White Matter Tractography and Diffusion-weighted Imaging

Advanced article

Article Contents

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Jean M Vettel, *U.S. Army Research Laboratory, Aberdeen, Maryland, USA*

Nicole Cooper, *U.S. Army Research Laboratory, Aberdeen, Maryland, USA*

Javier O Garcia, *U.S. Army Research Laboratory, Aberdeen, Maryland, USA*

Fang-Cheng Yeh, *University of Pittsburgh, Pittsburgh, Pennsylvania, USA*

Timothy D Verstynen, *Carnegie Mellon University, Pittsburgh, Pennsylvania, USA*

Human cognition requires coordinated communication across macroscopic brain networks. This coordination is fundamentally constrained by how populations of neurons are connected together. Understanding how structural connectivity between brain regions constrains or predicts variability within and between individuals is a pervasive topic of cutting edge research in neuroscience and the focus of multimillion dollar investments in brain research (e.g. Human Connectome Project, the White House's B.R.A.I.N initiative). Currently, diffusion-weighted imaging is the only noninvasive tool for studying the anatomical connectivity of macroscopic networks in the living human brain. Recent innovations in the acquisition and analysis of diffusion-weighted imaging provide an unprecedented opportunity to examine how an individual's unique structural wiring constrains brain function and cognition and how this unique wiring is sculpted by both genetics and experience across the lifespan.

Introduction

The human brain consists of approximately 86 billion neurons, with trillions of connections between individual neurons leading to a massively interconnected network (Azevedo *et al*., 2009). This network is composed of both gray matter (cell bodies) and white matter (axons), which together enable the brain's ability to decode, store and send information in support of human cognition and behaviour (Passingham *et al*., 2002). Consequently, coordinated communication across the brain is fundamentally constrained by patterns of interconnections and networks of specialised processing.

Gray matter is imaged and studied to understand the computational processing or neural representation of information. In humans, this research uses neuroimaging methods such as functional magnetic resonance imaging (fMRI), which tracks neuronal oxygen consumption during processing, or electroencephalography (EEG), which captures electrical activity generated when neurons pass electrochemical signals to each other. Analyses of gray matter activity identify what collections of neurons, or brain regions, are actively processing and communicating information during task performance. **See also**: **Cognitive Neuroscience**; **Cerebral Cortex**; **Brain Imaging: Observing Ongoing Neural Activity**; **History of Neuroscience**; **Neurons and Neural Networks: Computational Models**; **Brain Imaging: Localisation of Brain Functions**; **Oscillatory Neural Networks**

Serving a complementary role, white matter is imaged and studied to capture the trajectories of axons that relay communication between disparate brain regions. This type of research relies on diffusion-weighted imaging (DWI), also known as diffusion magnetic resonance imaging (dMRI), which uses an MRI (magnetic resonance imaging) scanner to measure the movement of water molecules in a small patch of imaged brain tissue, known as a voxel. Within each voxel, water diffusion is restricted in certain directions due to the tubular structure of axonal walls, leading to an anisotropic diffusion pattern. In contrast, if no axons are present in the voxel, water moves in all directions equally in isotropic diffusion (**Figure 1**). Analyses of white matter pathways identify the brain's structural connections that enable efficient and rapid communication among different brain regions. Currently, DWI is the only research tool for studying white

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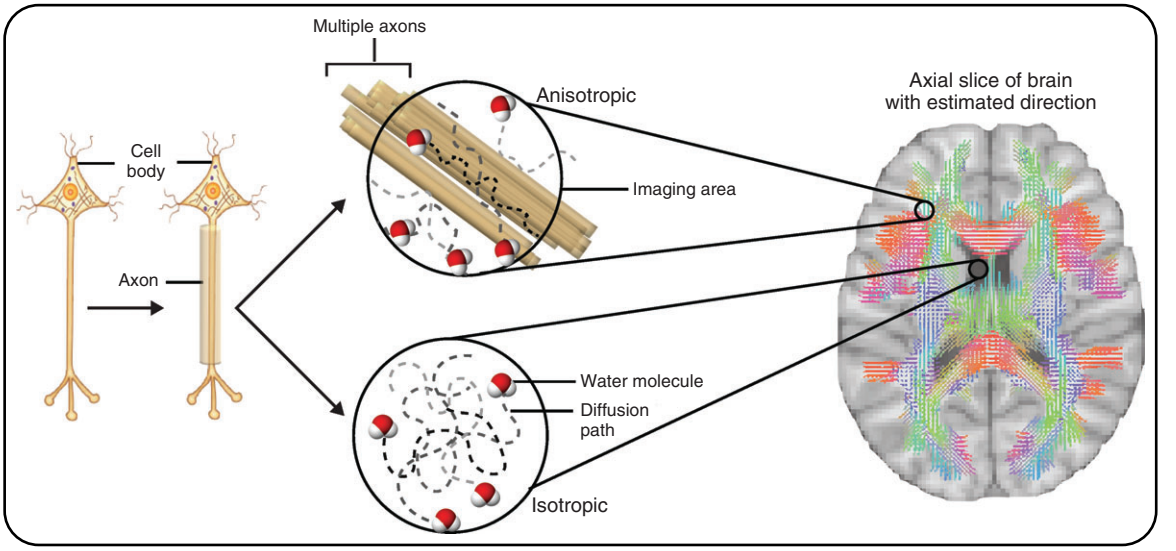

