Imaging connectivity: MRI and the structural networks of the brain

Jonathan D. Clayden, PhD

Institute of Child Health, University College London, UK

Correspondence to: Jonathan D. Clayden
E-mail: j.clayden@ucl.ac.uk

Summary

Magnetic resonance imaging (MRI) is a flexible and widely available neuroimaging technique. Structural MRI and diffusion MRI, in particular, provide information about connectivity between brain regions which may be combined to obtain a picture of entire neural networks, or the so-called connectome. In this review we outline the principles of MR-based connectivity analysis, discuss what relevant information it can provide for clinical and non-clinical neuroscience research, and outline some of the outstanding needs which future work will aim to meet.

KEY WORDS: connectivity, connectome, imaging, MRI, networks, white matter

Introduction

Neural computation is inextricably linked to connectivity. Without its extensive network of interconnections at every scale, the mammalian brain would not have the information processing capabilities that it does. Brain connectivity is also dynamic, both in the Hebbian sense that connection strengths between individual neurons are plastic (Ho et al., 2011), and in developmental terms, since the refinement of neural connections continues on a large scale for many years beyond birth (Tau and Peterson, 2010). Damage to the axon bundles connecting cortical regions is thought to underpin a range of neurological deficits, a principle commonly referred to as the "disconnection hypothesis" and discussed at length by Geschwind in a pair of seminal papers (Geschwind, 1965a,b). Techniques which allow for the health of neural white matter to be inferred *in vivo* therefore offer significant opportunities in clinical and non-clinical neuroscience. Here we will discuss the role of magnetic resonance imaging (MRI) in this context.

Brain connectivity can be considered at many different scales. At a fundamental level, intercommunication between individual neurons takes place at chemical or electrical synapses. The full pattern of synaptic connections in the nervous system of the nematode worm *Caenorhabditis elegans,* which contains just 302 neurons, has been painstakingly mapped out (White et al., 1986), but performing a similar feat for the hundred billion or so nerve cells of the human brain would be unimaginably difficult and, in all likelihood, not especially informative. More practical on the scale of entire neural systems is to consider connections made up of bundles of axons, linking together coherent gray matter nuclei or small cortical regions. Data from basic neuroscience, obtained using invasive techniques in non-human primates and other mammals, has provided tremendous insight into the connectivity of the visual cortices, for example, or the basal ganglia (Felleman and Van Essen, 1991; Parent and Hazrati, 1995).

Magnetic resonance imaging offers the opportunity to examine connectivity in the living brain. Although the technique is not without its challenges, and works at a relatively coarse scale, it is the focus of a great deal of current research due to its clinical feasibility. It is also the basis of various attempts currently being undertaken to characterize the human "connectome" in a meaningful way, notably in the context of the Human Connectome Project (http://www.humanconnectome.org; Van Essen and Ugurbil, 2012).

The focus of this review is specifically *structural* connectivity, the means of measuring it using MRI, and its key applications in neuroscience. Structural connectivity refers specifically to the identification and characterization of the axon bundles which embody connectivity. By contrast, "functional" connectivity has come to refer, in neuroimaging, to a correlation in the time courses of neural activity in spatially remote regions of gray matter; and "effective" connectivity describes patterns of influence by some neural systems over others. While functional connectivity may be measured relatively directly using functional MRI or encephalography, effective connectivity must generally be inferred using data in concert with a statistical framework such as a structural equation model (McIntosh and Gonzalez-Lima, 1994), or dynamic causal model (Friston et al., 2003). However, the relationship between functional and effective connectivity has been eloquently explored elsewhere, by Friston (1994) and others, and will not concern us further here.

The remainder of this review is organized as follows. We begin by discussing how MRI can be used in concert with computational techniques to derive information about brain connectivity. We then describe how this can be built up into a picture of connections across

the whole brain, and what information can be derived from this reconstructed connectome. We also outline some of the clinical studies in which this information has proven useful, and the role of cortical thickness information is discussed. Finally, we discuss the limitations of current approaches and future directions.

From molecules to connections

Although MRI is capable of producing highly detailed structural images of the human brain, the spatial resolution of clinical MRI is typically on the order of a millimeter. Neuronal axons, by contrast, are rarely more than a few microns in diameter; and it is therefore not possible to directly image axon bundles in the living brain using current technology.

