

How Form Constrains Function in the Human Brain

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Abstract

In neural systems, form and function are intimately linked; the communication dynamics across networked areas depends on the organization and integrity of the connections between them (i.e., axons and tracts). With the growth of diffusion-weighted imaging (DWI) and fiber tractography tools over the past decade, it has become possible to visualize the physical architecture of the human brain at an unprecedented resolution. This information has provided the first glimpses into the component circuitry supporting cognition, presenting a unique opportunity for cognitive neuroscientists. For the first time we can visualize the connections in the living brain, allowing us to measure individual differences in anatomical connectivity, relate this connectivity to brain function, and gain insights into the link between white matter architecture and behavior. In many ways, this technology is still in its infancy and its full potential has not yet been realized. Here, I outline the importance of understanding neuroanatomical connectivity as a hard constraint on neural computation. Beginning with an overview of the typical patterns of connectivity seen in neural systems, I go on to show how current neuroimaging tools can visualize several different types of connectivity in the brain. By highlighting recent findings showing how neuroanatomical organization and brain function are related during cognitive tasks, I emphasize the utility that structural brain mapping approaches can have for the broader social and behavioral sciences.

BACKGROUND

Two decades ago, in a commentary to the journal *Nature*, Francis Crick and Edward Jones threw down the proverbial gauntlet to the human neuroscience community. Highlighting the work being done to map the physical connections in the macaque brain, Crick and Jones lamented that the lack of such methods in humans fundamentally limits how much we can truly understand about the brain:

“Without [knowing anatomical connectivity] there is little hope of understanding how our brains work in the crudest way.” (*Crick & Jones, 1993*).

Indeed, the organization of white matter pathways within the brain defines the essential wiring diagram that acts as a hard constraint on neural processing (Felleman & Van Essen, 1991; Passingham, Stephan, & Kötter, 2002). Without the knowledge of how the different brain areas are connected together, it is impossible to truly understand how specific neural computations can lead to specific cognitive processes.

However, magnetic resonance (MR) physics was already working on a technology that would end up answering their challenge to map the physical connections *in vivo*. In fact, 3 years earlier, Michael Moseley and colleagues had published a series of studies showing how a new form of MRI (magnetic resonance imaging) called *diffusion-weighted imaging* (DWI; Bihan *et al.*, 1985) could be used to detect directionally dependent water diffusion in the cat brain (Moseley *et al.*, 1990). Subsequent work would go on to show that this water is constrained mostly within axons and could be used as a proxy to describe the geometry of underlying white matter pathways. Thus, by the time of Crick and Jones's commentary in *Nature*, physicists and radiologists were already working on methods to noninvasively capture the structural connections in the brain.

Over the past 20 years, DWI has grown to become arguably one of the most valuable tools in cognitive neuroscience. The increased popularity of DWI methods is most evident in the steadily increasing number of publications reporting DWI results over the past decade. According to Pubmed, the number of publications reporting on results using diffusion tensor imaging (DTI), the most popular DWI technique in cognitive neuroscience, has risen from 138 publications in 2003 to 1590 publications in 2013.

This accelerated adoption of DWI has led to a number of significant discoveries over the past decade. For example, DWI has been used to identify novel white matter pathways within human brain, such as the connectivity of the middle longitudinal fasciculus (Makris *et al.*, 2009; Wang *et al.*, 2012) and the existence of the frontal aslant tract (Catani *et al.*, 2012, 2013). When integrated with functional magnetic resonance imaging (fMRI), DWI is being used to map the human connectome and reveal fundamental properties of neural connectivity in our brains (Bullmore & Sporns, 2009). Clinically, DWI represents one of the most promising approaches to identifying diffuse axonal injury from head trauma such as concussion and traumatic brain injury (TBI; (Huisman *et al.*, 2004)) mainly due to its sensitivity to the directional motion of water, which is disturbed by axonal injury, rather than the density of water, which is measured by typical clinical MRI scans and not affected by axonal injury.

