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Permalink

https://escholarship.org/uc/item/0zm0j0fh

Journal

Journal of Neuroscience Research, 100(5)

ISSN

0360-4012

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Publication Date

2022-05-01

DOI

10.1002/jnr.24416

Peer reviewed

Diffusion MR imaging acquisition and analytics for microstructural delineation in pre-clinical models of TBI

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Abstract

Significant progress has been made toward improving both the acquisition of clinical diffusion weighted imaging (DWI) data and its analysis in the uninjured brain, through various techniques including a large number of model-based solutions that have been proposed to fit for multiple tissue compartments, and multiple fibers per voxel. While some of these techniques have been applied to clinical traumatic brain injury (TBI) research, the majority of these technological enhancements have yet to be fully implemented in the pre-clinical arena of TBI animal model-based research. In this review we describe the requirement for pre-clinical, MRI-based efforts to provide systematic confirmation of the applicability of some of these models as indicators of tissue pathology within the injured brain. We review how current DWI techniques are currently being used in animal TBI models, and describe how both acquisition and analytic techniques could be extended to leverage the progress made in clinical work. Finally, we highlight remaining gaps in the pre-clinical pipeline from data acquisition to final analysis that currently have no real, pre-clinical-based correlate.

Keywords

diffusion weighted imaging; structural connectivity; Traumatic brain injury; microstructure; pathology

Introduction

The field of magnetic resonance (MR) imaging has had an enormous impact in a large number of clinically-related central nervous system disorders, and traumatic brain injury (TBI) is no exception. Clinical research related publications involving TBI number over a thousand since 1993 and are increasing year after year. Given that white matter pathology

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is a hallmark of brain injury, it is no surprise that diffusion weighted imaging (DWI) has gained wide acceptance as the MR sequence to use for assessing the degree and extent of fiber tract pathology and microstructural disturbance. At least 440 clinical publications make use of some form of DWI as a dependent variable in studies since 1993. Clearly, imaging has become a cornerstone for TBI clinical research and as such, preclinical work has led the field in these endeavors, with the first DWI application in the stroke injured cat (Moseley et al. 1990). However, with the advent of parallel imaging capabilities through advances in computation power and improvements in radiofrequency coil design, together with the movement of clinical studies to high field systems such as 3 tesla and now increasingly to 7 telsa MRI scanners, increasingly complex data can now be obtained from clinical research subjects. In terms of scale of data acquisition and MR hardware, one could argue that the preclinical field may be in danger of becoming less relevant. However, given the multifactorial approaches that preclinical experimental designs can encompass within the same animal in addition to imaging, the potential achievements obtainable through the very richness of the data, can very easily outpace even the most radically-designed clinical study. Indeed, the increasing commonality of small animal, high field systems at 11Tesla and above, as well as the availability of benchtop MRI systems that require minimal local infrastructure, indicate that we can expect even more from preclinical imaging in the future to help advance the field. This is especially true for the development of new diffusion models that require additional ex vivo techniques such as histology, to confirm the tissue structure that the models predict.

In this brief review we will discuss the need for the continued development of MRI acquisition methods for preclinical imaging in TBI research, and in particular for DWI to match the level of refined analytics currently possible in clinical research data. We layout an idealized pipeline for robust DWI data acquisition, and a typical approach that may provide a systematic analysis of group level changes unbiased by brain region. We highlight areas of research that require improvement in hardware or sequence design in order to offer the potential for access to the most innovative parameters with which to interpret underlying TBI pathology. This review is by no means either an introductory text on DWI or an exhaustive analysis of published work- for that the reader is directed elsewhere to the many excellent reviews on those topics.

Preclinical DWI imaging for identification of tissue pathology after TBI- a brief history

Preclinical studies that have utilized DWI in some form to detect TBI-related pathology number 145 publications since 1994. The early studies were largely performed on the rat after either controlled cortical impact (CCI) or fluid percussion injury (FPI), and used diffusion weighted imaging to derive the apparent diffusion coefficient (ADC) of water and the trace of the diffusion tensor, a directionally-averaged DWI computed from the major gradient vectors as early probes of tissue microstructure (Hanstock et al. 1994; Ito et al. 1996; Alsop et al. 1996). These first studies identified regions of decreased ADC after injury that occurred in areas distinct from regions of increased T2, indicative of vasogenic edema. With the advent of faster hardware and new sequence designs that enabled the use

of echo planar imaging (EPI), experiments were able to proceed with the acquisition of dense image arrays that encoded many more diffusion vector matrices in a smaller amount of time. Present day studies are typically able to capitalize on the extra directionally-encoded diffusion information by fitting the data to a tensor model to derive the tensor indices: fractional anisotropy (FA), axial, radial and mean diffusivity (AD, RD, MD). A mouse CCI injury was one of the first studies to take advantage of that (Macdonald et al. 2007), in which it was shown that the DTI scalar indices reliably detected abnormalities in the corpus callosum when compared to classical B-amyloid precursor protein histology. This was followed-up by publications using the blast injury model (Rubovitch et al. 2011) and repeat injury model (Bennett, Donald, and Brody 2012), and then more recently the FPI model (Wright et al. 2017). The diffusion kurtosis model (Jensen et al. 2005), an extension of the tensor fit of DWI data, models the non-Gaussian diffusion presumed to occur due to the presence of tissue microstructural barriers. This has shown to be especially sensitive to gliosis after TBI clinically (Stokum et al. 2015) and after CCI injury in the rat (Zhuo et al. 2012). However, numerous other types of pathology can result in changes in kurtosis, so that the parameters derived from the fit are not solely a marker of gliosis.

Image Acquisition

Until relatively recently the vast majority of preclinical DWI studies used 2-dimensional, EPI mode to acquire the data in one or multiple shots to cross image k-space. This is most often paired with the acquisition of data using one 'b shell', or gradient-induced, diffusion-weighting, and around 30 directionally encoded diffusion directions organized in a collinear fashion around a sphere in order to accurately determine the primary diffusion vector within each imaging voxel. Using standard room temperature radiofrequency coils, these types of data can take around 30mins to acquire in the rat for 30 vectors, and 50mins in the mouse due to the need to acquire a greater number of averages to obtain enough signal-to-noise (SNR) to accurately fit these data.

Image parameters can be varied depending on the questions being asked with the data. For example, the diffusion weighting imposed by the gradient field - the b value, has been modelled to show that it can be increased significantly to eventually null the signal arising from the faster diffusion protons in the extra-axonal compartment (Assaf et al. 2004). This ability to obtain images sensitized to water diffusion within single compartments was estimated by fitting the fast decaying signal that occurs as b values increase, resulting in signal that is likely to be specific to the intra vs extra-axonal compartments (Veraart, Fieremans, and Novikov 2019). Similarly, the diffusion time ( ), the time occurring between the application of the diffusion-encoding gradients, provides a means with which to probe microstructure based on the distance between barriers that hinder water diffusion. Longer diffusion times probe larger spaces, with images bearing increased weighting toward free diffusion, and possibly to exchange between compartments. Much smaller diffusion times are of interest to provide sensitivity for obtaining signals arising from small structures such as single axons. However, the very small size of axons in rodents, on the order of 0.5um prevents currently implemented protocols and modelling schemes from providing this degree of precision (Pyatigorskaya et al. 2014).

The matrix size and the field of view of the 2-dimensional image plane, together with the slice thickness will of course influence the amount of signal in each voxel. Any change in image sequence parameters that result in smaller voxels will lower SNR per voxel. This will negatively influence the estimation of the amount of signal-loss due to diffusion weighting, and will also reduce the accuracy with which the primary diffusion direction within each voxel is determined. On the other hand, if the question being posed is one of microstructural changes, then small voxels may be required to probe tissue at higher spatial dimensions, in which case signal averaging is required, which necessarily prolongs the imaging time. If the question involves specific circuit analysis using tractographic interrogation of the brain based on the primary diffusion vector in each voxel, then larger voxels will provide the most accurate estimate of this, as long as each voxel is less than the size of the tracts of interest.