Figure 1 Principles of diffusion imaging. The axon of a neuron (represented as a cylinder) constrains the movement of water in small patch of imaged brain tissue, known as a voxel, using an MRI (magnetic resonance imaging) scanner, and this causes anisotropic water diffusion (top). When no axons are present, water moves equally in all directions in isotropic water diffusion (bottom).

matter pathways in the living human brain. **See also**: **Synaptic Integration**; **Neural Information Processing**; **Axon Guidance**; **Magnetic Resonance Imaging**

In this article, we provide a review of the current best practices and future directions of DWI research for newcomers to the methodology. The section titled 'DWI Acquisition and Analysis' discusses how water diffusion is measured, how water movement patterns are reconstructed to infer white matter integrity, and how fibre tractography algorithms use these reconstructed patterns to map structural networks. The section titled 'Application' highlights research that has applied innovative DWI analysis approaches to reveal new insights about brain–behaviour relationships. Finally, the section titled 'Pitfalls and Limitations' provides a succinct summary of current DWI limitations. 'References' for more advanced treatment of the introductory topics presented here are listed in the 'Further Readings' section.

DWI Acquisition and Analysis

Here, we first describe how diffusion images are acquired on an MRI scanner and then discuss how the most commonly used DWI scanning sequences trade off between the resolution of the diffusion image and the total scan time. Next, we provide the pros and cons of the two main classes of reconstruction approaches that quantify the pattern of water diffusion and estimate structural integrity in a voxel, and conclude with a description of two algorithmic approaches for tractography that rely on directional information from the voxels to estimate structural connectivity.

Measuring water diffusion

A DWI scanning sequence is an MRI protocol that defines how water diffusion is measured within a 3D brain volume. The movement of water in the brain can be hindered by the presence of axonal walls (**Figure 1**). DWI capitalises on this fact, assuming that strongly directional patterns of movement detected in the MR signal reflect characteristics of axons (or fibre tracts), such as axonal bundle size and orientation (Le Bihan and Johansen-Berg, 2012).

A DWI sequence uses a magnetic gradient to measure the movement of water molecules in a particular direction and for a fixed amount of time. At the beginning of the scan, the main magnetic field (the b0-field) aligns water molecules in the brain so that they are spinning like toy tops, all oriented in a common direction. During the scan itself, magnetic pulses occur that knock the water molecules off the main axis, tipping the toy tops off centre, and the MR signal captures the amount of water molecules that reorient themselves back in alignment with the main axis (the b0-field). Parameters of a DWI sequence modulate its sensitivity to the direction of movement and the time it takes the toy tops to reorient to the upright toy top position. Collectively, the MR signal in the resultant diffusion image records the displacement of the water molecules that travel along a specific direction.

There are two critical parameters in a DWI sequence that determine how the diffusion pattern will be sampled: the *b*-value (strength) and the *b*-vector (directions). The *b*-value is a time-by-distance measurement (s/mm^{-2}), and it reflects how well-directional movement can be resolved in the image. A higher *b*-value indicates a greater sensitivity to directional movement by increasing the diffusion time; that is, more diffusion time allows water molecules to collide with axonal barriers or traverse longer distances along the axis of the axon, but the longer intervals also lead to a decreased signal-to-noise ratio (Hagmann *et al.*, 2006). A *b*-value moderately sensitive to directional differences is 1500 s/mm^{-2}, whereas high values are typically over 3000 s/mm^{-2}. DWI sequences include a $b = 0$ (or b0) image where no directional gradient is applied, and these

images provide baseline activity that is compared with diffusion measured in images acquired with nonzero *b*-values. DWI sequences vary in what *b*-values are used to sample directional movement. The second critical parameter in a DWI sequence is the vector table. The *b*-vector is the direction of the diffusion gradient, and it captures what direction of water movement will be measured in the image. The range of possible directions and *b*-values sampled is called Q-space. Among different DWI sequences, the number of sampling directions ranges from only six directions to hundreds of directions.