Nevertheless, entire white matter tracts, which can be several millimeters across, often have a coherent orientation in any particular part of the brain, and this is exploited by diffusion MRI (dMRI). In this modality, the magnetic resonance signal is sensitive to the random thermal motion of water molecules within neural tissue. Since structures such as cell walls and myelin impede such motion, observing the characteristics of this self-diffusion in a particular part of the brain provides an insight into the underlying tissue microstructure (Le Bihan, 2003). In particular, the very linear structure of white matter tracts confers a strong orientational dependence, or anisotropy, on the mobility of free water. Very loosely, a millimeter or so of tract may be thought of as resembling a bundle of cylinders with a single orientation; and water molecules are freer to move along these cylinders than across them (Fig. 1).

The general technique for estimating the degree of water mobility, or diffusivity, in tissue using MRI was established in the mid-1960s (Stejskal and Tanner, 1965), and the effect of diffusion on the MRI signal was known for some time before that. But it was not until the 1990s, with the advent of diffusion tensor imaging (DTI), that a method for fully characterizing diffusion anisotropy was established (Basser et al., 1994). This was a major step forward, as it allowed the favored diffusion direction of water molecules, and hence the orientation of the underlying tract, to be inferred at each voxel (or 3D pixel) in an image of the brain. It was not long before postprocessing techniques which combined this local information to reconstruct entire white matter pathways followed (Conturo et al., 1999; Jones et al., 1999; Mori et al., 1999; Basser et al., 2000). The principle of this "tractography" is illustrated in figure 2, following the widely used approach of generating streamlines from seed points. Refinements to diffusion models and tractography algorithms have continued since, notably to allow for fiber crossings, but the general techniques remain broadly similar (Jones, 2008). A range of software tools for performing tractography is now available, and this has made its use relatively mainstream in clinical research applications. It has also been used for surgical planning and intraoperative navigation (Ciccarelli et al., 2008). However, it can be computationally intensive, and generally requires significant care and anatomical knowledge on the part of the user. Several approaches to automation have been described (O'Donnell and Westin, 2007; Clayden et al., 2009b; Zhang et al., 2010; Yendiki et al., 2011; Suarez et al., 2012), although none has yet attained widespread acceptance.

Diffusion tensor imaging and, to a lesser extent, its various successors have also been used to characterize white matter microstructure as such. Since diffusion anisotropy at the millimeter scale arises due to the coherent organization of axon bundles, it is logical to suppose that a reduction in observed anisotropy would follow a loss of coherence due to the effects of pathology. Indeed, there have been hundreds of clinical studies reporting reductions in anisotropy in parts of the brain, when compared with control cohorts or examined over the course of disease progression. Localized changes in diffusion parameters have also been detected after even relatively short periods of training in a new skill (Scholz et al., 2009; Sagi et al., 2012). The biophysical interpretation of anisotropy changes is

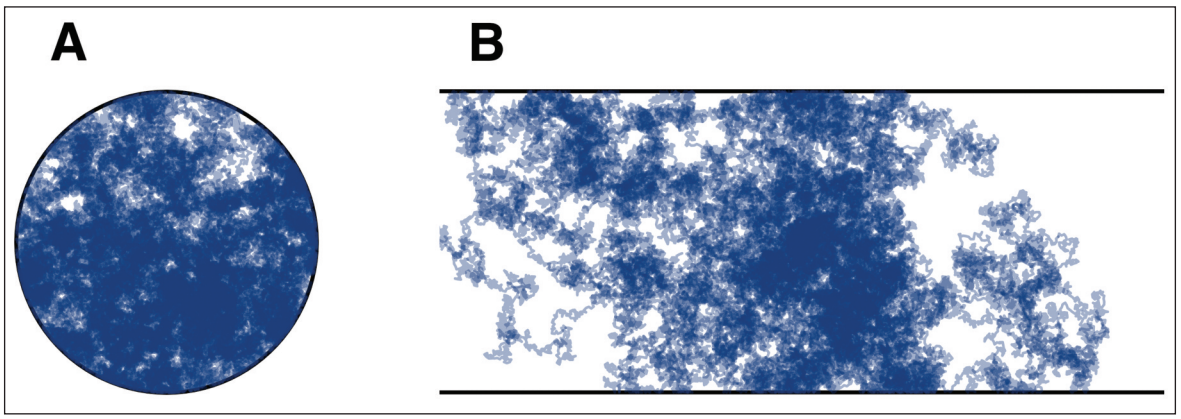

Figure 1 - Simulation of diffusion within an ideal impermeable cylinder, shown in cross- sections perpendicular (A) and parallel (B) to the axis of symmetry. Despite starting from the center of the figure in both cases, diffusing molecules progress further on average along the cylinder than across it.