Finally, the number of shots used within the EPI sequence is entirely pertinent to the quality of the data. Not only will more shots employed to cross k-space enable the use of lower echo times, resulting in improved SNR if bandwidth is held constant, but the image distortions are reduced which makes post-processing of data much easier, especially when considering the accuracy for subsequent co-registration of data to a brain template. Of course, a caveat of this method is the imaging time is extended by a factor of the number of shots. However, at least in our hands we have successfully replaced some data averaging (nex=8) with four-shot EPI (nex=2) and obtained good quality data with fewer geometric distortions to the brain, even in areas close to the ear canals (Fig. 1).

One further improvement to reduce the impact of the static B0 field interacting with small local susceptibility fields due to the brain structure (presence of the ear canals, large dural sinus etc.), and due to residual head movement, is to acquire either the B0 field map or images in which the phase direction is encoded with gradients of opposite polarity in order to calculate the phase distortion inherent to the brain for offline correction of all DWI data. Numerous schemes are available, with FSLtool's TOPUP being the most widely implement (Andersson, Skare, and Ashburner 2003; Smith et al. 2004). We have applied this to data acquired with the phased-encoding left-to right and observed an improvement in the fitted fiber-orientation data (Fig. 2). This correction has also been shown to be useful in spinal cord imaging of the rat (Motovylyak et al. 2018).

The acquisition of data with isotropic voxel resolution is considered the optimal protocol for obtaining data unbiased by anisotropic spatial resolution. Unfortunately, the signal averaging required to achieve this in 2-dimensional imaging mode would result in unfeasibility long scan times *in vivo, at least to acquire data with acceptable voxels dimensions with which to interpret structure*. Three-dimensional data acquisition schemes can be used in this regard by reducing the imaging field-of-view through use of outer volume suppression to prevent signal aliasing, resulting in scan times under 1hr for both rats and mice with the standard 30 diffusion vectors. One additional benefit of using 3D data acquisition is that the read-out direction can be set to the longest axis of the brain – the anteroposterior direction which not only restricts the time expensive phase-encoding to the shorter medial-lateral and dorsal-ventral axis, but it allows much more brain to be covered in the same time as 2D imaging accomplishes (Fig. 3).

Despite use of proper head stabilization, acquisition of data gated to the time between respirations can improve the quality of the data, with the limitation that scan times are significantly lengthened. This is especially true in the mouse where residual subcortical movement correlated to breathing may occur, despite there being no overall head movement. However, this is often not desirable, especially when a neuroprotective intervention is being studied after brain injury because most anesthetics, especially isoflurane, likely the most widely-used agent in rodent research, provide significant neuroprotective effects (Statler et al. 2006). In our own research we elect not to use gated acquisitions in order to obtain the shortest possible scan times.

Image Analysis

The approach to the analysis of DWI data is not only complicated by the increasingly complex array of sequences and computable indices that are available for probing tissue micro-architecture, but by the nature of brain injury, which itself is not only heterogeneous with regard to spatial variation within animal and within injured groups of animals or patients, but also in regard to the different types of pathology that underpin the MR signal. For example, hematomas are a common occurrence after brain injury and can be probed by susceptibility-weighted approaches that are sensitive to the signal inhomogeneity produced by paramagnetic deoxyhemoglobin (Immonen et al. 2009). However, the presence of iron may confound the DWI signal since it may result in increased FA and lowered MD values in the brain (Rulseh et al. 2013), and this will alter the interpretation of microstructure, and possibly even tractography data.

A region-of-interest (ROI) approach to analysis is a simple, useful, and often very sensitive method to use for image interrogation. This is true if prior or parallel knowledge from other techniques exists that faithfully restricts the field of interest without spatial bias. This has been used to great effect in neurotrauma research, and one might argue that this is the most sensitive technique to detect group differences due to the often large variability in injury severity and spatial extent of the injury. However, often there is no prior knowledge, and no other data acquired in parallel on the same brain to provide a systematic, unbiased basis for selection of ROIs. Group-wise analysis of data has become far more widespread in recent years with the advent of more robust methods to co-register rodent data into the same 3-dimensional space. By artificially expanding the image dimensions in the image header by a factor of 10 or more, the majority of tools optimized for the human brain can then provide a reasonable level of precision for co-registration of both rat and mice brains. However, the very first step of any analysis pipeline that will permit good image registration is the delineation of brain from extracranial tissues- i.e. brain extraction. Perhaps the most widely used method to achieve this is the FSL brain extraction tool (BET) (S. M. Smith 2002). A rodent version of BET does exist which uses a stretched sphere or rugby ball shape to begin the brain segmentation (Wood, Lythgoe, and Williams 2013), as well as the AFNI suite program "3dSkullstrip" used with the flag "-rat" (Cox 1996), an iterative approach from a masked template image using FSL BET (Crum et al. 2013), and the Rapid Automatic Tissue Segmentation (RATS) (Oguz et al. 2014), among other programs. While many of these programs work well for the naïve rodent brain, injury imposes a serious confound to the segmentation algorithms in use, so that more often than not manual intervention is

required. This is one area which requires progress to enable faster data analysis. In our own work, we have found that a combined rigid, affine and non-linear registration to a template rodent head without prior brain extraction of either target or moving image, produces acceptable brain masks in all cases, regardless of the severity of injury. While this approach is computationally expensive and time-intensive, it does completely automate the procedure.

The next step in the analysis of the raw diffusion data begins with denoising in order to correct for the non-Gaussian nature of the image noise which can bias the diffusion measurements (Jones and Basser 2004). We use the method of local estimation of noise by principle component analysis and random matrix theory (Veraart, Fieremans, and Novikov 2016). Also important is to correct for ringing artifact that arise due to sudden boundary transitions in an image resulting in edge artifacts (Fig 4). We use the Unring code written to deal with this (Kellner et al. 2016). The spatial alignment parameters derived from image alignment for correction of movement between volumes are required to correct the diffusion vectors used in the subsequent calculation of microstructural indices. Various schemes exist for this within the major software distributions used to fit the data. Similarly, correction of slice to slice errors within a volume is also warranted, as is the quality control of the whole data set and replacement of slices containing artifacts using non-parametrically-derived predictions, for example using FSL's Eddy tool (Andersson and Sotiropoulos 2016; Andersson et al. 2017; Andersson et al. 2016). As discussed earlier, if a field map or reverse phase b0 data have been acquired, the data can then be corrected for susceptibility-induced distortions at this point.

Numerous methods exist for delineation of group-wise-based microstructural deficits after TBI, and FSL's Tract Based Spatial Statistics (TBSS) software (Smith et al. 2006) is routinely used in clinical research. It was shown to be useful for not only delineating longitudinal changes in microstructure as indicated by changes in tensor indices after rat CCI injury in adult rats, but also in showing regions that were hitherto unknown to be involved in brain injury in this model (Harris et al. 2016). This data-driven, systems-level pipeline approach to analysis (Fig. 4) can be highly beneficial to a study since the method is unbiased to the operator. The confinement of the analysis to the center of the skeleton of the white matter throughout the brain provides a relatively, statistically robust way to conduct group comparisons by virtue of the relatively fewer multiple voxel comparisons made when compared to a whole brain grey+white matter analysis. Despite this however, it should be noted that the highly heterogenous nature of white matter injury after TBI means that only the most conserved areas of injury among rodents within the group will be detected by group-wise statistics. In addition, only those tracts that can be reliably aligned will be included in the maps, while areas of gross damage that occurs in severe TBI will lead to tract movement so that some tracts will not contribute. To some extent, this type of analysis is aided by using covariates of interest to weight the analysis, for example by injury severity. We have used T2-weighted data to compute tensor-based deformation-based Jacobian metrics of brain atrophy and expansion and found that this enhances the understanding of group-wise functional MRI statistics (Verley et al. 2018). As an alternative or an additional approach, ROI-based methods may be required to fully characterize the effects of injury and intervention.

