Limits to anatomical accuracy of diffusion tractography using modern approaches
Diffusion MRI fiber tractography is widely used to probe the structural connectivity of the brain, with a range of applications in both clinical and basic neuroscience. Despite widespread use, tractography has well-known pitfalls that limits the anatomical accuracy of this technique. Numerous modern methods have been developed to address these shortcomings through advances in acquisition, modeling, and computation. To test whether these advances improve tractography accuracy, we organized the 3-D Validation of Tractionography with Experimental MRI (3D-VoTEM) challenge at the ISBI 2018 conference. We made available three unique independent tractography validation datasets – a physical phantom and two ex vivo brain specimens - resulting in 176 distinct submissions from 9 research groups. By comparing results over a wide range of fiber complexities and algorithmic strategies, this challenge provides a more comprehensive assessment of tractography's inherent limitations than has been reported previously. The central results were consistent across all sub-challenges in that, despite advances in tractography methods, the anatomical accuracy of tractography has not dramatically improved in recent years. Taken together, our results independently confirm findings from decades of tractography validation studies, demonstrate inherent limitations in reconstructing white matter pathways using diffusion MRI data alone, and highlight the need for alternative or combinatorial strategies to accurately map the fiber pathways of the brain.
Scopus rating (2017): CiteScore 6.15 SJR 3.679 SNIP 1.806
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BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 6.31 SJR 3.967 SNIP 1.759
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BFI (2015): BFI-level 2
Scopus rating (2015): CiteScore 6.71 SJR 4.583 SNIP 1.852
Web of Science (2015): Impact factor 5.463
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 6.9 SJR 4.323 SNIP 2.03
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Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 3.654 SNIP 1.869
Web of Science (2010): Impact factor 5.937
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 3.954 SNIP 1.899
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 4.196 SNIP 1.771
Web of Science (2008): Indexed yes
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 3.467 SNIP 1.94
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 3.78 SNIP 1.921
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 3.481 SNIP 1.803
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 2.003 SNIP 1
Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 0.696 SNIP 0.404
Web of Science (2002): Indexed yes
Scopus rating (2001): SJR 0.528 SNIP 0.262
Imaging brain microstructure with diffusion MRI: Practicality and applications: practicality and applications
This article gives an overview of microstructure imaging of the brain with diffusion MRI and reviews the state of the art. The microstructure-imaging paradigm aims to estimate and map microscopic properties of tissue using a model that links these properties to the voxel scale MR signal. Imaging techniques of this type are just starting to make the transition from the technical research domain to wide application in biomedical studies. We focus here on the practicalities of both implementing such techniques and using them in applications. Specifically, the article summarizes the relevant aspects of brain microanatomy and the range of diffusion-weighted MR measurements that provide sensitivity to them. It then reviews the evolution of mathematical and computational models that relate the diffusion MR signal to brain tissue microstructure, as well as the expanding areas of application. Next we focus on practicalities of designing a working microstructure imaging technique: model selection, experiment design, parameter estimation, validation, and the pipeline of development of this class of technique. The article concludes with some future perspectives on opportunities in this topic and expectations on how the field will evolve in the short-to-medium term.

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Web of Science (2016): Impact factor 2.872
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): CiteScore 3.23 SJR 1.624 SNIP 1.032
Web of Science (2015): Impact factor 2.983
BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 3.45 SJR 1.635 SNIP 1.162
Web of Science (2014): Impact factor 3.044
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 3.9 SJR 1.681 SNIP 1.31
Web of Science (2013): Impact factor 3.559
Magnetic resonance temporal diffusion tensor spectroscopy of disordered anisotropic tissue

Molecular diffusion measured with diffusion weighted MRI (DWI) offers a probe for tissue microstructure. However, inferring microstructural properties from conventional DWI data is a complex inverse problem and has to account for heterogeneity in sizes, shapes and orientations of the tissue compartments contained within an imaging voxel. Alternative experimental means for disentangling the signal signatures of such features could provide a stronger link between the data and its interpretation. Double diffusion encoding (DDE) offers the possibility to factor out variation in compartment shapes from orientational dispersion of anisotropic domains by measuring the correlation between diffusivity in multiple directions. Time dependence of the diffusion is another effect reflecting the dimensions and distributions of barriers. In this paper we extend on DDE with a modified version of the oscillating gradient spin echo (OGSE) experiment, giving a basic contrast mechanism closely linked to both the temporal diffusion spectrum and the compartment anisotropy. We demonstrate our new method on post mortem brain tissue and show that we retrieve the correct temporal diffusion tensor spectrum in synthetic data from Monte Carlo simulations of random walks in a range of disordered geometries of different sizes and shapes.

