Structural human brain networks: hot topics in diffusion tractography

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Purpose of review
After more than 10 years of methodological developments and clinical applications, diffusion imaging tractography has reached a crossroad. Although the method is still in its infancy, the time has come to address some important questions. Can tractography reproduce reliably known anatomy or describe new anatomical pathways? Are interindividual differences, for example in tract lateralization, important to understand heterogeneity of clinical manifestations? Do novel tractography algorithms provide a real advantage over previous methods? Here we focus on some of the most exciting recent advancements in diffusion tractography and critically highlight their advantages and limitations.

Recent findings
A flourishing of diffusion methods and models are bringing new solutions to the well known limitations of classical tractography based on the tensor model. However, these methods pose also new challenges and require the convergence and integration of different disciplines before they can replace what is currently widely available.

Summary
Rigorous postmortem validation, clinical optimization and experimental confirmation are obligatory steps before advanced diffusion technologies can translate into clear benefits for neurological patients.

Keywords
diffusion imaging, spherical deconvolution, tractography, white matter connections

INTRODUCTION

> *'To interpret the activity of living human brains, their neuroanatomy must be known in detail. New techniques are urgently needed since most of the methods now used on monkeys cannot be used on humans' (Crick and Jones, 1993)* [1]

The study of brain connections has a long history dating back to postmortem blunt dissection performed by pioneer anatomists of the 18th and 19th century [2,3]. This method, although rudimentary in our eyes, allowed to delineate the trajectories of the major white matter bundles of the human brain. The development of animal tracing studies in the 20th century has further improved our knowledge of connections, adding more detailed descriptions of brain connectivity [4]. The ability to actively trace individual axons is unique to tracer studies, but these studies must be performed in nonhuman animals and their findings in other species remain to be confirmed. In 1994, a real breakthrough came with the development of diffusion tensor imaging (DTI) to study the organization of white matter in the living human brain. With this method it was possible, for the first time, to measure and extract *in vivo* and noninvasively the organization and integrity of white matter fibres by quantifying the movement of water molecules inside the tissue [5]. A few years later, tractography algorithms were proposed as a tool to mathematically reconstruct three-dimensional trajectories of the major white matter pathways [6–9]. Rapidly, this technique has become the most important tool for investigating the

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KEY POINTS

- Tractography methods reconstruct white matter pathways in the living human brain and can be used to assess interindividual anatomical differences.
- Atlases of white matter pathways can help to localize damaged tracts and improve clinicoanatomical correlation.
- New diffusion models and tractography algorithms have been developed to resolve fibre crossing and obtain truly tract specific characterization of diffusion properties for each fibre orientation.
- Direct validation of newly discovered tracts is possible by combining high-resolution diffusion imaging with postmortem histology.

connectional anatomy of the normal [10,11] and pathological human brain [12–18]. In parallel, a new breed of diffusion-imaging methods have been developed in the recent years with the aim to overcome two of the major limitations of DTI tractography: the inability to resolve multiple fibre orientations inside the same voxel (i.e. the *fibre-crossing problem*), and the lack of specificity of DTI indices (i.e. the *white matter integrity paradox*). In the next paragraphs we present 10 'hot topics' in the current diffusion imaging tractography field. We discuss advantages and limitations of some of the most recent advancements in the field and critically highlight challenges ahead.

TOPIC 1: REPRODUCING KNOWN ANATOMY

The ability to reproduce three-dimensional trajectories of white matter connections in the living human brain is a unique feature of tractography. For some tracts the details of the 'virtual reconstructions' match those derived from human postmortem blunt dissections [19] or histology [20,21]. This is particularly evident for tracts that reach cortical regions without crossing with other connections (e.g. dorsal cingulum' medial callosal fibres, and so on). For other tracts, the matching is rather incomplete due to the limitations of the diffusion tensor model and the intrinsic low spatial resolution of the human diffusion datasets.

In animals, axonal tracing methods have been used to validate, for example, tractography pathways based on diffusion spectrum imaging (DSI) [22]. Similarly, Dyrby *et al.* [23] attempted direct validation of tractography with in-vivo manganese in the minipig brain. A problem common to all the above studies is that the methods used to validate tractography have their own limitations (Table 1). Hence, validation remains a difficult task due to the lack of a universal gold standard for tracing connections. Use of functional methods could represent a valid alternative [24–27], although in this case these methods would allow definition of the function associated with a specific tract rather than confirming its exact anatomy (e.g., trajectory, volume, etc.)