Clinical data pipelines generally produce brain images segmented by grey and white matter and CSF. This information has been interleaved with tractography analysis to produce an algorithm that constrains the path of fiber tract to the underlying anatomy using a set of rules based on known anatomy – so called anatomically constrained tractography (Smith et al. 2012). When paired with spherical-deconvolution-informed filtering of tractograms (SIFT) to retrospectively prune fiber tracks globally in order to improve the fit between fiber tracks and the underlying DWI data to achieve more biologically plausible data (Smith et al. 2015b; Smith et al. 2015a). These techniques have been created specifically for the human brain, yet they remain to be tested in rodent brains and in trauma. The requirement of these techniques is obtaining tissue segmented brain images for input together with the DWI data. Part of the problem in the rodent is obtaining the necessary accurate segmentation of the brain which is difficult given the much lower amount of white matter compared to human. With the increasing availability of tissue priors for rodents– i.e. probabilistic images of tissue segmented from a series of rodent brains, the ability to automatically and accurately segment T2-weighted images of the naïve rodent brain is now relatively straightforward. However, at least in our laboratory, segmentation of images from TBI models is rather more complex and requires significant manual intervention. Clinically the problem of segmentation and the automated delineation of brain lesions is being approached using machine learning algorithms (Kamnitsas et al. 2017), and this is certainly an area that needs to be applied to pre-clinical data to improve tractographical analysis. We have begun to use these types of tractography analyses in the rodent in our work to derive fiber density and connectivity data (Fig. 5 & 6). A variation of these connectivity techniques has been applied to interpret the fluid percussion- injured rat brain (Wright et al. 2017), where the computation of the apparent fiber density between regions was informed by the underlying connectivity in a fixel-based analysis (Raffelt et al. 2012; Raffelt et al. 2015).

Modelling diffusivity

The diffusion image voxel is of course the signal-weighted average that arises from multiple cell types and structures that exist all over the brain. In order to provide a more accurate delineation of tissue microstructure, numerous model-based approaches have been proposed to delineate compartments within the brain by virtue of the different diffusional characteristics of proton spins. This has led to the ability to estimate the volume fraction of compartments, a measure of neurite density (Sune N. Jespersen et al. 2007; Sune N Jespersen et al. 2010), and axonal caliber (Assaf et al. 2008), so that when combined with T1, short-T2 or other contrast methods useful for approximating myelin content, the g-ratio of fiber-tracks can be derived (Campbell et al. 2018). In addition, models have generally assumed a single fiber orientation per voxel, such as the single tensor fit of the DWI signal, but 2 fiber models are now more commonplace in an attempt to address the problem of fiber-tracking in regions of crossing fibers (Tournier et al. 2008). While the subject of modelling diffusion signal has been extensively and recently reviewed, for example (Jelescu and Budde 2017; Novikov, Kiselev, and Jespersen 2018), we include a brief summary here limited to models that have been directly applied to TBI data. Not only are many of these biologically meaningful variables derived by modelling the diffusion signals controversial when computed from healthy brain data, but their derivation for use as

indicators of pathology in brain trauma should be carefully considered in the absence of any means for histologic assessment of ground truth.

One of the most widely used techniques for modelling the DWI signal is the 3-compartmental based model of neurite orientation dispersion and density imaging (NODDI) (Zhang et al. 2012). This technique has been applied to mild TBI where increased intracellular volume fraction and reduced orientation dependent dispersion index were found indicating greater neurite density and coherence of neurite orientation within white matter (Churchill et al. 2017). However, application to more general cases of TBI, including more severe injury, should be approached with caution since the large variation in structure and water content may violate many of the assumptions of the technique, which are specific to the normal brain. For example, NODDI is based on an implicit and pre-defined diffusivity within each compartment, so deviations from this assumption can manifest as changes in derived parameters if they are violated. In addition, the technique assumes a constant parallel diffusivity over the entire brain, and the majority of preclinical and clinical TBI studies have shown that not only is this to be altered spatially within the brain, but that it varies with time post-injury. Given the complex pathology that occurs after TBI for example, the propensity for axonal sprouting after injury (Harris et al. 2013) and the contribution of the gliotic fibers to the principle eigen vector in pericontusonal areas (Budde et al. 2011), cautious application of the technique should be used, ideally in preclinical models together with more gold-standard histological approaches. However, it should be noted that fitting a 2-compartment model (Jespersen et al. 2007) to *ex vivo* DWI data of the CCI-injured rat showed that MRI-derived neurite density was correlated to a histologically-derived neurite density (Wang et al. 2013). In addition, another *ex vivo* rodent study use the model free approach of Q-space imaging to derive an entropy parameter reflective of tissue organization to show that it was superior to FA for detecting reorganization (Fozouni et al. 2013). Finally, compartmental modelling combined with estimating water exchange rates has also been shown to be sensitive to compartment-specific diffusivity changes in the *ex vivo* brain after TBI (Davoodi-Bojd et al. 2014).

Balancing acquisition time versus structural information

For all the promise of the diffusion modelling techniques to derive meaningful parameters of complex tissue architecture, data for all these schemes do take a considerable amount of time to acquire and therefore are unlikely to be feasible for all experiments. To this end the double, or multiple-diffusion-encoded (DDE, MDE) techniques have been proposed, an alternative to diffusion modeling of signal arising from single or multiple pairs of diffusion-encoding gradients. This technique uses two or multiple sets of diffusion encoding field gradients placed serially within the sequence resulting in a more sensitive probe of tissue compartments, including compartment eccentricity, a deviation from spherical shape (Sune Nørhøj Jespersen et al. 2013a) or microscopic anisotropy as it is also known (Lawrenz, Koch, and Finsterbusch 2010; Shemesh et al. 2016). Unlike FA derived from fitting DTI data, the method proposes to reduce the confound that complex tissue architecture introduces to FA measurements, through reducing the effects of orientation dispersion of diffusion signal in each imaging voxel. A simulation study nicely showed that the DDE technique is highly applicable to the diseased CNS, since DDE-derived indices performed

better than DTI indices for complex and coherently arranged fibers, and to fibers simulated to have a beaded structure consistent with injury (Skinner et al. 2015). The technique has also been applied to the brain (Sune Nørhøj Jespersen et al. 2013b), and has recently been shown to be useful for detecting increases in apparent mean diameter of axons in the optic tract after brain injury in the mouse (Komlosh et al. 2018), and for predicting functional and histological outcome after spinal cord injury in rodents (Skinner et al. 2018).

Edema is an early and significant phenomenon after TBI and this can complicate not only the modelling of the diffusion signal and tract based analysis (Pasternak et al. 2009), but presumably the accuracy and usefulness of the tensor indices to indicate microstructure after TBI. Modelling the free water from the diffusion signal associated with microstructure has been shown to be more predictive of injury severity than conventional DTI measures, specifically at chronic time-points using 4-b shell acquisition scheme (Motovylyak et al. 2018). Optimization of the free water elimination technique in the brain has shown that only 2-b shells are required (Hoy et al. 2014) so that it could be usefully applied after TBI.

Considerable progress has been made in clinical application of diffusion imaging at both acquisition and analytic levels. However, the majority of studies have been applied to the normal brain, and there remains considerable progress to be made to understand how best to model the spatially and longitudinally varying pathology that occurs in the traumatically-injured brain. Simulation studies of diffusion parameters and pathology in traumatic injured CNS reiterate the very complex, multi-compartmental structure of the brain that influences all DWI-derived parameters (Skinner et al. 2015; Chanpimol et al. 2017)and prompt further evaluations for determining the diagnostic and predictive accuracy of such markers, such as after spinal cord injury (Skinner et al. 2018). Pre-clinical models of TBI are ideally suited to determining the suitability of model-based and model-free solutions for deriving parameters of tissue microstructure from the diffusion signal from within the complex tissue pathology that occurs in this disease. While the ability to obtain multiple acute and chronic, longitudinal datasets from each animal is a significant advantage over clinical work, it is the unrivaled ability to obtain parallel data together with end-point, detailed histology that is the most important benefit of preclinical research for interpreting *in vivo* markers of pathology. To leverage this advantage, the preclinical MRI field must continue to apply the technologically advances made in DWI data analytics in order to help guide the use of new biomarkers for the delineation of pathology in the injured brain.

