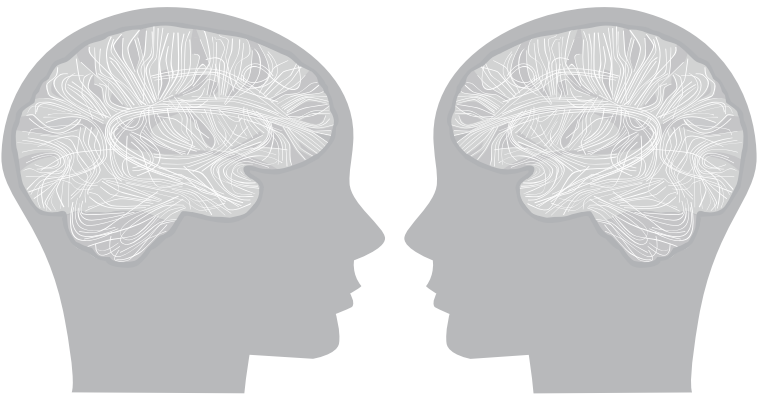
MICROSTRUCTURES OF LEARNING

Novel methods and approaches for assessing structural and functional changes underlying knowledge acquisition in the brain

May 23, 2014, Piratensalen, Grand Hotel, Lund, Sweden



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The Pufendorf Institute for Advanced Studies and the *HuMeNS**-
interdisciplinary group at Lund University
with support from the Birgit Rausing Language Program, Lund University

*Merle Horne (Coordinator), Magnus Lindgren, Markus Nilsson, Mikael Roll,
Yury Shtyrov, Freddy Ståhlberg & Daniel Topgaard

Symposium proceedings

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Edited by
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ISBN: 978-2-88919-480-3
doi: 10.3389/978-2-88919-480-3

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Tractometry and the hunt for the missing link: a physicist perspective

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SUMMARY

This article focuses attention on the pressing need to think carefully and deeply about the current state of the art in using measurements of tissue microstructure derived from MRI to explain individual differences in brain function, electrophysiology and or cognitive function[1]. Although initial effort in the application of microstructural imaging was on voxel-based metrics derived from diffusion tensor magnetic resonance imaging (DT-MRI), such as fractional anisotropy (FA) and the mean diffusivity (MD), there is increasing realisation of the limitations of this approach both in terms of biological specificity and in terms of interpretability of any results that emerge. This has led to the development of alternative approaches that are (i) looking at topologies of networks derived from diffusion-MRI-based fibre-tracking approaches, (ii) adopting "advanced" diffusion MRI metrics that go beyond the tensor model, or (iii) looking at data from non-diffusion-based MRI contrasts, such as those based on magnetization transfer, multi-component relaxometry, or susceptibility-weighted imaging. With the increasing availability of methods to extract such metrics, and ease of access, it should be stressed that our application of such methods is outpacing our understanding of what aspect of biology the metrics are actually capturing. As such, there is a danger of operating in an unprincipled and unstructured fashion. This article argues that the "missing link" is a non-invasive neuroimaging metric that is not only well understood, but which also can reasonably be expected to explain variance in brain function from a biological perspective, rather than a metric that is used purely as a matter of convenience.

Keywords: axons, connectivity, DTI, graph theory, microstructure, myelin, networks, tractography, tractometry, white matter

INTRODUCTION

The UK national rail network

The United Kingdom is served by a "national rail network" that comprises mainline and local train services that link small villages to large cities. An internet search for images of the "UK rail network" yields multiple schematic depictions of the available routes and connections between different stations distributed throughout the UK. Any of these schematic diagrams would lead an alien visitor to believe that all lines in the network are largely equivalent. In other words, the ability to travel from one station to another station is the same no matter where you are in the network. In other words, all train lines are created equally. However, anyone who has attempted to use this network on a regular basis knows that the ability to use the trainline is variable, with "leaves on the line" being a perennial problem, now part of humour in UK train-users (see http://www.networkrail.co.uk/timetables-and-travel/delays-explained/leaves/).

