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Review

Does diffusion MRI tell us anything about the white matter? An overview of methods and pitfalls

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ABSTRACT

One key pitfall in diffusion magnetic resonance imaging (dMRI) clinical neuroimaging research is the challenge of understanding and interpreting the results of a complex analysis pipeline. The sophisticated algorithms employed by the analysis software, combined with the relatively non-specific nature of many diffusion measurements, lead to challenges in interpretation of the results. This paper is aimed at an intended audience of clinical researchers who are learning about dMRI or trying to interpret dMRI results, and who may be wondering "Does dMRI tell us anything about the white matter?" We present a critical review of dMRI methods and measures used in clinical neuroimaging research, focusing on the most commonly used analysis methods and the most commonly reported measures. We describe important pitfalls in every section, and provide extensive references for the reader interested in more detail.

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1. Introduction

Diffusion magnetic resonance imaging (dMRI) is powerful. It measures microstructural properties of the brain and it enables the study of the living brain's connections. The popularity of dMRI in clinical research has grown tremendously since its introduction (Le Bihan et al., 1986) and since the development of the diffusion tensor model (Basser et al., 1994a,b). In fact, the number of publications related to the phrase "diffusion MRI" has increased from yearly totals in the hundreds in the early 1990s to over 25,000 publications in 2013 alone (Fig. 1).

However, despite the wealth of publications, performing clinical research using dMRI is absolutely not straightforward. There is a plethora of available processing and analysis methods for dMRI, including multiple software platforms, data models, algorithms, and philosophies. Complicating the picture further, changes in the most commonly measured quantities are not specific to a particular brain pathology. It is clear we can measure statistically significant brain changes with dMRI, but what do they mean? Today, the chief pitfall in applying dMRI to clinical research may well be the challenge of understanding and interpreting its meaning.

We note that other review articles have covered the basics of dMRI in depth (Le Bihan and Johansen-Berg, 2012) and have given detailed technical information on pitfalls that may occur (Jones and Cercignani, 2010; Jones et al., 2013). Our goal is not to duplicate these works; rather we intend to give a brief introductory overview of key concepts, with pointers to references that have more technical detail. Our experience with researchers new to dMRI is that they do not realize initially that the results cannot be compared across studies without knowledge of the methods employed in each study. Thus we focus especially on giving intuition for how methods applied in dMRI studies actually work, and their pitfalls or caveats, to give context for the clinical researcher beginning to read about and/or apply dMRI analyses. We assume the reader has some basic familiarity with dMRI, such as that given in an introduction (O'Donnell and Westin, 2011).

Readers interested in diffusion MRI analysis will benefit by starting with an existing pipeline. These pipelines may not overcome all pitfalls but are a good starting point. Example pipelines are available in FSL (http://fsl.fmrib.ox.ac.uk/), including preprocessing, motion correction, and voxelwise statistical analysis; Slicer (http://slicer.org/) including preprocessing (via DTIPrep extension), DTI tractography, and two-tensor tractography (via UKFTractography extension); and Enigma (http://enigma.ini.usc.edu) for diffusion MRI and genetics studies.

1.1. Roadmap

In the rest of this article, we first give very brief overviews of dMRI acquisition and reconstruction, followed by descriptions of many popular analysis methods and measurements. In each section we include

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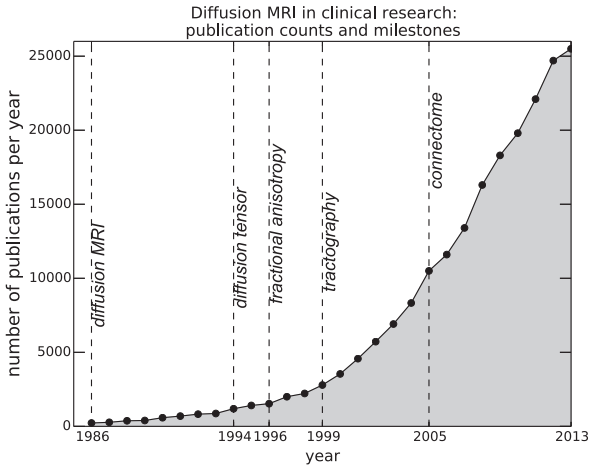

Fig. 1. The impact of diffusion MRI on clinical research has resulted in an enormous increase in the number of publications per year from 1986 to 2013. For reference, selected research milestones in the field are shown in italics above their year of publication. To create this graph, Google Scholar searches (Google, 2014) were performed on the phrase "diffusion MRI" limiting the date range to single years, and the total publication counts per year were recorded. One imagines that the total for 2013 will increase during the current year of 2014 as more papers are found by Google Scholar.

potential pitfalls. We conclude with a discussion of our original question, "Does dMRI tell us anything about the white matter?"