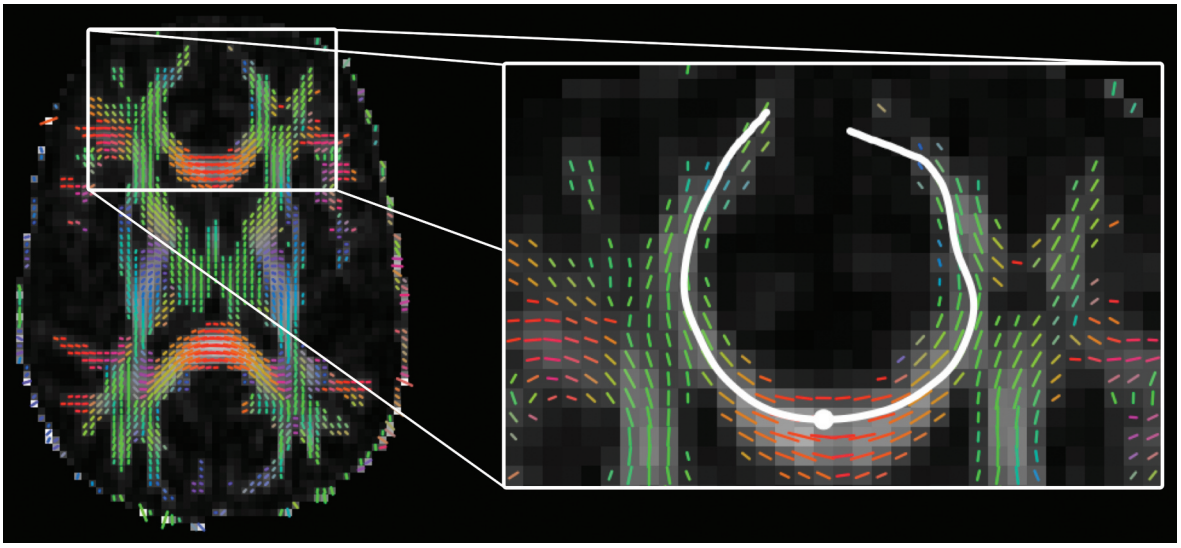

Figure 2 - Illustration of the principle of streamline tractography based on dMRI data. The principal direction of diffusion at each voxel location in the data is shown as a line, whose color corresponds to its orientation. The streamline, shown in white, is generated by beginning at a seed point (large white circle) and repeatedly stepping along the principal direction.

not fully understood, but a series of *ex vivo* experiments have suggested that the hindrance of cell membranes to water self-diffusion makes the biggest contribution to anisotropy, while myelin has a somewhat lesser effect (Beaulieu, 2002). Breakdown in axonal cell membranes and demyelination would therefore be expected to have some effect on observed anisotropy. Many authors have considered diffusivities perpendicular and parallel to the axons separately, in order to provide some distinction between different sources of change in anisotropy, but interpretation of these measures remains controversial (Wheeler-Kingshott and Cercignani, 2009), and so caution is advisable. Recently, novel dMRI-based experiments incorporating detailed tissue geometry models have been appearing, with the aim of directly estimating pseudohistological parameters such as axon radius from imaging data (Barazany et al., 2009; Alexander et al., 2010), and this is an enticing, if highly ambitious, avenue of current research.

The structural connectome

It was recognized soon after tractography first became established that it could be used as a tool to compare the connectivity "profiles" of different brain areas. Moreover, although afferent and efferent pathways cannot be distinguished using dMRI, the differences in the projections of streamlines generated from a set of seed points can be used to delimit functionally distinct cortical areas or subnuclei. This principle has been successfully applied to automatically segment subnuclei of the thalamus (Behrens et al., 2003) and basal ganglia (Draganski et al., 2008), as well as to separate adjacent, but functionally distinct, regions of cortex (Klein et al., 2007).

Going one step further, to build up a picture of the full structural connectivity network, is conceptually quite straightforward. Typically, a high-resolution structural MR image is used to parcellate the cortex into anatomically coherent subregions, tractography is performed throughout the brain, and the connectivity between each pair of regions is compiled into an abstract representation called a graph (Fig. 3, over). Graph-based approaches to structural connectivity analysis have become established in the dMRI literature in the last five years or so (Hagmann et al., 2008; Iturria-Medina et al., 2008), and are now an extremely fast-growing area of methodological and applied research.