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Organisations: Department of Applied Mathematics and Computer Science, Image Analysis & Computer Graphics, University of Copenhagen
The porcine corticospinal decussation: A combined neuronal tracing and tractography study

BACKGROUND: Pigs and minipigs are increasingly used as non-primate large animal models for preclinical research on nervous system disorders resulting in motor dysfunction. Knowledge of the minipig pyramidal tract is therefore essential to support such models. AIM AND METHODS: This study used 5 female Göttingen minipigs aging 11-15 months. The Göttingen minipig corticospinal tract was investigated, in the same animals, with in vivo neuronal tracing and with
Postmortem diffusion weighted MRI tractography to provide a thorough insight in the encephalic distribution of this primary motor pathway and its decussation at the craniocervical junction. RESULTS: The two methods similarly outlined the course of the pyramidal tract from its origin in the motor cortex down through the internal capsule to the craniocervical junction, where both methods displayed an axonal crossover at the pyramid decussation. The degree of crossover was quantified with unbiased stereology, where 81-93% of the traced corticospinal fibers crossed to the contralateral spinal cord. Accordingly, in the upper cervical spinal cord the corticospinal tract is primarily distributed in the contralateral lateral funiculus and in close relation to the gray matter, wherein some direct terminations on large ventral column gray matter neurons could be identified. DISCUSSION: The combination of neuronal tracing and tractography exploited the strengths of the respective methods to gain a better understanding of the encephalic distribution and craniocervical decussation of the Göttingen minipig corticospinal tract. Moreover, a quantification of the crossing fibers was obtained from the tracing data, which was not possible with tractography. Our data indicate that the porcine corticospinal system is quite lateralized down to the investigated upper cervical levels. However, further elucidation of this point will require a full examination of the corticospinal tracing pattern into the caudal spinal cord combined with an analysis of the direct versus indirect termination pattern on the lower motor neurons.
Validation strategies for the interpretation of microstructure imaging using diffusion MRI

Extracting microanatomical information beyond the image resolution of MRI would provide valuable tools for diagnostics and neuroscientific research. A number of mathematical models already suggest microstructural interpretations of diffusion MRI (dMRI) data. Examples of such microstructural features could be cell bodies and neurites, e.g. the axon’s diameter or their orientational distribution for global connectivity analysis using tractography, and have previously only been possible to access through conventional histology of post mortem tissue or invasive biopsies. The prospect of gaining the same knowledge non-invasively from the whole living human brain could push the frontiers for the diagnosis of neurological and psychiatric diseases. It could also provide a general understanding of the development and natural variability in the healthy brain across a population. However, due to a limited image resolution, most of the dMRI measures are indirect estimations and may depend on the whole chain from experimental parameter settings to model assumptions and implementation. Here, we review current literature in this field and highlight the integrative work across anatomical length scales that is needed to validate and trust a new dMRI method. We encourage interdisciplinary collaborations and data sharing in regards to applying and developing new validation techniques to improve the specificity of future dMRI methods.

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Image quality transfer and applications in diffusion MRI

This paper introduces a new computational imaging technique called image quality transfer (IQT). IQT uses machine learning to transfer the rich information available from one-off experimental medical imaging devices to the abundant but lower-quality data from routine acquisitions. The procedure uses matched pairs to learn mappings from low-quality to corresponding high-quality images. Once learned, these mappings then augment unseen low quality images, for example by enhancing image resolution or information content. Here, we demonstrate IQT using a simple patch-regression implementation and the uniquely rich diffusion MRI data set from the human connectome project (HCP). Results highlight potential benefits of IQT in both brain connectivity mapping and microstructure imaging. In brain connectivity mapping, IQT reveals, from standard data sets, thin connection pathways that tractography normally requires specialised data to reconstruct. In microstructure imaging, IQT shows potential in estimating, from standard “single-shell” data (one non-zero b-value), maps of microstructural parameters that normally require specialised multi-shell data. Further experiments show strong generalisability, highlighting IQT’s benefits even when the training set does not directly represent the application domain. The concept extends naturally to many other imaging modalities and reconstruction problems.
Disability in progressive MS is associated with T2 lesion changes

