed sensing related estimations [64,65]. The fiber distribution obtained from the deconvolution can depict the local axonal connections and assist further fiber tracking (Fig. 1). The main advantage of the model-based methods is the requirement for a fewer number of diffusion sampling directions, thereby leading to a substantial reduction of the scanning time. The principal drawback relates to the diffusion model depending upon certain assumptions to obtain an accurate parameter. In real world data, these assumptions can however, be violated leading to spurious results [66].

#### 3.2.2. Model-free methods

Instead of assuming a diffusion model, another emerging interest relates to the model-free approaches, which obtain empirical distribution of water diffusion by exhaustive sampling. The model-free methods use a distribution function to model the diffusion distribution. For example, q-space imaging [67] is used to estimate the ensemble *average propagator*, which is the distribution of spin displacement. To resolve the axonal direction from an average propagator, DSI [68] further integrates the radial distribution of an average propagator and calculates the orientation distribution function (ODF). This approach discards the radial information and focuses on the orientation information. The peak orientations on the ODF can be used as the fiber orientation for further fiber tracking [69]. As ODF does not contain information on the radial directions, the calculation of ODF does not necessarily require

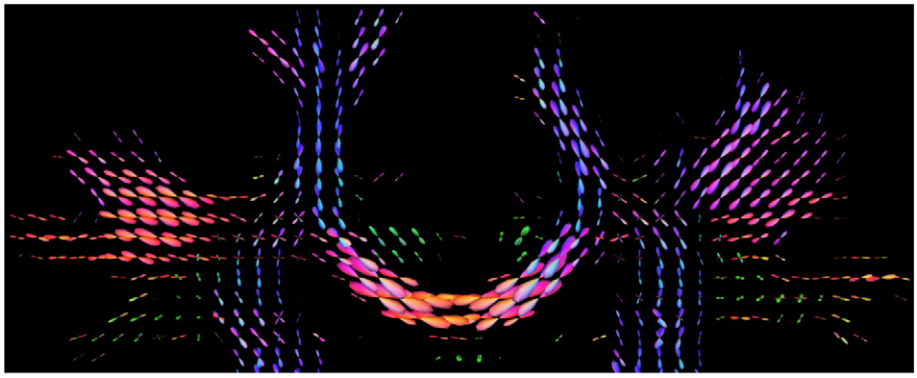

**Fig. 1.** The fiber orientation distribution obtained by diffusion deconvolution. This coronal slice is positioned at the centrum semiovale with corticospinal tracts being the vertically oriented tracts. The crossing region with the corpus callosum is also demonstrated.

exhaustive sampling. Only the signal responses at different orientations are needed to calculate the ODF. This idea leads to the high angular resolution diffusion imaging (HARDI) [17]. HARDI is a sampling strategy that acquires diffusion images using the same diffusion gradient strength. This is in contrast to the q-space imaging, which requires sampling on both different gradient strengths and directions. The simplified sampling scheme improves the feasibility of acquisition of the diffusion data. Diffusion ODF can be reconstructed from HARDI using q-ball imaging [70,71]. Despite this improvement, it is noteworthy that discarding radial information forfeits the rich information characterizing the tissue structure. A more flexible approach is to allow a method to make use of the radial information while offering the orientation information. This is enabled by generalized Q-sampling imaging (GQI) [72], which offers a length parameter to switch the focus between restricted diffusion and none restricted one. GQI has been shown to improve the quality of demonstration of the crossing fibers [63,65,73] and assist diffusion MRI-based fiber tracking [74].

### 3.3. Deterministic and probabilistic fiber tracking

Both model-based and model-free methods can provide the local fiber orientations within a voxel. The deterministic fiber tracking algorithm makes use of the local fiber orientations to delineate the whole trajectory. It starts from a seeding point and propagates along the fiber orientation until the termination criteria are met. Examples of this approach include the fiber assignment continuous tracking method [15] and streamline fiber tracking algorithm [75]. Both of these assume a single fiber orientation per voxel. With high angular resolution data, multiple fiber orientations can be resolved per voxel (Fig. 2). Further, a multiple fiber version of deterministic fiber tracking has been proposed to describe the complex connections of the fibers' geometry [69,74,76]. Despite this improvement, one major limitation in deterministic fiber tracking is the crossing-branching problem [77]. Deterministic fiber tracking prefers trajectories with less turning, thereby potentially missing the minor branches. One study showed that the percentages of false connections can range from 7% to 35% [74]. Identification of these false connections is an active research question. As opposed to deterministic fiber tracking, probabilistic fiber tracking was proposed to explore the *connection probability*. Although there are numerous versions of probabilistic fiber tracking algorithms, most of the reviewed papers used the probabilistic tracking routine from the FSL package [52]. In general, probabilistic fiber tracking utilizes the probabilistic distribution of fiber orientations to obtain a set of trajectories connecting to a voxel. The number of fibers connecting to a voxel can be used as an index to reveal the differences in connectivity.