2. dMRI acquisition: A brief overview

Diffusion magnetic resonance spectroscopy was invented in the 1960s (Stejskal and Tanner, 1965), later to be generalized from spectroscopy to imaging (Le Bihan et al., 1986) in the late 1980s, making it a potential clinical tool. The underlying principles of dMRI and the history of its first 25 years have been reviewed in detail (Le Bihan and Johansen-Berg, 2012). In short, water molecules serve as a probe of tissue structure at the micron level. Oriented tissues, such as white matter fiber tracts or heart muscle, affect the diffusion of water in a measurable way. In the brain, faster diffusion occurs along a fiber tract than perpendicular to it, giving rise to diffusion anisotropy, and enabling measurement of properties of the brain's connections and microstructure in vivo.

By applying magnetic field gradients such that signal is lost when water molecules diffuse along the gradient, a diffusion-weighted image (DWI) is acquired. The length of the diffusion experiment is typically a few tens of milliseconds (preferably <100 ms), in which water molecules can displace up to a few tens of microns. To measure the shape of water diffusion in three dimensions, many DWIs are acquired with magnetic field gradients of different orientations, often distributed evenly on a sphere (Jones et al., 1999a), and potentially with several strengths corresponding to several b-values as in multi-shell or diffusion spectrum imaging (Wedeen et al., 2005). Diffusion is often calculated relative to a baseline or B0 image that is not sensitized to diffusion. The diffusion-weighted and baseline images are then fit to a diffusion or fiber model for analysis. A standard echo-planar imaging (EPI) DTI acquisition (b-value near 1000 and 6–64 directions, for example) is available on most clinical scanners. Currently, acquisitions with multiple b-values and high numbers of gradient directions are not widely available and are limited to research protocols.

2.1. Pitfalls

A critical review with very detailed information on acquisition choices and tradeoffs, as well as data processing for artifact removal, is available (Jones et al., 2013). Information on dMRI acquisition pitfalls, including distortions due to eddy currents and magnetic susceptibility effects, is available in reviews (Basser and Jones, 2002; Le Bihan et al., 2006). The various distortions can complicate image alignment between dMRI and other MRI acquisitions. Additionally, since the information in diffusion imaging is contained in multiple DWIs, it is important to correct for possible artifactual differences between these images, such as head motion, that may cause spurious group differences (Yendiki et al., 2014). To ameliorate eddy current distortions and head motion, often an image registration approach is applied where all DWIs are affinely aligned to the baseline image. Susceptibility effects may also be corrected in software, especially if additional scanning information is available, such as a field map that measures the strength of the main magnetic field, or if the acquisition has two opposite phase encode directions (Andersson et al., 2003). The results of these two strategies are visually compared in Jones and Cercignani (2010). A book chapter reviewing possible corrections for these artifacts is available (Andersson and Skare, 2010).

Not all motion artifacts can be corrected using post-processing methods, however. For example, motion while the image is being acquired will cause artifacts such as signal drops, blurring and ghosting that go beyond displacing the image in space. Such motion artifacts could also be introduced by pulsation, which cannot be avoided by making sure the patient does not move. There are specialized sequences that are gated to the cardiac cycle, however cardiac gating complicates the acquisition and prolongs it, and is not commonly used.

Since not all artifacts can be identified or corrected by automatic tools, it is still considered good practice to assess the quality of all DWIs visually by a trained rater that is familiar with the different types of artifacts, and whether they can be corrected.

3. Reconstruction: Mathematical models for dMRI

At each voxel, traditionally some diffusion or fiber model is fit to the diffusion measurements. The most popular is the diffusion tensor (DTI) whose major eigenvector aligns with the principal diffusion direction, assumed to represent the underlying tract orientation (Fig. 2). For a review of DTI acquisition and processing see Le Bihan et al. (2001). The tensor model is able to represent just one fiber tract orientation per voxel, an anatomical implausibility in much, if not most of the brain (Tuch et al., 2002). This limitation has spurred a large body of research into higher-order and multiple-fiber models including spherical harmonics, multiple tensor models, ball-and-sticks models, orientation distribution functions, and more. See for example, selected methods (Tournier et al., 2004; Tuch, 2004; Wedeen et al., 2005; Behrens et al., 2007; Malcolm et al., 2010) and reviews covering the topic (Alexander, 2005; Jones et al., 2013).

3.1. Pitfalls

The DTI model can be fit to data with a single b-value near 1000 and a minimum of 6 (but today generally 20 or more) unique gradient directions. Acquisition schemes that are sufficient for the estimation of DTI are currently available on most clinical scanners. The length of the scan depends on the number of the measured gradients, where the minimal acquisition would require 1–2 min of a scan, and more robust DTI acquisitions could take 15 min or more. While longer scans provide more information, they are also more likely to cause increased discomfort to the subject, which in turn increases motion artifacts. Higher-order models have more stringent requirements for the DWIs (higher number of gradient directions and possibly multiple b-values), and often require altering the existing DTI protocols, as well as extensive additional post-processing steps.