Background: Progressive multiple sclerosis (MS) is characterized by diffuse changes on brain magnetic resonance imaging (MRI), which complicates the use of MRI as a diagnostic and prognostic marker. The relationship between MRI measures (conventional and non-conventional) and clinical disability in progressive MS therefore warrants further investigation. Objective: To investigate the relationship between clinical disability and MRI measures in patients with
progressive MS.
Methods: Data from 93 primary and secondary progressive MS patients who had participated in 3 phase 2 clinical trials were included in this cross-sectional study. From 3 T MRI baseline scans we calculated total T2 lesion volume and analysed magnetisation transfer ratio (MTR) and the diffusion tensor imaging indices fractional anisotropy (FA) and mean diffusivity (MD) in T2 lesions, normal-appearing white matter (NAWM) and cortical grey matter. Disability was assessed by the Expanded Disability Status Scale (EDSS) and the MS functional composite. Results: T2 lesion volume was associated with impairment by all clinical measures. MD and MTR in T2 lesions were significantly related to disability, and lower FA values correlated with worse hand function in NAWM. In multivariable analyses, increasing clinical disability was independently correlated with increasing T2 lesion volumes and MTR in T2 lesion. Conclusion: In progressive MS, clinical disability is related to lesion volume and microstructure.

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Scopus rating (2017): CiteScore 2.66 SJR 1.123 SNIP 0.944
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Scopus rating (2016): CiteScore 2 SJR 0.961 SNIP 0.729
Web of Science (2016): Impact factor 2.349
Scopus rating (2015): CiteScore 1.13 SJR 0.624 SNIP 0.512
Web of Science (2015): Impact factor 1.15
Scopus rating (2014): CiteScore 0.92 SJR 0.511 SNIP 0.401
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Scopus rating (2013): CiteScore 0.79 SJR 0.333 SNIP 0.385
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Effects of imaging gradients in sequences with varying longitudinal storage time—Case of diffusion exchange imaging
Purpose: To illustrate the potential bias caused by imaging gradients in correlation MRI sequences using longitudinal magnetization storage (LS) and examine the case of filter exchange imaging (FEXI) yielding maps of the apparent exchange rate (AXR). Methods: The effects of imaging gradients in FEXI were observed on yeast cells. To analyze the AXR bias, signal evolution was calculated by applying matrix exponential operators. Results: A sharp threshold for the slice thickness was identified, below which the AXR is increasingly underestimated. The bias can be understood in terms of an extended low-pass diffusion filtering during the LS interval, which is more pronounced at lower exchange rates. For a total exchange rate constant larger than 1 s⁻¹, the AXR bias is expected to be negligible when slices thicker than 2.5mm are used. Conclusion: In correlation experiments like FEXI, relying on LS with variable duration, imaging gradients may cause disrupting effects that cannot be easily mitigated and should be carefully considered for unbiased results. In typical clinical applications of FEXI, the imaging gradients are expected to cause a negligible AXR bias. However, the AXR bias may be significant in preclinical settings or whenever thin imaging slices are used.

General information
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Short parietal lobe connections of the human and monkey brain