### 3.4. Analytical approaches

#### 3.4.1. Voxel-based analysis

The diffusion indices can be analyzed at the voxel level. The regions of interest (ROI) can be manually selected by experts, and the indices within the region can then be used to compute group differences. The result however, may be subjective and not easily reproducible. A more objective approach is to use the analysis paradigm of voxel-based analysis (VBA) [78]. The mapping of the diffusion indices (for example, FA) is normalized to a stereotaxic space and statistical tests are applied to examine the significance of the group-wise differences. One should note that the transformation of direction-independent quantities such as FA and MD is straightforward. It does not require additional correction with respect to the directional information. This makes

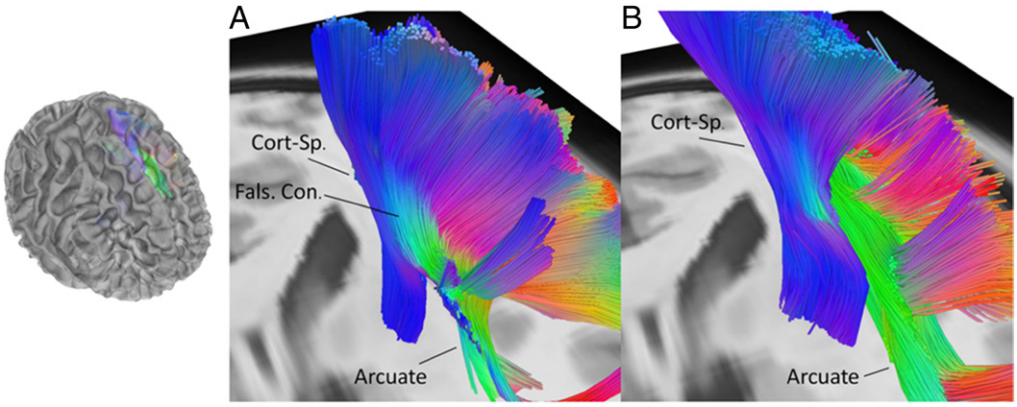


**Fig. 2.** A, Diffusion tensor imaging-based tractography leads to false continuation (Fals. Con.) between the arcuate and the corticospinal (Cort-sp.) tracts in the region of their crossing. B, An advanced fiber tracking method using GQI is able to resolve this issue displaying the orientation of the arcuate in an anteroposterior direction and that of corticospinal tract in the superoinferior direction without any major false continuation. Inset image demonstrates the angle pertinent to the viewing of the fiber tracts.

group-wise comparisons feasible with VBA. Reproducibility of this technique however, has been questioned due to the controversial effect related to the filter size [79]. The voxel-based approach further does not provide information with respect to the fiber orientations (directions), and cannot handle diffusion quantities of the crossing fibers.

*3.4.2. Tract-specific analysis*

Tract-specific analysis utilizes fiber trajectories from the fiber tracking to sample the diffusion indices [80–82]. The combination of tract-specific analysis and DSI extends the analysis to regions with crossing fibers [83,84]. Although the tract-specific approach can handle the problem of crossing fibers, it is reliant upon an accurate fiber tracking method to carry out a trustworthy analysis. Due to the limitation of the crossing-branching pattern, the fiber tracking algorithm may give rise to false connections. It further has reproducibility issues, as the results are not perfectly objective. Although this analytical approach can target a specific fiber pathway and analyze its integrity, it is reliant upon the user expertise in terms of selection of ROIs and segmentation of the obtained tracts. These therefore, lead to reproducibility issues, particularly when multiple users are involved [85–88].

*3.4.3. Skeleton-based approach*

Spatial transformation has been widely used in analyzing the structural characteristics of the human brain. Its use with the diffusion data however, is much more challenging as the transformation needs to consider the rotations of the axonal directions [89]. In DTI, the spatial transformation can be handled by a Jacobian matrix to correct the rotation problem [89,90]. The spatial transformation of HARDI can also be similarly corrected [91]. The spatial transformation for q-space imaging however, needs to consider the scaling effect at the radial direction. Another DTI-related analytical technique, tract-based spatial statistics (TBSS), [92] utilizes a mean FA skeleton. By projecting the diffusion indices to the skeleton, TBSS avoids the drawbacks of VBA, such as the smoothing and alignment issues. This enables localized statistical analysis in a stereotaxic space [93]. TBSS however, cannot reliably estimate and interpret the voxel-wise statistics at the crossing regions of fibers due to the inherent limitations associated with DTI. A recent improvement on TBSS has attempted to overcome this limitation by using the ball-and-stick model. Nonetheless, the skeleton used in TBSS assumes a single fiber orientation per voxel and does not make use of the information from the crossing fibers.

A solution to this problem is *diffusion MRI connectometry* [94], an analytical method that uses a multiple fiber skeleton (multiple fiber orientations per voxel) to sample the diffusion quantities on ODFs. Connectometry obtains statistical validation of fiber pathways with deviant ODF quantities. Instead of mapping the entire pathway before studying their differences, connectometry initially maps the difference at each fiber orientation in a voxel. It then connects the differences using fiber tracking to reveal the entire affected pathway, as shown in Fig. 3A. The sampled ODF values from a normal population are used to construct a *norm*, which can then be used to test the deviant cases, as shown in Fig. 3B. Importantly, the affected tracts are revealed with information regarding the sensitivity and specificity of the findings. The specificity of the results can be controlled using the false discovery rate.

## 4. Applications of advanced white matter imaging technique in neurosurgical and neurodegenerative disorders and neuroanatomical studies

In this section, the application of advanced white matter imaging techniques in clinical studies is presented along with the pertinent literature from conventional DTI-based approaches. An account of our preliminary experience is also included.