The most common way that DWI is used in cognitive neuroscience is in the evaluation of the microstructural integrity of underlying white matter pathways through measures such as fractional anisotropy (FA). These measures

provide local estimates of the diffusion of water molecules at fixed points in space, called *voxels* (short for “volumetric pixels” and reflect the spatial sampling of MRI-based imaging methods), with more restrictive water diffusion in a specific direction being used as a proxy for the health and integrity of underlying white matter. As a measure of integrity, these metrics appear to provide a good index of the health of axons and myelin when examined in animal studies (Budde, Xie, Cross, & Song, 2009; Klawiter *et al.*, 2011; Song *et al.*, 2005). Cross-sectional differences in FA are associated with group differences in physical health (Bolzenius *et al.*, 2013; Mueller *et al.*, 2011; Stanek *et al.*, 2011; Verstynen, Weinstein, *et al.*, 2012; Verstynen *et al.*, 2013), neurological pathologies (Bihan *et al.*, 2001; Dyrba *et al.*, 2013), and even broader social factors such as socioeconomic status (Gianaros, Marsland, Sheu, Erickson, & Verstynen, 2012). But these associations with behavior are not just limited to predicting differences across individuals. Longitudinal changes in FA have been associated with learning (Keller & Just, 2009; Sampaio-Baptista *et al.*, 2013; Scholz, Klein, Behrens, & Johansen-Berg, 2009). These promising findings, along with the relative conceptual and methodological ease of voxel-wise measures such as FA, these white matter integrity measures are quite appealing for a wide variety of applications in the social and behavioral sciences.

However, DWI allows for more than just a local estimate of white matter integrity. With the increased application of tractography methods to DWI data (for a review of tractography, see Jbabdi & Johansen-Berg, 2011), it has become possible to map a subset of the physical point-to-point connections in the human brain (Figure 1). This connectivity information is equally important to the behavioral scientist as integrity measures such as FA, if not more so. This is because connectivity analysis allows for visualization of the component circuitry of neural systems that regulate a vast number of cognitive processes (Passingham *et al.*, 2002). As tractography methods continue to improve, they will be used to ask some of the most fundamental questions about the human brain and its relation to cognition. In what follows, I highlight some of the most promising avenues of this structural mapping method for understanding the biological basis of human cognition.

STRUCTURAL CONNECTIVITY AND NEURAL COMPUTATION

In order to conceptualize the utility of neuroanatomical mapping approaches for social and behavioral sciences, it is important to understand that the physical wiring of brain circuits is a hard (i.e., nonmodifiable) constraint on how information flows through the network. There are two specific ways that anatomical connectivity can constrain function. First, the organization of connections between sets of neurons will determine the flow of information

