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

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Abstract

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: First, use of tractography for quantitative comparisons of specific white matter pathways in disease; second, evidence from tractography for the presence of qualitatively different pathways in congenital disorders or following recovery; third, 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

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 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 (MD), and its orientation dependence ('fractional anisotropy, 'FA') at each brain voxel (3D 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 MD and FA 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 (Figure 1). Before we incorporate diffusion imaging into every grant proposal and imaging examination, however, it is important to recognise 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 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, 17*, 18, 19] and tractography [20*] should improve this and already are providing sensible anatomical results [20-22]. Other limitations include the inability to differentiate anterograde 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 human 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: (i) To define paths within which quantitative comparisons can be made between subjects or over time. (ii) To demonstrate qualitative changes in tract location or presence. (iii) 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 FA or MD 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, 24*, 25, 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 [27, 28*, 29**, 30-33] (Figure 2), or to make use of values provided by the tractography algorithms themselves [34-36**], 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 revealed that patients with unilateral temporal lobe epilepsy have bilateral changes in the fornix and cingulum bundle, characterised by impaired tracking of these paths, and increased MD and reduced FA along them [37*]. The FA 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), consistent with degeneration [38] 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 reorganisation, measured as the laterality of FMRI 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 MD and radial diffusivity within the pyramidal tract in patients presenting with motor symptoms [39], whereas patients presenting with optic neuritis show reduced probability of connection along the optic radiations [40]. White matter changes in patients who have developed multiple sclerosis are also pathway-specific, and correlate with the pattern of motor versus cognitive symptoms [41].

Tractography of the corticospinal tract reliably shows that this pathway has reduced FA and increased MD in patients with amyotrophic lateral sclerosis [34,42,43]. 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 [34], and identifies distinctions between patients with ALS versus primary lateral sclerosis [23] and those with sporadic versus familial forms of ALS [44].

In neuropsychiatry, although there have now been multiple reports of white matter changes in schizophrenia [45], there is little consensus in the pattern of change [46], possibly due in part to methodological variability [47*]. 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 [48].

Could tractography visualise adaptive reorganisation?

In addition to pinpointing areas of pathology, could tractography shed light on possible compensatory mechanisms in disease? One recent report suggests that unexpected *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 [35]. 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 FA within specific pathways relates to behavioural performance on related sensory and

cognitive tasks [26,49*, 50*, 51, 52], and that specific functional systems show training-related changes [53**].

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 1/2 of the primary somatosensory cortex [54**]. 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 visualise 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 (2005) 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 [22,55,56].

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 [38]. 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 [57,58], raising the possibility that novel anatomical pathways mediate these cross modal responses. Tractography of visual pathways in five early blind patients showed that while cortico-cortical connections with visual cortex were similar to healthy controls, thalamo-cortical visual pathways were much more difficult to trace in the blind group, despite being present in all healthy controls [36**]. Quantitative comparisons of diffusion measures along the expected thalamo-cortical visual pathways revealed reduced FA and increased MD 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 hemispherectomised 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 [59].

Improved models of normal human white matter anatomy

Understanding patterns of cognitive, sensory and motor impairments resulting from localised 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 connectional in the two species both using tractography and in comparison to the ‘gold standard’ of previously published invasive tract tracing studies in macaque [60*]. 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 [61]. 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 [62*, 63, 64*, 65*]. 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 visualise 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 [64*] (Figure 1). A further study identified an additional ventral route in the left hemisphere, connecting Broca’s and Wernicke’s areas via the uncinate fascicle/extreme capsule [62*]. 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 [66,67], corpus callosum [68], or cerebral peduncle [69], could prove useful in predicting clinical outcomes following discrete lesions within specific pathways. Within grey matter, cortical [65*,70,71] and subcortical [72-74] structures can be differentiated based on tractography-defined patterns of anatomical connectivity [75]. 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 [30,76-78]. 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 tumors or epileptogenic tissues, tractography could provide information on the location of critical structures to avoid [79**,80]. Careful consideration of the information provided by standard pre-operative 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 [81**]. By seeding tractography from areas defined using functional imaging, however, it is possible to improve tracing of pathways displaced by a tumor [29] (Figure 3), or passing through low anisotropy regions of perifocal oedema [82].