Across DWI sequences described in the literature, there are currently three general classes of diffusion sampling schemes that vary in what *b*-values and *b*-vectors they use. *Single-shell Schemes* sample a set of directions at the same *b*-value, and the directions are usually equally distributed on a sphere to maximise sensitivity to diffusion direction. *Multishell Schemes* improve upon single-shell schemes by combining multiple single-shell schemes acquired with different *b*-values. Finally, *Grid Schemes* sample a specific grid arrangement of *b*-vectors and *b*-values that have a variety of directions and strengths sampled under a maximum *b*-value. Across all of the schemes, the end product of a DWI sequence is a collection of diffusion images (3D brain volumes), and the MR signal represented in each brain volume captures the diffusion time (*b*-value) and amount of water movement in each voxel for direction (*b*-vector).

Each of the diffusion-sampling schemes can be configured to trade off between the resolution of the diffusion image and total scan time (Hagmann *et al*., 2006). A DWI sequence with coarse resolution of just a few directions can be acquired in just a few minutes, whereas a DWI sequence with fine resolution of many directions can take 30–45 min to acquire. The best trade-off must be determined based on what structural resolution is needed to investigate the experimental hypotheses for a particular study. The three most commonly used diffusion sequences rely on different sampling schemes: diffusion tensor imaging (DTI) and high-angular resolution diffusion imaging (HARDI) typically employ a single-shell scheme, whereas diffusion spectrum imaging (DSI) relies on a grid scheme.

The most prevalent sequence used in the literature is DTI, and the bulk of existing knowledge on brain structure has employed this approach. DTI's core advantage is its short scan length, averaging 4–8 min with modern multiband imaging protocols, since typical DTI sequences use only a few dozen directions (minimum of 6 required); however, DTI's core disadvantage arises from its inability to detect crossing fibre tracts (Van *et al*., 2010). Brain modelling efforts estimate that crossing fibres are present in approximately 63–90% of all voxels (Jeurissen *et al*., 2013), indicating a strong limitation when using DTI to examine structural integrity in whole-brain analyses.

Both HARDI and DSI improve the resolution of directional water movement by sampling more diffusion directions, typically several hundred, and this greatly improves the resolution in the MR signal. However, this resolution occurs at a trade-off with a longer scan time, often ranging from 12 to 35 min, and a longer scan time increases the risk for participant head movement and discomfort during the scan. Although the difference between HARDI and DSI is tightly tied to the physics of the image acquisition, the general intuition is that DSI samples directions in a different spatial pattern than HARDI. In addition, DSI employs a set of different *b*-values whereas traditional HARDI uses the same *b*-value (Tuch *et al*., 2002). These differences enable DSI images to detect multiple speeds of diffusion and provide a richer characterisation of the distribution of water diffusion in all possible directions. This increased resolution from DSI comes at a cost: the sequence takes more time to acquire, artefacts are more difficult to remove, fewer analysis methods have been developed for it, and sophisticated setup is required on the MRI scanner. However, more important than their differences, both HARDI and DSI can capture crossing fibres to overcome the core limitation in DTI.

Reconstructing diffusion patterns within a voxel

The diffusion images from a DWI scanning sequence contain a scalar value that represents the overall MR signal intensity in each voxel (the amount of total water movement following the magnetic pulse). The next step in DWI analysis uses reconstruction algorithms to convert the raw MR signal measured in different directions (*b*-vector) to an estimate of the pattern of water diffusion within each voxel (**Figure 2**). Most reconstruction methods available today can be categorised into two classes: *model-based methods* or *model-free methods*. Here, we will first describe model-based methods and their most common set of voxel-based structural metrics (FA (fractional anisotropy), AD (axial diffusivity), RD (radial diffusivity) and MD (mean diffusivity)) and then we will discuss model-free methods and their prevalent voxel-based structural metrics (QA (quantitative anisotropy) and ISO (isotropic water signal)).

As one of their core advantages, model-based methods (**Figure 2**, centre row) can reconstruct patterns of water movement in each voxel from DWI sequences with minimal directions, such as DTI. However, this reconstruction approach requires strong assumptions about the underlying diffusion distribution. This approach is susceptible to error when the model's assumptions about water diffusion are violated (Alexander *et al*., 2002), such as voxels where there are complex fibre crossings. Once the model is fit for each voxel, structural metrics are derived to characterise the white matter integrity in the voxel. FA is the most commonly used white matter measure from DTI. An FA value of 1 indicates water that moves in a perfect line (anisotropic), as would be the case if all water is contained in a single set of axons. An FA value of 0 indicates perfectly spherical (isotropic) diffusion, suggesting that no axon restricts the movement of the water molecules (**Figure 1**). Larger FA values are assumed to reflect greater density and volume of underlying white matter.