Acknowledgements:

References

Alsop DC, Murai H, Detre JA, McIntosh TK, and Smith DH. 1996. "Detection of Acute Pathologic Changes Following Experimental Traumatic Brain Injury Using Diffusion-Weighted Magnetic Resonance Imaging." J Neurotrauma 13 (9): 515–21. [PubMed: 8913968]

Andersson, Jesper LR, Graham Mark S, Drobnjak Ivana, Zhang Hui, Filippini Nicola, and Bastiani Matteo. 2017. "Towards a Comprehensive Framework for Movement and Distortion Correction of Diffusion MR Images: Within Volume Movement." NeuroImage 152 (May): 450–66. doi:10.1016/j.neuroimage.2017.02.085. [PubMed: 28284799]

Andersson, Jesper LR, Graham Mark S, Zsoldos Enik, and Sotiropoulos Stamatios N. 2016. "Incorporating Outlier Detection and Replacement into a Non-Parametric Framework for Movement and Distortion Correction of Diffusion MR Images." NeuroImage 141 (November): 556–72. doi:10.1016/j.neuroimage.2016.06.058. [PubMed: 27393418]

Andersson, Jesper LR, Skare Stefan, and Ashburner John. 2003. "How to Correct Susceptibility Distortions in Spin-Echo Echo-Planar Images: Application to Diffusion Tensor Imaging." NeuroImage 20 (2). United States: 870–88. doi:10.1016/S1053-8119(03)00336-7. [PubMed: 14568458]

Andersson, Jesper LR, and Sotiropoulos Stamatios N. 2016. "An Integrated Approach to Correction for Off-Resonance Effects and Subject Movement in Diffusion MR Imaging." NeuroImage 125 (January): 1063–78. doi:10.1016/j.neuroimage.2015.10.019. [PubMed: 26481672]

Assaf Yaniv, Tamar Blumenfeld-Katzir Yossi Yovel, and Basser Peter J.. 2008. "Axcaliber: A Method for Measuring Axon Diameter Distribution from Diffusion MRI." Magnetic Resonance in Medicine 59 (6): 1347–54. doi:10.1002/mrm.21577. [PubMed: 18506799]

Assaf Yaniv, Freidlin Raisa Z., Rohde Gustavo K., and Basser Peter J.. 2004. "New Modeling and Experimental Framework to Characterize Hindered and Restricted Water Diffusion in Brain White Matter." Magnetic Resonance in Medicine 52 (5): 965–78. doi:10.1002/mrm.20274. [PubMed: 15508168]

Bennett, Rachel E, Mac Donald Christine L, and Brody David L. 2012. "Diffusion Tensor Imaging Detects Axonal Injury in a Mouse Model of Repetitive Closed-Skull Traumatic Brain Injury." Neuroscience Letters, February. doi:10.1016/j.neulet.2012.02.024.

Budde, Matthew D, Janes Lindsay, Gold Eric, Turtzo Lisa Christine, and Frank Joseph A. 2011. "The Contribution of Gliosis to Diffusion Tensor Anisotropy and Tractography Following Traumatic Brain Injury: Validation in the Rat Using Fourier Analysis of Stained Tissue Sections." Brain : A Journal of Neurology 134 (Pt 8). England: 2248–60. doi:10.1093/brain/awr161. [PubMed: 21764818]

Campbell, Jennifer SW, Leppert Ilana R., Narayanan Sridar, Boudreau Mathieu, Duval Tanguy, Cohen-Adad Julien, Bruce Pike G, and Stikov Nikola. 2018. "Promise and Pitfalls of G-Ratio Estimation with MRI." NeuroImage 182 (July 2017). Elsevier Ltd: 80–96. doi:10.1016/j.neuroimage.2017.08.038. [PubMed: 28822750]

Chanpimol Shane, Seamon Bryant, Hernandez Haniel, Harris-love Michael, and Blackman Marc R. 2017. "Simulation of Changes in Diffusion Related to Different Pathologies at Cellular Level After Traumatic Brain Injury." Mag Reson in Med 76 (1): 290–300. doi:10.1186/s40945-017-0033-9.Using.

Churchill Nathan W., Caverzasi Eduardo, Graham Simon J., Hutchison Michael G., and Schweizer Tom A.. 2017. "White Matter Microstructure in Athletes with a History of Concussion: Comparing Diffusion Tensor Imaging (DTI) and Neurite Orientation Dispersion and Density Imaging (NODDI)." Human Brain Mapping 38 (8): 4201–11. doi:10.1002/hbm.23658. [PubMed: 28556431]

Cox Robert W. 1996. "AFNI: Software for Analysis and Visualization of Functional Magnetic Resonance Neuroimages." Computers and Biomedical Research. doi:10.1006/cbmr.1996.0014.

Crum William R., Giampietro Vincent P., Smith Edward J., Gorenkova Natalia, Stroemer R. Paul, and Modo Michel. 2013. "A Comparison of Automated Anatomical-Behavioural Mapping Methods in a Rodent Model of Stroke." Journal of Neuroscience Methods 218 (2). Elsevier B.V.: 170–83. doi:10.1016/j.jneumeth.2013.05.009. [PubMed: 23727124]

Davoodi-Bojd Esmaeil, Chopp Michael, Hamid Soltanian-Zadeh Shiyang Wang, Ding Guangliang, and Jiang Quan. 2014. "An Analytical Model for Estimating Water Exchange Rate in White Matter Using Diffusion MRI." PloS One 9 (5). United States: e95921. doi:10.1371/journal.pone.0095921. [PubMed: 24836290]

Fozouni Niloufar, Chopp Michael, Nejad-Davarani Siamak P, Zhang Zheng Gang, Lehman Norman L, Steven Gu, Ueno Yuji, et al. 2013. "Characterizing Brain Structures and Remodeling after TBI Based on Information Content, Diffusion Entropy." PloS One 8 (10). United States: e76343. doi:10.1371/journal.pone.0076343. [PubMed: 24143186]

Hanstock CC, Faden AI, Bendall MR, and Vink R. 1994. "Diffusion-Weighted Imaging Differentiates Ischemic Tissue from Traumatized Tissue." Stroke 25 (4): 843–48. [PubMed: 8160231]

Harris NG, Verley DR, Gutman BA, and Sutton RL. 2016. "Bi-Directional Changes in Fractional Anisotropy after Experiment TBI: Disorganization and Reorganization?" NeuroImage 133 (June). United States: Elsevier Inc.: 129–43. doi:10.1016/j.neuroimage.2016.03.012. [PubMed: 26975556]

Harris Neil G, Nogueira Marcia S M, Verley Derek R, and Sutton Richard L. 2013. "And Increases Functionally Active Sprouting Axons after Brain Injury" 1269: 1257–69. doi:10.1089/neu.2012.2737.

Hoy Andrew R., Koay Cheng Guan, Kecskemeti Steven R., and Alexander Andrew L.. 2014. "Optimization of a Free Water Elimination Two-Compartment Model for Diffusion Tensor Imaging." NeuroImage 103. Elsevier B.V.: 323–33. doi:10.1016/j.neuroimage.2014.09.053. [PubMed: 25271843]

Immonen, Riikka J, Kharatishvili Irina, Grohn Heidi, Pitkanen Asla, and Grohn Olli H J. 2009. "Quantitative MRI Predicts Long-Term Structural and Functional Outcome after Experimental Traumatic Brain Injury." NeuroImage 45 (1). United States: 1–9. doi:10.1016/j.neuroimage.2008.11.022. [PubMed: 19101638]

Ito J, Marmarou A, Barzo P, Fatouros P, and Corwin F. 1996. "Characterization of Edema by Diffusion-Weighted Imaging in Experimental Traumatic Brain Injury." Journal of Neurosurgery 84 (1). United States: 97–103. doi:10.3171/jns.1996.84.1.0097. [PubMed: 8613843]

Jelescu, Ileana O, and Budde Matthew D. 2017. "Design and Validation of Diffusion MRI Models of White Matter." Frontiers in Physics 28. doi:10.3389/fphy.2017.00061.

