



## Review

## Mapping connectivity in the developing brain



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## ABSTRACT

Recently, there has been a wealth of research into structural and functional brain connectivity, and how they change over development. While we are far from a complete understanding, these studies have yielded important insights into human brain development. There is an ever growing variety of methods for assessing connectivity, each with its own advantages. Here we review research on the development of structural and/or functional brain connectivity in both typically developing subjects and subjects with neurodevelopmental disorders. Space limitations preclude an exhaustive review of brain connectivity across all developmental disorders, so we review a representative selection of recent findings on brain connectivity in autism, Fragile X, 22q11.2 deletion syndrome, Williams syndrome, Turner syndrome, and ADHD. Major strides have been made in understanding the developmental trajectory of the human connectome, offering insight into characteristic features of brain development and biological processes involved in developmental brain disorders. We also discuss some common themes, including hemispheric specialization – or asymmetry – and sex differences. We conclude by discussing some promising future directions in connectomics, including the merger of imaging and genetics, and a deeper investigation of the relationships between structural and functional connectivity.

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## 1. Introduction

After birth, the brain undergoes remarkable changes as it adapts and learns in a new environment. Over a century of neuroanatomical research has revealed how the brain changes structurally and functionally throughout development; the last thirty years have also seen the widespread use of brain imaging to probe functional activation and coherence, as well as other dynamic brain changes (reviewed by Casey et al., 2000). In addition to understanding these changes, it is equally important to understand how the underlying structural and functional connectivity of the mature adult brain are set up and refined in childhood and adolescence. With novel variants of MRI – such as diffusion imaging and resting state functional MRI – we now have the technology to image neural pathways reliably, and to assess relationships between the activity of different brain regions, opening up new avenues for research.

Diffusion weighted imaging (DWI) is a method that allows us to visualize the diffusion of water along axons and thus visualize axonal pathways. Originally based on the observation that the MRI signal is reduced when water is diffusing (Stejskal and Tanner, 1965), increasingly elaborate scanning methods were developed to assess the primary directions in which water is diffusing, at each location in the living brain. By modeling the directional diffusion of water as an ellipsoidal shape, or “tensor”, at each voxel in the brain, diffusion tensor imaging (or DTI) may be used to follow the major fiber bundles of the white matter, and map smooth tracts running from one brain region to another. More recently, high angular resolution diffusion imaging (HARDI) has been developed, offering some advantages over DTI, as it can better map tracts in regions with crossing fibers (Jahanshad et al., 2011). Fractional anisotropy (FA), the degree to which water tends to diffuse in one concentrated direction (along the axon), is one of the most common measures used to assess axon integrity. Apparent diffusion coefficient (ADC) or mean diffusivity (MD) measures the overall magnitude of diffusion, regardless of the directions; low values for mean diffusivity indicate greater organization. As a general rule of thumb – which has many exceptions – higher FA and lower MD tend to reflect more highly developed, more strongly myelinated tracts, with a higher axonal conduction speed. Many comparisons of diseased versus normal subjects find lower FA and higher MD in disease—this is also a general trend in the studies below, but is not universally the case.

The improved ability to disentangle fibers that mix and cross results from collecting more diffusion-weighted images at more angles, in conjunction with mathematical models that can resolve more than one dominant fiber direction in any given voxel (Cetingul et al., 2012a, 2012b). HARDI – essentially a more advanced form of diffusion imaging than DTI – differs from DTI in collecting diffusion data in more directions. It models the overall diffusion profile at each point in the brain using orientation distribution functions (ODFs) instead of tensors. ODFs estimate the probability of diffusion in each direction at each voxel, instead of assigning a single dominant diffusion direction to a given voxel (Tournier et al., 2004). For these reasons, HARDI is better at resolving crossing fibers (such as the corpus callosum and the long association fibers), a major issue for DTI (Tuch et al., 2002). These can then be separated and individually analyzed, giving a more accurate view of the brain’s anatomical connections (Zhan et al., 2009a; Jin et al., 2012). As more directional scans are collected, longer scan times are needed, and

this has provoked major efforts to speed up diffusion imaging (Zhan et al., 2011).

Resting-state fMRI (rsfMRI) is a branch of research based on the idea that distant brain regions can be functionally coupled, whether or not they are structurally connected. Rs-fMRI data can be collected either in the presence or absence of a task. This coupling can be measured through the blood oxygenation level dependent (BOLD) time-courses of these distant regions. The phenomenon of synchronized low-frequency fluctuations (~0.01–0.1 Hz) in the BOLD signal of known functional networks was first found by Biswal et al. (1995), and led to the discovery of a number of temporally coherent networks (Damoiseaux et al., 2006; Fox et al., 2005) that have been replicated across individuals (Beckmann et al., 2005) and have high test-retest reliability, even in children (Thomason et al., 2011). There are three main methods to assess functional connectivity that we will consider here: seed-based, ICA (i.e., independent components analysis), and graph theory. In the seed-based approach, the researcher extracts the time course of a seed (region of interest) and then correlates that time course with the time courses of the rest of the voxels in the brain, to search for matches (Fox and Raichle, 2007). Brain regions with a high degree of positive correlation with the seed – i.e., those with a very similar time course – are thought to be functionally coupled. ICA (independent components analysis) is model-free, meaning that the researcher does not select a seed or ROI. Rather, the four-dimensional resting-state data can be decomposed into time courses and associated spatial maps, describing the temporal and spatial characteristics of the components making up the data (Beckmann et al., 2005). The same intrinsic connectivity networks (ICNs) can be seen with both seed-based and ICA approaches, and each method offers some advantages and disadvantages. Many possible roles have been attributed to ICNs, including memory functions, organization and coordination of neuronal activity, and priming the brain for coordinated activity (Fox and Raichle, 2007; Seeley et al., 2007). ICNs are altered in a wide range of psychiatric and developmental disorders, further motivating the need to establish how they develop in healthy individuals (Greicius, 2008), as well as metrics of normal brain function based on resting state data.

More pragmatically, there is also a major effort to understand how quickly information on brain connectivity can be collected, with techniques available today. When young children are assessed, scan times should be as short as possible without sacrificing important information, to avoid placing undue burden on the participants (Jahanshad et al., 2010; Zhan et al., 2008, 2009b, 2012a). Ongoing work is also determining how the chosen scanning protocols affect the maps of brain connectivity that are recovered (Zhan et al., 2012b). Clearly, the ability to pool and compare data collected worldwide on brain connectivity – including changes across development – depends on understanding how connectivity measures might depend on the scanners, protocols and methods used to extract maps of the brain’s connections.

In this review, we will cover developmental changes in functional and structural connectivity in healthy, typically developing individuals (Table 1), along with a few illustrative examples of how connectivity may be disrupted in developmental disorders (Table 2). There is a much wider body of research covering how functional and structural connectivity are affected in individuals with neurological or psychiatric disorders, but those are beyond the scope of this review (Greicius, 2008; Lim and Helpert, 2002; Sexton et al., 2009; Seyffert and Silva, 2005; Uddin et al., 2010; please also

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