Conclusions

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.

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References

1. Basser PJ, Mattiello J, LeBihan D. Estimation of the effective self-diffusion tensor from the NMR spin echo. *J Magn Reson B*. 1994; 103:247. [PubMed: 8019776]
2. Kim J, Lee SK, Lee JD, et al. Decreased fractional anisotropy of middle cerebellar peduncle in crossed cerebellar diaschisis: diffusion-tensor imaging-positron-emission tomography correlation study. *AJNR Am J Neuroradiol*. 2005; 26:2224–2228. [PubMed: 16219826]
3. Shiga K, Yamada K, Yoshikawa K, et al. Local tissue anisotropy decreases in cerebellopetal fibers and pyramidal tract in multiple system atrophy. *J Neurol*. 2005; 252:589–596. [PubMed: 15834652]
- *4. Hickman SJ, Wheeler-Kingshott CA, Jones SJ, et al. Optic nerve diffusion measurement from diffusion-weighted imaging in optic neuritis. *AJNR Am J Neuroradiol*. 2005; 26:951–956. [PubMed: 15814951] Apparent diffusion correlates with visual evoked potential amplitude and behavioural measures in optic neuritis demonstrating a potential role different to that of anisotropy in interrogating white matter integrity.
5. Buffon F, Molko N, Herve D, et al. Longitudinal diffusion changes in cerebral hemispheres after MCA infarcts. *J Cereb Blood Flow Metab*. 2005; 25:641–650. [PubMed: 15689956]
6. Muller MJ, Greverus D, Dellani PR, et al. Functional implications of hippocampal volume and diffusivity in mild cognitive impairment. *Neuroimage*. 2005; 28:1033–1042. [PubMed: 16084115]
7. Barnea-Goraly N, Menon V, Eckert M, et al. White matter development during childhood and adolescence: a cross-sectional diffusion tensor imaging study. *Cereb Cortex*. 2005; 15:1848–1854. [PubMed: 15758200]
8. Schmithorst VJ, Wilke M, Dardzinski BJ, Holland SK. Cognitive functions correlate with white matter architecture in a normal pediatric population: a diffusion tensor MRI study. *Hum Brain Mapp*. 2005; 26:139–147. [PubMed: 15858815]
9. Snook L, Paulson LA, Roy D, et al. Diffusion tensor imaging of neurodevelopment in children and young adults. *Neuroimage*. 2005; 26:1164–1173. [PubMed: 15961051]
10. Charlton RA, Barrick TR, McIntyre DJ, et al. White matter damage on diffusion tensor imaging correlates with age-related cognitive decline. *Neurology*. 2006; 66:217–222. [PubMed: 16434657]
11. Persson J, Nyberg L, Lind J, et al. Structure-Function Correlates of Cognitive Decline in Aging. *Cereb Cortex*. 2005