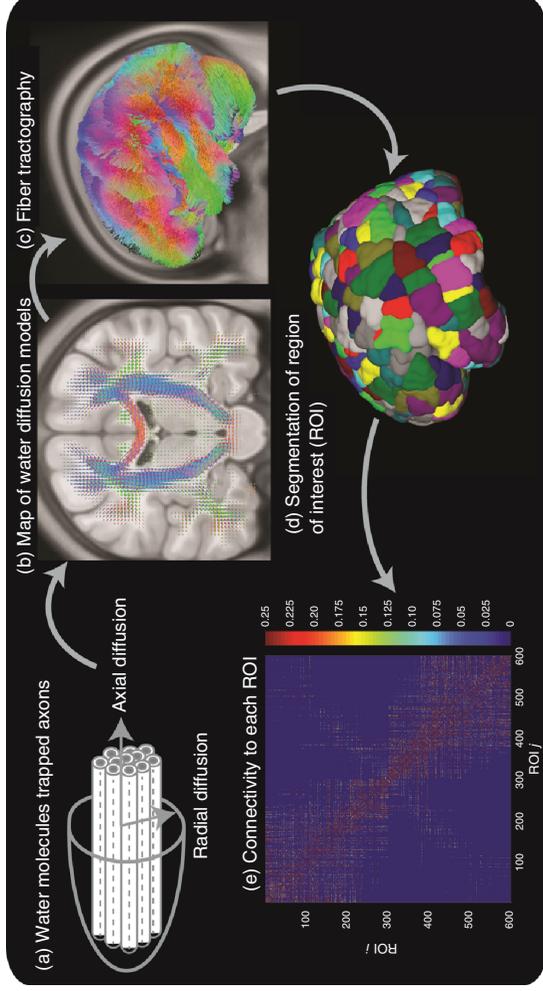


Figure 1 An outline of a typical fiber tractography analysis. (a) Water trapped in axons diffuses primarily along the length of the axon (axial diffusivity) and less so in the orthogonal direction (radial diffusivity). (b) This directionally dependent diffusion signal is measured with DWI and modeled at each volumetric pixel, called a *voxel*. The map shows a distribution of orientation distribution functions in MNI template space (Yeh & Tseng, 2011). (c) The whole-brain map of water diffusion at each voxel is then explored using automated tractography algorithms to produce a map of connections throughout the brain. (d) Brain areas can then be segmented into a set of regions of interest (ROI) using a number of approaches (anatomical segmentation is shown here). (e) The connectivity between each ROI pair is then estimated, providing a structural connectivity map.

across the circuit and define the tuning properties (e.g., directional tuning, receptive fields) of connected units. Second, the integrity of the connections between two nodes can influence the strength of information transfer within the circuit. Here, I focus on the utility of organizational patterns in neural circuits to explain the functional processing related to cognition.

Before going into too much detail about the computational utility of anatomical connectivity, it is important to first know the general classes of connections that are seen in the brain. Work in animal systems has revealed several common connection patterns seen in neural circuits (for an excellent review of this work, see Thivierge & Marcus, 2007). These patterns include the following:

Convergence. Many-to-one connections (e.g., corticostriatal systems)

Divergence. One-to-many-connections (e.g., pedunculopontine efferents)

Reciprocity. Symmetrically looped connections (e.g., thalamicocortical loops)

Lateral Connectivity. Mutual connections within a layer (e.g., retinal ganglion cells)

Topography. Point-to-point mappings that preserve spatial and functional arrangements (e.g., retinotopy of projections from the lateral geniculate nucleus to the primary visual cortex).

Each of these connectivity patterns contributes to a specific class of computations (Figure 2). For example, neural network models have shown how convergent inputs allow for networks to perform information integration from multiple inputs, such as what happens during sensory integration across sensory modalities (Denève, Duhamel, & Pouget, 2007; Deneve, Latham, & Pouget, 2001). On the other hand, lateral connectivity within a layer allows for stability in local computations (Deneve, Latham, & Pouget, 1999; Deneve, Pouget, & Latham, 1999; Ma, Beck, Latham, & Pouget, 2006) and provides a physical architecture that allows for adaptive plasticity within a local circuit (Verstynen & Sabes, 2011; Wu, Amari, & Nakahara, 2002; Wu & Amari, 2005; Wu, Chen, Niranjana, & Amari, 2003). Finally, topography constrains the way that information is represented as it passes from one region to the next and thus defines the representational structure of the system (Jbabdi, Sotiropoulos, & Behrens, 2013). The complete class of functional computations that are constrained by each connectivity pattern is still unknown. Nor is it certain that this is even an exhaustive list of connectivity patterns (see also Thivierge & Marcus, 2007). What is certain, however, is that the properties of network computations are fundamentally limited by how the system is wired together (Passingham *et al.*, 2002).