*4.1. Intracranial mass lesions and applications in neurosurgery*

One of the key advantages of using advanced white matter imaging in our preliminary experience [95], has been the ability to obtain

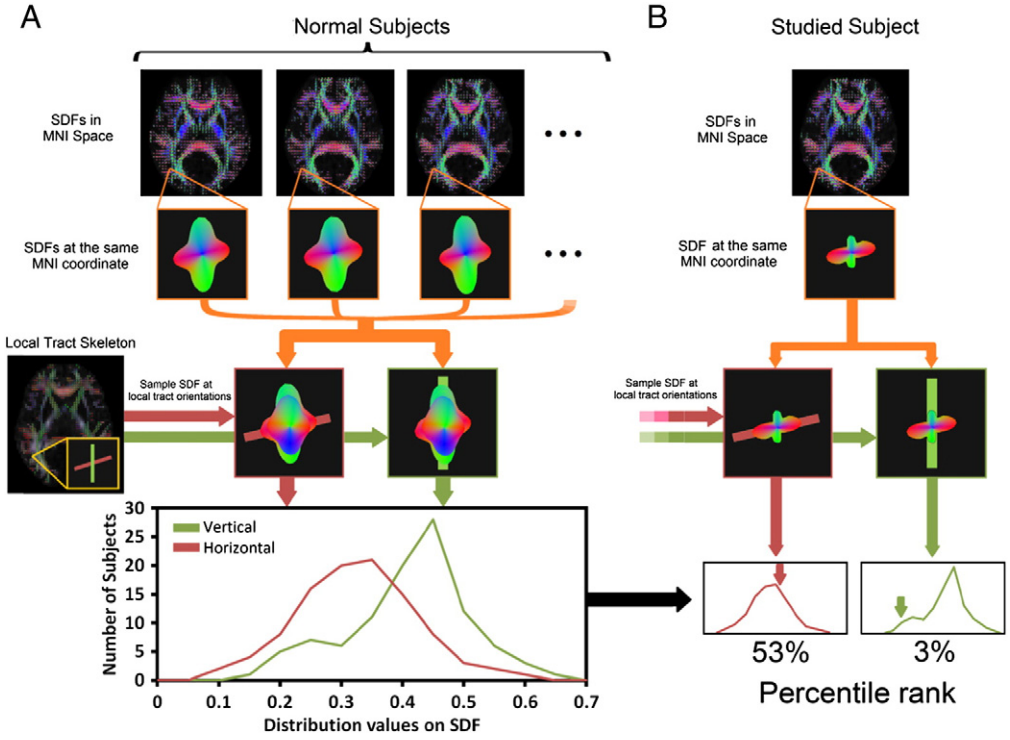


**Fig. 3.** Diffusion MRI connectometry. A, The spin distribution functions (SDFs) are reconstructed in the MNI template space using q-space diffeomorphic reconstruction and sampled at the local fiber orientations to obtain the diffusion quantity of corresponding fiber. The sampled SDF values from a normal population construct a norm that can be used to test the deviant cases. B, The data of a studied study (*e.g.*, a patient with tract damage) are reconstructed in the template space and sampled using same procedure. The sampled SDF values are compared with the norm to calculate the percentile rank for further statistical testing.

superior qualitative data in terms of depiction of multiple perilesional tracts in a three dimensional fashion around mass lesions like CMs and tumors. This has greatly assisted with accurate surgical planning. In a recent study [96], we further assessed the relationship specifically of supratentorial CMs to the relevant perilesional white matter tracts. We attempted to characterize the associated changes both qualitatively (in terms of displacement or disruption) and quantitatively, using mean anisotropy index (derived from ODF). This was done both for the overall affected white matter tracts and for the specific perilesional segments. Supratentorial CMs represent an ideal model for assessing the usefulness of an advanced white matter imaging technique in investigating perilesional tracts. By definition, CMs, within their core do not possess any intervening brain parenchyma and therefore, white matter. Use of the more conventional DTI in brainstem CMs' resection, which are surgically challenging with a higher annual average symptomatic hemorrhage rate of 2.7% to 5% [97–99], has been reported [100–104]. Only isolated case reports have described the utility of DTI with supratentorial CMs [105,106]. A further DTI study detailed the perilesional quantitative characteristics of these vascular malformations [34]. In our preliminary series, we demonstrated the utility of GQI-based tractography in illustrating the precise spatial relationship of CMs to multiple perilesional white matter tracts in a three dimensional fashion (Fig. 4). This was helpful for surgical planning and for demonstrating associated disruption and/or displacement, both of which occurred perilesionally [96]. These changes were supported by the anisotropy index (an indirect marker of fiber integrity and organization like FA in DTI) with the perilesional values being lower compared to the contralateral homologous segment for disruption. The reverse was true for displacement. In cases with suspected disruption, the results needed cautious interpretation due to the lack of any histopathological data.

### 4.2 . Case example

These advantages can be demonstrated (Fig. 4) using a case example of a 66-year-old right handed female with a symptomatic 10 mm left parietal lobe hemorrhagic CM [96]. Due to the lesion's proximity to the sensory cortex and its potential effect on the arcuate fasciculus (AF), perilesional white matter tracts were evaluated preoperatively. Perilesionally, tractography demonstrated posterior displacement of the AF (with the lateral margin being free of these fibers); anteromedial displacement of the thalamopostcentral; and an unaffected corticospinal tract (CST) (Fig. 4). The functional MRI (fMRI) confirmed the left hemisphere to be language dominant with Broca's in the inferior frontal gyrus. Using information from the fiber tractography, she underwent an image-guided surgical approach through the post-central sulcus for lesionectomy. Resection of the gliotic plane was limited due to the proximity of the fiber tracts. Postoperatively she had no neurological deficits. In this case, qualitative data in terms of displacement of AF was supported quantitatively, as the mean anisotropy value for the perilesional segment was higher in relation to the value for the contralateral equivalent segment.