TOPIC 2: INTERINDIVIDUAL VARIABILITY

One of the major contributions of tractography to brain anatomy is the identification of left and right asymmetries in the cerebral white matter pathways. By extracting surrogate measurements of tract volume, such as the number of streamlines or the space occupied by them, several studies revealed a left lateralization of short and long association pathways such as the direct connections of the arcuate fasciculus (between posterior temporal and inferior frontal regions) [27], the optic radiations [20], the frontal aslant tract [28▪] and the U-shaped fibres connecting primary motor and somatosensory cortex [28▪]. Other tracts, such as the anterior fronto-parietal segment of the arcuate fasciculus [29▪] and the connections from temporal to superior parietal cortex [30] are right lateralization. There is also preliminary evidence that the degree of lateralization of these tracts is associated with handedness [28▪], verbal memory performances [27] and visuo-spatial tasks [29▪]. These findings could be relevant in clinical settings where quantification of the degree of anatomical lateralization may help to predict recovery, for example, in stroke patients with neglect or aphasia [31].

TOPIC 3: ATLASING CORTICAL AND SUBCORTICAL CONNECTIVITY

Until the advent of tractography, our knowledge of white matter anatomy was based on a small number of influential 19th and early 20th century postmortem dissection atlases [32–34]. In common with their contemporary counterparts [35], these atlases emphasize the constant or average anatomy of representative participants at the expense of normal variability between participants. In the recent years, several groups have used DTI to produce group atlases of the major white matter tracts [2,19,36–38]. By extracting anatomical location of each tract from several participants, these atlases provide probability maps of each pathway and quantify their anatomical variability. These atlases help the clinician to establish a relationship of focal

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Table 1. Methods for tracing or tracking brain connections

Method	Advantages	Limitations
Blunt dissections	Applicable to human brains	Only for postmortem tissue
	Direct anatomical method	User driven and operator dependent
	Identify large tracts	Variable quality of the prepared sample
		Destructive
		Qualitative only
		Limited ability to visualize crossing bundles (false negatives)
		Produce artifactual trajectories (false positives)
		Time consuming
Staining degenerating myelin (e.g. Marchi's method)	Direct anatomical method	Only for postmortem tissue
	Identify large and small tracts	Fibre delineation limited by the volume and location of the lesion
	Operator-independent	Variable quality of the prepared sample
	Applicable to human and animal brains	Destructive
		Qualitative only
		Time consuming
		3D reconstruction limited
Axonal tracing	Direct anatomical method	Not suitable for humans
	Identify large and small tracts	Fibre delineation depends on the injection site
		Variable quality of results depending on the tracer used
	Allow direct testing of specific hypotheses	Qualitative only
	Reveal fibre directionality	Limited number of tracts per sample
		Destructive
		Time consuming
		3-Dimensional reconstruction limited
Neurohistology	Direct anatomical method	Small field of view
	Identify small local networks	3-Dimensional reconstruction limited
	Not user driven	Time consuming
	Allows to distinguish neurochemical properties of the fibres (e.g., cholinergic, etc.)	Destructive
Cortical electrophysiology	*In vivo*	Not anatomical
	Allows comparative studies between species	Time consuming
	Functional information	Small number of hypothesis tested in the same sample
	Small number or single neuron connectivity	Invasive
	Directionality can be inferred	Presence of artifacts (e.g., noise, movement, and so on)
Tractography	*In vivo*	Indirect anatomical method
	Applicable to human and animal brains	Low spatial resolution
	Noninvasive	Presence of artifacts
	Time efficient	Operator dependent
	Allow to study large populations	Limited visualization of bending, merging and crossing fibres
	Correlation with behavioural and other functional measures	
	Quantitative	
	Multiple hypothesis testing	
	Not destructive	

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lesions with nearby tracts and improve clinicoanatomical correlation [20]. It remains to be established, however, how much of this variability is due to a true underlying anatomical difference (as suggested by correlations between structural differences and behavioural performances [27,29▪]) or is the result of methodological limitations (Fig. 1) [39].