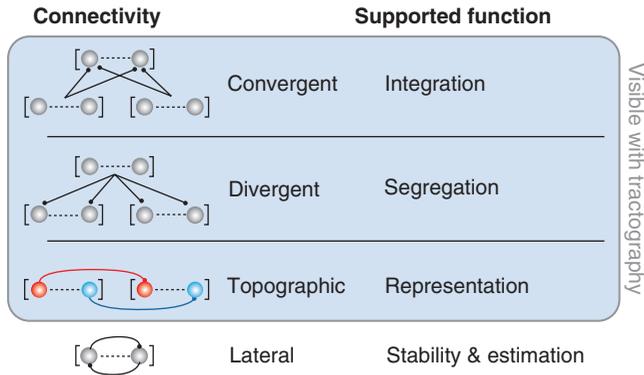


Figure 2 An example of some of the most common connectivity patterns seen in neural circuits [see Thivierge and Marcus (2007) for a more detailed description of these patterns]. The patterns highlighted in the box show patterns that can be detected using DWI methods.

With the advent of DWI-based fiber tractography algorithms, it has become possible to virtually map the underlying white matter pathways in the living human brain and capture some of these connectivity patterns (for a complete review of DWI, see Hagmann *et al.*, 2006). These algorithms use the geometry of water diffusion in the brain that is measured with DWI and iteratively map the likelihood, either probabilistically or deterministically, that any two voxels in the brain are connected.

While these tools have shown great promise in mapping underlying white matter pathways, current DWI-based methods can only resolve a subset of the overall connectivity patterns in the brain. This is largely due to the spatial resolution of DWI (i.e., millimeters) and the inability to identify the directionality of connections (i.e., it is not possible to tell if a detected connection emits from point A to point B or vice versa or both). Nonetheless, fiber tractography approaches are already providing key insights about brain–behavior associations linked to two general connectivity patterns: convergence/divergence connectivity and topography. The functional utility of each pattern is considered in turn.

INTEGRATION AND SEGREGATION

With current DWI-based tractography methods it is impossible to tell whether a connection between any three regions reflects a divergent set of connections, a convergent set of connections, or both. Considered together, convergence and divergence patterns describe the integration and segregation of information within a circuit. With the adoption of graph-analytic methods to describe neural connectivity, we now know a lot about the

general patterns of integration and segmentation within the human brain (Bullmore & Sporns, 2009; Leergaard, Hilgetag, & Sporns, 2012). These machine learning analytics summarize how easily information can travel across brain areas by looking at the paths it takes to get from one area to the next (Sporns, 2013). These descriptive topology metrics have been used to identify differences in connectivity patterns in clinical neurological and psychiatric conditions such as multiple sclerosis, schizophrenia, and Alzheimer's disease (for a review of these findings and limitations of clinical connectometry, see Griffa *et al.*, 2013).

One major limitation of this approach is that it is not clear how these graph metrics aid our understanding of neural function or map onto cognitive abilities.

What does a more modular structural network mean for the function of the system or behavior? How does altered structural connectivity between groups, for example, sex differences, provide a mechanism for the altered computations that lead to any behavioral differences seen in these groups? Metrics of "small worldness" are excellent at providing summary statistics of network structure, but they are generally agnostic with regard to the underlying functions of the network itself.

However, that is not to say that measures of convergence and divergence have no utility for understanding brain function. In fact, measures of structural convergence have recently been shown to be useful for predicting functional activity during face processing (Saygin *et al.*, 2011). While participants passively viewed a series of faces, Zeynep Saygin and colleagues recorded hemodynamic responses across the entire brain using fMRI. They then estimated the structural connectivity between the fusiform face area (FFA; a region on the fusiform gyrus with selective responses to faces) and the rest of the brain using a probabilistic form of tractography that was applied to DTI data. The pattern of task-related responses in the FFA was then modeled as a function of the activity in the other brain regions, with the amount of influence of each brain region determined by the amount of connectivity they had with the FFA. Compared to several null models, Saygin and her colleagues found that a portion of the variance in FFA responses could be explained by the structural connectivity with other brain areas. This intriguing finding alludes to the possibility that the degree of convergent (or reciprocal divergent/convergent pathways) might have some predictive utility for explaining task-related activity, at least in sensory regions.