The parietal lobe has a unique place in the human brain. Anatomically, it is at the crossroad between the frontal, occipital, and temporal lobes, thus providing a middle ground for multimodal sensory integration. Functionally, it supports higher cognitive functions that are characteristic of the human species, such as mathematical cognition, semantic and pragmatic aspects of language, and abstract thinking. Despite its importance, a comprehensive comparison of human and simian intraparietal networks is missing. In this study, we used diffusion imaging tractography to reconstruct the major intralobar parietal tracts in twenty-one datasets acquired in vivo from healthy human subjects and eleven ex vivo datasets from five vervet and six macaque monkeys. Three regions of interest (postcentral gyrus, superior parietal lobule and inferior parietal lobule) were used to identify the tracts. Surface projections were reconstructed for both species and results compared to identify similarities or differences in tract anatomy (i.e., trajectories and cortical projections). In addition, post-mortem dissections were performed in a human brain. The largest tract identified in both human and monkey brains is a vertical pathway between the superior and inferior parietal lobules. This tract can be divided into an anterior (supramarginal gyrus) and a posterior (angular gyrus) component in both humans and monkey brains. The second prominent intraparietal tract connects the postcentral gyrus to both supramarginal and angular gyri of the inferior parietal lobule in humans but only to the supramarginal gyrus in the monkey brain. The third tract connects the postcentral gyrus to the anterior region of the superior parietal lobule and is more prominent in monkeys compared to humans. Finally, short U-shaped fibres in the medial and lateral aspects of the parietal lobe were identified in both species. A tract connecting the medial parietal cortex to the lateral inferior parietal cortex was observed in the monkey brain only. Our findings suggest a consistent pattern of intralobar parietal connections between humans and monkeys with some differences for those areas that have cytoarchitectonically distinct features in humans. The overall pattern of intraparietal connectivity supports the special role of the inferior parietal lobule in cognitive functions characteristic of humans.

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Thalamocortical Connectivity and Microstructural Changes in Congenital and Late Blindness

There is ample evidence that the occipital cortex of congenitally blind individuals processes nonvisual information. It remains a debate whether the cross-modal activation of the occipital cortex is mediated through the modulation of preexisting corticocortical projections or the reorganisation of thalamocortical connectivity. Current knowledge on this topic largely stems from anatomical studies in animal models. The aim of this study was to test whether purported changes in thalamocortical connectivity in blindness can be revealed by tractography based on diffusion-weighted magnetic resonance imaging. To assess the thalamocortical network, we used a clustering method based on the thalamic white matter projections towards predefined cortical regions. Five thalamic clusters were obtained in each group representing their cortical projections. Although we did not find differences in the thalamocortical network between congenitally blind individuals, late blind individuals, and normal sighted controls, diffusion tensor imaging (DTI) indices revealed significant microstructural changes within thalamic clusters of both blind groups. Furthermore, we find a significant decrease in fractional anisotropy (FA) in occipital and temporal thalamocortical projections in both blind groups that were not captured at the network level. This suggests that plastic microstructural changes have taken place, but not in a degree to be reflected in the tractography-based thalamocortical network.

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Organisations: Department of Applied Mathematics and Computer Science, Image Analysis & Computer Graphics, Copenhagen University Hospital, University of Copenhagen
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Web of Science (2018): Indexed yes
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Scopus rating (2017): CiteScore 3 SJR 1.348 SNIP 0.768
Web of Science (2017): Impact factor 3.161
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.21 SJR 1.581 SNIP 0.877
Web of Science (2016): Impact factor 3.054
BFI (2015): BFI-level 1
Scopus rating (2015): CiteScore 3.47 SJR 1.957 SNIP 1.146
Web of Science (2015): Impact factor 3.568
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 3.35 SJR 2.182 SNIP 0.973
Web of Science (2014): Impact factor 3.582
BFI (2013): BFI-level 1
Scopus rating (2013): CiteScore 3.24 SJR 2.218 SNIP 0.829
Web of Science (2013): Impact factor 3.608
BFI (2012): BFI-level 1
Scopus rating (2012): CiteScore 2.82 SJR 1.919 SNIP 0.692
Web of Science (2012): Impact factor 2.864
BFI (2011): BFI-level 1
Scopus rating (2011): CiteScore 1.93 SJR 1.268 SNIP 0.906
Web of Science (2011): Impact factor 2
BFI (2010): BFI-level 1
The challenge of mapping the human connectome based on diffusion tractography

Tractography based on non-invasive diffusion imaging is central to the study of human brain connectivity. To date, the approach has not been systematically validated in ground truth studies. Based on a simulated human brain data set with ground truth tracts, we organized an open international tractography challenge, which resulted in 96 distinct submissions from 20 research groups. Here, we report the encouraging finding that most state-of-the-art algorithms produce tractograms containing 90% of the ground truth bundles (to at least some extent). However, the same tractograms contain many more invalid than valid bundles, and half of these invalid bundles occur systematically across research groups. Taken together, our results demonstrate and confirm fundamental ambiguities inherent in tract reconstruction based on orientation information alone, which need to be considered when interpreting tractography and connectivity results. Our approach provides a novel framework for estimating reliability of tractography and encourages innovation to address its current limitations.