Graph representations are appealing for their simplicity, since they collapse the complexities of brain connectivity into a set of abstract interconnected "nodes". They are also extremely well-understood in mathematical terms, since graph theory as a field has been developed over centuries. Numerical values can be derived which represent a whole spectrum of topological features of the network represented by the graph (Rubinov and Sporns, 2010), such as the average number of connections to each brain region represented by a node, or the average number of connections which must be traversed to get between any pair of nodes. In common with many complex networks, brain networks have also been described as having "small-world" topology (Watts and Strogatz, 1998), with a number of key hubs acting as gateways between local clusters of interconnected gray matter regions.

The availability of relatively intuitive graph-based measures of network characteristics, such as overall construction "cost" (the density of connections present), and "efficiency" (inversely related to the typical path length between nodes), has catalyzed the appli-

cation of these techniques in neuroscience. Figure 4 illustrates some of these concepts using two simple graphs. For example, Wen et al. (2011) have presented evidence of a relationship between a global measure of neural network efficiency and several aspects of cognitive performance in old age. It has also been reported that global efficiency is lower in Alzheimer's disease patients, when compared to controls (Lo et al., 2010), and that path lengths are longer in frontal and temporal regions in schizophrenia (van den Heuvel et al., 2010), amongst other clinical findings. Similar results have been reported using network analysis based on functional connectivity.

However, while graph-based findings can certainly be instructive, it is important not to overinterpret the results of these analyses. The tidy, well-behaved graphical representation obscures the practical vagaries of the underlying data, but the graph is implicitly subject to all of the caveats applying individually to each step of the process used to generate it. Moreover, there is very little consensus regarding the details of the pipeline that should be used, but the choice of nodes, tractography algorithm and various thresholds can have a very significant effect on the reconstructed network (Zalesky et al., 2010; Bastiani et al., 2012). One must therefore not be fooled into thinking that the connectome obtained is definitive.

Finally, it is not always clear that the network properties of the brain as a whole are relevant. Global efficiency, for example, provides putative information on the ease

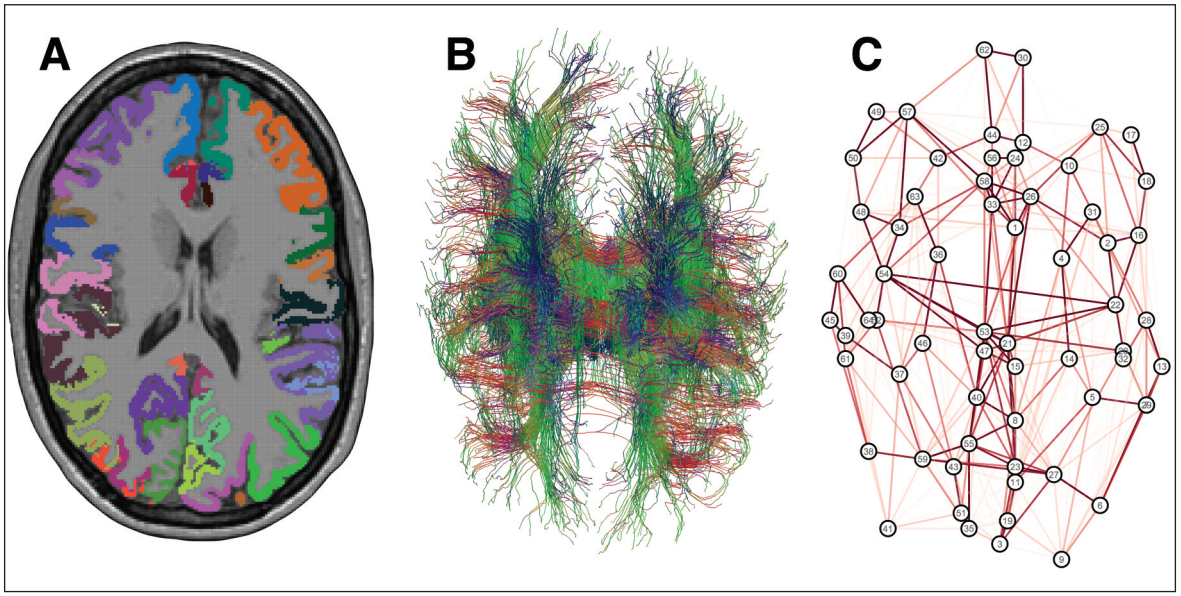

Figure 3 - Key stages in the creation of a structural connectivity graph using magnetic resonance images: cortical parcellation (A), whole-brain tractography (B), and the final graph representing the pattern of connections between regions (C).