TOPOGRAPHY

While convergence and divergence describe the path that information travels across a brain network, topography describes the way that information

is represented as it travels from region to region. Recently, there has been a growing interest in resolving topographic patterns of structural connectivity in the human brain. Over the past few years, my colleagues and I, as well as other researchers, have shown how DWI-based tractography methods can resolve fine topographic patterns in the human brain. For example, using diffusion spectrum imaging (DSI), a high-angular resolution form of DWI, we have shown how it is possible to visualize the somatotopic organization of corticospinal pathways using DSI (Verstynen, Jarbo, Pathak, & Schneider, 2011). These pathways are particularly difficult to resolve as they pass through the midbrain and because they compact into an area of space about 5 mm^2 in diameter. Yet, it is still possible to detect the general somatotopic organization of these fibers using tractography on DSI data (Figure 3a). More recently, we have shown how this approach can capture both global (centimeters) and local (millimeters) topographic patterns in corticostriatal pathways (Verstynen *et al.*, 2012) (Figure 3b). This type of topographic analysis is not particularly specialized to DSI imaging approaches. Work from Iona Fine's laboratory has shown how tractography on DTI data can reveal the retinotopy of the interhemispheric connections in the splenium that connect the two primary visual cortices (Bock *et al.*, 2013; Saenz & Fine, 2010). This organization of the callosal pathways only encompasses a few voxels (i.e., a few millimeters) of tissue space, but even at this small distance, tractography approaches can detect these general patterns. Taken together, these findings illustrate the utility of DWI-based methods at capturing fine topologies at the macroscopic level in the human brain.

But what informative value does topography have for understanding brain function or cognition? In functional activity, understanding the topography of different functional responses can provide clues as to the nature of processing that an area does (see Schlerf, Verstynen, Ivry, & Spencer, 2010 for an example of this in the cerebellum). Recently, Jbabdi and colleagues argued that similar principles apply when looking at the structural organization of brain networks (Jbabdi *et al.*, 2013), that is, knowing how information is organized as it projects from one area to the next can provide insights into network-level representations.

My colleagues and I looked at how the organization of connections from the intraparietal sulcus (IPS) could explain patterns of attentional modulation of the early visual cortex (Greenberg *et al.*, 2012). Using functional localizers, we mapped out the boundaries of V1, V2, and V3, as well as the topographic representation of spatial attention in the IPS. Using tractography on DSI data, we then mapped the structural connections between these functionally defined regions. With a fairly high resolution we were able to confirm that regions of the posterior IPS that were selective for attending to a specific area of space were most strongly connected to early visual areas that also attended to that