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BFI (2019): BFI-level 2
Web of Science (2019): Indexed yes
The corpus callosum establishes the anatomical continuity between the 2 hemispheres and coordinates their activity. Using histological tracing, single axon reconstructions, and diffusion tractography, we describe a callosal projection to the caudatus and putamen in monkeys and humans. In both species, the origin of this projection is more restricted than that of the ipsilateral projection. In monkeys, it consists of thin axons (0.4–0.6 µm), appropriate for spatial and temporal dispersion of subliminal inputs. For prefrontal cortex, contralateral minus ipsilateral delays to striatum calculated from axon diameters...
and conduction distance are <2 ms in the monkey and, by extrapolation, <4 ms in humans. This delay corresponds to the
performance in Poffenberger's paradigm, a classical attempt to estimate central conduction delays, with a
neuropsychological task. In both species, callosal cortico-striatal projections originate from prefrontal, premotor, and motor
areas. In humans, we discovered a new projection originating from superior parietal lobule, supramarginal, and superior
temporal gyrus, regions engaged in language processing. This projection crosses in the isthmus the lesion of which was
reported to dissociate syntax and prosody. The projection might originate from an overproduction of callosal projections in
development, differentially pruned depending on species.

General information
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Karolinska Institutet, University of Fribourg, University of Rome La Sapienza
Contributors: Innocenti, G. M., Dyrby, T. B., Andersen, K. W., Rouiller, E. M., Caminiti, R.
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BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): CiteScore 5.87 SJR 3.892 SNIP 1.633
Web of Science (2017): Impact factor 6.308
Web of Science (2017): Indexed yes
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Scopus rating (2016): CiteScore 5.5 SJR 4.103 SNIP 1.614
Web of Science (2016): Impact factor 6.559
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): CiteScore 6.68 SJR 4.929 SNIP 1.872
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 6.86 SJR 4.887 SNIP 1.994
Web of Science (2014): Impact factor 8.665
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 7.26 SJR 5.386 SNIP 1.899
Web of Science (2013): Impact factor 8.305
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
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ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): CiteScore 7.2 SJR 5.187 SNIP 1.893
Web of Science (2011): Impact factor 6.544
ISI indexed (2011): ISI indexed yes
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Scopus rating (2010): SJR 5.074 SNIP 1.843
Individual Differences in the Alignment of Structural and Functional Markers of the V5/MT Complex in Primates

Extrastriate visual area V5/MT in primates is defined both structurally by myeloarchitecture and functionally by distinct responses to visual motion. Myelination is directly identifiable from postmortem histology but also indirectly by image contrast with structural magnetic resonance imaging (sMRI). First, we compared the identification of V5/MT using both sMRI and histology in Rhesus macaques. A section-by-section comparison of histological slices with in vivo and postmortem sMRI for the same block of cortical tissue showed precise correspondence in localizing heavy myelination for V5/MT and neighboring MST. Thus, sMRI in macaques accurately locates histologically defined myelin within areas known to be motion selective. Second, we investigated the functionally homologous human motion complex (hMT+) using high-resolution in vivo imaging. Humans showed considerable intersubject variability in hMT+ location, when defined with myelin-weighted sMRI signals to reveal structure. When comparing sMRI markers to functional MRI in response to moving stimuli, a region of high myelin signal was generally located within the hMT+ complex. However, there were considerable differences in the alignment of structural and functional markers between individuals. Our results suggest that variation in area identification for hMT+ based on structural and functional markers reflects individual differences in human regional brain architecture.
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Scopus rating (2017): CiteScore 5.87 SJR 3.892 SNIP 1.633
Web of Science (2017): Impact factor 6.308
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
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BFI (2015): BFI-level 2
Scopus rating (2015): CiteScore 6.68 SJR 4.929 SNIP 1.872
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BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 6.86 SJR 4.887 SNIP 1.994
Web of Science (2014): Impact factor 8.665
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 7.26 SJR 5.386 SNIP 1.899
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ISI indexed (2013): ISI indexed yes
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Scopus rating (2012): CiteScore 7.28 SJR 5.077 SNIP 1.916
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BFI (2011): BFI-level 2
Scopus rating (2011): CiteScore 7.2 SJR 5.187 SNIP 1.893
Web of Science (2011): Impact factor 6.544
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BFI (2010): BFI-level 2
Scopus rating (2010): SJR 5.074 SNIP 1.843
Web of Science (2010): Impact factor 6.844
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 5.158 SNIP 1.896
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 4.992 SNIP 1.762
Scopus rating (2005): SJR 4.464 SNIP 1.773
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 4.128 SNIP 1.676
Scopus rating (2003): SJR 4.824 SNIP 1.887
Scopus rating (2002): SJR 4.666 SNIP 1.673
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Scopus rating (2000): SJR 3.708 SNIP 2.05
Scopus rating (1999): SJR 3.955 SNIP 2.182