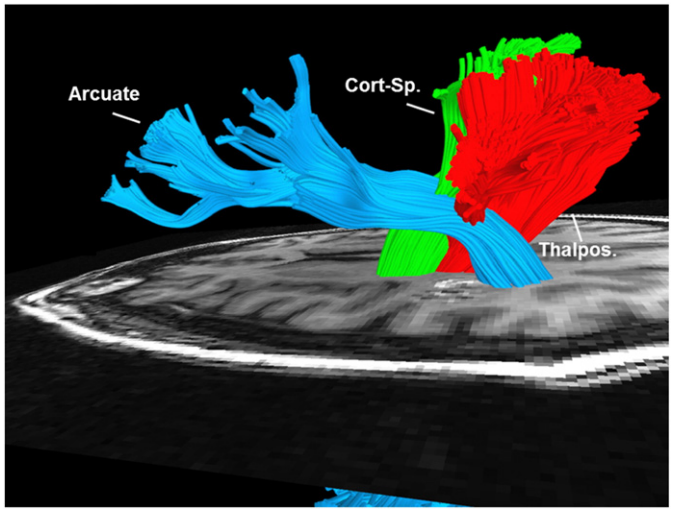


**Fig. 4.** Advanced fiber tracking analysis (note MRI scan has been flipped) showed posterior displacement of the arcuate around the left parietal cavernous malformation with anteromedial displacement of the thalamopostcentral (Thalpos.) fibers with no effect on the corticospinal (Cort-Sp.) tract and with lateral margin being free of the traversing superior longitudinal fasciculus fibers, allowing a surgical approach through the post-central sulcus. Multiple crossing perilesional fibers are demonstrated.

Limitation of DTI with respect to discerning multiple perilesional tracts is accentuated in the presence of a space occupying mass with its associated edema. There is increasing emerging data regarding the utility of advanced white matter imaging techniques in mass lesions [107–109]. A recent study [107] evaluated the differences between GQI and DTI in the preoperative mapping of fiber tractography in peritumoral edema of cerebral tumors. Five patients underwent 3-T MRI scans with subsequent reconstruction of the tracts using both GQI and DTI. GQI-based tractography was able to fully display the intact fibers in the edematous zone in comparison with DTI. These tracts were found to be incomplete, missing or ruptured with DTI. Although conventional neurosurgical wisdom does not permit the resection of the edematous zone around the cerebral neoplasms, demonstration of the fiber tracts in that zone in their correct orientation will aid surgical trajectory planning and potential tract preservation. A further study [108] compared another advanced white matter imaging technique (HARDI- compressed sensing) with DTI for evaluation of eight patients with gliomas in the temporal lobe in proximity to the optic radiation. This technique displayed the optic radiation better compared with the DTI-based results in all cases. The advantage was particularly highlighted for cases where high grade gliomas had significant associated peritumoral edema or were large and in close proximity to the reconstructed fiber tract. The key focus of the ongoing investigations in the application of white matter imaging techniques in patients with cerebral tumors has been aptly directed towards accurately reconstructing the perilesional tracts in their anatomical entirety in the surrounding edematous zones. It is noteworthy that despite its limitations, DTI has been an important adjunct in the resection of intracranial mass lesions including tumors [36,110] and CMs [101,102,104] and has been widely used in clinical and research studies. Further, the short image acquisition time for DTI makes it more clinically accessible.

### 4.3. Neurodegenerative disorders

#### 4.3.1. Amyotrophic lateral sclerosis

ALS is a neurodegenerative disorder, marked by progressive failure of both upper (UMN) and lower motor neurons (LMN). LMN symptoms in ALS obscure the UMN symptoms and therefore, contribute at least partly to the potential delay in the diagnosis and subsequent treatment. Although the diagnosis of ALS is based on clinical examination and electrophysiological studies among others [111], an imaging biomarker is potentially useful for monitoring *pathological* progression and for evaluating efficacy of treatments in future trials. Previous studies in ALS, using DTI have shown that white matter pathology, predominantly in the motor pathways, can be detected and potentially tracked longitudinally over time. This makes white matter pathology a candidate as an outcome measure for future trials. Multiple DTI [31–33,112–115] studies in ALS have therefore been carried out to investigate the involvement of the white matter tracts. The white matter pathology has been examined for potential correlation with clinical markers of progression like the revised ALS functional rating scale [111,116]. These studies have relied on the DTI-based indices like FA or ADC for quantification of the observed changes in the integrity of white matter tracts, for example CST or corpus callosum. In general, these studies have demonstrated a reduction in the values of FA, when compared with controls or when monitored in a longitudinal fashion [113,115,

117,118] over time along the CST. These changes have therefore, indirectly demonstrated the disease progression in ALS. Another noteworthy point in ALS with respect to monitoring white matter disease, is the presence of extramotoric changes. These changes have been demonstrated in multiple studies, notably so in the corpus callosum [119]; cingulum and hippocampal formation [120]; and cerebellum [117]. A previous pathological study in ALS [121] based on *post-mortem* examination had shown evidence of degenerating fibers in the pre-central gyrus (and CST); post-central gyrus; the adjacent frontal and parietal gyri; corpus callosum; and basal ganglia. Overall these changes suggest a multisystem neurodegenerative process, which so far using the DTI and VBA in a complementary fashion, have been elucidated to varying extents [33,118,122,123]. Although these studies have been promising in demonstrating the white matter changes in ALS, use of DTI and its associated quantitative indices is limited as a quantitative marker in ALS. This is related to the DTI-based quantitative indices suffering from partial volume effects [18,28]. Other limitations pertinent to all tractography-based studies are also applicable including the inherent variability, particularly between observers. These are due to issues related to the ROIs chosen and the manual nature of the analysis. Changes in the imaging data in terms of the signal to noise ratio across multiple scans, is another issue affecting reproducibility. VBA addresses some of these limitations, however it does not provide directional information for the affected tracts.