What this tells us is that while it is *necessary* to have a schematic map of the network connections in order to understand possible routes that one may take to visit different parts of the network, the information is *insufficient* to determine *a priori* how effectively one may use any particular parts of the network, and therefore the efficiency of using the network as a whole. Thus, while the designer of a rail network may be gratified to have minimized the travel distance between any two train stations, in terms of time or number of train changes required, and perhaps at the amount of steel needed to make that network, suggesting that the *layout* of the network is efficient, the passenger's perspective is very different. If the condition of the track is such that the passenger is unable to travel efficiently, incurs unacceptable delays, misses a vital interchange, or does not arrive at the same station at the same time as a friend travelling on another route, frustration is ensured. As far as the passenger is concerned, there is a dysfunction of the network.

1 Henceforth, we will use the term "function" as a generic term to include measurements of activity as observed by neuroimaging, measurements of electrophysiology and/or performance on a task, unless we specify a specific aspect of "function."

Brain networks

Networks are studied increasingly in neuroscience (Sporns, 2010), whether these are derived from mapping statistical relationships between time-varying "functional" signals (Biswal et al., 1995; Schoffelen and Gross, 2009; Friston, 2011), correlation of structural attributes such as cortical thickness (He et al., 2007; Chen et al., 2008), or by inferring continuous white matter pathways between cortical nodes using white matter *tractography*. Here we focus on the latter. In most cases, the researcher employs an algorithm that will use diffusion MRI data to derive discrete estimates of a continuous white matter pathway, either in a deterministic or probabilistic fashion, to infer a continuous trajectory, which is then asserted as a "tract" or a "connection" (Jones, 2008; Behrens and Sporns, 2012).

If a deterministic algorithm is used, then one obtains something akin to a national rail network map, with each connection being represented "democratically." With a sufficient number of pathways thus reconstructed, the data can be subjected to a graph theory analysis (Iturria-Medina et al., 2007; Hagmann et al., 2008; Bullmore and Sporns, 2009; Kaiser, 2011), allowing one to compute measures of network integration and segregation, including measures such as clustering coefficient, minimum path length, "small-worldness" and efficiency (Hagmann et al., 2008; Bullmore and Sporns, 2009; Kaiser, 2011). Using this approach, researchers have found differences in graph theory metrics in disease (Petrella, 2011; Griffa et al., 2013) and associations between graph theory metrics and cognition, for example (e.g., van den Heuvel et al., 2009; Ajilore et al., 2014).

When such analyses are performed purely on the connections themselves by considering "binary" edges (present or not), one might be surprised by these results since they implicitly assume that the only difference between individuals is in the *layout* of the wiring, and that any individual differences in the *make up* of the white matter fibres is less interesting/irrelevant/non-existent (or, implicitly, correlates strongly with the presence of an edge in the graph). They implicitly disregard as uninteresting any individual differences in the make up of the fibres. Of course, such a supposition makes no sense whatsoever when considering single pathways between two nodes, or a single fascicle, such as the arcuate fasciculus when studied in a language paradigm. Discarding the microstructural information (and even that on shape/length) and reducing the information to "there is a connection" leaves no variance in information. In addition, the criteria by which the binary edges are determined are often arbitrary and can have a huge effect on graph theory analysis results (Langer et al., 2013; Drakesmith et al., 2014).

In practice, of course, researchers have adopted several approaches to "weight" the edges of a graph. The first class of approach is a "frequency" approach. Some apply information obtained from a probabilistic tracking algorithm, and use the variance in the number of successfully reconstructed pathways between two nodes to explore covariance with "function" (e.g., Parker et al., 2005; Broser et al., 2012). The "probabilistic tractography score" is often interpreted as a quantitative marker of "connectivity" in this context. This approach to obtaining inter-individual or inter-tract variances has also been employed in graph theory analyses to "weight" the edges of the graph (Vorburger et al., 2013; Weiler et al., 2014). A closely related approach to probabilistic tracking is simply to use cortical nodes with an extended area, i.e., containing multiple voxels, and count how many "streamlines" can be reconstructed successfully between the nodes, often referred to as "streamline count" (Wang et al., 2012; Hecht et al., 2013). This is, however, a challenging parameter to work with due to sources of bias such as length and curvature (e.g., Jones, 2010).