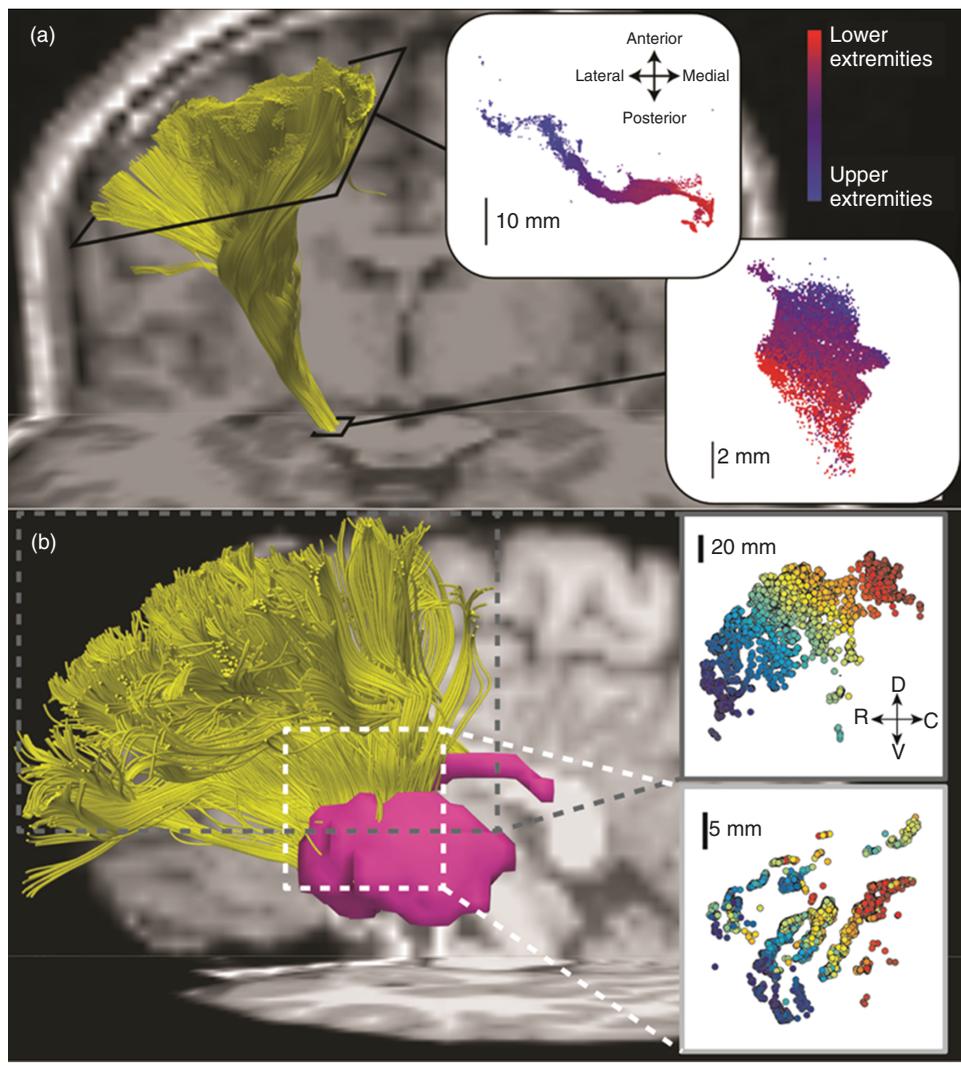


Figure 3 (a) Somatotopic organization of the corticospinal projections from the central sulcus for a single subject. Top inset shows organization of fiber start points at the cortex and bottom image shows organization of fiber positions in the crus cerebri of the midbrain. Reprinted from Verstynen *et al.* (2011). (b) Organization of corticostriatal projections that originate in the middle frontal gyrus for a single subject. Coloring reflects position of the fiber start point in the cortex, with more rostral fibers shown in cooler colors and more caudal fibers shown in warmer colors. Upper inset shows the fiber start points along the sagittal plane in the cortex and lower inset shows fiber end points along the sagittal plane in the striatum. Reprinted from Verstynen, Badre, *et al.* (2012).

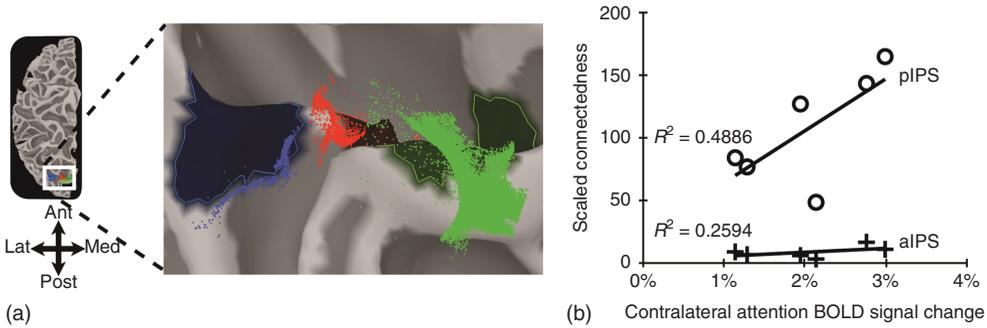


Figure 4 (a) Position of fiber endpoints (dots) that terminate in functionally defined regions of the intraparietal sulcus, at the cortical surface. Colors reflect functionally defined regions based on a spatial attention mapping paradigm: attention to upper visual field, blue; attention to lateral visual field, red; attention to lower visual field, green. (b) Percent BOLD signal change due to attentional modulation, in six extra striate regions, plotted relative to the number of anatomical connections from three topographically organized regions in the anterior intraparietal sulcus (aIPS) and posterior intraparietal sulcus (pIPS). Both panels reprinted from Greenberg *et al.* (2012).