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**Single-Shot-RARE for rapid 3D hyperpolarized metabolic ex vivo tissue imaging: RF-pulse design for semi-dense spectra**

MRS of hyperpolarized (HP) 13C-enriched compounds is a promising method for in vivo cancer diagnosis. Sentinel lymph node ex vivo tissue sample histology used in clinical routine for breast cancer metastasis diagnosis requires time consuming sample analysis. 3D-HP-MRSI can potentially speed up the diagnosis given a sensitive marker that can be efficiently imaged in tissue after homogenous injection. The entire sample can be confined within the imaged volume giving the possibility of complete spatial non-selectivity of the radio frequency (RF) pulses in the RF pulse design with no chemical shift localization errors. Since only a few product signals are of interest for this application, a combination of under-sampled temporal encoding, frequency selective excitation and the Single-Shot-RAREsequence offers favourable SNR characteristics. Small peak separations are challenging, however, since they require narrow excitation transition-bands. We have designed a 3D-MRSI pulse sequence for hyperpolarized ex vivo sample imaging for semi-dense compound spectra (few components, relatively small separations), ultimately aimed to be used for metastasis detection in excised lymph nodes.

**General Information**

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**Using Diffusion Tractography to Predict Cortical Connection Strength and Distance: A Quantitative Comparison with Tracers in the Monkey**

Tractography based on diffusion MRI offers the promise of characterizing many aspects of long-distance connectivity in the brain, but requires quantitative validation to assess its strengths and limitations. Here, we evaluate tractography’s ability to estimate the presence and strength of connections between areas of macaque neocortex by comparing its results with published data from retrograde tracer injections. Probabilistic tractography was performed on high-quality postmortem diffusion imaging scans from two Old World monkey brains. Tractography connection weights were estimated using a fractional scaling method based on normalized streamline density. We found a correlation between log-transformed tractography and tracer connection weights of r = 0.59, twice that reported in a recent study on the macaque. Using a novel method to estimate interareal connection lengths from tractography streamlines, we regressed out the distance dependence of connection strength and found that the correlation between tractography and tracers remains positive, albeit substantially reduced. Altogether, these observations provide a valuable, data-driven perspective on both the strengths and limitations of tractography for analyzing interareal corticocortical connectivity in nonhuman primates and a framework for assessing future tractography methodological refinements objectively.

SIGNIFICANCE STATEMENT Tractography based on diffusion MRI has great potential for a variety of applications, including estimation of comprehensive maps of neural connections in the brain (“connectomes”). Here, we describe methods to assess quantitatively tractography’s performance in detecting interareal cortical connections and estimating connection strength by comparing it against published results using neuroanatomical tracers. We found the correlation of tractography’s estimated connection strengths versus tracer to be twice that of a previous study. Using a novel method for calculating interareal cortical distances, we show that tractography-based estimates of connection strength have useful predictive power beyond just interareal separation. By freely sharing these methods and datasets, we provide a valuable resource for future studies in cortical connectomics.
An Ex Vivo Imaging Pipeline for Producing High-Quality and High-Resolution Diffusion-Weighted Imaging Datasets