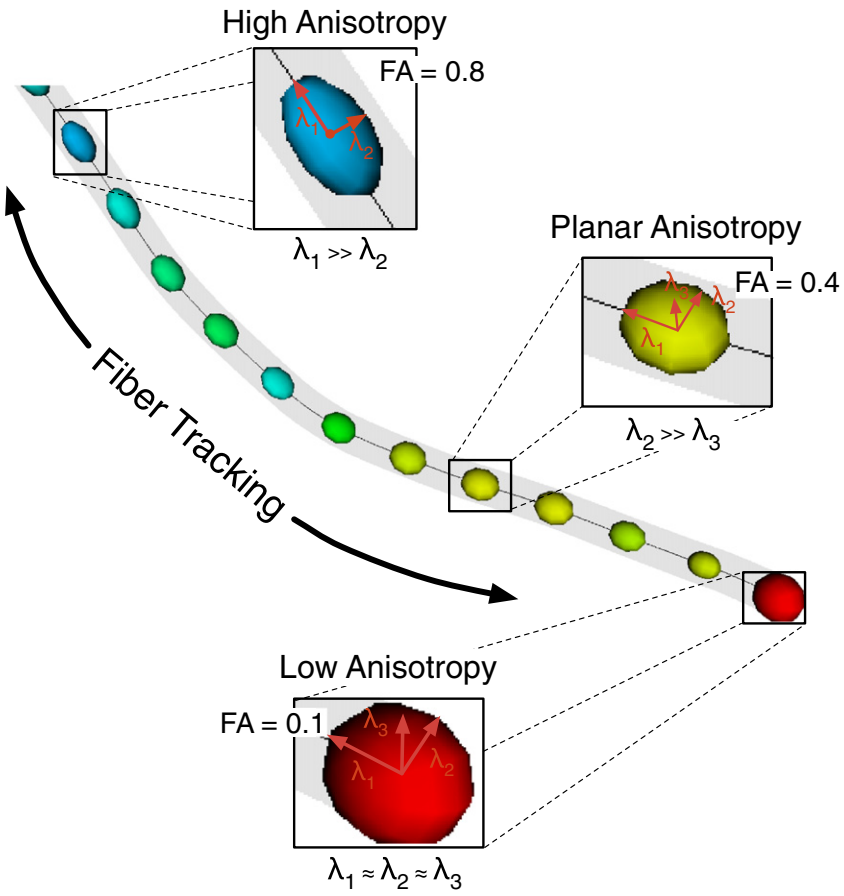

Fig. 2. A visual example illustrating the diffusion tensor model and the major concepts of diffusion anisotropy, fiber tracking or tractography, and eigenvectors and eigenvalues. A fiber trajectory from tractography (middle) is shown as a thin black line and shaded in gray, while selected diffusion tensors along it are displayed as ellipsoids and colored according to fractional anisotropy (FA). High (blue), medium (yellow), and low (red) FA tensors may be seen. FA values range from 0.1 to 0.8 in this small dataset. Three example tensors are shown in more detail with eigenvectors drawn in red. The eigenvectors form an orthogonal coordinate system and correspond to the axes of the ellipsoids. Each eigenvector is scaled proportional to the square root of the corresponding eigenvalue. The eigenvector corresponding to the largest eigenvalue was followed during fiber tracking and is therefore tangent to the fiber from tractography. Equations describing the relative relationships of the eigenvalues are shown for each zoomed tensor. The tractography and diffusion ellipsoid rendering was performed in 3D Slicer (www.slicer.org).

4. dMRI scalar measurements: Anisotropies and more

Diffusion anisotropy enables modeling of the oriented cellular structures in brain tissue. Diffusion anisotropy in the brain is caused mainly by cellular membranes, with some contribution from myelin, as described in a thorough review that also discusses diffusion anisotropy's history and complex relationship to pathology (Beaulieu, 2002).

The most commonly reported value in clinical studies, the fractional anisotropy or FA (Basser and Pierpaoli, 1996), measures how different the ellipsoidal shape of the diffusion tensor is from that of a sphere. Other anisotropy measures have been proposed for the tensor (Westin et al., 2002) and for many flavors of higher-order models. The other commonly reported value is the mean diffusivity (MD), equivalent to one-third of the trace of the tensor (the sum of its eigenvalues). Many DTI reviews describe these measures (Le Bihan et al., 2001; Jellison et al., 2004). Most clinical research thus far has used the FA, MD, and/or other scalar measures, as opposed to studying the entire tensor, fiber model, or diffusion model.

4.1. Pitfalls

Interpretation of changes in scalar measurements is complex due to their non-specificity. For example, many factors (e.g. cell death, edema, gliosis, inflammation, change in myelination, increase in connectivity of crossing fibers, increase in extracellular or intracellular water, etc.) may cause changes in FA. Thus the common description of FA as "white matter integrity" is a misnomer. Rather, FA is a measure that is sensitive to neuropathology in its many forms, as well as to local changes or anatomical differences in connectivity. Reviews that discuss the topic of non-specificity of FA include Assaf and Pasternak (2008), Le Bihan and Johansen-Berg (2012), and Jones et al. (2013). The MD also suffers from non-specificity: it is affected by tissue geometry and has been shown to be lower in areas of complex fiber configuration (Vos et al., 2012).