area of space. Thus, there was a consistent topography of spatial information between visual areas in the occipital lobe and attention areas in the parietal lobe (Figure 4a). More importantly, however, we showed that this topography of connectedness positively correlated with the degree of attentional modulation seen in early visual cortex (Figure 4b). Therefore, the efficiency of point-to-point organization of connections from the posterior IPS to the early visual cortex could reflect a potential mechanism for attentional modulation in the primary visual cortex.

LIMITATIONS

Thus far I have outlined the emerging utility of DWI-based imaging tools for understanding how the physical architecture of connections in the brain might constrain brain function. However, there are several important limitations that are, as of yet, unresolved with these DWI approaches.

Bias. In many cases, the tractography output from DWI data is biased toward detecting connections between gyri (the folds of cortical tissue), with substantial loss in connectivity to sulcal regions (the wrinkles of cortical tissue). This significantly limits the scope of connectivity that can be estimated within the brain.

Artifacts. Just like its cousin method fMRI, there are many sources of noise in the DWI signal. Many of these sources can bias results toward a spurious finding between groups. For example, it was recently shown that spurious

head motion can introduce a change in the FA signal that resembles what is also seen in demyelination (Yendiki, Koldewyn, Kakunoori, Kanwisher, & Fischl, 2013). For a comprehensive review of noise sources in DWI, see Jones & Cercignani, 2010.

Directionality. Currently it is not possible to tell the direction mapped connections from the DWI signal, that is, if axons are going from region A to region B or vice versa. Thus, any inferences made from DWI data are restricted to undirected graphs and networks.

Spatial Resolution. Being an MRI-based method means that the spatial resolution of DWI is on the order of millimeters and centimeters. This is an order of magnitude higher than the spatial range of individual neurons. As with the directionality problem, any models or inferences made from DWI data are restricted to large networks of millions of neurons, rather than local networks of dozens of neurons or less.

Mapping to Function. Where possible I tried to highlight findings linking white matter architecture to either brain function or cognition. However, the precise mapping between these measures of white matter and functional properties of brain systems remains elusive. For example, in an integrated DWI and transcranial magnetic stimulation (TMS) study, DWI-based measures of corticospinal tract integrity, including FA, were not correlated with the conduction excitability of the corticospinal pathways when stimulated with TMS (Hübers, Klein, Kang, Hilker, & Ziemann, 2012). Thus, variability in FA did not predict individual differences in how signals are propagated from the motor cortex to the spinal motor neurons. While it is difficult to make an inference from this null result, it does suggest that the precise mapping between structure and function using DWI based methods is still ambiguous.

Validation. Until more studies are done incorporating histological or microdissection methods with DWI results, it is difficult to know the false-positive or false-negative rates of tractography data or how measures such as FA relate to the true number of underlying axons in a voxel.

Despite these limitations, some of which are shared with other neuroimaging methods, DWI still represents the best available tool for mapping white matter pathways in humans and understanding how they relate to cognition.

PUTTING IT TOGETHER

While DWI is most widely used to measure the integrity of white matter pathways, tractography approaches are just beginning to allow us to explore deeper questions about principles of neural organization and how the specific organization of brain pathways leads to behavior. Current studies are just beginning to get a handle on the phenomenological relationships

between structural connections and brain function. One day it may be possible to go beyond characterizing specific white matter–behavior relationships and identify the fundamental principles regarding how certain connection patterns (e.g., convergence, topography) constrain information processing in neural networks. Knowing these principles can provide a deeper understanding of the mechanisms by which neural circuits give rise to cognition.

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