Jensen Jens H., Helpern Joseph A., Ramani Anita, Lu Hanzhang, and Kaczynski Kyle. 2005. "Diffusional Kurtosis Imaging: The Quantification of Non-Gaussian Water Diffusion by Means of Magnetic Resonance Imaging." Magnetic Resonance in Medicine 53 (6): 1432–40. doi:10.1002/mrm.20508. [PubMed: 15906300]

Jespersen Sune N., Kroenke Christopher D., Østergaard Leif, Ackerman Joseph J.H., and Yablonskiy Dmitriy A.. 2007. "Modeling Dendrite Density from Magnetic Resonance Diffusion Measurements." NeuroImage 34 (4): 1473–86. doi:10.1016/j.neuroimage.2006.10.037. [PubMed: 17188901]

Jespersen, Sune N, Bjarkam Carsten R, Nyengaard Jens R, Chakravarty M Mallar, Hansen Brian, Vosegaard Thomas, Østergaard Leif, Yablonskiy Dmitriy, Nielsen Niels Chr, and Vestergaard-Poulsen Peter. 2010. "Neurite Density from Magnetic Resonance Diffusion Measurements at Ultrahigh Field: Comparison with Light Microscopy and Electron Microscopy." NeuroImage 49 (1): 205–16. doi:10.1016/j.neuroimage.2009.08.053. [PubMed: 19732836]

Jespersen Sune Nørhøj, Lundell Henrik, Sønderby Casper Kaae, and Dyrby Tim B.. 2013a. "Orientationally Invariant Metrics of Apparent Compartment Eccentricity from Double Pulsed Field Gradient Diffusion Experiments." NMR in Biomedicine 26 (12): 1647–62. doi:10.1002/nbm.2999. [PubMed: 24038641]

Jespersen Sune Nørhøj, Lundell Henrik, Sønderby Casper Kaae, and Dyrby Tim B. 2013b. "Orientationally Invariant Metrics of Apparent Compartment Eccentricity from Double Pulsed Field Gradient Diffusion Experiments." NMR in Biomedicine 26 (12): 1647–62. doi:10.1002/nbm.2999. [PubMed: 24038641]

Jones Derek K., and Basser Peter J.. 2004. "'Squashing Peanuts and Smashing Pumpkins': How Noise Distorts Diffusion-Weighted MR Data." Magnetic Resonance in Medicine 52 (5): 979–93. doi:10.1002/mrm.20283. [PubMed: 15508154]

Kamnitsas Konstantinos, Ledig Christian, Newcombe Virginia F.J., Simpson Joanna P., Kane Andrew D., Menon David K., Rueckert Daniel, and Glocker Ben. 2017. "Efficient Multi-Scale 3D CNN

with Fully Connected CRF for Accurate Brain Lesion Segmentation." Medical Image Analysis 36. Elsevier B.V.: 61–78. doi:10.1016/j.media.2016.10.004. [PubMed: 27865153]

Kellner Elias, Dhital Bibek, Kiselev Valerij G., and Reisert Marco. 2016. "Gibbs-Ringing Artifact Removal Based on Local Subvoxel-Shifts." Magnetic Resonance in Medicine 76 (5): 1574–81. doi:10.1002/mrm.26054. [PubMed: 26745823]

Komlosh Michal E., Benjamini Dan, Hutchinson Elizabeth B., King Sarah, Haber Margalit, Avram Alexandru V., Holtzclaw Lynne A., Desai Abhishek, Pierpaoli Carlo, and Basser Peter J.. 2018. "Using Double Pulsed-Field Gradient MRI to Study Tissue Microstructure in Traumatic Brain Injury (TBI)." Microporous and Mesoporous Materials 269. Elsevier Ltd: 156–59. doi:10.1016/j.micromeso.2017.05.030. [PubMed: 30337835]

Lawrenz Marco, Koch Martin A., and Finsterbusch Jürgen. 2010. "A Tensor Model and Measures of Microscopic Anisotropy for Double-Wave-Vector Diffusion-Weighting Experiments with Long Mixing Times." Journal of Magnetic Resonance 202 (1): 43–56. doi:10.1016/j.jmr.2009.09.015. [PubMed: 19854085]

Macdonald C, Dikranian K, Song S, Bayly P, Holtzman D, and Brody D. 2007. "Detection of Traumatic Axonal Injury with Diffusion Tensor Imaging in a Mouse Model of Traumatic Brain Injury." Experimental Neurology 205 (1): 116–31. doi:10.1016/j.expneurol.2007.01.035. [PubMed: 17368446]

Moseley ME, Cohen Y, Mintorovitch J, Chileuitt L, Shimizu H, Kucharczyk J, Wendland MF, and Weinstein PR. 1990. "Early Detection of Regional Cerebral Ischemia in Cats: Comparison of Diffusion- and T2-Weighted MRI and Spectroscopy." Magn.Reson Med 14: 330–46. [PubMed: 2345513]

Motovylyak Alice, Skinner Nathan P., Schmit Brian D., Wilkins Natasha, Kurpad Shekar N., and Budde Matthew D.. 2018. "Longitudinal *In Vivo* Diffusion Magnetic Resonance Imaging Remote from the Lesion Site in Rat Spinal Cord Injury." Journal of Neurotrauma 10: neu.2018.5964. doi:10.1089/neu.2018.5964.

Novikov Dmitry S., Kiselev Valerij G., and Jespersen Sune N.. 2018. "On Modeling." Magnetic Resonance in Medicine 79 (6): 3172–93. doi:10.1002/mrm.27101. [PubMed: 29493816]

Oguz Ipek, Zhang Honghai, Rumple Ashley, and Sonka Milan. 2014. "RATS: Rapid Automatic Tissue Segmentation in Rodent Brain MRI." Journal of Neuroscience Methods 221. Elsevier B.V.: 175–82. doi:10.1016/j.jneumeth.2013.09.021. [PubMed: 24140478]

Pasternak Ofer, Sochen Nir, Gur Yaniv, Intrator Nathan, and Assaf Yaniv. 2009. "Free Water Elimination and Mapping from Diffusion MRI." Magnetic Resonance in Medicine 62 (3): 717–30. doi:10.1002/mrm.22055. [PubMed: 19623619]

Pyatigorskaya Nadya, Le Bihan Denis, Reynaud Olivier, and Ciobanu Luisa. 2014. "Relationship between the Diffusion Time and the Diffusion MRI Signal Observed at 17.2 Tesla in the Healthy Rat Brain Cortex" 500: 492–500. doi:10.1002/mrm.24921.

