Just pretty pictures? What diffusion tractography can add in clinical neuroscience

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Purpose of review

Diffusion tractography uses non-invasive brain imaging data to trace fibre bundles in the human brain *in vivo*. This raises immediate possibilities for clinical application but responsible use of this approach requires careful consideration of the scope and limitations of the technique.

Recent findings

To illustrate the potential for tractography to provide new information in clinical neuroscience we review recent studies in three broad areas: use of tractography for quantitative comparisons of specific white matter pathways in disease; evidence from tractography for the presence of qualitatively different pathways in congenital disorders or following recovery; use of tractography to gain insights into normal brain anatomy that can aid our understanding of the consequences of localised pathology, or guide interventions.

Summary

Diffusion tractography opens exciting new possibilities for exploring features of brain anatomy that previously were not visible to us *in vivo*.

Keywords

diffusion imaging, tractography, white matter

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Abbreviation

MRI   magnetic resonance imaging

Introduction

Imaging has proved to be a useful tool in clinical neuroscience, providing in-vivo markers of disease severity or response to therapy and shedding light on processes of progression and recovery. This review considers whether diffusion magnetic resonance imaging (MRI) tractography can provide a new source of useful information in clinical neuroscience.

Diffusion imaging is sensitive to diffusion of free water. This is useful for imaging of brain anatomy because, within white matter, diffusion is orientation-dependent: there is greater hindrance to diffusion across a fibre bundle than along it. By acquiring multiple images, each sensitive to diffusion at a different orientation, we can fit a model (e.g., the diffusion tensor [1]) to our measurements and quantify the mean diffusion, and its orientation dependence ('fractional anisotropy') at each brain voxel (three-dimensional pixel). Recent studies confirm the sensitivity of these measures to microstructural changes in disease [2,3,4•,5,6] and in normal development [7–9] and ageing [10–12].

Here, we focus specifically on 'tractography', the technique of tracing brain pathways using diffusion data. By fitting a diffusion model we can estimate not only mean diffusion and fractional anisotropy but also the orientation of maximum diffusion at each voxel. Tractography is performed by following these orientation estimates to reconstruct a pathway that, within a coherent bundle, corresponds to the underlying fibre pathway [13]. Previously, such white matter anatomy could only be studied by post-mortem dissection or invasive tracing in non-human animals. The ability to trace the white matter pathways of the whole human brain from a single in-vivo scan raises immediate possibilities for clinical application and there has been a rapid increase in publications using tractography in clinical populations.

Tractography certainly produces spectacular images (Fig. 1). Before we incorporate diffusion imaging into every grant proposal and imaging examination, however, it is important to recognize its limitations, and to consider what it can provide other than pretty pictures.

Limitations of tractography

Diffusion tractography does not trace fibres in the sense that injected tracers trace fibres; tractography shows us

Figure 1 Routes between Broca's and Wernicke's areas in the human brain
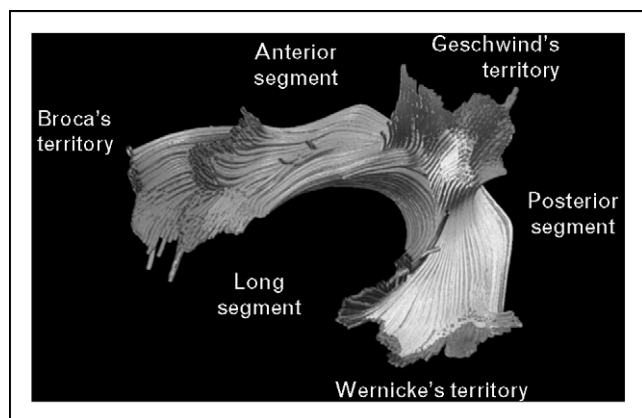
A direct path, corresponding to the arcuate fasciculus, and an indirect path via the inferior parietal cortex (Geschwind's territory), consisting of an anterior segment, and a posterior segment. Reproduced with permission [63•].

the path of least resistance to water diffusion. In some contexts (e.g. in the corpus callosum), the tractography-derived pathway corresponds well to the underlying fibre pathway but in other contexts it does not. The size of our imaging voxels is typically a few millimetres cubed so a single voxel could contain tens of thousands of axons. Most methods assume that fibres at each voxel are well described by a single orientation estimate, and so the methods perform poorly in regions of fibre crossing or complexity or with small or tortuous pathways. Methodological developments in orientational [14] and spatial [15] resolution, and in diffusion modelling [16–19] and tractography [20•] should improve this and already are providing sensible anatomical results [20•,21,22]. Other limitations include the inability to differentiate antero-grade and retrograde connections, to detect the presence of synapses, or to determine whether a pathway is functional. In summary, the limitations mean that false positives and negatives will occur and so the presence or absence of a particular pathway in a tractography result should always be interpreted with care.