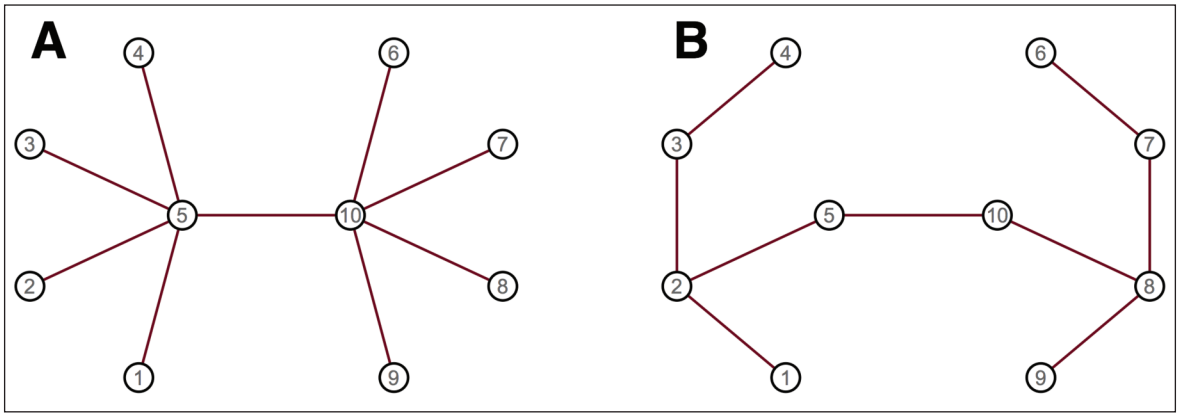

Figure 4 - Two simple graphs with the same number of nodes and connections, but different topologies. Graph A has higher "efficiency", because a maximum of three connections need to be traversed to get from any one node to any other, compared to up to seven for graph B. However, if either of the central "hub" nodes, 5 and 10, were to be destroyed and removed from the graph, a larger proportion of nodes in graph A would be disconnected. Graph B is therefore, in some senses, less vulnerable to attacks targeted at these nodes.

by which any two cortical regions may communicate with each other, but in most cases it is unlikely that a specific neurological condition would be the result of an impairment of all-to-all interregional communication. Decomposing the structural connectome into coherent subnetworks may well be a valuable alternative strategy, although once again there are various methodological approaches available (Clayden et al., 2013). As is often the case, prior knowledge from other sources is likely to be very valuable in focusing attention on a subnetwork relevant to a particular cognitive ability, or perhaps connections mediated by a particular neurotransmitter.

Cortical thickness

Although tractography provides a well-established and relatively direct way to obtain structural connectivity information, it is not the only such method that uses MR images. A common alternative is to consider correlations in cortical thickness between regions. The pipeline in this case is to acquire one or more high-resolution structural MR images, parcellate the cortex as before, and then calculate the average distance from the pial surface to the white matter boundary within each parcellated region (Fischl and Dale, 2000; Kim et al., 2005). Across a cohort of subjects, the correlations between each pair of cortical thickness estimates can then be obtained and used as an indirect measure of connectivity between them. Unlike with dMRI, connectivity cannot be straightforwardly estimated for a single individual using this approach.

It is far from obvious that correlation in cortical thickness should imply the existence of a connection between two regions, and indeed the anatomical underpinnings of this observation remain unclear. Nevertheless, Lerch et al. (2006) demonstrated that areas in which cortical thickness is correlated with that in Broca's area corresponded closely to the gray matter surrounding the arcuate fasciculus, the language pathway to which that region is connected. A fair degree of agreement with dMRI-based connectivity information has also been reported at the network level (Gong et al., 2012).

Graph-based studies using cortical thickness correlation as their measure of corticocortical connectivity have found relationships between network properties and age during development (Khundrakpam et al., 2013), and differences in clustering topology between grapheme-color synesthetes and controls (Hanggi et al., 2011), amongst other findings. Indeed, cortical thickness is not the only anatomical measure which has been used in this way: Bassett et al. (2008) built up graphs using correlations in gray matter volume, for example, showing differences in the locations of network hubs between schizophrenics and controls.