Raffelt David A., Smith Robert E., Ridgway Gerard R., Tournier J. Donald, Vaughan David N., Rose Stephen, Henderson Robert, and Connelly Alan. 2015. "Connectivity-Based Fixel Enhancement: Whole-Brain Statistical Analysis of Diffusion MRI Measures in the Presence of Crossing Fibres." NeuroImage 117. Elsevier B.V.: 40–55. doi:10.1016/j.neuroimage.2015.05.039. [PubMed: 26004503]

Raffelt David, Donald Tournier J, Rose Stephen, Ridgway Gerard R., Henderson Robert, Crozier Stuart, Salvado Olivier, and Connelly Alan. 2012. "Apparent Fibre Density: A Novel Measure for the Analysis of Diffusion-Weighted Magnetic Resonance Images." NeuroImage 59 (4). Elsevier Inc.: 3976–94. doi:10.1016/j.neuroimage.2011.10.045. [PubMed: 22036682]

Rubovitch Vardit, Ten-Bosch Meital, Zohar Ofer, Harrison Catherine R., Tempel-Brami Catherine, Stein Elliot, Hoffer Barry J., et al. 2011. "A Mouse Model of Blast-Induced Mild Traumatic Brain Injury." Experimental Neurology 232 (2). United States: 280–89. doi:10.1016/j.expneurol.2011.09.018. [PubMed: 21946269]

Rulseh, Aaron M, Keller Ji í, Tint ra Jaroslav, Kožíšek Milan, Vymazal Josef, Tinte Jaroslav, Keller Ji í, et al. 2013. "Chasing Shadows: What Determines DTI Metrics in Gray Matter Regions? An in Vitro and in Vivo Study." Journal of Magnetic Resonance Imaging : JMRI 38 (5): 1103–10. doi:10.1002/jmri.24065. [PubMed: 23440865]

Shemesh Noam, Jespersen Sune N., Alexander Daniel C., Cohen Yoram, Drobnjak Ivana, Dyrby Tim B., Finsterbusch Jurgen, et al. 2016. "Conventions and Nomenclature for Double Diffusion Encoding NMR and MRI." Magnetic Resonance in Medicine 75 (1): 82–87. doi:10.1002/mrm.25901. [PubMed: 26418050]

Skinner Nathan P., Kurpad Shekar N., Schmit Brian D., and Budde Matthew D.. 2015. "Detection of Acute Nervous System Injury with Advanced Diffusion-Weighted MRI: A Simulation and Sensitivity Analysis." NMR in Biomedicine 28 (11): 1489–1506. doi:10.1002/nbm.3405. [PubMed: 26411743]

Skinner Nathan P., Lee Seung Yi, Kurpad Shekar N., Schmit Brian D., Muftuler L. Tugan, and Budde Matthew D.. 2018. "Filter-Probe Diffusion Imaging Improves Spinal Cord Injury Outcome Prediction." Annals of Neurology 84 (1): 37–50. doi:10.1002/ana.25260. [PubMed: 29752739]

Smith Robert E., Tournier Jacques-donald Donald, Calamante Fernando, and Connelly Alan. 2012. "Anatomically-Constrained Tractography: Improved Diffusion MRI Streamlines Tractography through Effective Use of Anatomical Information." NeuroImage 62 (3). Elsevier Inc.: 1924–38. doi:10.1016/j.neuroimage.2012.06.005. [PubMed: 22705374]

Smith RE, Tournier JD, Calamante F, Connelly A. 2015a. "SIFT2: Enabling Dense Quantitative Assessment of Brain White Matter Connectivity Using Streamlines Tractography." NeuroImage 119. Elsevier Inc.: 338–51. doi:10.1016/j.neuroimage.2015.06.092. [PubMed: 26163802]

Smith RE, Tournier JD, Calamante F, Connelly A. 2015b. "The Effects of SIFT on the Reproducibility and Biological Accuracy of the Structural Connectome." NeuroImage 104 (2015). Elsevier Inc.: 253–65. doi:10.1016/j.neuroimage.2014.10.004. [PubMed: 25312774]

Smith Stephen M., Jenkinson Mark, Woolrich Mark W., Beckmann Christian F., Behrens Timothy E.J.J, Johansen-Berg Heidi, Bannister Peter R., et al. 2004. "Advances in Functional and Structural MR Image Analysis and Implementation as FSL." NeuroImage 23 Suppl 1 (January): S208–19. doi:10.1016/j.neuroimage.2004.07.051. [PubMed: 15501092]

Smith Stephen M. 2002. "Fast Robust Automated Brain Extraction." Human Brain Mapping 17 (3): 143–55. doi:10.1002/hbm.10062. [PubMed: 12391568]

Smith, Stephen M, Jenkinson Mark, Johansen-Berg Heidi, Rueckert Daniel, Nichols Thomas E, Mackay Clare E, Watkins Kate E, et al. 2006. "Tract-Based Spatial Statistics: Voxelwise Analysis of Multi-Subject Diffusion Data." NeuroImage 31 (4): 1487–1505. doi:10.1016/j.neuroimage.2006.02.024. [PubMed: 16624579]

Statler Kimberly D., Alexander Henry, Vagni Vincent, Holubkov Richard, Dixon C. Edward, Clark Robert S.B., Jenkins Larry, and Kochanek Patrick M.. 2006. "Isoflurane Exerts Neuroprotective Actions at or near the Time of Severe Traumatic Brain Injury." Brain Research 1076 (1): 216–24. doi:10.1016/j.brainres.2005.12.106. [PubMed: 16473332]

Stokum, Jesse A, Sours Chandler, Zhuo Jiachen, Kane Robert, Shanmuganathan Kathirkamanthan, Gullapalli Rao P, Stokum Jesse A, et al. 2015. "A Longitudinal Evaluation of Diffusion Kurtosis Imaging in Patients with Mild Traumatic Brain Injury A Longitudinal Evaluation of Diffusion Kurtosis Imaging in Patients with Mild Traumatic Brain Injury" 9052 (October). doi:10.3109/02699052.2014.947628.

Tournier J.-Donald, Yeh Chun-Hung, Calamante Fernando, Cho Kuan-Hung, Connelly Alan, and Lin Ching-Po. 2008. "Resolving Crossing Fibres Using Constrained Spherical Deconvolution: Validation Using Diffusion-Weighted Imaging Phantom Data." NeuroImage 42 (2): 617–25. doi:10.1016/j.neuroimage.2008.05.002. [PubMed: 18583153]

Tournier J. Donald, Calamante Fernando, Gadian David G., and Connelly Alan. 2004. "Direct Estimation of the Fiber Orientation Density Function from Diffusion-Weighted MRI Data Using Spherical Deconvolution." NeuroImage 23 (3): 1176–85. doi:10.1016/j.neuroimage.2004.07.037. [PubMed: 15528117]

Veraart Jelle, Fieremans Els, and Novikov Dmitry S.. 2016. "Diffusion MRI Noise Mapping Using Random Matrix Theory." Magnetic Resonance in Medicine 76 (5): 1582–93. doi:10.1002/mrm.26059. [PubMed: 26599599]

Veraart Jelle, Fieremans Els, and Novikov Dmitry S. 2019. "NeuroImage On the Scaling Behavior of Water Diffusion in Human Brain White Matter." NeuroImage 185 (October 2018). Elsevier Ltd: 379–87. doi:10.1016/j.neuroimage.2018.09.075. [PubMed: 30292815]

Verley Derek R., Torolira Daniel, Pulido Brandon, Gutman Boris, Bragin Anatol, Mayer Andrew, and Harris Neil G. 2018. "Remote Changes in Cortical Excitability after Experimental Traumatic Brain Injury and Functional Reorganization." Journal of Neurotrauma 35 (20): 2448–61. doi:10.1089/neu.2017.5536. [PubMed: 29717625]

Wang Shiyang, Chopp Michael, Nazem-Zadeh Mohammad-Reza, Ding Guangliang, Nejad-Davarani Siamak P, Changsheng Qu, Lu Mei, et al. 2013. "Comparison of Neurite Density Measured by MRI and Histology after TBI." PloS One 8 (5). United States: e63511. doi:10.1371/journal.pone.0063511. [PubMed: 23717439]

Wood Tobias, Lythgoe David, and Williams Steven. 2013. "RBET: Making BET Work for Rodent Brains." In Proc. Intl. Soc. Mag. Reson. Med, 21:2706. ISMRM.

Wright, David K, Johnston Leigh A, Kershaw Jeff, Ordidge Roger, O'Brien Terence John, Shultz Sandy Richard, Brien Terence J O, et al. 2017. "Changes in Apparent Fibre Density and Track-Weighted Imaging Metrics in White Matter Following Experimental Traumatic Brain Injury." Journal of Neurotrauma 10 (13). United States: neu.2016.4730. doi:10.1089/neu.2016.4730.