Importantly, there are multiple ways that FA may change, and these changes are quantified in four voxel-based metrics of white matter that are prominent in the current literature: FA, AD, RD and MD. Differences in underlying cellular microstructure structure may be reflected in diffusion along the principal axon direction, called AD, or may manifest in diffusivity in the orthogonal plane to AD, called RD. Structural changes may also arise in the overall degree of diffusivity, called MD, which is independent of the overall shape of the underlying diffusion pattern. Due to the

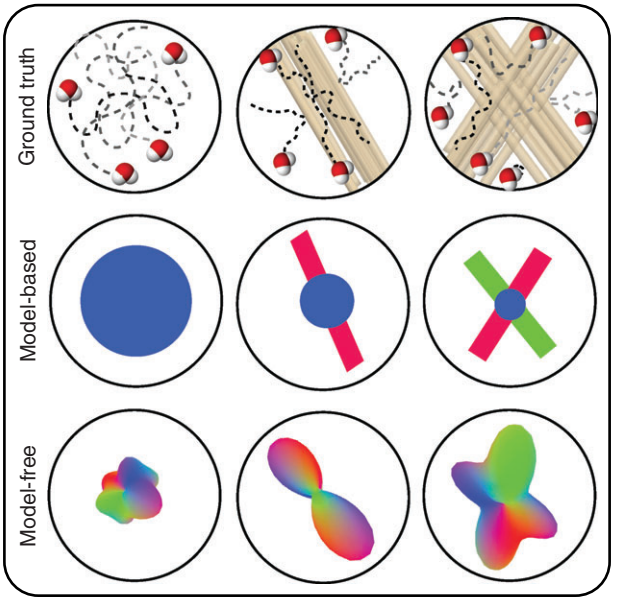

Figure 2 Model-based and model-free estimations of water diffusion. Most imaged voxels in DWI (diffusion-weighted imaging) belong to one of the three categories: no axons present (left column), axons aligned in one primary direction (middle column), or crossing axons oriented in different directions (right column). The first row depicts possible patterns of water diffusion, whereas the second and third rows illustrate two types of reconstruction methods and how they estimate the corresponding diffusion pattern. In row 2, a model-based method known as the ball-and-stick method estimates the overall magnitude of diffusion (represented as a ball) and the fibre direction (represented as oriented sticks). In row 3, a model-free method estimates an orientation distribution function (ODF), and the model captures multiple peaks in the empirical distribution of the water diffusion (represented by the ellipsoids) when crossing fibres are present.

inability to resolve crossing fibre tracts in traditional approaches, there are other advanced model-based methods available, such as the ball-and-stick model (Behrens *et al*., 2003), that improve the description of complicated white matter structures.

In contrast to model-based approaches, model-free methods (**Figure 2**, bottom row) directly estimate the empirical distribution of water diffusion, rather than fit to an assumed distribution. One early model-free method was the DSI reconstruction method (developed in conjunction with the DSI imaging sequence). This approach uses the probability of water diffusion in all directions in 3D space to estimate an object in each voxel called an orientation distribution function (ODF; see bottom row of **Figure 2**). Since a diffusion structure is not assumed, there is little risk of violating the model and less risk for overfitting. However, the downside of model-free methods is that they often need more samples, which means a longer acquisition time. Fortunately, recent developments of simultaneous multiple slice acquisition (i.e. multiband imaging; Feinberg and Setsompop, 2013) have dramatically shortened the required imaging time, thereby reducing the drawback of model-free reconstruction approaches.

In model-free reconstruction methods, the ODF provides metrics of structural integrity in the voxel. The two most common metrics are QA, characterising the peaks of directional diffusion, and the ISO, quantifying the background diffusion signal. As its core advantage, however, the ODF identifies multiple peaks in its empirical distribution of diffusion, revealing the presence of axons with crossing trajectories (see bottom row of **Figure 2**). Consequently, the ODF overcomes the core limitation in the traditional model-based analyses of DTI data that are prominent in the early DWI literature. Using model-free methods, voxel-based metrics can reveal intra- or inter-subject differences in any brain region, and they provide a versatile and sensitive measure to study voxel-based metrics of axonal structure.

Of course, not all reconstruction approaches fall cleanly in this model-based versus model-free dichotomy, including the increasingly popular constrained spherical deconvolution (CSD) approach (Tournier *et al*., 2004). Similar to model-based methods, CSD assumes an underlying distribution for voxels with a known fibre population, but similar to model-free methods, CSD produces an ODF for the fibre distribution (but typically termed fibre orientation distribution, FOD). The advantage of hybrid approaches such as CSD is the intersection of the primary benefits of both model-based and model-free methods – requiring fewer diffusion orientations in the DWI sequence but still estimating a sharp, precise ODF. However, their disadvantage is also the combination of the flaws from both, including sensitivity to model violations and outliers that lead to a higher likelihood of identifying false fibres.