Although we must keep in mind the limitations of tractography, we also should not lose sight of the fact that it is the only technique for tracing white matter pathways in a living brain and that it does so using data that can be acquired in minutes. This raises immediate opportunities for novel clinical investigations. We review recent studies that illustrate how tractography can provide clinically relevant information that was not previously available: to define paths within which quantitative comparisons can be made between subjects or over time; to demonstrate qualitative changes in tract location or presence; and to provide novel information on

normal anatomy, relevant to understanding disease or planning surgical interventions.

## Quantitative tractography provides a marker for degeneration

Studies reporting changes in fractional anisotropy or mean diffusion in disease vary substantially in how accurately they can pinpoint the location of changes. Often, pathology occurs locally. Defining which pathways are affected, and which are not, is critical to understanding disease development and progression, and to targeting interventions. The location of changes can be inferred from regions of interest analyses [4•,6,9–12], voxel-wise comparisons [5,7,8], or projecting diffusion values onto a tract-based template [23–26]. These approaches, however, all make assumptions about the correspondence in tract location across subjects. An alternative strategy is to use tractography to extract a specific pathway and then to calculate diffusion measures along that pathway (Fig. 2) [27,28••,29••,30–33], or to make use of values provided by the tractography algorithms themselves (O. Ciccarelli et al., in preparation) [3,35], such as path probability, although the physiological interpretation of such tracking measures is debatable.

Using tractography to identify regions of interest in this way, a recent study [36•] revealed that patients with unilateral temporal lobe epilepsy have bilateral changes in the fornix and cingulum bundle, characterized by impaired tracking of these paths, and increased mean diffusion and reduced fractional anisotropy along them. The fractional anisotropy reduction was driven by increased radial diffusivity (i.e., increased diffusion perpendicular to the principal diffusion direction, thought to reflect degeneration of the usual barriers to diffusion in this direction [37]), consistent with degeneration of pathways connecting to the hippocampus (where the primary pathology occurs). It is intriguing that these white matter changes are bilateral, whereas conventional MRI and pathology studies typically report unilateral abnormalities in such patients. Bilateral diffusion changes in the uncinate fascicle, connecting medial temporal and inferior frontal regions, have also been reported in a similar patient group [25]. Interestingly, these uncinate changes correlated with functional reorganization, measured as the laterality of functional MRI activation during verbal fluency tasks, demonstrating a direct correspondence between the white matter changes and their functional consequences [25].

Quantitative studies using tractography have also identified specific white matter changes in patients with clinically isolated syndromes suggestive of multiple sclerosis. There is increased mean diffusion and radial diffusivity within the pyramidal tract in patients presenting with motor symptoms [38], whereas patients presenting with

Figure 2 Motor and sensory pathways in premature infants

(a) Tracing of motor (darker grey, more anterior) and sensory (paler grey) pathways in a premature infant. (b) Quantitative measurements from along these pathways show increasing fractional anisotropy (FA) with age, probably reflecting a combination of increasing packing density and myelination. Reproduced with permission [28••].
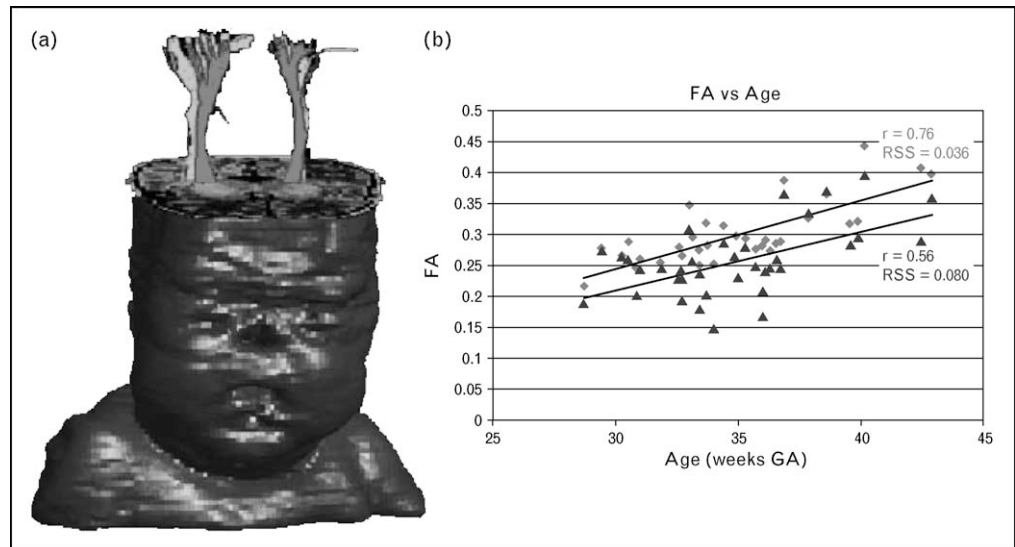
optic neuritis show reduced probability of connection along the optic radiations [39]. White matter changes in patients who have developed multiple sclerosis are also pathway-specific, and correlate with the pattern of motor versus cognitive symptoms [40].