Zhang Hui, Schneider Torben, Wheeler-Kingshott Claudia A., and Alexander Daniel C.. 2012. "NODDI: Practical in Vivo Neurite Orientation Dispersion and Density Imaging of the Human Brain." NeuroImage 61 (4). Elsevier Inc.: 1000–1016. doi:10.1016/j.neuroimage.2012.03.072. [PubMed: 22484410]

Zhuo Jiachen, Xu Su, Proctor Julie L., Mullins Roger J., Simon Jonathan Z., Fiskum Gary, and Gullapalli Rao P.. 2012. "Diffusion Kurtosis as an in Vivo Imaging Marker for Reactive Astrogliosis in Traumatic Brain Injury." NeuroImage 59 (1). United States: 467–77. doi:10.1016/j.neuroimage.2011.07.050. [PubMed: 21835250]

Significance Statement

Magnetic resonance diffusion imaging of the brain has become a primary tool with which to identify regions of pathology, chiefly axonal injury that occurs subsequent to a traumatic brain injury (TBI). While there has been significant progress made in clinical-based research work in the normal brain that is now beginning to be applied to clinical TBI research, there remain gaps in how pre-clinical research is conducted. We highlight areas of pre-clinical research that use diffusion imaging that require further progress to be able to fully validate the continuing advancements made in the clinical field.
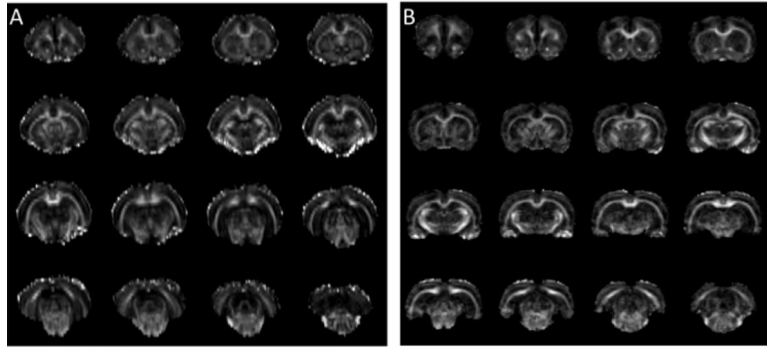
Fig. 1.
Effect of the number of echo planar shots to cross k space on image shape in 2-dimensional DWI data. [A] A single versus [B] 4 shots were used to compute fractional anisotropy maps from a naïve rat brain. Nex=8 and 2 respectively, all other acquisition parameters were kept constant. Imaging time and DWI SNR was ~13mins/44:1 and 28mins / 74:1 in 1- vs 4-shot respectively.
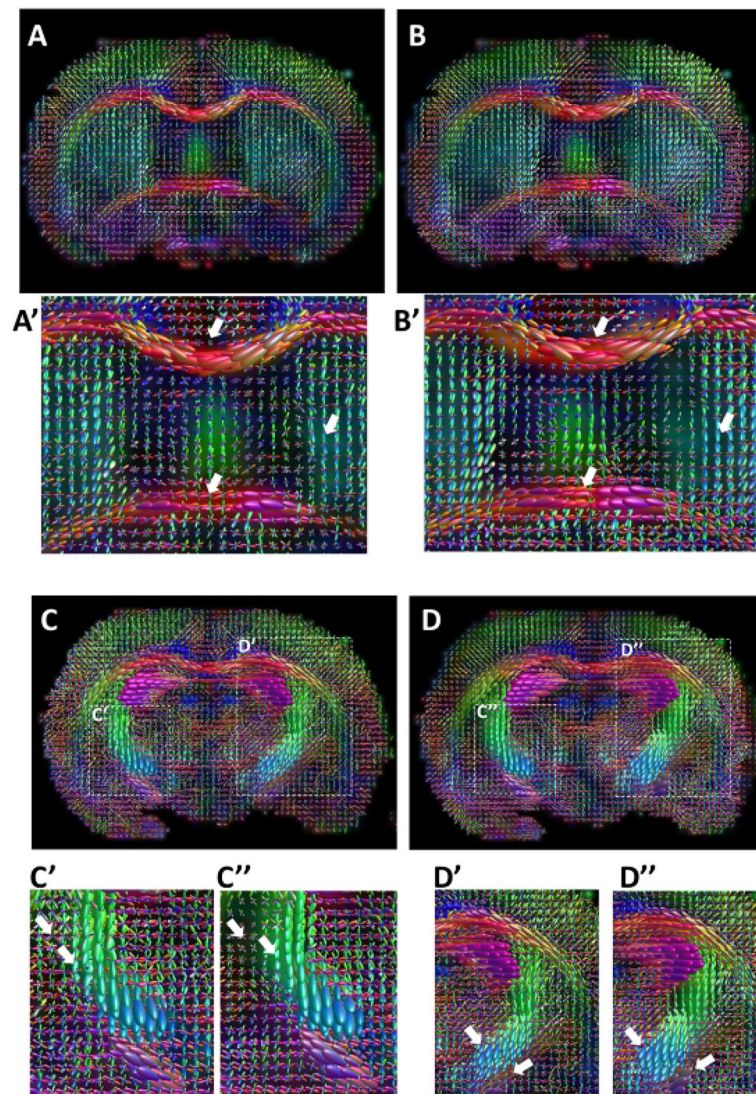
Fig. 2.
Effect of phase distortion correction on fitted fiber-orientation directions (FODs) in representative DWI data of a naïve, adult rat brain comparing uncorrected [A, C and insets A', C', D'] versus phase-corrected images [B, D, and insets B',C",D"]. Images colors indicate directional-encoded information of the primary diffusion vector or FOD, computed from the tensor and represented by X (red), Y (green) and Z (blue) primary movement of protons. There is greater primary vector water directionality after phase correction [A vs B and inset A' vs B'] as indicated by larger, single FOD lobes in corpus callosum, anterior commissure, and in mixed grey/white matter regions (white arrows). Similar findings occur in the more posterior corticospinal tracts and adjacent grey/white matter [C vs D, and insets C' vs C", and D' vs D"]. Data were fitted using spherical constrained deconvolution implemented in MRtrix3 (J. D. Tournier et al. 2004).
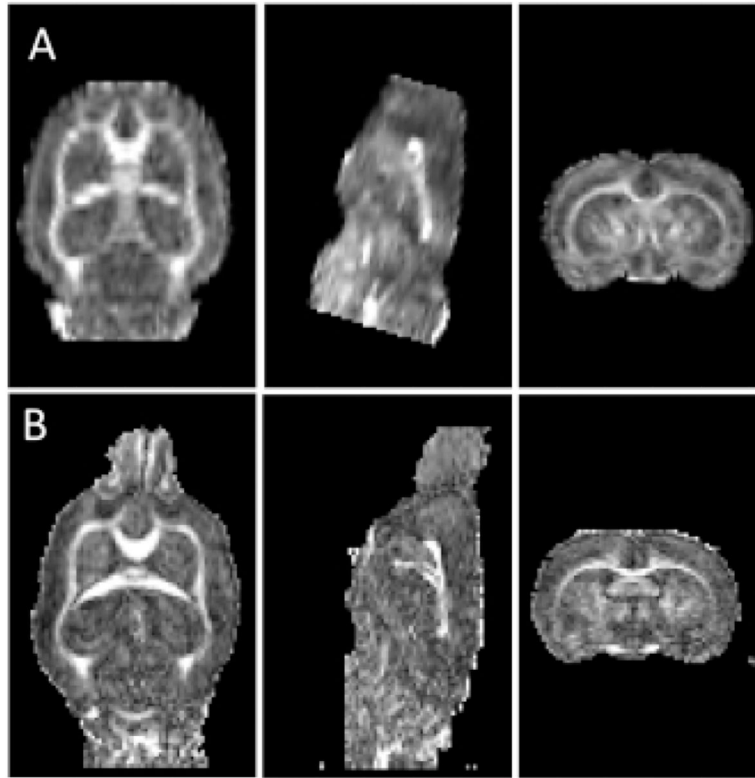
Fig. 3.
Axial, sagittal and coronal fractional anisotropy images computed from DWI data acquired by [A] two- and [B] three-dimensional protocols from the naïve adult rat (single shell of 30 directions for both, but b=1000 and 2800 S/mm2, respectively) and 4 b0s. Although both data were acquired in ~30 mins, a greater antero-posterior brain coverage results from 3D acquisition and with high spatial resolution (2D= 234×234×750um compared to 250um3 isotropic for 3D).
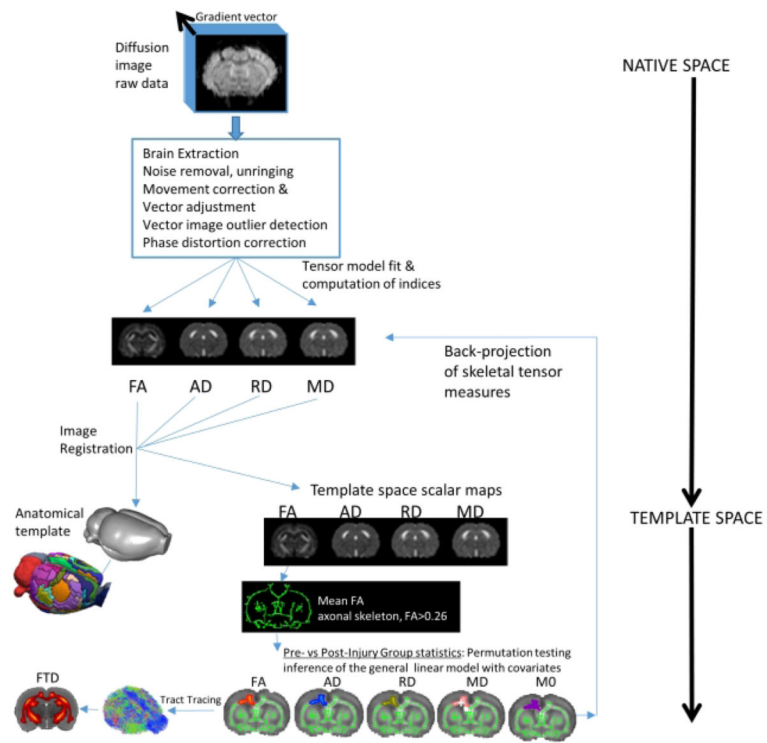
Fig. 4.
Systems level approach to determining differences in connectivity in the rodent brain after injury using a Tact Based Spatial Statistics approach to generate statistical parametric maps of diffusion tensor indices fractional anisotropy (FA), axial, radial and mean diffusivity (AD, RD, MD), tensor mode (MO), fiber track density (FTD).
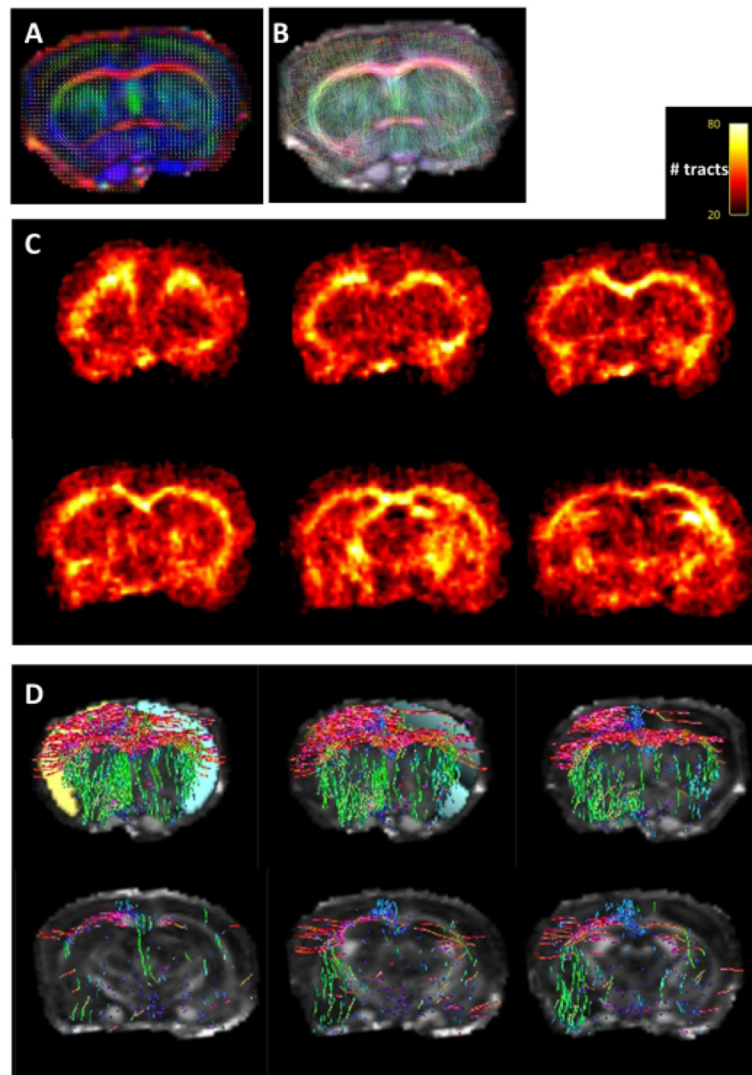
Fig. 5.