TOPIC 4: ANATOMICAL PROBABILITY AND TRACTOGRAPHY UNCERTAINTY

The 'probability' maps reproduced in current diffusion atlases must not be confused with the maps produced by 'probabilistic' tractography [40–42]. Compared to deterministic approaches in which the estimated fibre orientation (e.g. direction of maximum diffusivity for the tensor model) is assumed to represent the best estimate to propagate streamlines, probabilistic methods generate multiple solutions to reflect also the variability or 'uncertainty' of the estimated fibre orientation [43▪▪,44]. These methods, therefore, provide additional information on the reproducibility of each tractography reconstruction by mapping the intrinsic uncertainty of individual diffusion datasets. The uncertainty quantified by probabilistic tractography is mainly driven by the magnetic resonance noise, partial volume effects and inaccuracy of the chosen diffusion model. Therefore, the probability of individual maps should not be considered as a direct measure of the anatomical probability of the tract. Indeed, in some cases artifactual trajectories can have high probability similar to true anatomical pathways. Ultimately, in datasets without noise both deterministic and probabilistic approaches based on the same diffusion model would generate identical tractography maps. Understanding these basic assumptions underlying probabilistic tractography is important to interpret correctly its results.

TOPIC 5: NOVEL DIFFUSION MODELS

One of the major improvements for both probabilistic and deterministic tractography is the introduction of novel advanced diffusion models to estimation multiple fibre orientations. Several models have been proposed.

Multiparametric methods (e.g., Multitensor [45,46] or 'Ball and Stick' models [40,42]) are model-dependent approaches in which the diffusion data are fitted with a chosen model that assumes a discrete number of fibre orientations (e.g., two or more).

Nonparametric, model-independent methods such as DSI [47], qBall imaging [48,49], or diffusion orientation transform [50] have been developed to better characterize the water molecular displacement by using a spherical function or the diffusion orientation distribution function (dODF). The multilobe shape of the dODF provides information on the number of fibre orientations, their orientation and the weight of each fibre component.

A third group of methods try to take advantage of both approaches by extracting directly the underlying fibre orientation (i.e., fibre-ODF) using a specific diffusion model for white matter fibres. The latter approaches are usually described as spherical deconvolution methods [51–58] and they generally show higher angular resolution (i.e. the ability to resolve crossing fibres at smaller angles) compared with methods based on dODFs [59]. Spherical deconvolution methods are becoming the methods of choice in an increasing number of studies as they require acquisition protocols that are

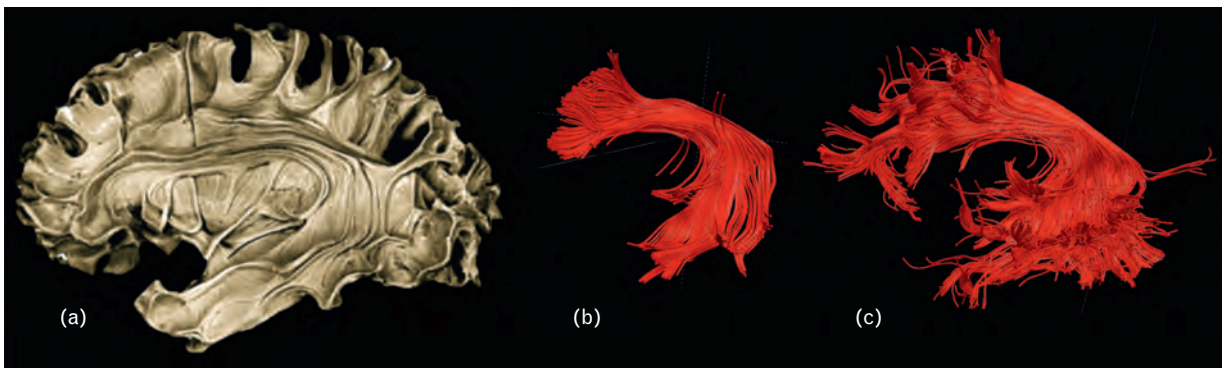

FIGURE 1. The anatomy of the arcuate fasciculus derived from (a) postmortem blunt dissections, and from in-vivo tractography based on (b) diffusion tensor imaging and (c) spherical deconvolution. The images in (b) and (c) are from the same individual and differences in the reconstructed arcuate fasciculus are mainly due to methodological limitations of both methods. Image (a) modified from [39].

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close to clinical DTI protocols (e.g. low number of diffusion gradient directions and b-values that are accessible in most clinical scanners).

TOPIC 6: VISUALIZING NEW TRACTS

Advanced diffusion models that resolve multiple white matter trajectories offer the possibility of describing tracts that are not visible using current DTI methods and identify new tracts. By using spherical deconvolution tractography, for example, it is possible to visualize and quantify the volume of the three segments of the superior longitudinal fasciculus, a tract previously described only in the monkey brain (Fig. 2) [29▪,60]. Recently, the same method has been used to reveal new details of the short frontal lobe connections [28▪]. Although an exact knowledge of these short fibres represents a significant step forward in our understanding of human anatomy, it is important to be aware that tractography based on advanced diffusion methods is prone to produce a higher number of false positives compared to DTI tractography. Hence, validation of these tracts with complementary methods [26] is necessary before applying these anatomical models to clinical populations [3].