The second class of approach is to sample localised quantitative metrics of tissue microstructure (and thus obtain a distribution of the metric) along a particular pathway or fascicle, i.e., graph edge (e.g., Jones et al., 2005a,b). To this end, the most commonly used metrics are those derived from the tensor model, i.e., fractional anisotropy (Basser and Pierpaoli, 1996; Pierpaoli and Basser, 1997), mean diffusivity, "longitudinal" and "radial" diffusivities. For critical perspectives on these metrics see Wheeler-Kingshott and Cercignani (2009) and Szczepankiewicz et al. (2015). A small number studies have used other indices such myelination as estimated by magnetization transfer imaging (e.g. van den Heuvel et al., 2010). Looking at individual fasciculi, this approach is termed "tract-specific" analysis (Kanaan et al., 2006), while in graph-based analyses it is referred to as a "weighted graph" approach.

Network usage

At this stage, we should return to our analogy of the passenger on the train network and the importance of being able to predict our ability to travel along the train track as intended, so that we might arrive at the right place at the right time, and synchronise with others travelling on the same network. It is this aspect that will explain a large amount of variance in differences in efficiency between rail networks or in brain function between individuals. The question is this: to what extent does the probabilistic score, streamline count or tensor-based metric, either on a tract-specific basis, or in a graph analysis, give us *relevant* information?

The probabilistic score is simply how many times one can reconstruct a pathway between two points (Jones, 2010). While microstructural information may be used in the derivation of those pathways (e.g., low anisotropy used to terminate the propagation of a particular instance of a streamline), the probabilistic score does not provide a measure of the microstructural make up *per se*. DT-MRI-based metrics are heavily influenced by the microstructural make up of the tissue, and so perhaps take us one step closer to ascertaining the *quality* of the connection. However, as has been discussed many times in the past, the shape of the tensor is influenced by many factors including "interesting"

sources of variances, such as axonal density, diameter, myelination (Beaulieu, 2002), but one "uninteresting" source of variance dominates, i.e., the intra-voxel orientational dispersion or "*architectural paradigm*" (Beaulieu, 2002; Szczepankiewicz et al., 2015). To the best of our knowledge, the relative orientation of one axon to its neighbours in a voxel has no impact on its ability to carry an action potential. Thus, as previously noted, we should not be surprised when a DT-MRI-based metric does not explain variance in brain function. Rather, we might be more surprised when it does! It is, perhaps, in these instances that individual differences in "uninteresting" sources of variance are small, e.g., the function under assessment is reliant on information along a fibre pathway that is relatively *invariant* in intra-voxel orientational dispersion. It is in these situations that the DT-MRI metrics may be biased more towards the interesting sources of variance, such as myelin and axon morphometrics, explaining our previous proposal that "diffusion tensor MRI does well only some of the time" (De Santis et al., 2014).

A consequence of this argument would be that DT-MRI is probably more informative when comparing groups that have similar overall brain structure than when comparing widely different brains. For example, interpreting DT-MRI when comparing brains of Alzheimer's disease patients to healthy controls is less informative than comparing the brains of a strictly defined control group (e.g., males, 25 years old, minimal variation in intracranial volume) before and after intervention such as cognitive training.

Tractometry and going beyond the tensor

Several DT-MRI studies have demonstrated a significant group difference or within-group microstructure-function correlation when taking the average parameter along a specific pathway (reconstructed with tractography) when a voxel-based search of the same data reveals nothing significant (Keedwell et al., 2012; Postans et al., 2014; Bracht et al., 2015). While only conjecture, this is likely to be attributable to the increased statistical power derived from averaging along the tract, effectively grouping the estimates from multiple noisy voxel-wise estimates, rather than considering each voxel in isolation. This then motivates the need for "tractometry" (Bells et al., 2011), which is the derivation of microstructural metrics along specific white matter pathways, whether it is averaging the parameter across the whole tract, or just a segment thereof.