Tracking fibre pathways across voxels

Once the fibre directions are reconstructed within a voxel (**Figure 2**), fibre tractography approaches can be applied to map the trajectories of axon bundles. In general, tracking methods can be categorised into two classes of algorithms: *deterministic* and *probabilistic*. These two approaches have different aims, and the pros and cons of each are discussed in this section.

Deterministic tractography uses a seed-based approach to traverse through imaged voxels and delineate the path of major fibre pathways (Mori and van Zijl, 2002). Starting with a seed point in the white matter, a deterministic algorithm traverses along local fibre directions in a recursive, step-by-step process until a set of termination criteria are met. Various combinations of termination criteria can be applied, such as an angular threshold (i.e. not allowing the algorithm to make too sharp of a turn), an anisotropy threshold (i.e. threshold by which a voxel is determined to be in gray matter vs white matter) or anatomical masks (i.e. explicit declarations of gray matter vs white matter voxels). At the end of the tracking process, the final data object is a streamline that reflects the most likely trajectory of a bundled fibre pathway. Critically, multiple iterations of a deterministic algorithm that use the same parameters in the mapping process will yield the same fibre tractography output.

Probabilistic tractography also uses a seed-based approach to traverse through white matter pathways, but instead of delineating the specific trajectory of individual fibre bundles, these algorithms estimate a probability of connectedness between the specified seed voxel and all other voxels (Behrens *et al*., 2007). This procedure yields a different result when the algorithm is run from the same seed voxel because the progression along potential pathways is randomised. The end result of probabilistic tracking is a map of voxel weights that indicate the likelihood

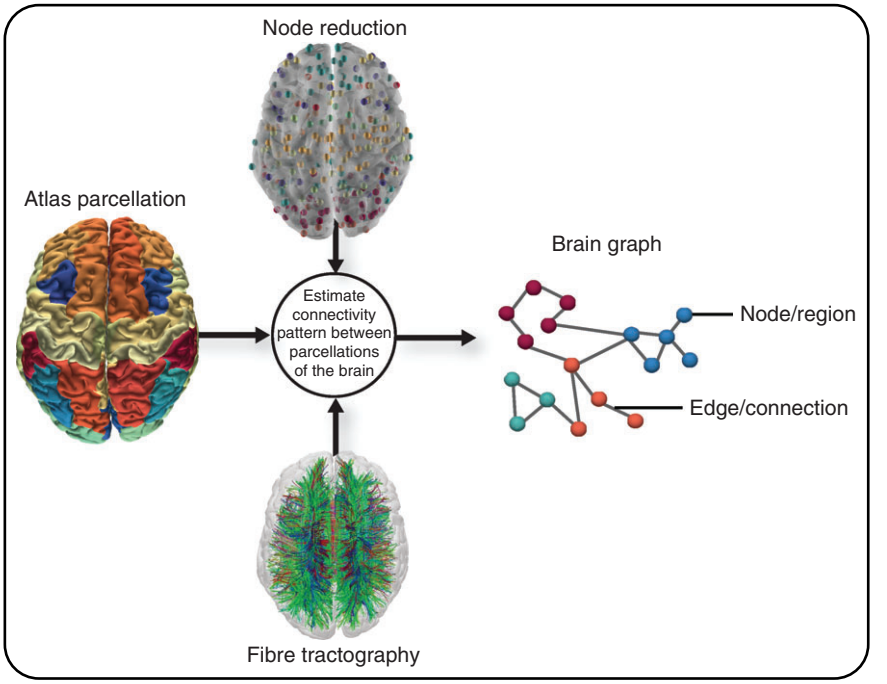

Figure 3 Estimating brain networks. To examine brain network properties, gray matter is parcellated into distinct brain regions using a brain atlas (left). These regions then serve as the nodes of a graph (middle top) and the DWI structural connections, or fibre tractography, as edges (middle bottom) in a brain graph (right) that represents a brain network. The resultant brain graph can be used to investigate how structural connectivity relates to individual differences in function and performance.

of connectedness between a seed region and all other voxels. This distribution can be analysed as the estimated strength of connectivity.

Fibre tractography data is primarily used to characterise end-to-end structural connectivity between pairs of brain regions, and these estimates have been productively employed to study brain networks, often called the human connectome (Bullmore and Sporns, 2009). Here, a brain network is formulated as a graph to leverage analytic approaches from network science (Bassett and Sporns, 2017). Gray matter voxels are parcellated into brain regions that serve as the nodes of the graph, and estimated white matter tractography between these regions serves as the edges (**Figure 3**). These graphs delineate what brain regions have structural connectivity that enables direct communication between them, providing an immensely insightful framework to examine when structural connectivity can account for or predict functional network activity and/or variability in human behaviour.