Much of the difficulty in interpretation of dMRI measures is fundamentally caused by the fact that the scale at which diffusion is measured with dMRI (mm scale) is much larger than the size scale of the individual axons and cells that are probed by the diffusing water (micron scale). Thus what is measured is a voxel-averaged quantity that must be computationally modeled to extract any biologically relevant parameters. This is a difficult inverse problem. For intuition into the problem, a table of size scales pertaining to dMRI measurements in the brain is available (O'Donnell and Westin, 2011).

In addition to the non-specificity issue, the analysis of FA and MD is not theoretically ideal, as the FA and MD measures are not mathematically orthogonal. This means that changes in FA are potentially reflected as changes in MD and vice versa. Sets of orthogonal measures have been proposed, including the mode that differentiates between "cigar" and "pancake" tensor shapes, unlike FA that is high in both shapes (Ennis and Kindlmann, 2006). Use of axial and radial diffusivities or individual diffusivities (eigenvalues) in addition to FA may also clarify the picture to some extent (Song et al., 2003; Alexander et al., 2007; Assaf and

Pasternak, 2008). However, as mentioned above, all DTI derived parameters, including the individual diffusivities, represent averaging over many cellular domains, and are therefore non-specific.

There are many practical challenges in conducting a scalar measurement based study. Statistically, it is difficult to compare dMRI measures across scanners (or even within-scanner if, for example, a software upgrade has affected the dMRI acquisition). Repeated scans on two scanners measured the coefficient of variation (CV = standard deviation/average) and found that within-scanner FA and trace measures were reproducible (CV of 1.9% and 2.6%, respectively) but across-scanner measures were biased (CV of 4.5% and 7.5%, respectively) (Pfefferbaum et al., 2003). A more recent study found that inter-site bias in FA could be corrected with a global scaling factor (Vollmar et al., 2010). The same study provided a useful table of results comparing studies on DTI test–retest reliability in both 1.5 T and 3.0 T scanners (Vollmar et al., 2010).

Furthermore, while the trace and MD vary little within the brain, the FA is highly spatially variable (high in tract centers and abruptly dropping on tract borders, areas near CSF, or voxels where tracts cross). This complicates its analysis across subjects (see Section 5 for more detail). Additionally, when cerebrospinal fluid (CSF) and white matter are both present in a voxel, CSF contamination can bias results. This may be corrected with mathematical modeling that includes an isotropic or free water component (Pasternak et al., 2009; Metzler-Baddeley et al., 2012). The amount of free water in white matter may change depending on age or pathology, and eliminating its effect can increase the specificity of the DTI measures to changes that occur in the tissue (Pasternak et al., 2012; Rathi et al., 2014).

New approaches under investigation aim to disambiguate measurements from dMRI by calculating more biologically relevant tissue parameter(s), such as free water, axon diameters, disambiguated anisotropies, and more (Assaf and Basser, 2005; Assaf et al., 2008; Shemesh et al., 2010). Often, this requires advanced scanning paradigms as well as novel computational methods. Another possibility for improving specificity is to combine dMRI results with other imaging modalities, such as magnetic resonance spectroscopy, magnetization transfer, positron emission tomography, or functional MRI (Mandl et al., 2010; Du et al., 2013).

5. dMRI studies: Methods that analyze voxels

Once a parameter of interest has been calculated, most commonly FA and/or MD, statistical analyses are applied across the group.

One popular style of analysis performs statistics at the voxel level, requiring image registration to align or normalize all subjects' data to a common coordinate system. This paradigm is called voxel-based morphometry or VBM (Ashburner and Friston, 2000). The VBM strategy analyzes the whole brain without any a priori hypothesis needed as to the location of an effect, and it can be performed automatically, thus it is an extremely popular technique.

Another popular analysis style can be applied when a hypothesis about the location of an effect is available. A region of interest (ROI) is defined, and data are measured (usually averaged) within the ROI. The ROI definition may be done via image segmentation, however in dMRI, ROIs are often defined using tractography (see Sections 6 and 7 for more detail on tractography and tractography-based measurements).

A voxel-based approach designed to address issues specific to dMRI is called tract-based spatial statistics or TBSS (Smith et al., 2006). Despite the frequent misconception in researchers new to dMRI, the TBSS approach actually analyses data at selected *voxel locations*, not in "tracts" from tractography. The difference between TBSS and standard VBM is that TBSS analyzes only high FA data from each subject that is likely to correspond to the core of a tract, while avoiding low FA values that are not considered to be the core.