12. Pfefferbaum A, Adalsteinsson E, Sullivan EV. Frontal circuitry degradation marks healthy adult aging: Evidence from diffusion tensor imaging. *Neuroimage*. 2005; 26:891–899. [PubMed: 15955499]
13. Mori S, Crain BJ, Chacko VP, van Zijl PC. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. *Ann.Neurol*. 1999; 45:265. [PubMed: 9989633]
14. Tuch DS, Reese TG, Wiegell MR, et al. High angular resolution diffusion imaging reveals intravoxel white matter fiber heterogeneity. *Magn Reson.Med*. 2002; 48:577. [PubMed: 12353272]
15. Nunes RG, Jezzard P, Behrens TE, Clare S. Self-navigated multishot echo-planar pulse sequence for high-resolution diffusion-weighted imaging. *Magn Reson Med*. 2005; 53:1474–1478. [PubMed: 15906309]
16. Alexander DC. Multiple-fiber reconstruction algorithms for diffusion MRI. *Ann N Y Acad Sci*. 2005; 1064:113–133. [PubMed: 16394152]
- *17. Tuch DS. Q-ball imaging. *Magn Reson Med*. 2004; 52:1358–1372. [PubMed: 15562495]
Beautiful data from Macaque monkeys demonstrating the potential of high angular resolution diffusion techniques: a real technical achievement.
18. Tournier JD, Calamante F, Gadian DG, Connelly A. Direct estimation of the fiber orientation density function from diffusion-weighted MRI data using spherical deconvolution. *Neuroimage*. 2004; 23:1176–1185. [PubMed: 15528117]
19. Perrin M, Poupon C, Rieul B, et al. Validation of q-ball imaging with a diffusion fibre-crossing phantom on a clinical scanner. *Philos Trans R Soc Lond B Biol Sci*. 2005; 360:881–891. [PubMed: 16087433]
- *20. Parker GJ, Alexander DC. Probabilistic anatomical connectivity derived from the microscopic persistent angular structure of cerebral tissue. *Philos Trans R Soc Lond B Biol Sci*. 2005; 360:893–902. [PubMed: 16087434] This paper demonstrates the shape of things to come in tractography. Considering complex fibre architecture within a voxel allows the authors to track the to the entirety of the motor strip, instead of just the medial surface as is often shown.
21. Tuch DS, Wisco JJ, Khachaturian MH, et al. Q-ball imaging of macaque white matter architecture. *Philos Trans R Soc Lond B Biol Sci*. 2005; 360:869–879. [PubMed: 16087432]
22. Wedeen VJ, Hagmann P, Tseng WY, et al. Mapping complex tissue architecture with diffusion spectrum magnetic resonance imaging. *Magn Reson Med*. 2005; 54:1377–1386. [PubMed: 16247738]
23. Ciccarelli, O.; Behrens, TEJ.; Johansen-Berg, H., et al. Tract-based spatial statistics (TBSS) to investigate mechanisms of brain damage in ALS and PLS; 12th International conference for Functional Mapping of the Human Brain, 2006, Florence, Italy; 2006;
- *24. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage*. 2006 in press. Voxelwise comparison techniques are renowned for being difficult to interpret and prone to artifact. This paper introduces a new method for comparing diffusion properties from the centre of white matter pathways, improving robustness and interpretability.
25. Voets, NL.; Smith, SM.; Johansen-Berg, H., et al. Trans-synaptic degeneration of white matter pathways contributes to language reorganisation in Temporal Lobe Epilepsy; 12th International conference for Functional Mapping of the Human Brain, 2006, Florence, Italy; 2006;
26. Johansen-Berg, H.; Della-Maggiore, V.; Smith, SM.; Paus, T. Integrity of white matter in the corpus callosum correlates with bimanual co-ordination skills; 12th International conference for Functional Mapping of the Human Brain, 2006, Florence, Italy; 2006;
27. Gong G, Jiang T, Zhu C, et al. Side and handedness effects on the cingulum from diffusion tensor imaging. *Neuroreport*. 2005; 16:1701–1705. [PubMed: 16189481]
- **28. Berman JI, Mukherjee P, Partridge SC, et al. Quantitative diffusion tensor MRI fiber tractography of sensorimotor white matter development in premature infants. *Neuroimage*. 2005; 27:862–871. [PubMed: 15978841] This paper is an elegant demonstration of using tractography to derive quantitative measures. Tractography is performed in preterm infants, and diffusion measures along the motor and sensory pathways show significant correlations with age.

Intriguingly, even at such an early stage of myelination, diffusion anisotropy is higher along the motor than the sensor pathways.