Tractography of the corticospinal tract reliably shows that this pathway has reduced fractional anisotropy and increased mean diffusion in patients with amyotrophic lateral sclerosis (ALS) (O. Ciccarelli *et al.*, in preparation) [41,42]. Key challenges in this heterogeneous disease include defining markers or predictors of progression and differentiating subtypes. Preliminary results show that the degree or location of degeneration within the corticospinal tract correlates with rate of disease progression (O. Ciccarelli *et al.*, in preparation), and identifies distinctions between patients with ALS versus primary lateral sclerosis [23] and those with sporadic versus familial forms of ALS [43].

In neuropsychiatry, although there have now been multiple reports of white matter changes in schizophrenia [44], there is little consensus in the pattern of change [45], possibly due in part to methodological variability [46]. Recent tractography studies also give a complex picture: differences between patients and controls may vary substantially with age of investigation [32], while patients with very late onset psychosis fail to show any consistent changes relative to healthy subjects [47].

Could tractography visualize adaptive reorganization?

In addition to pinpointing areas of pathology, could tractography shed light on possible compensatory mechanisms in disease? One recent report suggests that unex-

pected increases in tract integrity measures in the unaffected hemisphere of patients with cerebral palsy due to unilateral periventricular white matter injury could reflect adaptive compensation [34]. Although this interpretation is possible, we should keep in mind the fact that tractography-based metrics are not fibre counts but rather measure ease of tracking: an alternative explanation, for example, is that loss of callosal inputs from a damaged hemisphere results in easier tracing of the perpendicularly oriented cortico-bulbar tracts. Nevertheless, the possibility remains that tractography could be used not only as a marker of degeneration, but also of increased myelination or packing density, potentially reflecting positive adaptive change. Support for the idea that variation in diffusion parameters reflects functionally relevant variation in pathway function is found in evidence from healthy subjects showing that fractional anisotropy within specific pathways relates to behavioural performance on related sensory and cognitive tasks [26,48•,49•,50,51], and that specific functional systems show training-related changes [52••].

In addition to increased use of existing tracts, it is possible that more extensive adaptive changes occur in response to damage. Astounding new results using conventional tract tracing show that recovery following an experimental motor cortex lesion in the squirrel monkey is associated with growth of novel connections from ventral premotor cortex to areas 1 and 2 of the primary somatosensory cortex [53••]. This remarkable finding raises the possibility that rerouting of axon trajectories (or possibly even sprouting of new axons) mediates functional recovery. This study was even able to visualize the rerouting of fibres around the lesions site: on approaching the lesion, axons from premotor cortex

appeared to deviate from their course and change track to head towards somatosensory cortex. Beautiful, painstakingly acquired results such as these put the pretty pictures we can generate with diffusion tractography into sharp perspective. Clearly, with diffusion tractography we are limited to looking at the system at a completely different scale: while the traditional tract tracers reconstruct the routes of the footpaths and side alleys of brain circuitry, the diffusion tractographers are rather like passengers in an aeroplane, trying to produce a roadmap based on the blurred streetlights of distant expressways. The big plus of imaging, however, is that we can look at the whole system in one shot, and in a living human patient. Therefore, the demonstration that such extensive rewiring could occur following naturally occurring damage, such as stroke, raises the challenge of searching for markers (albeit indirect) of this rewiring in the human brain *in vivo*. Admittedly, we will not be able to track the fibres shown by Dancause *et al.* [53••] using anything even close to existing technology and approaches. Yet it is not inconceivable that imaging could one day provide a marker for such changes. Local features in diffusion data, for example, may provide markers for subtle changes in cortical architecture, such as might be expected with a shift in the balance of intracortical fibre orientations [22,54,55].