The missing link: current status

So, what of the "Missing Link"? The provocative title refers to the fact that we have yet to come up with a principled white matter metric to explain variance in brain function. More specifically, to the best of our knowledge, there is a marked absence of any formal *theoretical* link between individual differences in any MRI-derived measure of tissue microstructure and individual differences in brain function. Thus, for example, while DT-MRI does indeed do well "some of the time" (De Santis et al., 2014) in that, for example, there are numerous reports of correlations between DT-MRI metrics and cognition (Johansen-Berg, 2010; Kanai and Rees, 2011; Roberts et al., 2013a), but doubtless there are at least an equal number of studies that have been conducted that have NOT found any correlation or group difference which have not been reported in the literature. Further, only a small number of studies with "counter-intuitive" results have appeared in the literature (e.g., choice reaction time correlating positively with FA in the visual pathway (Tuch et al., 2005), or negative correlation between years of training in karate and FA (Roberts et al., 2013b). While not specific to diffusion MRI, or even neuroimaging more broadly this positive reporting bias (Fanelli, 2010; Ioannidis, 2011; Francis, 2014; http://www.badscience.net/2011/08/brain-imaging-studies-report-more-positive-findings-than-their-numbers-can-support-this-is-fishy/) and subsequent plethora of positive results in the literature clearly has an impact on researchers coming into the field looking for a structural substrate. When coupled with the modest data acquisition requirements for a DT-MRI experiment, increasing availability of easy-to-use and push-button analysis packages, the increasing ubiquity of DT-MRI based studies is understandable. The exquisite sensitivity of diffusion-based metrics, and thus their tendency to yield some form of difference or correlation in many instances, makes them particularly attractive. Granted, in cases where a correlation or group difference is found, they yield *some* insight in that they show that *something* in the white matter explains differences, but can go no further. Given the degenerate nature of the metrics, one is simply unable to say whether this "*something*" relates to axonal morphometrics, myelin morphometrics, some combination of the two or even, perhaps, something entirely unrelated such as subject motion (Yendiki et al., 2013).

Thus, while DT-MRI yields sensitivity, it comes at a price of lack of biological *specificity.* It is this degeneracy that has partly motivated the gradual adoption of neuroimaging approaches to offer increased biological specificity, attempting to hone in and capture variance in just one particular attribute of neural microstructure (Alexander et al., 2011; Assaf et al., 2013), e.g., "axonal" markers (Assaf et al., 2004, 2008; Alexander et al., 2010; Nilsson et al., 2013a), or "myelin" markers (MacKay et al., 1994; Henkelman et al., 2001; Laule et al., 2007; Deoni et al., 2008; Wharton and Bowtell, 2012, 2014; Liu et al., 2014; Haacke et al., 2015), summarised below. Ultimately, the hope is that by increasing the biological specificity, one might also increase the sensitivity by being able to invest scan-time resources in the most informative metrics.

Summary of microstructural imaging approaches and what they offer

Diffusion MRI utilizes diffusing water molecules as a probe of tissue microstructure. Diffusion tensor MRI, diffusional kurtosis imaging (DKI) (Jensen and Helpern, 2010; Wu and Cheung, 2010), and q-space diffusion MRI

(King et al., 1994; Assaf et al., 2002; Cohen and Assaf, 2002) are techniques that use statistical tools to model and extract features of the molecular displacement probability distribution, or diffusion propagator. DT-MRI yields the average diffusion tensor, while DKI and related methods yield the intra-voxel variance of diffusion coefficients or tensors, in addition to the average. In q-space MRI, features such as the width of the diffusion propagator are extracted, which can be associated with axon diameters (Assaf et al., 2008; *Alexander et al., 2010*). While these techniques are highly sensitive, they cannot tell which specific feature is responsible for a certain level of change, because they provide single metrics that cannot disentangle the contributions of features of the tissue such as axonal orientation, density, myelination *et cetera* (Cohen and Assaf, 2002; Szczepankiewicz et al., 2015).