- **29. Schonberg T, Pianka P, Hendler T, et al. Characterization of displaced white matter by brain tumors using combined DTI and fMRI. *Neuroimage*. 2006 One of the best examples of tractography in tumour neurosurgery. This paper shows the value of functional localisation of tractography seeds and targets, when anatomical identification is made difficult by displaced tissue. Furthermore, in the fibres compressed by the tumour, parallel diffusivity is increased and perpendicular diffusivity is decreased, reflecting the increased packing density of the axons.
- 30. Voets, NL.; Johansen-Berg, H.; Stein, JF., et al. Abnormal limbic connectivity in a patient undergoing subgenual cingulate Deep Brain Stimulation for chronic depression following thalamic stroke; 12th International conference for Functional Mapping of the Human Brain, 2006, Florence, Italy; 2006;
- 31. Kanaan RA, Shergill SS, Barker GJ, et al. Tract-specific anisotropy measurements in diffusion tensor imaging. *Psychiatry Res*. 2006; 146:73–82. [PubMed: 16376059]
- 32. Jones DK, Catani M, Pierpaoli C, et al. Age effects on diffusion tensor magnetic resonance imaging tractography measures of frontal cortex connections in schizophrenia. *Hum Brain Mapp*. 2005
- 33. Partridge SC, Vigneron DB, Charlton NN, et al. Pyramidal tract maturation after brain injury in newborns with heart disease. *Ann Neurol*. 2006
- 34. Ciccarelli O, Behrens TE, Altmann DR, et al. Probabilistic diffusion tractography: a potential tool to assess the rate of disease progression in ALS. submitted.
- 35. Thomas B, Eyssen M, Peeters R, et al. Quantitative diffusion tensor imaging in cerebral palsy due to periventricular white matter injury. *Brain*. 2005; 128:2562–2577. [PubMed: 16049045]
- **36. Shimony JS, Burton H, Epstein AA, et al. Diffusion Tensor Imaging Reveals White Matter Reorganization in Early Blind Humans. *Cereb Cortex*. 2005 Primary visual cortex (V1) in early blind patients shows a functional response to other sensory stimuli. This paper confirms that pathways from visual thalamus to V1 are reduced in such patients, but does not find any new pathways from thalamic nuclei associated with other sensory inputs. This suggests the neural plasticity is mediated by cortico-cortical and not thalamo-cortical projections.
- *37. Concha L, Beaulieu C, Gross DW. Bilateral limbic diffusion abnormalities in unilateral temporal lobe epilepsy. *Ann Neurol*. 2005; 57:188–196. [PubMed: 15562425] Patients with unilateral temporal lobe epilepsy are found to have altered diffusion characteristics in the temporal-lobe limbic pathways. Strikingly, despite the unilateral nature of the disease, anisotropy changes are found bilaterally in the cingulum and fornix bundles.
- 38. Pierpaoli C, Barnett A, Pajevic S, et al. Water diffusion changes in Wallerian degeneration and their dependence on white matter architecture. *Neuroimage*. 2001; 13:1174. [PubMed: 11352623]
- 39. Pagani E, Filippi M, Rocca MA, Horsfield MA. A method for obtaining tract-specific diffusion tensor MRI measurements in the presence of disease: application to patients with clinically isolated syndromes suggestive of multiple sclerosis. *Neuroimage*. 2005; 26:258–265. [PubMed: 15862226]
- 40. Ciccarelli O, Toosy AT, Hickman SJ, et al. Optic radiation changes after optic neuritis detected by tractography-based group mapping. *Hum Brain Mapp*. 2005; 25:308–316. [PubMed: 15834863]
- 41. Lin X, Tench CR, Morgan PS, et al. ‘Importance sampling’ in MS: use of diffusion tensor tractography to quantify pathology related to specific impairment. *J Neurol Sci*. 2005; 237:13–19. [PubMed: 16109428]
- 42. Abe O, Yamada H, Masutani Y, et al. Amyotrophic lateral sclerosis: diffusion tensor tractography and voxel-based analysis. *NMR Biomed*. 2004; 17:411–416. [PubMed: 15386625]
- 43. Aoki S, Iwata NK, Masutani Y, et al. Quantitative evaluation of the pyramidal tract segmented by diffusion tensor tractography: feasibility study in patients with amyotrophic lateral sclerosis. *Radiat Med*. 2005; 23:195–199. [PubMed: 15940067]
- 44. Blain CR, Williams VC, Turner MR, et al. Tract-specific measurements within the corticospinal tract in sporadic ALS and patients homozygous for the D90A SOD1 gene mutation. *Proc.Intl.Soc.Mag.Reson.Med*. 2005