Quality not quantity

Moving from quantitative comparisons of diffusion values along existing pathways, to demonstration of qualitative changes in white matter anatomy is challenging. Typically, defining false positives or negatives in tractography relies on prior anatomical knowledge and so interpretation of the presence of an unexpected pathway, or the absence of an expected tract, is difficult [37]. Early acquired blindness is an interesting test case: functional imaging of this group shows that responses can be evoked in their (intact) visual cortices during somatosensory or auditory stimulation [56,57], raising the possibility that novel anatomical pathways mediate these cross-modal responses. Tractography of visual pathways in five early blind patients showed that while corticocortical connections with visual cortex were similar to healthy controls, thalamocortical visual pathways were much more difficult to trace in the blind group, despite being present in all healthy controls [35]. Quantitative comparisons of diffusion measures along the expected thalamocortical visual pathways revealed reduced fractional anisotropy and increased mean diffusion in the patients, consistent with axonal degeneration, demyelination or atrophy. Interestingly, however, no 'new' anatomical pathways to V1, for example from non-visual regions of thalamus, that could potentially mediate novel cross-modal responses, were apparent in the early blind participants. Preliminary results in hemispherectomized subjects show that projections from the (present but degenerated) superior

colliculus of the removed hemisphere to the intact hemisphere were apparent in two patients with blindsight but absent in two patients without blindsight, suggesting that crossed collicular projections could mediate residual visual processing in blindsight [58].

Improved models of normal human white matter anatomy

Understanding patterns of cognitive, sensory and motor impairments resulting from localized brain damage depends on good models of functional brain anatomy. Although much is known from classical neuroanatomy, there is a definite role for diffusion tractography to provide additional novel evidence, particularly for brain regions in which homologies between species are not straightforward, such as the prefrontal cortex which is disproportionately expanded in humans relative to non-human primates. By acquiring diffusion data both in humans and in macaque monkeys, we were able to demonstrate generally good correspondence between prefrontal connections in the two species both using tractography and in comparison to the 'gold standard' of previously published invasive tract tracing studies in macaques [59]. In a study of the parietal cortex, where again inter-species homologies are not straightforward, we compared the distribution of connections in the human brain from three areas known to connect to distinct subregions of macaque parietal cortex [60]. The termination points of these pathways in human parietal cortex identified three regions around the intraparietal sulcus, which could therefore be argued to be the human homologues of the macaque subregions that receive equivalent connections.

Another system for which it is difficult to extrapolate from animal data is the language network. The anatomy of language networks is key to understanding patterns of aphasic deficits and has been the subject of a number of tractography studies [61•,62,63•,64•]. The textbook view of aphasias holds that left inferior frontal lesions result in Broca's aphasia, posterior temporal lesions produce Wernicke's aphasia, and damage to the fibre bundle that connects them (the arcuate fasciculus) results in 'conduction aphasia'. In fact, however, there is wide variety in the pattern of language deficits that result from white matter damage in this region, raising the possibility that multiple language-relevant fibre systems pass through this area in the human brain. This possibility was recently tested using tractography to visualize pathways between Broca's and Wernicke's areas in healthy human brains. One study identified two distinct dorsal paths: a direct path, corresponding to the arcuate fasciculus, and a novel indirect path, via the inferior parietal cortex (Fig. 1) [63•]. A further study identified an additional ventral route in the left hemisphere, connecting Broca's and Wernicke's areas via the uncinate fascicle/extreme