Biophysical models hold the potential to at least partly provide the missing link. The CHARMED model (Yendiki et al., 2013) predicts the diffusion-weighted MRI signal in terms of axon density and average diameter, while extensions such as AxCaliber (Assaf et al., 2004) extend the average diameter with a distribution described by its mean and variance. The NODDI model (Zhang et al., 2012) assumes an effective axonal diameter of zero, but includes axonal (or "neurite") orientation dispersion. Estimation of the axon diameter is demanding in terms of MRI hardware performance (Dyrby et al., 2012; Setsompop et al., 2013; McNab et al., 2014; Huang et al., 2015). Just as in light microscopy, diffusion MRI has a resolution limit below which axon diameters cannot be reliably quantified (Nilsson et al., 2013a). Although the resolution limit does depend on the analysis model, protocol and the design of the gradient waveforms, it is ultimately determined by the maximal amplitude of the magnetic field gradient that the scanner can produce. Current clinical scanners and present analysis models do not permit accurate quantification of axon diameters below 2–4 μm; below this limit axon diameters are inseparable from zero. This is why the effective diameter is assumed as zero in the NODDI model, given that most axons are smaller than the limit. All of these three models (CHARMED) (Assaf et al., 2004), AxCaliber (Assaf et al., 2008) assume slow exchange between the intra-axonal and the extracellular spaces, but inter-compartmental exchange can under limited circumstances be modelled and estimated using the modified Kärger model (Nilsson et al., 2013a) and extensions such as filter-exchange imaging (FEXI) (Lasič et al., 2011; Nilsson et al., 2013b). From a more general perspective, the diffusion MRI signal can be modelled using multiple components, each described by a scalar or a distribution on the anisotropy, orientation and the size or diffusivity of the component. When testing a multitude of different models with different compositions on in vivo or ex vivo data, three tissue components are typically required (extracellular, intracellular, and water confined in spherical cells or freely diffusing cerebrospinal fluid), but it is not entirely clear that the data supports reliable estimation of the axon diameter (Ferizi et al., 2014). Parameters such as axon density, the amount of extracellular "free" water, and orientation dispersion, have higher explanatory power and can be reliably quantified using optimized protocols (Zhang et al., 2012). These parameters can be beneficial for localizing brain regions impacted by diseases, but improved models and hardware (e.g. Nilsson et al., 2013a,b; McNab et al., 2014; Huang et al., 2015) will be needed to provide accurate estimates of axon diameters below the current resolution limit.

Methods other than diffusion MRI can also contribute to the "missing link". Such methods take advantage of relaxometry (MacKay et al., 1994; Laule et al., 2007; Deoni et al., 2008), magnetization transfer (Wolff and Balaban, 1989; Henkelman et al., 1993, 2001; Sled and Pike, 2001; Xu et al., 2014) and magnetic susceptibility (Wharton and Bowtell, 2012, 2014; Haacke et al., 2015). In their basic implementation, these techniques yield voxel-averaged metrics that are sensitive to changes in the tissue structure, but that lack specificity in the same manner as FA from DT-MRI does. Relaxometry is sensitive to the proton density (PD) and the longitudinal and transverse relaxation rates (T_1 and T_2, respectively), which reflect on the chemical environment of water molecules. Multi-echo experiments demonstrate a distribution of these values within the voxels (MacKay et al., 1994), where different T_1 and T_2 values can be associated to myelin water, intracellular water, and extracellular water. Methods such as multi-component driven equilibrium single pulse observation of T_1 and T_2 [mcDESPOT (Deoni et al., 2008)] provide a means to estimate these compartment-specific values in clinically realistic times. The water fraction with short T_2 has been designated as the myelin water fraction (MWF) (MacKay et al., 1994). Since brain function may be modulated by the myelin content but not the white matter T_2-value, the MWF is one step closer to contributing to the "missing link" than T_2. However, the MWF is blind to whether a change in myelin content occurs in small or large axons, and may thus not be sufficient to predict individual differences in brain function. Another approach to quantify white matter content is to utilize magnetization transfer (Wolff and Balaban, 1989; Henkelman et al., 1993, 2001; Sled and Pike, 2001; Ramani et al., 2002), where the MR signal is sensitized to macromolecular content, i.e., myelin density, by a process where macromolecular protons (such as those found in myelin) are saturated by an off-resonance ["magnetisation-transfer" (MT) pulse] while in constant exchange with free water. By comparing the MR signal with and without the application of the MT pulse, the magnetization transfer ratio (MTR) can be obtained (Wolff and Balaban, 1989). High MTR in WM is believed to be associated with the proteins and lipids in myelin. However, the MTR value depends on many aspects of the protocol in use, including the RF pulses, B_0 and B_1 homogeneity (particularly at higher field strengths) as well as intrinsic MR properties such as the T_1. This led to the development of several approaches to model out these additional sources of variance, to move toward a quantitative parameter (the macromolecular proton fraction) that gets closer to a physiological property of tissue, and therefore one step closer to the assembling the missing link. Finally, quantitative susceptibility mapping (e.g., Wharton and Bowtell, 2012, 2014; Liu et al., 2014; Haacke et al., 2015) shows promise to add another dimension to imaging of brain structure and function, especially at ultra-high field strengths. Due to the geometrical arrangement of myelinated axons, and the differential in magnetic