45. Kubicki M, McCarley R, Westin CF, et al. A review of diffusion tensor imaging studies in schizophrenia. *J Psychiatr Res.* 2005
46. Kanaan RA, Kim JS, Kaufmann WE, et al. Diffusion tensor imaging in schizophrenia. *Biol Psychiatry.* 2005; 58:921–929. [PubMed: 16043134]
- *47. Jones DK, Symms MR, Cercignani M, Howard RJ. The effect of filter size on VBM analyses of DT-MRI data. *Neuroimage.* 2005; 26:546–554. [PubMed: 15907311] A cautionary tale about the application of simple voxel-wise group statistics for diffusion imaging. Much care is needed in analysis and interpretation.
48. Jones DK, Catani M, Pierpaoli C, et al. A diffusion tensor magnetic resonance imaging study of frontal cortex connections in very-late-onset schizophrenia-like psychosis. *Am J Geriatr Psychiatry.* 2005; 13:1092–1099. [PubMed: 16319302]
- *49. Tuch DS, Salat DH, Wisco JJ, et al. Choice reaction time performance correlates with diffusion anisotropy in white matter pathways supporting visuospatial attention. *Proc Natl Acad Sci U S A.* 2005; 102:12212–12217. [PubMed: 16103359] A different perspective on the tractography problem. By choosing a task that is mediated by the visual pathways and correlating diffusion anisotropy with performance, the authors are able to isolate the optic radiations impressively. However, care is needed in interpretation: in this study, faster reaction times are associated with lower anisotropy.
- *50. Beaulieu C, Plewes C, Paulson LA, et al. Imaging brain connectivity in children with diverse reading ability. *Neuroimage.* 2005; 25:1266–1271. [PubMed: 15850744] Voxelwise statistics reveal locations where anisotropy correlates with reading ability in children. Tractography from these regions generate motor and language pathways.
51. Madden DJ, Whiting WL, Huettel SA, et al. Diffusion tensor imaging of adult age differences in cerebral white matter: relation to response time. *Neuroimage.* 2004; 21:1174. [PubMed: 15006684]
52. Schulte T, Sullivan EV, Muller-Oehring EM, et al. Corpus callosal microstructural integrity influences interhemispheric processing: a diffusion tensor imaging study. *Cereb Cortex.* 2005; 15:1384–1392. [PubMed: 15635059]
- **53. Bengtsson SL, Nagy Z, Skare S, et al. Extensive piano practicing has regionally specific effects on white matter development. *Nat Neurosci.* 2005; 8:1148–1150. [PubMed: 16116456] Diffusion imaging suggests functionally induced white matter plasticity due to piano training, but the pattern of differences varied depending on the age of training. Of particular interest is a correlation between hours of piano practice and FA in motor pathways for those who practised as children, but in the arcuate fasciculus in those who practised as adolescents and adults.
- **54. Dancause N, Barbay S, Frost SB, et al. Extensive cortical rewiring after brain injury. *J Neurosci.* 2005; 25:10167–10179. [PubMed: 16267224] Beautiful tract tracing study in squirrel monkeys. Following an experimental M1 lesion and subsequent partial recovery, connections from ventral premotor cortex have apparently deviated from their usual course towards the lesion site and re-routed, to form novel connections with areas 1 and 2 of the somatosensory cortex.
55. Tuch DS, Reese TG, Wiegell MR, Wedeen VJ. Diffusion MRI of complex neural architecture. *Neuron.* 2003; 40:885–895. [PubMed: 14659088]
56. Behrens TE, Jenkinson M, Robson MD, et al. A consistent relationship between local white matter architecture and functional specialisation in medial frontal cortex. *Neuroimage.* 2006; 30:220–227. [PubMed: 16271482]
57. Burton H, McLaren DG, Sinclair RJ. Reading embossed capital letters: An fMRI study in blind and sighted individuals. *Hum Brain Mapp.* 2005
58. Kujala T, Palva MJ, Salonen O, et al. The role of blind humans' visual cortex in auditory change detection. *Neurosci Lett.* 2005; 379:127–131. [PubMed: 15823429]
59. Leh, S.; Johansen-Berg, H.; Ptito, A. Identifying pathways to blindsight in hemispherectomized subjects using DTI; 12th International conference for Functional Mapping of the Human Brain, 2006, Florence, Italy; 2006;
- *60. Crosson PL, Johansen-Berg H, Behrens TE, et al. Quantitative investigation of connections of the prefrontal cortex in the human and macaque using probabilistic diffusion tractography. *J Neurosci.* 2005; 25:8854–8866. [PubMed: 16192375] Tractography is applied to frontal circuitry using diffusion data from human and macaque. Similarities in connection patterns are used to test