Building upon the findings from DTI studies, one study adopted a two-step approach to evaluating white matter disease in a longitudinal fashion in ALS patients in relation to markers of clinical progression [124]. The first *primary* step involved an adaptation of the diffusion connectometry [125] analysis to identify the affected white matter tracts followed by a detailed 'tractography' approach towards the quantitative evaluation of these identified abnormal fiber pathways. This approach was tailored to test both 'individual' and 'group' data against a control population. In line with the current literature, our study [124] identified the involvement of both motoric and extramotoric white matter pathways (Fig. 5).

Another endeavor associated with DTI in ALS has been the evaluation of its use as a diagnostic tool and as an aid in enabling discrimination between the different motor neurone disease (MND) phenotypes. Despite the existence of current diagnostic criteria [111], a potential imaging diagnostic tool may prevent delay in diagnosis and allow earlier discrimination between the different disease phenotypes. A recent meta-analysis [126] concluded that the discriminatory capability of DTI to make a diagnosis of ALS was only modest. Potential reasons may be the clinico-pathological heterogeneity in ALS and the use of group studies. These reasons become more pertinent with inclusion of different phenotypes. Although there is increasing evidence that the different MND phenotypes lie within a spectrum [33,127] with overlapping white matter abnormalities, the anatomical location and the extent of these changes vary. This therefore, makes group comparison studies difficult.

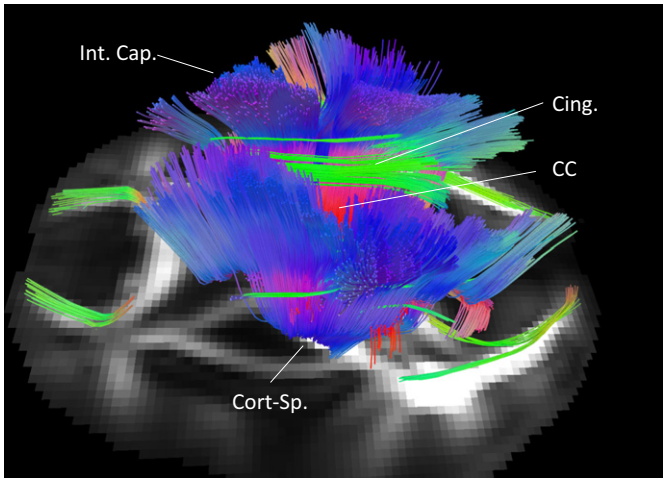


**Fig. 5.** In a patient with ALS, approximately 42 months into the disease onset, there were demonstrated bilateral changes in the motoric and extramotoric pathways; involved tracts included corticospinal tract (Cort-sp.); the internal capsule (Int. Cap.); corpus callosum (CC) and cingulum (Cing.) among other tracts.

*4.3.2. Huntington's disease*

Previous studies (PREDICT-HD and TRACK-HD) in Huntington's disease (HD) patients have shown that white matter pathology can be tracked longitudinally and reliably over 12 to 24 month periods. As the white matter pathology correlates with some clinical characteristics, it is potentially a strong candidate as an outcome measure for future clinical trials [128]. DTI among other MR techniques has been previously employed in the demonstration of white matter pathology in premanifest and symptomatic HD [129–131]. The primary aim in HD has been to use DTI to develop an imaging biomarker for disease progression rather than as a diagnostic tool. Premanifest HD in this respect is of particular importance, as a reproducible marker of disease (pathological) progression in terms of an imaging biomarker will be invaluable in this group. This is related to the fact that this group has limited markers of clinical and imaging progression (as seen on standard MRI). In future, this imaging biomarker may be used to evaluate the efficacy of novel treatments. There is further emerging evidence regarding early extrastriatal involvement in HD, including in premanifest disease [132,133], and its correlation with measures of clinical progression [134,135]. White matter projections including corticostriatal projections, cingulum and uncinate fasciculus (UF) have been implicated in the pathophysiology of HD [132]. Other tracts of interest include corticostriatal projections [dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex to striatum]; thalamocortical projections; callosal fibers; CST; inferior occipito-frontal fasciculus (IOF); and thalamopostcentral fibers. These can be difficult to reconstruct reliably using DTI-based tractography. These are currently being investigated in the premanifest and the manifest HD patients in a longitudinal fashion using both DTI and advanced white matter imaging techniques.

Based on the current literature largely derived from DTI and structural MRI studies, changes in the white matter seem to be present before the clinical manifestation of motor symptoms in gene-positive premanifest HD patients. With the use of white matter imaging techniques, these can be evaluated over time. An example of this approach is the evaluation of quantitative parameters such as percentage changes in anisotropy and volumes for fiber tracts of interest over longitudinal scans. Changes in these parameters over longitudinal scans will indirectly track pathological progression. Similarly, tract-specific qualitative and quantitative data can be expected to deteriorate with clinical progression in early manifest HD (as defined by total functional capacity (TFC $\geq$ 8) and potentially correlate with measures of clinical progression. In light of this evidence, the current focus is therefore, on the longitudinal scanning of premanifest and early manifest HD patients. There are conflicting reports about changes in the DTI-based quantitative markers, for example FA, in denoting the structural integrity of the subcortical nuclei [129]. Cortical changes [133] including thinning in the premanifest and manifest groups, are also an additional area of evaluation with potential different patterns of cortical changes possibly providing explanations for the widespread clinical heterogeneity in HD. Possible correlation between areas of cortical thinning and white matter changes can be expected. This is based on the assumption that the anatomy of white matter degeneration should correspond to the regions of cortical gray matter atrophy. An example of use of the advanced white matter imaging technique in HD is provided using a patient (age: 41; CAG: 42) at the premanifest stage (Fig. 6), who underwent two scans six months apart. During this scan interval, the score on behavioral assessment increased from 9 to 13. There were quantitative