susceptibility between white matter components and surrounding tissue, they distort the surrounding magnetic field in a characteristic way, which may be utilized to estimate properties such as axonal orientations (Wharton and Bowtell, 2012) and potentially also axonal morphometrics such as myelin thickness (Wharton and Bowtell, 2014). Remarkably, few attempts have been made to provide a joint model of white matter that predicts the outcome of diffusion, relaxation, magnetization transfer and susceptibility mapping experiments simultaneously.

In contrast to DT-MRI, these approaches have not yet found widespread adoption in neuroscience, which is likely attributable to several reasons. Firstly, the neuroscience community has wholesale adopted diffusion tensor MRI. Consequently, in any study reporting on white matter microstructure, reporting the fractional anisotropy, for example, is expected. Moreover, as previously noted, given the likely "success" in getting a positive result with DT-MRI, any reluctance to relinquish a grip on DT-MRI would be completely understandable. Additional metrics require additional acquisition time, invoking additional scan costs, resource contention, and participant tolerance. Secondly, many of these approaches are still under active development. Thus, while for DT-MRI there are commonly found strategies for data acquisition (e.g., $b = 1000$ s/mm^2, 30–60 uniformly distributed directions) (Jones et al., 1999) and standardized protocols (Jones and Leemans, 2011), metrics of anisotropy (FA being the most prevalent), and data analysis (e.g., Smith et al., 2006; Leemans et al., 2009), the same cannot be said of the other metrics. Third, even if there was consensus, there is relatively limited availability of user-friendly interfaces. Fourth, while DT-MRI is widely used *despite* us not really having an understanding of what the metrics are telling us from a biologically specific perspective, it seems that the community developing these alternative approaches is more hesitant in releasing them for general use, while efforts to understand and interpret what they are telling us are on-going.

Quantitative, interpretable metrics – now what?

Consider a Utopian world, in which we have developed fully robust non-invasive methods to quantify axonal morphometrics (including axon diameter, axon density, membrane permeability), myelin metrics (including myelin thickness), g-ratio (Stikov et al., 2011; Melbourne et al., 2014; Stikov et al., 2014; Campbell et al., 2014) and so forth. Moreover, each metric has been validated using more invasive methods, and finally there is a consensus on the optimal way to acquire, pre-process and analyse the data. What then? We would then be equipped with a set of tools to quantify disparate attributes of white matter microstructure and would be in the position of being able to repeat the exercise of looking for correlations between these new metrics and aspects of brain function. We may, for example, find a positive association between a myelin metric and task performance, or between coherence in electrophysiological recordings between two cortical regions and the mean axon diameter in the pathway connecting them. This gives us yet further insights into associations between microstructure and function – but remains unprincipled. In other words, to the best of our knowledge, there is no theory that links task performance to axon diameter or myelin thickness. Granted, we understand that action potentials are conducted more quickly in axons with larger diameters (Hursh, 1939), which has recently been explored with diffusion MRI and EEG by Horowitz et al. (2014), and that myelin further increases the conduction velocity (Waxman and Bennett, 1972; Waxman, 1980). Moreover, we understand that there is a theoretical optimal ratio of the outer diameter of the axon (axon + myelin) to the inner axon diameter, characterized by the "g-ratio" (Rushton, 1951), in that the conduction velocity is optimised when the g-ratio is 0.6. However, consider a thought experiment in which all axons happened to be of the same diameter across our cohort. In this special case, one may reasonably anticipate that deviations from the optimal g-ratio, and therefore (in our *Gedanken* that all axon diameters are the same), variance in our myelin metric might be expected to explain variance in conduction velocity, albeit non-linearly since both more and less myelin results in a departure from the optimal g-ratio. However, the likelihood of there being no intra- or inter-individual variance in axon diameter seems particularly low, especially in light of histological evidence (e.g. Aboitiz et al., 1992). If, as is more likely, there is variance in axon diameter, then the impact of any additional variance in myelin metrics may be less significant. It is, of course, important to consider the distance between nodes of Ranvier, which also impacts on conduction through the axon. To the best of our knowledge, there has been no MR-based approach that allows quantification of the inter-nodal distance, although it has been shown that inter-nodal distance correlates with axon diameter, at least in healthy rabbits (Hess and Young, 1952). Moreover, it is not just the mean but also the *distribution* of axon diameters that is likely important to consider. In myelinated axons, a diameter of 0.7 µm appears to optimize the energy per transmitted bit of information (Perge et al., 2009). The presence of large axons, whose diameter correlates with brain size between species in contrast to mean diameters of myelinated and unmyelinated axons (Wang, 2008; Wang et al., 2008) indicates they must support another type of function than small axons that motivate the extra energy required to use them.