homologues between the two species. Most notably pars opercularis in human showed connection patterns more similar to a ventral premotor region than to any prefrontal region in macaque.

61. Rushworth MF, Behrens TE, Johansen-Berg H. Connection Patterns Distinguish 3 Regions of Human Parietal Cortex. *Cereb Cortex*. 2005
- *62. Parker GJ, Luzzi S, Alexander DC, et al. Lateralization of ventral and dorsal auditory-language pathways in the human brain. *Neuroimage*. 2005; 24:656–666. [PubMed: 15652301] Two routes (dorsal and ventral) are identified that connect Broca's and Wernicke's regions and their homologues in the right hemisphere. In each case diffusion anisotropy is higher in the left hemisphere, suggesting an anatomical asymmetry in these pathways.
63. Nucifora PG, Verma R, Melhem ER, et al. Leftward asymmetry in relative fiber density of the arcuate fasciculus. *Neuroreport*. 2005; 16:791–794. [PubMed: 15891571]
- *64. Catani M, Jones DK, ffytche DH. Perisylvian language networks of the human brain. *Ann Neurol*. 2005; 57:8–16. [PubMed: 15597383] Careful inspection of the same dorsal pathway shown in ref 62 in the language system reveals a third (indirect) route, via the inferior parietal cortex.
- *65. Friederici AD, Bahlmann J, Heim S, et al. The brain differentiates human and non-human grammars: Functional localization and structural connectivity. *Proc Natl Acad Sci U S A*. 2006; 103:2458–2463. [PubMed: 16461904] Combined FMRI and tractography study of human inferior frontal cortex. Regions which have distinct functional responses during grammar processing also have distinct connectivity profiles.
66. Zarei M, Johansen-Berg H, Jenkinson M, et al. Two dimensional map of cortical connections in the human internal capsule. submitted.
67. Holodny AI, Gor DM, Watts R, et al. Diffusion-tensor MR tractography of somatotopic organization of corticospinal tracts in the internal capsule: initial anatomic results in contradistinction to prior reports. *Radiology*. 2005; 234:649–653. [PubMed: 15665224]
68. Huang H, Zhang J, Jiang H, et al. DTI tractography based parcellation of white matter: application to the mid-sagittal morphology of corpus callosum. *Neuroimage*. 2005; 26:195–205. [PubMed: 15862219]
69. Ramnani N, Behrens TE, Johansen-Berg H, et al. The Evolution of Prefrontal Inputs to the Cortico-pontine System: Diffusion Imaging Evidence from Macaque Monkeys and Humans. *Cereb Cortex*. 2005
70. Johansen-Berg H, Behrens TE, Robson MD, et al. Changes in connectivity profiles define functionally distinct regions in human medial frontal cortex. *Proc.Natl.Acad.Sci.U.S.A*. 2004; 101:13335. [PubMed: 15340158]
71. Anwander, A.; Schubotz, RI.; Tittgemeyer, M., et al. DTI-Tractography Based Parcellation of Human Precentral Cortex; 11th International conference for Functional Mapping of the Human Brain, 2005, Toronto, Canada; 2005; Available on CD-Rom in NeuroImage
72. Lehericy S, Ducros M, Krainik A, et al. 3-D Diffusion Tensor Axonal Tracking shows Distinct SMA and Pre-SMA Projections to the Human Striatum. *Cereb.Cortex*. 2004
73. Johansen-Berg H, Behrens TE, Sillery E, et al. Functional-Anatomical Validation and Individual Variation of Diffusion Tractography-based Segmentation of the Human Thalamus. *Cereb.Cortex*. 2005; 15:31. [PubMed: 15238447]
74. Devlin JT, Sillery EL, Hall DA, et al. Reliable identification of the auditory thalamus using multi-modal structural analyses. *Neuroimage*. 2006
75. Behrens TE, Johansen-Berg H. Relating connectional architecture to grey matter function using diffusion imaging. *Philos Trans R Soc Lond B Biol Sci*. 2005; 360:903–911. [PubMed: 16087435]
76. Sillery E, Bittar RG, Robson MD, et al. Connectivity of the human periventricular-periaqueductal gray region. *J Neurosurg*. 2005; 103:1030–1034. [PubMed: 16381189]
77. Johansen-Berg, H.; Behrens, TEJ.; Matthews, PM., et al. Connectivity of a subgenual cingulate target for treatment-resistant depression; 12th International conference for Functional Mapping of the Human Brain, 2006, Florence, Italy; 2006;
78. Hadjipavlou G, Dunckley P, Behrens TEJ, Tracey I. Determining anatomical connectivities between cortical and brainstem pain processing regions in humans: a diffusion tensor imaging study in healthy controls. *Pain*. in press.