Figure 3 Tracing of pathways displaced by a tumour
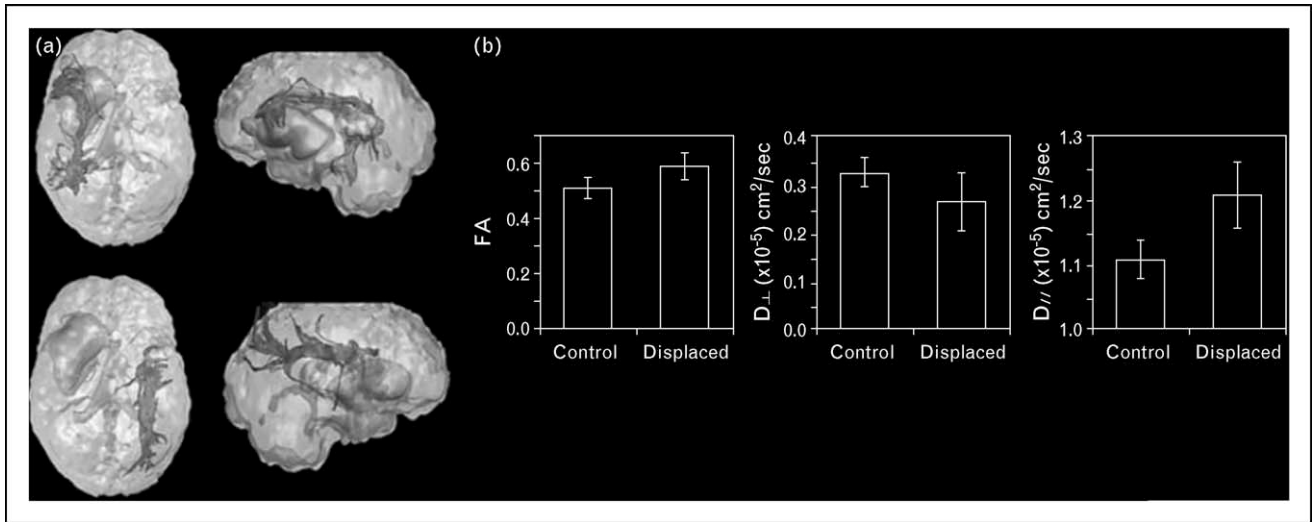
(a) Tracing the superior longitudinal fasciculus (dark grey path) around a tumour (large shape, anterior, visible on all four brain views) using functional landmarks (small, pale grey shapes, located at the anterior and posterior ends of the SLF, visible in top two views only). Bottom two images show that tracing is much less successful when based on anatomical, rather than functional, landmarks. (b) Quantitative measurements show that the displaced tract has elevated fractional anisotropy. This probably reflects increased packing density with tract compression, as there is decreased diffusion perpendicular to the tract, and increased diffusion along it. Reproduced with permission [29••].

capsule [61•]. These distinct routes for language processing provide a framework for understanding specific patterns of deficits arising from discrete white matter damage and lead to testable predictions of anatomical–clinical correlates.

Tractography for parcellation and surgical targeting

Finally, we consider the use of tractography to parcellate grey or white matter. Tractography-based maps of white matter bundles such as the internal capsule (M. Zarei *et al.*, in preparation) [65], corpus callosum [66], or cerebral peduncle [67] could prove useful in predicting clinical outcomes following discrete lesions within specific pathways. Within grey matter, cortical [64•,68,69] and subcortical [70–72] structures can be differentiated based on tractography-defined patterns of anatomical connectivity [73]. A potentially useful application of these developments could be improved targeting of surgical interventions such as deep brain stimulation for movement, pain, or mood disorder [30,74–76]. Targeting is typically based on conventional MRI, which does not always provide adequate definition of structures of interest, and brain atlases, which do not consider inter-individual anatomical variability. Tractography could enable accurate definition of grey matter targets within individual patients.

When neurosurgery aims to remove tumours or epileptogenic tissues, tractography could provide information on the location of critical structures to avoid [77••,78]. Careful consideration of the information provided by standard preoperative tractography, however, highlights its limitations: the edges of a tractography-derived boundary do not necessarily correspond to the edges of the tract and so care is needed when using this information surgically [79••]. By seeding tractography from areas defined using functional imaging, however, it is possible to improve tracing of pathways displaced by a tumour (Fig. 3) [29••], or passing through low anisotropy regions of perifocal oedema [80].

Conclusion

As diffusion tractography moves into the clinical setting, we must keep in mind its limitations. Although the technique is already providing clinically relevant markers in disease, the interpretation of changes is complex. Despite these caveats, diffusion tractography offers exciting opportunities to test hypotheses that could previously not be addressed in the living human.

Acknowledgements

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The authors provide a cautionary tale making the point that the 'edges' of a tractography-derived pathway do not accurately estimate the edges of the underlying pathway and so care is needed when using this information to guide surgical intervention. Potentially, however, improved tractography methods could reduce this discrepancy.

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