Diffusion tensor (DT) imaging and related multifiber reconstruction algorithms allow the study of in vivo microstructure and, by means of tractography, structural connectivity. Although reconstruction algorithms are promising imaging tools, high-quality diffusion-weighted imaging (DWI) datasets for verification and validation of postprocessing and analysis methods are lacking. Clinical in vivo DWI is limited by, for example, physiological noise and low signal-to-noise ratio. Here, we performed a series of DWI measurements on postmortem pig brains, which resemble the human brain in neuroanatomical complexity, to establish an ex vivo imaging pipeline for generating high-quality DWI datasets. Perfusion fixation ensured that tissue characteristics were comparable to in vivo conditions. There were three main results: (i) heat conduction and unstable tissue mechanics accounted for time-varying artefacts in the DWI dataset, which were present for up to 15 h after positioning brain tissue in the scanner; (ii) using fitted DT, q-ball, and persistent angular structure magnetic resonance imaging algorithms, any b-value between \( \sim 2,000 \) and \( \sim 8,000 \) s/mm\(^2\), with an optimal value around 4,000 s/mm\(^2\), allowed for consistent reconstruction of fiber directions; (iii) diffusivity measures in the postmortem brain tissue were stable over a 3-year period. On the basis of these results, we established an optimized ex vivo pipeline for high-quality and high-resolution DWI. The pipeline produces DWI data sets with a high level of tissue structure detail showing, for example, two parallel horizontal rims in the cerebral cortex and multiple rims in the hippocampus. We conclude that high-quality ex vivo DWI can be used to validate fiber reconstruction algorithms and to complement histological studies. Hum Brain Mapp, 2011. © 2010 Wiley-Liss, Inc.
Modelling Brain Tissue using Magnetic Resonance Imaging

Diffusion MRI, or diffusion weighted imaging (DWI), is a technique that measures the restricted diffusion of water molecules within brain tissue. Different reconstruction methods quantify water-diffusion anisotropy in the intra- and extra-cellular spaces of the neural environment. Fibre tracking models then use the directions of greatest diffusion as estimates
of white matter fibre orientation. Several fibre tracking algorithms have emerged in the last few years that provide reproducible visualizations of three-dimensional fibre bundles. One class of these algorithms is probabilistic tractography. Although probabilistic tractography currently holds great promise as a powerful non-invasive connectivity-measurement tool, its accuracy and limitations remain to be evaluated. Probabilistic tractography was assessed post mortem in an in vitro environment. Postmortem DWI benefits from the possibility of using high-field experimental MR scanners and long scanning times, thereby significantly improving the signal-to-noise ratio (SNR) and anatomical resolution. Moreover, many of the degrading effects observed in vivo, such as physiological noise, are no longer present. However, the post mortem environment differs from that of in vivo both due to a lowered environmental temperature and due to the fixation process itself. We argue that the perfusion fixation procedure employed in this thesis ensures that the postmortem tissue is as close to that of in vivo as possible. Different fibre reconstruction models were tested on a range of different b-values (a b-value is a summary measurement of the strength of the applied diffusion gradients). We conclude that for robust reconstruction of fibre directions, and subsequently for tractography, b-values in the range of ~2000 s/mm² and ~8000 s/mm² should be used. Within a two year period, no statistical inter- or intra-brain difference in the diffusion coefficient was found in perfusion fixed minipig brains. However, a decreasing tendency in the diffusion coefficient was found at the last time points about 24 months post mortem and might be explained by an ongoing chemical reaction due to the fixative used. Short-term instabilities within the first 15 hours of DWI scanning were observed and found likely to be caused by the preparation of the postmortem tissue prior to MR scanning. This artefact can be avoided e.g. by simply excluding DWI volumes obtained in the first time period of the scanning session. Probabilistic tractography was validated against two invasive in vivo neuronal tracers that were used to derive a gold standard. A high spatial agreement between tractography and the gold standard was found, and some of the widely known limitations of tractography methods could be confirmed e.g. uncertainty in regions containing crossing fibres, and definition of tract termination. In the thesis we delve behind the published results to describe all the practical issues that had to be considered in order to ensure a reliable outcome, and a successful experiment. This includes the selection of independent anatomical data to be used to derive a gold standard, the selection of a gyrated animal model in place of the human brain, objective selection of the seed region to initiate, and a waypoint region to constrain the tractography results.