Application

By allowing for a noninvasive measurement of structural connectivity, DWI provides unprecedented opportunities to examine how the functions of neural networks, and subsequent behaviours, are constrained by the peculiarities of how an individual brain is wired together (Verstynen, 2015). Based on space constraints, we highlight just two interesting applications of DWI to study the role of genetics and learning on the wiring of the brain, demonstrating DWI's potential to address questions of how nature and nurture influence the human connectome. Inquisitive readers can explore other interesting DWI applications. Some of our favourites highlight DWI's utility to understand brain development in paediatric and adolescent populations (Yoshida *et al*., 2013), identify microstructural changes underlying diseases such as Alzheimer (Sexton *et al*., 2011) and schizophrenia (Ellison-Wright and Bullmore, 2009) and develop novel clinical approaches for neurosurgery (Fernandez-Miranda *et al*., 2012) and brain stimulation treatments (Muldoon *et al*., 2016; Bortoletto *et al*., 2015). **See also**: **On Human Brain Networks in Health and Disease**; **Philosophy of Neuroscience**

Nature: how does genetics contribute to the wiring of the brain?

Diffusion imaging provides an informative lens to investigate how genetics (nature) contributes to the organisation of the brain's connections. Studies have used FA from DTI (**Figure 4**) to show that there is a high degree of heritability in the integrity of white matter pathways in twins (Chiang *et al*., 2009; Pfefferbaum *et al*., 2001), akin to the strong heritability of gray matter volume in twins (Schmitt *et al*., 2007). This means that a high degree of white matter integrity in one twin predicts the same high degree in the other. However, this research also revealed that heritability was highly variable across different regions of the brain, with weaker genetic influence in less anisotropic areas (Chiang *et al*., 2008).

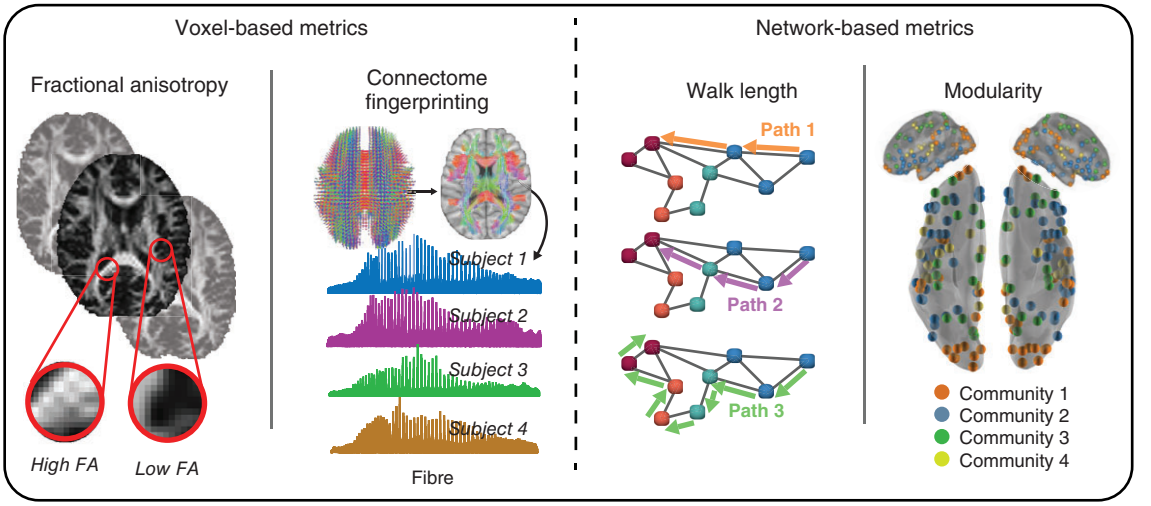

Figure 4 Voxel-based and network-based metrics of structural integrity. On the left, two voxel-based metrics are depicted: voxels with high fractional anisotropy (FA) reflect greater density in large, primary fibres, whereas a local connectome fingerprint also captures variability in crossing fibres, creating a neural signature of an individual's unique structural connectivity. On the right, two network-based metrics are depicted: a measure known as walk length defines the number of nodes that are traversed on the path from an origin to a destination node, whereas a measure known as modularity identifies communities based on the density of structural connections.

A more sensitive measure of local white matter integrity has been proposed called the local connectome (Yeh *et al*., 2015). Unlike FA, which captures only the primary direction of water diffusion in a voxel, the local connectome characterises the orientation and integrity of multiple fibres within a voxel. This allows for a more complex representation of local white matter along a pathway. The local connectome fingerprint is an ordered vector of hundreds of thousands of individual fibres throughout the brain (**Figure 4**) and is highly sensitive to unique patterns of local white matter architecture. In fact, local connectome fingerprints can classify whether two images come from the same person with over 99.9% accuracy (Yeh *et al*., 2016).