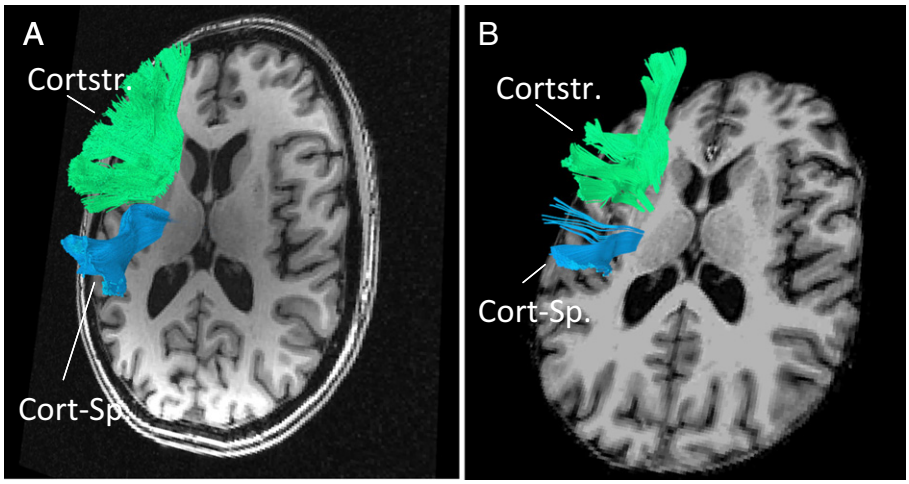


**Fig. 6.** Axial MR (advanced white matter imaging) (A, earlier; B, 6 months later) of a patient with premanifest Huntington's disease demonstrating qualitative reduction in dorsolateral prefrontal cortex projections to striatum or corticostriatal (Cortstr.) projections; corticospinal (Cort-Sp.) tract (blue) is also shown.

reductions (volume and anisotropy) in multiple fiber tracts of interest bilaterally for this patient including in the genu and splenium of the corpus callosum. In terms of demonstrated tracts (Fig. 6), the percentage reductions in the anisotropy values were: left side [DLPFC to striatum (14.8%); CST (18%)] and right side [DLPFC to striatum (16.6%); CST (14.5%)]. Despite a decrease in the corticostriatal projections, there was no corresponding decrease in the striatal or extrastriatal subcortical nuclei volumes, as measured using the Freesurfer analysis. Although the behavioral scores changed over the scan duration, there was no evidence of motor symptoms or change in the motor scores despite a quantitative decrease in the CST bilaterally. Although our experience is preliminary, advanced white matter imaging in conjunction with other MR-based analytical techniques, seems to be a promising tool for development as an imaging biomarker in HD.

### 4.4. Neuroanatomical studies

Several neuroanatomical studies, including on CST; corticostriatal projections; arcuate; MdLF; and claustrum have been facilitated with the help of GQI-based tractography [73,136–139]. GQI-based tractography has been found to be useful in terms of demonstrating the fiber tracts reliably along their anatomical course with accurate cortical end points [95]. The findings from the GQI-based tractography have been consistent with the neuroanatomical knowledge. With limitations associated with all tractography techniques, dissection of the white matter tracts has been immensely valuable in validating these findings and the neuroanatomical features.

Claustrum is one such example of a structure, which has been studied *via* fiber dissection, an advanced white matter imaging technique [139] and previously with DTI. Connectivity features and the structural significance of the claustrum have been postulated to relate to consciousness [140]. Most of the previous studies on claustrum have involved histological studies involving injected tracers and neurophysiological recordings in animals. These are difficult to extrapolate to the human brain, leaving its role largely unknown. Based on the anatomical studies, the claustrum [139] is divided into two parts: the dorsal claustrum (also referred to as compact [141,142] or insular claustrum [143–145]) and the ventral claustrum (also named fragmented [141, 142], prepiriform, amygdalar, or temporal claustrum [144,145]). The dorsal claustrum is a continuous irregular lamina of gray matter lying between the putamen (from which it is separated by the external capsule) and the insular cortex (from which it is separated by the extreme capsule) (Fig. 7). The ventral claustrum consists of a group of diffuse or island-like gray masses fragmented by the UF and the IOF (Fig. 7). White matter anatomy of the claustrum has been studied using the fiber microsurgical dissection technique (the Klinger technique) in the *post-mortem* human brains [146]. The gray matter of the short and long insular gyri is carefully removed to expose the extreme capsule and the claustrum. After removal of the dorsal extreme capsule, the fibers of the dorsal external capsule are seen to converge into and merge with the gray matter of the dorsal claustrum, forming a characteristic spoke-and-wheel pattern with its center at the dorsal claustrum (Fig. 7). The fibers of the UF (connecting orbital-frontal cortex with the medial temporal lobe and temporal pole) and IOF (connecting prefrontral to the parieto-occipital regions) traverse the most anterior