5.1. Pitfalls

The main assumption underlying VBM is that the normalization will place corresponding anatomy at the same location across subjects. Precise voxelwise alignment of FA across subjects is challenging due to its high spatial variability and to CSF contamination near ventricles. In VBM, the challenge of anatomical variability is often addressed by smoothing (spatial averaging) to "spread out" the data, bringing it into better spatial correspondence while also improving the Gaussianity of the voxelwise distributions of data across subjects. However, VBM may not give consistent results across dMRI studies. FA changes in VBM studies are highly dependent on the size of the smoothing kernel (Jones et al., 2005), and reported coordinates of significant difference in VBM of FA in schizophrenia are extremely inconsistent across studies (Melonakos et al., 2011).

TBSS was developed to address the difficult FA image registration problem, where the "cores" of the white matter tracts do not align sufficiently after image registration (Smith et al., 2006). Improved image registration is needed not only to identify corresponding anatomical regions across subjects, but also to attempt to generate results based on microstructural, not macrostructural, brain changes. If the image registration is not adequate, even though FA measures microstructural tissue properties in individual subjects, groupwise changes in FA can be caused by macrostructural changes (such as an increase in ventricle size or change in tract thickness).

Thus the TBSS method limits VBM analyses to the likely cores of major fiber tracts, i.e. regions of high FA. To do this, first an analysis region is calculated as a groupwise white matter skeleton, a surface of high FA voxels from a group average FA map. Then the TBSS method uses a heuristic to find and analyze high FA values for each subject. The heuristic is a local search to find a maximal FA voxel by looking in directions perpendicular to the skeleton. Using TBSS, high FA values may be found for analysis despite challenges in FA registration. However it is not guaranteed that the FA values selected for analysis at each skeleton voxel actually belong to the same anatomical tract across all subjects. It has been shown that the FA variance interacts with the anatomy and the imaging matrix in TBSS (Edden and Jones, 2011). Unsurprisingly, central structures are less variable than peripheral structures in terms of FA variance, but much more surprisingly, the rotation of the brain in the scanner affects the skeleton thickness and therefore the local sensitivity to differences (Edden and Jones, 2011).

All voxel-based analyses are heavily dependent on the image registration or normalization method employed. Methods for registration of dMRI data have been compared (Park et al., 2003; Zhang et al., 2007; Wang et al., 2011), demonstrating that high-dimensional normalization and use of multiple channels/full tensor information is superior to registration based on a single scalar value such as FA. However, many studies are still performed with simpler registration methods based for example on FA.

Finally, it should be noted that while the above mentioned methods provide a statistic, a rigorous statistical analysis and hypothesis testing are required for any inference. Similar to other imaging modalities, familywise errors must be addressed due to the many statistical tests (multiple comparisons) that are performed (one for each voxel) (Nichols and Hayasaka, 2003). Currently, specialized statistical approaches designed for dMRI analysis are not widely available, with the exception of FSL that includes a rigorous statistical analysis tuned for application to the white matter skeleton results of TBSS. Other novel statistical approaches include methods that steer away from conventional group analysis, moving toward identification of abnormalities in an individual subject when compared to a group of normal controls. This is important when the suspected pathology varies in its spatial location between patients (White et al., 2009; Lipton et al., 2012; Bouix et al., 2013).

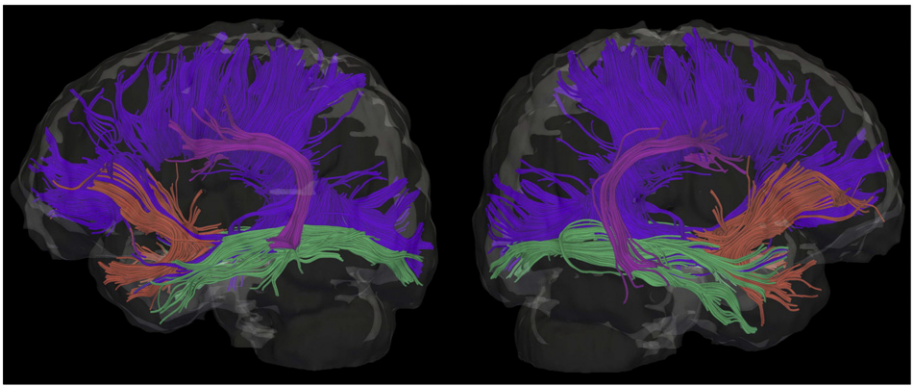

Fig. 3. An example of single-tensor streamline tractography showing the corpus callosum (purple), arcuate fasciculus (pink), uncinate fasciculus (orange), and inferior longitudinal fasciculus (green) tracts segmented with an atlas created by spectral clustering, using the methods described in O'Donnell and Westin (2007). The two views are from the left and right sides of the brain. Some subtle differences can be seen across hemispheres, potentially due to anatomical differences and/or to properties of the data and computational pipeline.

6. dMRI studies: Methods that trace connections

Tractography is the name given to any computational method that attempts to reconstruct white matter fiber tracts or "trace brain connections" based on dMRI data (Fig. 3). For DTI reviews that teach anatomy of major white matter fiber tracts, see Jellison et al. (2004) and Catani and Thiebaut de Schotten (2008). For a recent review on the field of tractography and future directions, see Jbabdi and Johansen-Berg (2011).