The local connectome also reveals genetic contributions to structural connectivity. By comparing the structural similarity between twins and siblings relative to unrelated individuals, a fingerprint analysis revealed a robust, although limited, role for genetic influence on structural connections. Results demonstrated approximately 12% similarity between identical/monozygotic twins and roughly 5% similarity between fraternal/dizygotic twins and nontwin siblings (Yeh *et al*., 2016). Thus, while heritability may be high in particular pathways, the brain's global connectivity is only moderately determined by genetics. **See also**: **Identical Twins Reared Apart**

Nurture: how does learning contribute to the wiring of the brain?

Based on the value placed on education and professional training across the lifespan, one captivating and persistent question in neuroscience centres on the mechanisms underlying neuroplasticity. Research over the last decade has confirmed that DWI can capture structural changes after both short-term learning and long-term expertise acquisition, marking one of its dominant applications in healthy subject populations.

One productive experimental design in this research area combines a training paradigm with pre- and post-training DWI scans. In a landmark study that largely inspired this DWI application, a group of adults underwent a 6-week protocol to learn a new visuo-motor skill, juggling, and they demonstrated training-related increases in FA (Scholz *et al*., 2009). A similar study found FA changes following a 6-week training for a complex balancing task (Taubert *et al*., 2010). Importantly, individual differences in learning are reflected in the amount of structural change measured (Johansen-Berg, 2010; Tomassini *et al*., 2011). These results confirm that FA can capture plasticity in large primary axon fibres at short timescales and reflect individual differences.

Training paradigms have also combined tractography with analytic tools from network science to further characterise the properties of learning-induced structural change. In one study, participants learned a new visuo-motor task, similar to playing a set of piano arpeggios, over the course of 6 weeks. Individual differences in learning rate were reflected in structural wiring among visual regions and between visual and motor cortices (Kahn *et al*., 2016). This analysis used tractography to create a structural network and employed a method from network science, walk strength, to examine indirect connections. A walk is defined as a path from one node in the graph (brain region) to another (**Figure 4**). This study found that as walk length increased, individual differences in motor–visual connectivity were increasingly correlated with learning rate. By combining tractography and network science methods, these results suggest that DWI can identify a role for physically extended sets of polysynaptic structural connections between motor and visual cortices that support the acquisition of a visuo-motor skill.

Research has also combined tractography with network science to study the development of expertise, examining how learning changes structural connectivity over long timescales. Instead of

pre- and post-training DWI scans, this research compares a group of experts to controls. In this study, collegiate baseball players discriminated simulated baseball pitches in a scanning session that collected functional (fMRI/EEG) and structural (DWI) data, and a set of age-matched controls did the same (Muraskin *et al*., 2017). After using tractography to create a structural connectome, a modularity analysis divided the whole brain into five communities, where a community was defined by dense connections among its members but sparse connections to brain regions outside of the community (**Figure 4**). Compared with controls, experts showed stronger connectivity between two of the modules that linked motor and frontal regions with cerebellar regions, and interestingly, the regions that showed expertise-related structural differences also showed expertise-related functional differences. Thus, DWI not only reveals plasticity from long-term expertise development, but its combination with functional imaging can also reveal structure–function couplings that expand our understanding of organisational principles of the human brain. **See also**: **Cortical Plasticity: Use-dependent Remodelling**

Pitfalls and Limitations

Although DWI has demonstrated promise as a research and clinical tool, proper applications of the method can only occur with a realistic understanding of its limitations. We provide a review of three dominant challenges in the field. First, the current tractography algorithms rely on local decisions when traversing from one voxel to the next, often with no prior assumptions about the direction of underlying white matter pathways. As a result, these algorithms will frequently make incorrect turns, leading to the identification of false fibre pathways (Daducci *et al*., 2016; Reveley *et al*., 2015). Second, no reliable methods to remove noise from head motion and physiology exist (Le Bihan and Johansen-Berg, 2012). This can be particularly problematic when looking at individual differences in white matter architecture in cases where a subject-specific variable (e.g. obesity) is correlated with a noise source (e.g. head motion). Finally, it is not well understood how anisotropy in the DWI signal relates to the anatomical components of the underlying biological tissue (e.g. axonal fibre integrity, myelin sheath structure and glia content), and this lack of knowledge limits the interpretation of differences or changes in the DWI signal itself. Ongoing efforts to validate methods to image and reconstruct the diffusivity signal employ animal models (Budde *et al*., 2011) and phantom devices of artificial tissue (Fillard *et al*., 2011; Daducci *et al*., 2014), but analysis in biological tissue tends to produce different results than these two surrogate models (Lichenstein *et al*., 2016). Thus, continued research to overcome DWI limitations will be critical to improve the methods and thereby advance our understanding of structural connectivity and its relation to individual differences.