Challenges and opportunities

In the decade and a half since diffusion tractography was first put forward, there have been a number of efforts to validate it: for example, by comparing the results to *ex vivo* dissection or invasive tracing (Dyrby et al., 2007; Lawes et al., 2008). There have also been major efforts to reconstruct pathways in fixed tissue using techniques such as three-dimensional polarized light imaging (Axer et al., 2011), to give a very high-resolution "gold standard" for comparison with *in vivo* reconstructions. While the results of validation work have been broadly encouraging, there have also been some cautionary tales of the risks of overreliance on the technique in a clinical context (Kinoshita et al., 2005); and further refinements to the reliability of tractography are certainly needed.

A key area holding back the possibilities of structural connectomics is the lack of robust imaging-based measures of connectivity. Two common choices are the number of streamlines which connect each pair of gray matter regions, and the average anisotropy of voxels through which those streamlines pass. There are also variants of these measures which try to correct for the size of each target region, whole brain volume, and so on. The intuition for each of these measures is relatively obvious. The number of streamlines forming a connection can be viewed as a proxy for its cross-sectional area, which is assumed to relate to the bandwidth of the connection – its capacity for transmitting information. But there are several practical issues undermining this assumption, arguably the most crucial of which is the well-known tendency for long pathways to be underrepresented due to the accumulation of small errors during tractography (Morris et al., 2008; Clayden et al., 2009a). This issue does not directly apply to the anisotropy-based approach, which is assumed to provide information on the integrity of the white matter forming the relevant connection. However, in this case there are other issues due to the low resolution of the imaging data: how should one deal with voxels on the periphery of the tract, which may incorporate irrelevant tissue? Either way, it is not difficult to imagine falsely positive (or negative) results emerging due to limitations of the image processing, rather than any characteristic of neuroscientific interest. A similar issue exists to some extent in functional connectivity work (Smith et al., 2011), but it is partly mitigated by the shorter image processing pipeline which is required to get from raw data to connectivity estimate in that case.

Consensus on methodology is unlikely ever to become universal, due to the different requirements of individual studies, but researchers should be aware of the impact of their choices. DTI has the advantage of being applicable to almost any diffusion data set, and is relatively robust to noise, but makes tracking small pathways that run near to major ones almost impossible. As a result, a connectome reconstructed using DTI would be expected to be more sparse than one using a higher-order model (Bastiani et al., 2012). Likewise, using a large number of small regions of interest as nodes will tend to produce a much less densely connected graph than one which uses whole brain lobes (Zalesky et al., 2010). Aspects of the image acquisition, such as

resolution, will also have a significant influence on the networks obtained; and the effects of such characteristics can be hard to predict. For group comparisons in particular, consistency in all of these matters is key.

Another major challenge is the integration of structural and functional connectivity information. Several attempts at this have already been made, and many more are ongoing, but the unique difficulties of each individual technique are further compounded when trying to create a unified picture. Recent work has demonstrated that there is a certain amount of basic agreement between the methods, but functional connectivity is generally found to be more variable than structural connectivity, and not wholly explained by it (Park et al., 2008; Skudlarski et al., 2008; Honey et al., 2009). In particular, Honey et al. reported that consistent functional connectivity can be observed between regions which are not directly connected anatomically. Resolving these differences is an important aim for future work, and may prove to be the cornerstone of a future robust approach to reconstructing the human connectome.

Parallel to the methodological challenges are unaddressed questions of a more neuroscientific nature. What is the "typical" pattern of structural connectivity in a healthy adult? What about in a child? How much variation is there in the connectome from person to person? How does connectivity change during development or ageing, due to disease processes, or in response to treatment or training? Can connectivity "fingerprints" help predict developmental or clinical outcomes? If carefully and thoughtfully applied, MRI will be a key tool in answering some of these questions.

Concluding remarks

In this review we have given an overview of methods for studying so-called structural connectivity using MRI. We have also illustrated how they are used, what can be learned from them, and some of the difficulties that they face. Graph methods and connectome approaches have gained a great deal of visibility in the last few years, although they bring their own pitfalls as well as some inspiring new possibilities. In the end, MRI methods currently offer the only means to study structural connectivity in the living brain, and are therefore very likely to be central to future discoveries in this area as techniques continue to be refined.

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