- **79. Powell HW, Parker GJ, Alexander DC, et al. MR tractography predicts visual field defects following temporal lobe resection. *Neurology*. 2005; 65:596–599. [PubMed: 16116123] Nice example of how tractography could provide information that could guide clinical decision making: pre-operative DTI reveals the extent of Meyer's loop in the optic radiations. If surgery encroaches on this pathway then visual field deficits are apparent following surgery – but see also reference 81 below.
80. Bartsch AJ, Homola G, Biller A, et al. Diagnostic Functional MRI: Illustrated Clinical Applications and Decision-Making. *Journal of Magnetic Resonance Imaging*. in press.
- **81. Kinoshita M, Yamada K, Hashimoto N, et al. Fiber-tracking does not accurately estimate size of fiber bundle in pathological condition: initial neurosurgical experience using neuronavigation and subcortical white matter stimulation. *Neuroimage*. 2005; 25:424–429. [PubMed: 15784421] 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. The authors suggest that pathway volumes are consistently underestimated with the tractography they employed.
82. Bartsch, AJ.; Behrens, TEJ.; Biller, A., et al. Clinical tractography despite perifocal oedema; Scientific Meeting of the World Federation of Neuroradiological Societies, Adelaide, Australia; 2006;

Figure 1.

Routes between Broca's and Wernicke's Areas in the human brain: A direct path (red), corresponding to the arcuate fasciculus, and an indirect path via the inferior parietal cortex ('Geschwind's territory'), consisting of an anterior segment (green), and a posterior segment (yellow) (from ref. 64).

Figure 2.

Left: Tracing of motor (red) and sensory (green) pathways in a premature infant. Right: Quantitative measurements from along these pathways show increasing FA with age, probably reflecting a combination of increasing packing density and myelination (from ref. 28).

Figure 3.

Left: Tracing the superior longitudinal fasciculus (red) around a tumor (yellow) using functional landmarks (blue). Bottom two images show that tracing is much less successful when based on anatomical landmarks. Right: Quantitative measurements show that the displaced tract has elevated FA. This probably reflects increased packing density with tract compression, as there is decreased diffusion perpendicular to the tract, and increased diffusion along it (from ref. 29).