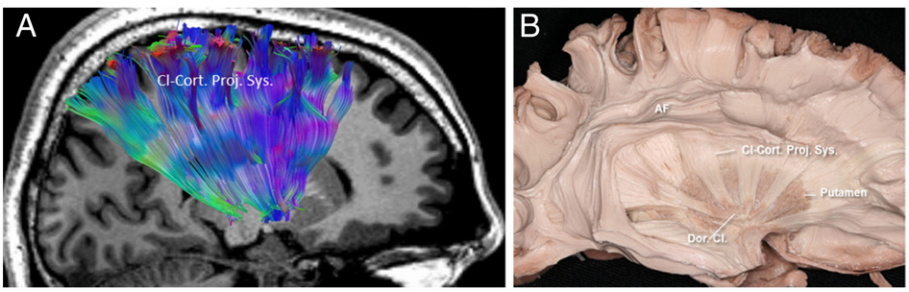


**Fig. 7.** A, Reconstruction of the claustro-cortical projection system (Cl-Cort. Proj. Sys.) using advanced white matter imaging technique; these fibers form the dorsal portion of the external capsule and converge into the dorsal claustrum. B, Fiber microdissection of the *post-mortem* human brain demonstrating the dorsal claustrum (Dor. Cl.) and the claustro-cortical projection system with the latter having been partially dissected to expose the underlying putamen; arcuate fasciculus (AF).

and inferior parts of the claustrum to create the gray matter islands that form the ventral claustrum. Based on fiber dissection studies, the so-called dorsal external capsule seems to be mainly composed of the claustro-cortical projection system. This projection system interconnects the claustrum with multiple cortical areas. The conventional "static" conceptualization of the external capsule as a group of fibers located deep to the claustrum is therefore, replaced with a more dynamic view of the external capsule or the claustro-cortical system [146,147]. One DTI study reported on the claustro-cortical projection system in the human brain [146]. This demonstrated that the external capsule was composed of multiple fiber bundles originating from the superior frontal; pre-central; post-central; superior parietal; and parieto-occipital regions and converging in the area of the dorsal claustrum. This led to the conclusion that the dorsal external capsule was mainly composed of the projection and not association fibers. Further a topographical organization in the dorsal claustrum and external capsule was also evident [139]. Posterior cortical areas projected into the posterior part of the dorsal claustrum and the more anterior cortical areas converged into the anterior part. Although the findings from this DTI study were exciting, the claustro-cortical fibers were not seen to be truly ending in the claustrum. These fibers were instead converging on the claustrum with evidence of false continuation in between the fiber tracts at the level of the claustrum. The cortical terminations of the claustro-cortical fibers were further approximated by using an overlaid T1 structural sequence. With advanced white matter imaging, connectivity features of the claustrum have been demonstrated in better detail including the representation of its endpoint projection pattern onto the cerebral cortex [139]. The claustrum fiber bundles show a ribbon-like pattern, highly resembling the fiber microdissection findings (Fig. 7) [139]. The claustro-cortical fibers terminate at the level of the dorsal claustrum. Further analysis of the cortical terminations of the claustro-cortical fibers reveal connections with the superior and rostral middle frontal gyrus; pre-motor; primary motor; somatosensory; and posterior parietal cortex areas with predominant connectivity being observed with the associative cortical areas. These findings therefore, support the role of claustrum in multi-model integration of the sensory and motor information.

MdLF [73] elucidates this approach further regarding integration of the fiber dissection studies with tractography. This pathway had been originally described in the monkeys as interconnecting the superior temporal and the angular gyri. DTI studies had supported its existence in the human beings with a connectivity pattern similar to that in monkeys and with a potential role in the language system. Using a combination of microdissection and tractography derived from advanced white matter imaging of normal subjects (Fig. 8), we found that the MdLF, in fact, connected the superior temporal gyrus with the superior parietal lobule with only minor connections with the angular gyrus. This led to speculation regarding its potential role in the auditory system.

## 5. General considerations, limitations and future directions

### 5.1. General considerations

Related to the general limitations discussed above with respect to tractography, is the possibility of missing affected fiber tracts. This is related to the ROIs being chosen based on a known pathology or the location of a lesion. Diffusion connectometry is a better approach in this respect, as no manual selection of ROIs is involved. Qualitative data from tractography-based studies with DTI or advanced white matter imaging techniques should be interpreted with a sound knowledge of the perilesional or loco-regional anatomy [36,96]. In the setting of mass lesions, this problem is accentuated further as an abnormal trajectory of a fiber may be either technical in origin or be real. Good neuroanatomical knowledge therefore, may help with an accurate interpretation of the data. In order to reduce the subjectivity of the interpretation of qualitative data, particularly in the setting of mass lesions, the use of a combined qualitative and quantitative approach [96] may be helpful. This approach can be adapted depending upon the relevant application and potentially provide information on the integrity of a fiber tract of interest with implications for prognostication and neurological recovery. Of particular importance in longitudinal studies, is the variability in the quantitative parameters that can occur across scan sessions irrespective of the pathology. In order to ascertain this and also the normal range of differences in anisotropy values and/or volumes for tracts of interest that can exist between sides (left *versus* right) related to hemisphere dominance, one strategy is to scan several normal subjects on multiple occasions. Establishing these parameters will assist with interpretation of the findings in both longitudinal studies and studies involving mass lesions in the brain.

Another issue pertains to the phantom studies. Various diffusion phantoms have been used to verify ADC of pure water and water inside the tissue at a microscopic level. Recently solid fiber-based phantoms are being used to verify the issues concerning anisotropy and direction of the fibers. One solution involves building of a textile based *hollow fiber phantom*, which can potentially simulate restricted diffusion. Restricted water diffusion can quantify axonal bundle, which may therefore lead to a more robust quantitative metric reflecting changes in the morphology and integrity of the fibers.