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Segmentation of age-related white matter changes in a clinical multi-center study
Age-related white matter changes (WMC) are thought to be a marker of vascular pathology, and have been associated with motor and cognitive deficits. In the present study, an optimized artificial neural network was used as an automatic segmentation method to produce probabilistic maps of WMC in a clinical multi-center study. The neural network uses information from T1- and T2-weighted and fluid attenuation inversion recovery (FLAIR) magnetic resonance (MR) scans, neighboring voxels and spatial location. Generalizability of the neural network was optimized by including the Optimal Brain Damage (OBD) pruning method in the training stage. Six optimized neural networks were produced to investigate the impact of different input information on WMC segmentation. The automatic segmentation method was applied to MR scans of 362 non-demented elderly subjects from 11 centers in the European multi-center study Leukoaraiosis And Disability (LADIS). Semi-manually delineated WMC were used for validating the segmentation produced by the neural networks. The neural network segmentation demonstrated high consistency between subjects and centers, making it a promising technique for large studies. For WMC volumes less than 10 ml, an increasing discrepancy between semi-manual and neural network segmentation was observed using the similarity index (SI) measure. The use of all three image modalities significantly improved cross-center generalizability compared to neural networks using the FLAIR image only. Expert knowledge not available to the neural networks was a minor source of discrepancy, while variation in MR scan quality constituted the largest source of error.

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Validation of in vitro probabilistic tractography

Diffusion weighted imaging (DWI) and tractography allow the non-invasive study of anatomical brain connectivity. However, a gold standard for validating tractography of complex connections is lacking. Using the porcine brain as a highly gyrated brain model, we quantitatively and qualitatively assessed the anatomical validity and reproducibility of in vitro multi-fiber probabilistic tractography against two invasive tracers: the histochemically detectable biotinylated dextran amine and manganese enhanced magnetic resonance imaging. Post mortem DWI was used to ensure that most of the sources known to degrade the anatomical accuracy of in vivo DWI did not influence the tracking results. We demonstrate that probabilistic tractography reliably detected specific pathways. Moreover, the applied model allowed identification of the limitations that are likely to appear in many of the current tractography methods. Nevertheless, we conclude that DWI tractography can be a precise tool in studying anatomical brain connectivity.

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Segmentation of Age-Related White-Matter Changes in a large-scale, multi-centre study

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Semi-Quantitative Assessment of Inflammation in dMRI using Data Mining Techniques

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Standardizing MR Image Intensity In Multi-Center Studies

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The prefrontal cortex of the Göttingen minipig brain defined by neural projection criteria and cytoarchitecture

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Validation of Diffusion Tensor Imaging for in vivo tracing of cortico-thalamic projections in the Göttingen minipig brain

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**Projects:**

**Identification of new brain areas involved in body weight control and appetite regulation**
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Dahl, A. B., Main Supervisor, Department of Applied Mathematics and Computer Science
Dyrby, T. B., Supervisor, Department of Applied Mathematics and Computer Science
Hecksher-Sørensen, J., Supervisor
01/12/2018 → 30/11/2021
Project: PhD

**Biomedical modelling of the brain network using MRI**
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Project: PhD

**Multi-modal microstructure imaging of biological tissue**
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Project: PhD

Cryogenic Single and Array Coils for Magnetic Resonance Systems
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Award relations: Cryogenic Single and Array Coils for Magnetic Resonance Systems
Project: PhD

Quantitative evaluation of peptide analogue distribution in mouse tissue using 3D computer modelling
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Award relations: Quantitative evaluation of peptide analogue distribution in mouse tissue using 3D computer modelling
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Kvantitativ tractografi: Statistisk modellering af hjernens neurale forbindelser med diffusion tensor imaging
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Award relations: Kvantitativ tractografi: Statistisk modellering af hjernens neurale forbindelser med diffusion tensor imaging
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Computational modeling of MR/PET in brain tumor patients for optimized radiation therapy planning
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Project: PhD

Modeling Structural Brain Connectivity
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Determination of magnetic resonance imaging biomarkers for multiple sclerosis treatment effects
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Project: PhD

Mapping the functional integration in the human basal ganglia by means of multi-modal magnetic resonance imaging
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Award relations: Mapping the functional integration in the human basal ganglia by means of multi-modal magnetic resonance imaging
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