In vivo mouse diffusion imaging. Spin echo, DWI 3D isotropic data from a single, adult, naive mouse were acquired using 0 and 3000s/mm2 B values and were fit by constrained spherical deconvolution [A], processed by spherical-deconvolution-informed filtering of tractograms [B], used for computation of tract-density images [C], and processed for homotopic sensory-motor cortex connectivity using seed-based analysis [D]. Colors in [A and B] are red, green, blue=x, y, z direction of fiber tracts, respectively.
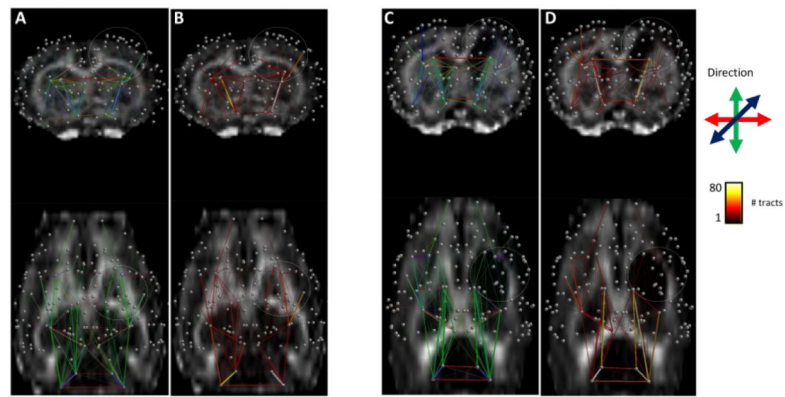
Fig. 6.

In vivo rat brain structural connectivity in a [A,B] naïve and [C,D] injured rat at 4wks post-injury showing fiber-tract direction [A,C] and number [B,D] overlaid on a map of fractional anisotropy. Spin echo, DWI 2D data were acquired from a [A,B] single, adult naïve and [C,D] an injured rat injured by controlled cortical impact and studied at 4 wks post-injury. Data were acquired using 0 and 1000s/mm2 B values and were fit by constrained spherical deconvolution, registered to a rat brain atlas containing 148 parcellated regions, in order to compute the rodent structural connectome. Data are shown as grey nodes (brain regions, no units) and edges where the color [A,C] indirects direction of the tract and [B,D] the number of fiber tracts between regions (color scale 1–80). Data show obvious decreases in connectivity in the primary, cortical injury region and at the level of the thalamus (hatched circle area).