This one example presupposes that conduction velocity is the primary target of interest. However, the conduction *time*, in other words, the time to propagate a signal from one region to another will also be a function of the length of the connection between them. This, alone, argues against a voxel-wise search for correlations between these microstructural metrics and function. Now, suppose that we have a forward model [e.g., based on cable theory (Tasaki and Matsumoto, 2002)] that allows us to predict conduction velocities from tractometry of relevant quantities and, through robust tractography, the length of a pathway, to enable prediction of conduction delays. What then? Is there a theory that indicates that the conduction delay should always be minimised? And if so, are

conduction delays "absolute" (so that one might expect correlation between conduction delay and task performance across a cohort), or "relative" (i.e., different individuals operate at overall different "rates" – so that we should not anticipate correlations across a cohort). Fields argues that what is important for optimal brain function is not that the conduction velocity is as high as possible, or that conduction delays are minimized, but that signals arriving from different parts of the brain arrive *in synchrony* (Stanford, 1987; Sugihara et al., 1993; Pajevic et al., 2014). Extrapolating, one might expect that deviations from synchrony may lead to deviations from optimality and therefore reduction in performance/function. However, deviation from synchrony does not necessarily mean deviation from optimality. Many EEG/MEG task elicit reductions in synchrony as well as increases, with the best known example being an increase in alpha synchrony when eyes are closed compared to open. More synchronous signals have lower entropy and suggest that increase in synchrony reflect *less* information processing (e.g. Anderson and Jakobsson, 2004; Qi et al., 2004). One possibility is that the conduction velocities of different fibre populations coming into an area of cortex should be tailored to maximise *the amount of information* received by the cortex, rather than synchrony *per se.*

The complexity of the problem of deriving the missing link in the "Tractometry" framework is further exacerbated by evidence for conduction velocity varying *along* white matter pathways (Baker and Stryker, 1990; Traub and Mendell, 1988); thus the tissue should be characterised at each point of every axon and used in the forward model. Recently, Tomassy et al. (1988) have also reported evidence for wide variation in myelin content along single axons, further exacerbating the problem of establishing the missing link between measurements of microstructure at the voxel scale to function. Thus, the ability to use microstructural data in a forward model to predict accurately individual differences in function in terms of differences in white matter structure seems a long way off.

CONCLUSION

In conclusion, while diffusion tensor imaging is a sensitive technique, and therefore yields useful information that *something* in the white matter might be different, it lacks the biological specificity needed to gain any further insight. This is acknowledged and many groups are developing complementary approaches to provide higher biological specificity. While promising, these have not yet enjoyed widespread dissemination nor, therefore, widespread adoption. There would be considerable change of behaviour needed for these metrics to REPLACE diffusion tensor imaging.

However, even if adopted into widespread practice, we would be only be able to relate individual differences in function to differences in specific white matter attributes in a phenomenological manner at best. A more principled approach that generates forward models, predicting function from structure, and states *a priori* exactly how and why a particular imaging metric (or combination thereof) will explain variance in a particular aspect of brain function, would fashion the deployment of advanced microstructural imaging in neuroscience into a more rigorous science. However, before this can happen, much more work is needed on the "hunt for the missing link."

ACKNOWLEDGMENTS

The authors wish to thank Dr Mark Drakesmith, Cardiff University for helpful comments on the manuscript. DKJ is also grateful to the Wellcome Trust, United Kingdom, for supporting this work through an Investigator Award.

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