Accurately estimating the course of the brain's connections from dMRI is a difficult technical problem, therefore many methods for performing tractography have been developed. First introduced in 1999 (Conturo et al., 1999; Jones et al., 1999b; Mori et al., 1999; Weinstein et al., 1999; Basser et al., 2000), DTI streamline methods repeatedly follow the principal diffusion direction (the tensor's principal eigenvector) with many small spatial steps, where each step is usually 1 mm or less. Some tractography methods use additional information from the tensor to "continue through" regions of crossing fibers (Westin et al., 2002; Lazar et al., 2003) that are not well represented by the eigenvector. Probabilistic tractography techniques were then developed (Behrens et al., 2003) to perform tracking by sampling from distributions on fiber orientation, rather than by following only the principal diffusion direction. Currently available flavors of tractography methods, with examples given as citations, include deterministic (Conturo et al., 1999; Jones et al., 1999b; Mori et al., 1999; Weinstein et al., 1999; Basser et al., 2000), probabilistic (Behrens et al., 2003; Friman et al., 2006), regularized (Poupon et al., 2000), geodesic (O'Donnell et al., 2002), global (Jbabdi et al., 2007; Aganj et al., 2011; Mangin et al., 2013), with a prior or an atlas (Hagler et al., 2009; Yendiki et al., 2011), with many different models (Behrens et al., 2007; Malcolm et al., 2010), in individual subject data (most studies), and in population average data (Goodlett et al., 2009; Aganj et al., 2011). Colorful tractography visualizations of the brain's connections have even inspired art contests (http://www.neurobureau.org/).

Reviews are available that describe tractography methods in much more detail (Jones, 2008; Jbabdi and Johansen-Berg, 2011; O'Donnell andWestin, 2011) and discuss issues and impacts of tractography (Johansen-Berg and Behrens, 2006).

6.1. Pitfalls

With the many available options, and new methods under development, it is difficult to choose a tractography method, or to compare results across studies. Recent studies have assessed the quality of the results of various tractography algorithms (Fillard et al., 2011; Bastiani et al., 2012), generally concluding that more sophisticated models are an improvement over the single tensor DTI model.

The nomenclature for tractography is confusing. The output of many tractography methods is a set of trajectories, approximating brain connections. Other methods output connection probabilities or strengths that may be viewed as images. The output of tractography methods may be referred to as trajectories, streamlines, tracts, fibers, tracks, tractograms, or other similar names. However, the field seems to be converging toward exclusive use of the words "tract" and "fiber" (Fig. 4). Often the word "tract" is reserved for some anatomically plausible connection comprised of many trajectories or of many voxels with high connection strength, while the word "fiber" refers to some computational result that is smaller, usually a single deterministic or probabilistic streamline trajectory.

Tractography can be variable both within and across subjects. Several studies have quantified its reproducibility on a within-subject basis. The CV of tract volume (with probabilistic tractography) between repeated scans of the same subject was found to be quite high, between 10% and 15% when the tract was seeded in DTI space (Heiervang et al., 2006). Compared to tract volume, MD and FA had much lower CVs (2–7%) when measured in tracts in repeated scans (Heiervang et al., 2006). We note that MD/trace was more reproducible than FA in repeated scans (Heiervang et al., 2006), likely due to MD's lower spatial variability within the brain parenchyma, thus its relative insensitivity to the tract measurement region, compared to FA which is highly spatially

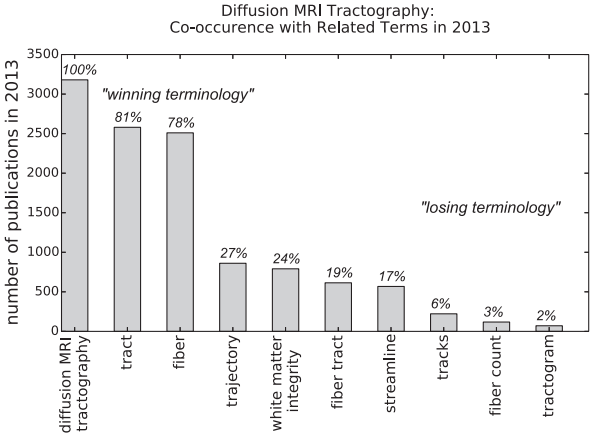

Fig. 4. What should one call the computational output of an algorithm to estimate brain connections? This survey of terminology used in papers related to dMRI tractography in 2013 employs paper counts estimated by Google Scholar (y-axis). Searches were performed with the words "diffusion" "MRI" and "tractography," (leftmost bar) plus additional terms (all other bars) to investigate their co-occurrence. In papers that relate to dMRI tractography, the nouns "tract" and "fiber" seem to be winning, as they are present in about 80% of papers, while their combination "fiber tract" is present in 19%.

variable due to crossing fibers in addition to any neuropathology. However FA was more reproducible than MD across scanners (Pfefferbaum et al., 2003). The selection of the tract itself may be another source of variability: interactive tract selection protocols (of deterministic streamline tractography) were shown to have reasonable inter-rater reproducibility for FA measurement (in repeated analyses of the same subject, not repeated scans) with CVs near 1% Wakana et al. (2007).