TOPIC 7: QUANTIFICATION AND CLINICAL APPLICATIONS

By extracting quantitative diffusion indices, such as fractional anisotropy and mean diffusivity, along the dissected tract it is possible to characterize the microstructural properties of tissue in the normal and pathological brain and provide quantitative measurements for group comparisons or individual case studies [61,62]. The interpretation of these indices, however, is not always straightforward, especially in regions containing fibre crossing. An example of the complexity of this problem is the increase of fractional anisotropy commonly seen in the normal-appearing white matter regions distant to the lesioned area. Before interpreting these changes as indicative of 'plasticity or remodelling', other explanations should be taken into account. In voxels containing both degenerating and normal fibres, increases in fractional anisotropy values

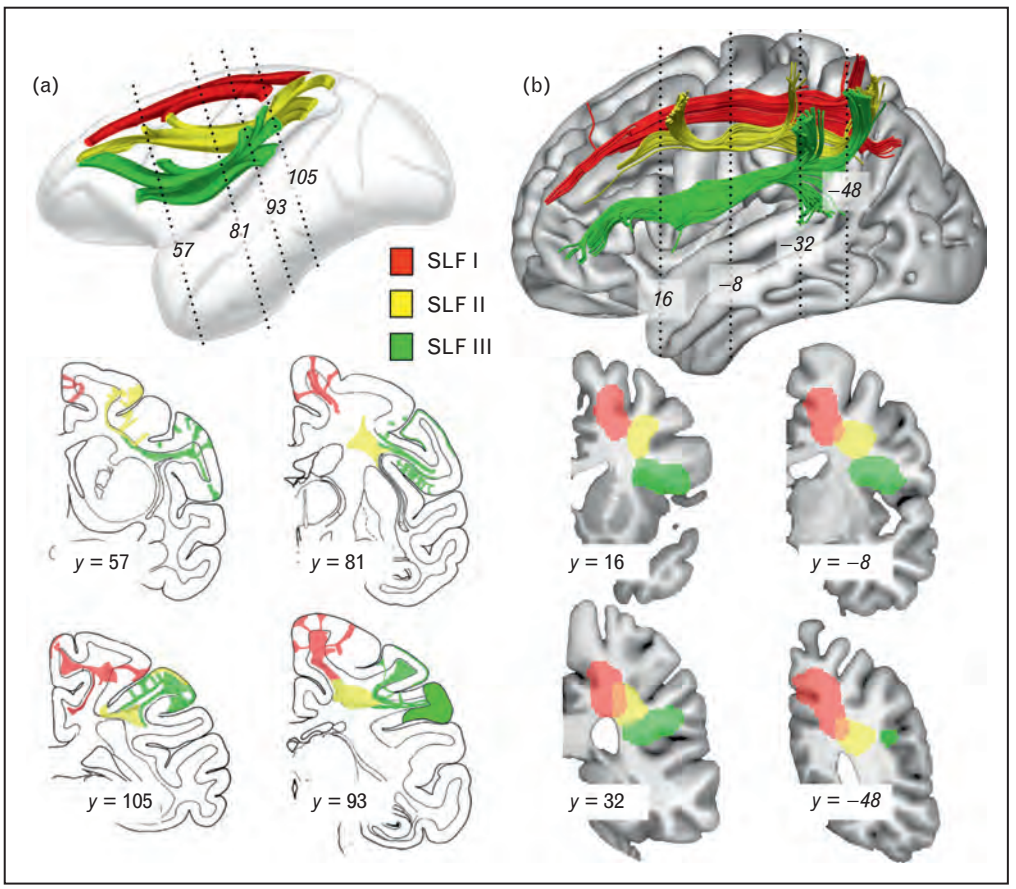

FIGURE 2. Visualization of the three branches of the superior longitudinal fasciculus (SLF) in (a) monkey brain using axonal tracing and (b) human brain using spherical deconvolution tractography [60].