One of the criticisms has been the scanning time, which in our experience has not been prohibitive even for patients with intracranial lesions. One trend in diffusion field is to use fast scanning sequences at half their original length. Further work is being done towards improving the conventional diffusion sequence by using a multi-band acquisition sequence [148]. This leads to a substantial reduction of scanning time to 10 to 15 min and improved patient comfort during clinical studies without compromising accuracy. It is noteworthy that experience with the advanced white matter imaging techniques is

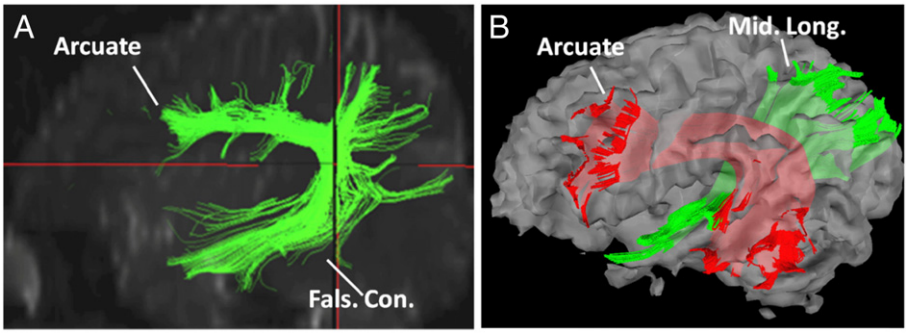


**Fig. 8.** A, Diffusion tensor imaging reconstruction of the arcuate fasciculus demonstrating the false continuation (Fals. Con.) between the fibers of the middle longitudinal fascicle (Mid. Long.) and the fibers at the termination of the arcuate in temporal lobe. B, Advanced white matter imaging reconstruction demonstrated the two tracts with the middle longitudinal fasciculus (Mid. Long.) seen to be connecting the superior temporal gyrus with the superior parietal lobule (with minor connections with the angular gyrus).

preliminary in research and clinical areas. Much of the experience has been acquired with DTI and with its applications in clinical research studies. Even with conventional DTI, guidelines for its use in the clinical setting, for example in the resection of a neoplasm, are not completely clear. Use of the DTI is guided by its availability, institutional and surgeons' preference.

### 5.2. Intracranial mass lesions

The anisotropy index, derived from the advanced white matter imaging technique, could be potentially affected by the susceptibility artifact due to the presence of blood products with mass lesions [96]. This could give rise to *artifactual* disruption. With lack of histopathological data, using any quantitative index including FA, to support tract disruption may therefore be considered speculative. One solution is to undertake pre- and postoperative scans in patients. This will allow both qualitative and anisotropy data to be recorded and checked for consistency with the preoperative results after a potential lesionectomy. One will expect a potentially disrupted tract and its associated qualitative and quantitative characteristics (and related deficits) to remain mostly unchanged after the lesionectomy. The reverse will be true for the displaced tracts.

A further limitation pertains to detecting minor degrees of change in the integrity of fiber tracts, where an overall or even a perilesional segment's anisotropy index in relation to the contralateral side may not be sensitive enough to provide the information. An 'automated' anisotropy profile, using multiple points in the perilesional and contralateral white matter tracts, will provide a better picture of the craniocaudal integrity of the tract [96]. This approach may be useful towards prognostication. In view of the preliminary accuracy of cortical termination points from tractography [95,139], its correlation with the fMRI [96] data and with results from the intraoperative white matter stimulation for cerebral lesions, is being examined. This may also assist with future anatomical studies. In these studies, integration of tractography with functional modalities like fMRI or magnetoencephalogram may allow a more reliable speculation regarding the role of a specific tract.

### 5.3. Neurodegenerative disorders

One current issue is to establish the normal variability in the quantitative parameters to allow meaningful interpretation of observed changes in these values across scan sessions in patients with neurological disorders. A further issue pertains to the heterogeneity of the disease population, enrolled in the studies and its potential impact on the results. The control population are sex and age-matched to the patient population. It remains to be elucidated as to how the heterogeneity of both control and disease population may impact the variability in the measurement of the quantitative parameters. In the ALS study, this has been partially accounted for by enrolling patients with ALS, as defined according to the El-Escorial criteria [111] before potentially focusing in the future on other MND phenotypes. In the HD study, the focus is on the early manifest and premanifest patients. Despite these measures, patients with similar clinical disease burden or phenotype may have pathological heterogeneity making the data interpretation challenging.

### 5.4. Neuroanatomical studies

Well-established knowledge on white matter human neuroanatomy has largely relied upon the translational studies in monkeys' brains. Neuroanatomical studies, however using *in vivo* tractography techniques, have revealed that there are multiple discrepancies between the microstructural connectivity features of human and animal brains. In fact, the precise structural connectivity of the brain remains largely unknown. With the advancements in the white matter mapping techniques, one now has the opportunity to unravel many of the mysteries surrounding the structure and function of the human brain, as intended by the government-funded initiative, the so-called *Human Connectome Project*.

## 6. Conclusion

In this review article, we have presented the technological advances leading up to the development of DTI and more advanced techniques aimed at imaging the white matter. We have discussed the relative advantages and limitations associated with different white matter imaging techniques and analytical approaches. The general limitations associated with tractography studies have also been presented. The use of an advanced white matter imaging technique to obtain superior qualitative data in terms of accurate demonstration of multiple crossing fibers in a three dimensional manner around intracranial lesions is clearly useful in neurosurgery for decision making and surgical approach planning. In terms of assessing injury to a tract, a preliminary combined qualitative and quantitative approach has been discussed with potential applications for prognostication. Adaptation of the analytical approaches, for example the connectometry and its subsequent use in conjunction with the data from tractography, has enabled longitudinal studies in the neurodegenerative disorders. These have provided us with preliminary, yet encouraging results. Apart from ongoing technical advancements towards improvement of the advanced white matter imaging techniques, future studies will need to be combined with functional imaging modalities. In particular, these studies will provide information at the level of the cortex for correlation with the *end points* of the fiber tracts.

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