Across-subject variability of tractography, or even entire tracts that are absent, is another feature of tractography that may be caused either by actual anatomical differences, or by various pitfalls. "Absent" tracts can be meaningful and due to anatomical structure: in 62.5% of subjects the arcuate fasciculus was present only in the left hemisphere when using single-tensor streamline tractography (Catani et al., 2007). However, this should be interpreted as an anatomical asymmetry in the language-related arcuate fasciculus tract, as opposed to a confirmation of its complete absence in the right hemisphere in many healthy people. A small, thin arcuate, if present, would likely be traceable with another combination of dMRI data and tractography algorithm.

Anatomical errors in tractography are prevalent. For images illustrating "false-negative" (missing fibers) and "false-positive" (anatomically incorrect) tractography, see Catani (2007) and O'Donnell and Westin (2011). False-negative errors can be due to the measurement model, such as the failure to trace lateral connections of the corticospinal tract with the single-tensor model (Behrens et al., 2007; Jones, 2008; Qazi et al., 2009; O'Donnell and Westin, 2011; Farquharson et al., 2013). This phenomenon of "missing fibers" is due to "crossing fibers" that are not modeled by DTI, a pitfall that has been discussed in detail (Jones, 2008). In addition to missing fibers, spurious false-positive trajectories are produced that cross from one anatomical structure to another. This occurs especially when using sophisticated multiple fiber models.

Spurious fibers that are considered to be anatomically incorrect are removed in various ways in published studies. Fiber removal may be done for any tract. We illustrate it with the example of two studies that reconstructed the corticospinal tract using two different tractography methods, probabilistic and spherical deconvolution. In these particular studies, errant fibers were removed in two ways. First, fibers were not shown if the number of fiber trajectories passing through a voxel was less than a threshold (Behrens et al., 2007; Farquharson et al., 2013). Second, fibers were included and excluded using regions of interest (motor cortex) and disinterest (midsagittal regions to prevent crossing into the contralateral hemisphere) (Behrens et al., 2007; Farquharson et al., 2013).

The extensive anatomical knowledge that is needed to "clean up" and reconstruct tracts diminishes the expectation of discovering any truly "new" pathway that has not been seen historically in dissection studies. The state of the art of tractography, in general, aims to reconstruct known connections. However, the potential to study these connections and their variability in vivo, in health and disease, is an amazing opportunity.

7. dMRI studies: Methods that analyze connections

Two main categories of method, tract-based quantification and graph-theoretical connectome analysis, are popular for analyzing the results of tractography. In tract-based quantification, anatomically labeled fiber tracts are used as regions of interest to measure FA, MD, or another parameter. Thousands of successful studies have been performed. In the quickly-growing field of connectomics (Sporns et al., 2005), the tracts are reduced to a connectivity matrix according to the regions of interest they connect, enabling the study of the brain's connections using graph theory. Many recent reviews are available regarding connectome analysis (Toga et al., 2012; Johansen-Berg, 2013).

7.1. Pitfalls

Both categories of method inherit the pitfalls discussed earlier for tractography, as well as for measurement of scalar indices such as FA that are widely used in both categories. However there are additional pitfalls that are worth mentioning. Recent reviews discuss pitfalls and limitations in connectomics (Van Essen and Ugurbil, 2012; Fornito et al., 2013), so we focus more on limitations and caveats when measuring properties of anatomically labeled fiber tracts from tractography.

Before any measurement can be made using tractography, whether it is the mean FA in the corpus callosum or the number of streamlines connecting cortical region A to B, some segmentation or division of the tracts into relevant regions must be performed. This segmentation problem is a challenge for tract-based quantification, in which the anatomical structure of interest must be selected in some way, whether automatic or interactive. Furthermore, the combination of tractography algorithm and segmentation method may not succeed for smaller tracts in all subjects, thus studies are often limited to the major ones such as corpus callosum, arcuate, uncinate, cingulum, corona radiata, etc. The segmentation problem is also a challenge in connectomics: defining the regions of interest or nodes of the connectome graph (that induce a segmentation or grouping of the tracts) is considered to be a hard and open problem. A recent review discusses the methods and issues related to tractography segmentation in both tract-based quantification and connectomics (O'Donnell et al., 2013).