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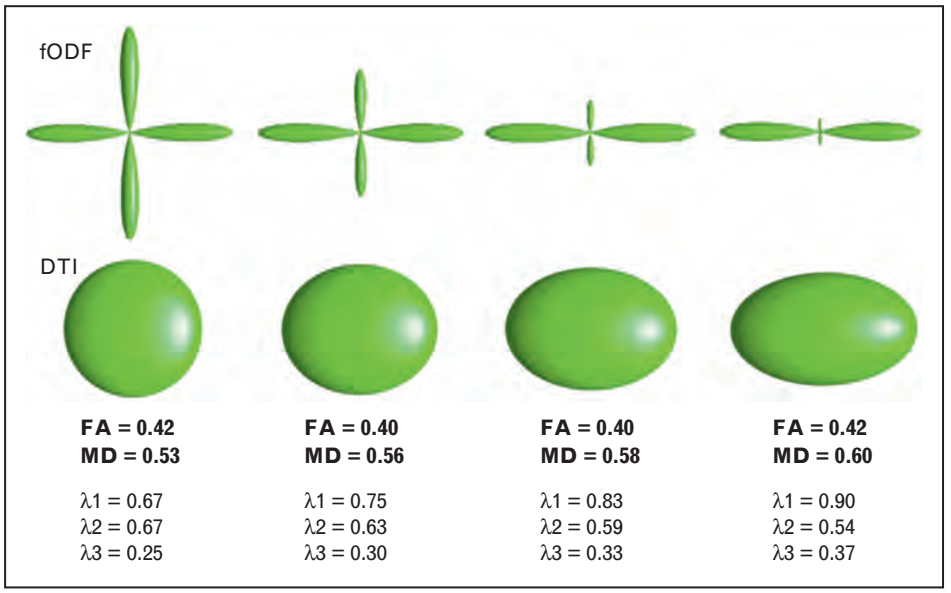

FIGURE 3. Diffusion changes in a crossing configuration. This figure shows how average fibre orientation distribution function (fODF), tensor ellipsoids and diffusivity values change according to the simulated degeneration of the vertical fibre component, while the horizontal component remains intact. Please note that the changes in the overall fractional anisotropy (FA) do not reflect the constant degeneration of the vertical fibre and therefore do not represent a direct quantitative measurement of fibre integrity. DTI, diffusion tensor imaging; MD, mean diffusivity. MD, λ1, λ2, and λ3 values are in [$\times 10^{-3}$ mm^2/s].

are, in fact, more likely due to the axonal degeneration of the perpendicular fibres (Fig. 3) [63].

The lack of specificity of current diffusion indices (i.e., diffusion changes depend on a number of biological, biochemical and microstructural factors) [44] and the intrinsic voxel-specific rather than fibre-specific information derived from current indices has stimulated scientists to work on new methods and novel diffusion indices [58,64▪,65]. Tractometry [66,67] is an interesting approach that tries to combine tractography with the quantitative mapping along individual tracts of complementary neuroimaging measurements based on, for example, relaxometry, magnetization transfer ratio [68], myelinated water fraction [69] or multicompartmental diffusion indices [70,71]. More recently, true tract-specific indices based on spherical deconvolution that better describe the microstructural diffusion changes of individual crossing fibres within the same voxel have been proposed. Changes in the hindrance modulated orientation anisotropy [64▪], for example, have a greater sensitivity than conventional fractional anisotropy values to detect degeneration that occurs only in one population of fibres, whereas the others crossing fibres remain intact (Fig. 4) [64▪]. In the future, tractography combined with other methods will allow to extract even more specific tissue microstructure indices, such as axonal diameter distributions or axonal density [72–74].

TOPIC 8: FUTURE TRACTOGRAPHY ALGORITHMS

Most of the current tractography algorithms are still based on the same tracking strategies originally introduced by the first tractography approaches [6–9]. These strategies apply rules to avoid, for example, unrealistic fibre bending (i.e., angular thresholds) or tracking outside white matter regions (i.e., anisotropy thresholds) and are effective in reducing some of the artifactual reconstructions [9,75,76]. However, when tractography is performed using multifibre approaches, new strategies are necessary because of the increased risk of false-positive reconstructions. Different approaches have been recently proposed to guide the propagation of the tractography algorithm across regions with multiple fibre orientations and try to discriminate between crossing, kissing and bending configurations. Some of these approaches use 'directional consistency' or similarity between fibre orientations across neighbouring voxels [77,78], others use tract-specific properties [58,64▪] or microstructural characteristics (e.g. axonal diameter) [79] to propagate and differentiate tracts.