Conclusion

Research using DWI has fostered widespread excitement about tackling fundamental questions concerning how structural connectivity may constrain or explain intra- and inter-subject variability in human behaviour. DWI sequences require experimenters to determine a trade off between resolution and time, and interpretation of DWI differences must take these technical limitations into consideration. The bulk of existing literature has used DTI to study the larger fibre bundles in the brain, but recent advancements in image acquisition and analysis have revealed structural differences at a finer resolution. Research using these newer methods extend and complement the existing DTI findings, and recent research has made significant progress to better understand the interaction of genetics and learning on the wiring in the brain. Continued efforts to combine DWI with sophisticated analytic tools, such as those from network science, will expand our ability to identify predictive patterns in the DWI signal. While our existing knowledge of structure–function–behaviour relationships is captivating, the imaging technique is likely in its infancy for its impact on our knowledge of the human brain. The field is ripe with opportunity and awaiting innovations from multidisciplinary approaches.

Glossary

AD (axial diffusivity) One of the four common metrics of structural integrity derived from DTI data, and it captures the amount of diffusion along the principal axon direction within a voxel.

Anisotropic diffusion Water movement that is restricted in certain directions, and in DWI imaging, this restriction is interpreted as the presence of axonal walls in the imaged voxel.

Deterministic tractography One of the two types of algorithms that use voxel-based estimates of diffusion direction to estimate the path of major fibre pathways that connect brain regions, and deterministic algorithms will always yield the same result if run with the same tracking parameters.

DSI (diffusion spectrum imaging) A DWI imaging sequence that often employs a grid scheme that samples hundreds of directions at multiple *b*-values, and the same name designates a model-free reconstruction method.

DTI (diffusion tensor imaging) A DWI imaging sequence relies on a single-shell scheme to sample a small set of directions (minimum of 6) at the same *b*-value; this is the original and most prominent DWI method, but it is unable to detect crossing fibres that strongly limits its use in whole-brain structural analyses.

DWI (diffusion-weighted imaging) A noninvasive neuroimaging method that measures the movement of water molecules and is used in reconstruction algorithms to estimate the direction of structural connections between brain regions.

FA (fractional anisotropy) The most common metric of structural integrity derived from DTI data, and a value of 0 means isotropic diffusion (interpreted as no axons present) and a value of 1 means anisotropic diffusion (interpreted as axons aligned in a primary direction) within a voxel.

Grid schemes One of the three general classes of diffusion imaging schemes that trade off sensitivity to directional water movement and total DWI scan time, and this class improves

resolution of directional movement by sampling a grid arrangement of directions and *b*-values.

HARDI (high-angular resolution diffusion imaging) A diffusion sampling scheme with hundreds of directions typically sampled at the same *b*-value.

ISO (isotropic water signal) A metric of structural integrity derived from model-free reconstruction methods, and it quantifies the background diffusion signal within a voxel.

Isotropic diffusion Water movement is equal in all directions, and in DWI imaging, this unrestricted movement is interpreted as the absence of axonal walls in the imaged voxel.

MD (mean diffusivity) One of the four common metrics of structural integrity derived from DTI data, and it captures the overall degree of diffusivity that is independent of the overall shape/direction of the underlying diffusion pattern within a voxel.

MRI (magnetic resonance imaging) A scanner that uses magnetic gradients to image biological tissue in awake, behaving humans without the use of any chemical agents.

Multishell schemes One of the three general classes of diffusion-imaging schemes that trade off sensitivity to directional water movement and total DWI scan time, and this class improves resolution of directional movement by sampling several single-shell schemes with different *b*-values.

ODF (orientation distribution function) A metric of structural integrity derived from model-free reconstruction methods, and it captures the probability of water movement in all directions within a voxel.

Probabilistic tractography One of the two types of algorithms that use voxel-based estimates of diffusion direction to estimate the path of major fibre pathways that connect brain regions, and probabilistic algorithms can yield different mapping results since the progression along potential pathways is randomised on each iteration of the tracking algorithm.

QA (quantitative anisotropy) A metric of structural integrity derived from model-free reconstruction methods, and it captures the peaks of directional diffusion within a voxel.

RD (radial diffusivity) One of the four common metrics of structural integrity derived from DTI data, and it captures the amount of diffusion in the direction orthogonal to the principal axon direction measured by AD within a voxel.

Single-shell schemes One of the three general classes of diffusion imaging schemes that trade off sensitivity to directional water movement and total DWI scan time, and this class samples a set of directions, which are equally distributed on a sphere, at the same *b*-value.

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