The process of defining tracts for tract-based quantification can be a source of variability in any study. The common paradigm of interactive selection ("virtual dissection") of fiber tracts (Stieltjes et al., 2001; Catani et al., 2002) has an important inter-rater spatial variability: kappa overlap measures in the neighborhood of 0.6 and 0.7 indicated "substantial" agreement (Wakana et al., 2007). A clustering method was found to reduce variability across raters (Voineskos et al., 2009), and many automated methods have been proposed to identify tracts based on a variety of atlases (Wakana et al., 2004; O'Donnell and Westin, 2007; Hagler et al., 2009; Guevara et al., 2012). However, atlas creation and representation is still an interesting open problem (Toga et al., 2006), and detailed neuroanatomical knowledge and interactive virtual dissection play an important role in studies of white matter anatomy today (Catani et al., 2013).

In quantitative tractography, what should one measure? Some of the tract-based measurements that are made rely heavily on the parameters of the tractography method employed. The most reviled example is the reporting of a count of the number of streamline trajectories as the "fiber count" (Jones et al., 2013). The fiber count is apparently losing popularity, as it was present in only 3% of dMRI tractography publications as estimated using Google Scholar (Fig. 4). The "fiber count" is highly dependent on the number of times tractography was seeded in each voxel, and the properties of the tractography method employed. Many studies use this number: it is often employed in connectome matrices and in anatomical comparisons across hemispheres, for example. However it is crucial to realize that it is not a count of neuroanatomical fibers, and that tractography has a spatial scale of mm, not microns. In addition, the fiber count is not a meaningful number for comparison across studies with differing tractography methods, thus there is a danger in reporting this number directly. Parameters with real physical measurement units or dimensionless quantities, such as tract volumes in mm^3, laterality indices, and graph-theoretic measures, are more possible to compare across studies. Finally, studies have shown that measurement of scalar values along a tract can reveal localized differences that may be missed when taking the mean within the entire tract (O'Donnell et al., 2009; Colby et al., 2012).

8. Discussion: Does dMRI tell us anything about the white matter?

It is clear that dMRI provides useful information about brain structure to aid clinical decision making. For example, in a prospective

study of 238 neurosurgical patients, the use of dMRI improved patient outcomes and prolonged survival (Wu et al., 2007). And importantly, diffusion-weighted imaging is now the most sensitive and specific technique for early stroke detection (Jauch et al., 2013).

But in clinical research, does dMRI tell us anything about the white matter? It is clear that the information in dMRI, as tantalizingly nonspecific as it may be, has inspired much investigation into the anatomy and alterations of the brain's tissue microstructure. As the only existing method that can probe the white matter microstructure in the living brain, dMRI is sensitive to changes present in many diseases. Recent reviews have highlighted findings in schizophrenia (Fitzsimmons et al., 2013; Samartzis et al., 2014), traumatic brain injury (Shenton et al., 2012), autism (Travers et al., 2012), and attention deficit/hyperactivity disorder (van Ewijk et al., 2012). That short list of recent reviews is only the tip of the impressive dMRI study iceberg (see again Fig. 1). We note also that dMRI can be as important and informative in gray matter as in white matter (Sagi et al., 2012; Zatorre et al., 2012; Bouix et al., 2013; Rathi et al., 2014), though the gray matter measures may be less reproducible than the white matter measures (Vollmar et al., 2010). However, there is a growing awareness of the non-specificity of many dMRI findings (Assaf and Pasternak, 2008; Melonakos et al., 2011; Le Bihan and Johansen-Berg, 2012; Vos et al., 2012; Jones et al., 2013).

Though the dMRI field is maturing, methods for acquisition, computational processing and modeling of the data are continually being developed and improved. New research directions aim to address the issues of non-specificity and data interpretation by measuring dMRI parameters that may more closely relate to the physiological parameters of brain tissue (Assaf and Basser, 2005; Assaf et al., 2008; Shemesh et al., 2010). Partial volume effects due to CSF contamination may be corrected (Pasternak et al., 2009; Metzler-Baddeley et al., 2012). Additional approaches for improving the specificity of dMRI findings involve measuring data from complimentary modalities. Diffusion weighted MR spectroscopy (Du and Öngür, 2013; Du et al., 2013) gives additional microstructural insight via diffusion profiles of metabolites. Magnetization transfer imaging (Kubicki et al., 2005; Mandl et al., 2010, 2015-in this issue) enables calculation of the magnetization transfer ratio, a putative myelin marker. Moving forward, we expect that improved modeling and acquisition techniques, in conjunction with multimodal analyses, may more closely relate changes in dMRI to changes in brain cells and their environment.

However, in clinical research today, interpreting any dMRI study is a challenge. The final pitfall we will describe is that of comparing results across studies: the dMRI protocol may vary, and the methods may vary. Thus researchers must be cautious and aware of the strengths and limitations of the methods employed, both when comparing the results of different studies, and when interpreting their own results. An awareness of the complex acquisition and processing pipelines used in dMRI clinical research should enable a more nuanced interpretation of the findings of any study.

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Contributors

OP and LJO conceptualized the structure of the manuscript. LJO wrote and edited the manuscript and created the figures. OP contributed to the writing and editing of the manuscript.

Both authors contributed to and have approved the final manuscript.

Conflict of interest

The authors state that no potential conflicts of interest are associated with this manuscript.

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