Global tractography is an alternative method [80–82] in which the entire tract is generated simultaneously without a direct propagation of streamlines. By piecing together smaller tracts, the entire pathways is globally fitted to a chosen model that maximizes the consistency of the whole tract with

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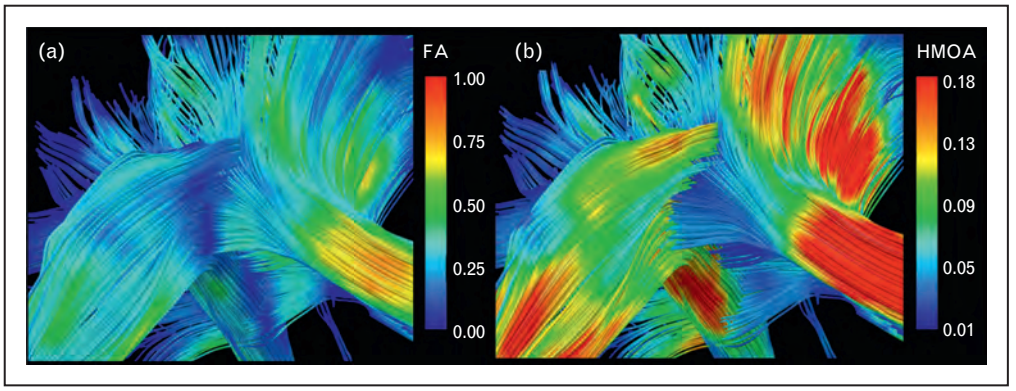

FIGURE 4. Mapping diffusion indices along crossing white matter tracts. The arcuate fasciculus and the lateral projections of the corpus callosum cross at the level of the corona radiata. (a) Fractional anisotropy (FA) values provide an average, voxel-specific description of the anisotropic properties of the selected brain region and, therefore, identical FA values are attributed to both crossing fibres. (b) The hindrance modulated orientational anisotropy (HMOA) index shows distinct diffusion characteristics for the two crossing tracts, lower HMOA for the callosal projections and higher HMOA for the arcuate fibres. Modified from [64▪].

the corresponding diffusion data. Because of small local errors, the final pathway can be formed by different anatomical tracts; for this reason anatomical constraints (or priors) are applied to distinguish between true tracts and artifacts [83].

TOPIC 9: CONNECTOMICS

Investigating the entire connectivity of the human brain remains today one of the most challenging tasks in neuroscience. Developing and applying novel techniques to visualize and study large brain networks is essential to achieve a complete reconstruction of the human brain connectome [84▪,85]. Whole brain tractography approaches combined with powerful network analysis tools are currently in development [86,87] and may offer in the future a new tool to investigate connectivity in the healthy and pathological brain. However, most of the connectomic results rely on the anatomical accuracy of tractography methods and their ability to describe white matter trajectories between distant cortical regions. Inevitably, the limitations of current tractography algorithms bias the final connectomic results. For example, most distant hubs are likely to be understimated with analysis based on probabilistic tractography [44]. Improving tractography methods is, therefore, essential to provide solid foundations for mapping the human connectome.

TOPIC 10: SPATIAL RESOLUTION, ULTRARESOLUTION AND VALIDATION

Despite improvements in diffusion models and algorithms the low spatial resolution and the lack of histological validation remain two of the major limitations of in-vivo diffusion tractography. Little is still known about the true correspondence between tractography reconstructions, diffusion indices and the real underlying tissue organization. The development of new magentic resonance hardware and new diffusion sequences have recently shown that higher spatial resolutions can be achieved *in vivo* [88,89,90▪]. Even higher resolutions have been reached in preliminary studies on animals and human postmortem brains on preclinical magnetic resonance systems [91–95]. The development of 'microtractography' approaches based on ultrahigh resolution datasets (e.g. 100 micron and below) has the potential to offer unique tractography reconstructions to characterize small connections and bridging the gap between in-vivo neuroimaging and histological analyses. At such resolution, reconstructions can be directly validated with neurohistological analysis, and will offer opportunities to study network organization at different scales [90▪,96].

CONCLUSION

Diffusion remains one of the most exciting and challenging fields in neuroimaging. Clinicians should not be discouraged by the fast-paced proliferation of techniques and methods currently applied to study white matter pathways. Most of these methods offer new opportunities to visualize in-vivo white matter connections in the normal and pathological human brain and revitalize disconnectionist accounts of neurological disorders. However, these methods still need full validation before they can be applied to clinical routine.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 513).

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