



Development of large-scale functional networks from birth to adulthood: A guide to the neuroimaging literature



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ABSTRACT

The development of human cognition results from the emergence of coordinated activity between distant brain areas. Network science, combined with non-invasive functional imaging, has generated unprecedented insights regarding the adult brain's functional organization, and promises to help elucidate the development of functional architectures supporting complex behavior. Here we review what is known about functional network development from birth until adulthood, particularly as understood through the use of resting-state functional connectivity MRI (rs-fcMRI). We attempt to synthesize rs-fcMRI findings with other functional imaging techniques, with macro-scale structural connectivity, and with knowledge regarding the development of micro-scale structure. We highlight a number of outstanding conceptual and technical barriers that need to be addressed, as well as previous developmental findings that may need to be revisited. Finally, we discuss key areas ripe for future research in order to (1) better characterize normative developmental trajectories, (2) link these trajectories to biologic mechanistic events, as well as component behaviors and (3) better understand the clinical implications and pathophysiological basis of aberrant network development.

Introduction

The human brain is organized into multiple distributed functional brain networks that can be measured at multiple spatiotemporal scales

Coordinated neuronal activity between anatomically disparate regions is an essential feature of human brain function. Across all stages of postnatal development, brain activity to a large degree is consolidated within so-called “resting-state networks” (RSNs). RSNs are defined as distinct modules of regions that exhibit highly synchronized activity even in the absence of external stimuli. RSNs have proven to be highly reproducible in the adult brain (Doucet et al., 2011; Gordon et al., 2016; Power et al., 2011; Yeo et al., 2011) and have become an influential framework for interpreting functional and structural neuroimaging data. Patterns of functional connectivity (FC) within and between the major RSNs are increasingly understood as intrinsic properties of brain function, given that they strongly predict patterns of interregional co-activation across different tasks (Cole et al., 2014; Smith et al., 2009) and are associated with task-relevant

behavioral performance (Cole et al., 2012; Lewis et al., 2009).

Interregional FC arises from anatomical projection strengths (Messe et al., 2014; Shen et al., 2012), correlated gene expression (Richiardi et al., 2015), and synaptic receptor densities (Turk et al., 2016; van den Heuvel et al., 2016b) – properties that, in turn, undergo experience-dependent and activity-dependent modulation over the lifespan (Huttenlocher, 2002; Markham and Greenough, 2004; Scholz et al., 2009). This intricate structural-functional interplay underscores that the ontogeny of functional networks likely reflects programmed neurodevelopmental events (e.g. neurogenesis, cell death, myelination, pruning, synaptic plasticity, and glial development) (Innocenti and Price, 2005; Stiles and Jernigan, 2010) and that FC aberrations may point towards the etiological bases of neuropsychiatric disorders (e.g. Swartz and Monk, 2014; van den Heuvel et al., 2016a). Thus, exploring the normal trajectory of functional network development and its relationships with these underlying biological processes should be a central mission of both basic and clinically relevant neurodevelopmental research.

Current views regarding network development have been heavily informed by resting-state functional connectivity MRI (rs-fcMRI),

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which measures the correlations in spontaneous, low-frequency activity between investigator-defined regions. This review will accordingly provide in-depth discussions of the developmental rs-fcMRI literature, its limitations, and unique insights gained from complementary approaches, especially electroencephalography and magnetoencephalography (EEG/MEG). We will begin by discussing emerging themes in the analysis of functional network data. We will then synthesize current findings regarding FC changes from birth to adulthood, and place them within the context of co-occurring macro- and micro-scale structural modifications. Finally, we will discuss some of the implications with regard to neurodevelopmental disorders and highlight several crucial knowledge gaps that are likely to guide research efforts in the near future.

Analytic approaches to functional connectivity are evolving rapidly

Correlated resting-state activity was first identified in bilateral sensorimotor cortex by Biswal et al. (1995), followed soon after by similar findings of bilaterally correlated activity in early visual and early auditory cortex (Cordes et al., 2001; Kiviniemi et al., 2000; Lowe et al., 1998). These discoveries were made using “seed” regions outlined based on *a priori* anatomical boundaries. Correlations were then quantified between the seed region’s fMRI timecourse and all other voxels of the brain, producing an FC map. More data-driven approaches were developed based on the concept of independent components analysis (Beckmann and Smith, 2004), which decomposes brain activity into a set of spatial maps (i.e. components) that minimally overlap. ICA maps reproducibly reveal early visual, early auditory, and primary sensory/motor components, as well as other components comprising distributed portions of the frontal, parietal, and temporal association cortices (Damoiseaux et al., 2006).

Building upon these advances, the neuroimaging community has increasingly focused on interrogating the brain as an integrated complex system. In this context, graph theory has emerged as a powerful new approach. A ‘graph’ is simply a network of things, referred to as nodes, and the connections between those things, referred to as edges. The network’s behavior can thus be modeled as a set of properties that emerge from the network’s unique global structure and local features (Sporns, 2014). Graph theoretic studies typically construct functional brain networks using regions as nodes and correlations in activity as edges. Past reviews have already written eloquently about the rationales for applying this approach to study development (Power et al., 2010; Vertes and Bullmore, 2015), which we will only briefly summarize and expand upon here.

First, most individual cognitive abilities arise not solely from a particular brain area, but from networks of activity spanning multiple distributed regions (Petersen and Sporns, 2015). From social cognition in infancy (Eggebrecht et al., 2017) to cognitive control and decision-making in adolescence (Dwyer et al., 2014; van Duijvenvoorde et al., 2015), specific cognitive capacities co-evolve with complex network effects within and between different RSNs, throughout postnatal development. Second, structural connectivity shapes and constrains functional networks across the lifespan (Betz et al., 2014; Hagmann et al., 2012; Vertes and Bullmore, 2015). Cross-modal network analysis is therefore crucial for elucidating normative mechanisms of cognitive development and the pathophysiology of neurodevelopmental disturbances. As a proof-of-principle, recent studies have found that even purely local, experimentally induced perturbations (e.g. exogenous stimulation or inactivation) result in widespread, complex neurophysiological changes, which are at least partly explainable as local interactions with global network structure (Andoh et al., 2015; Grayson et al., 2016; Gu et al., 2015a; Masic et al., 2015). By extension, one could reason that developmental modifications in brain FC, whether normative or pathological, are also best understood via an emerging network science that merges structural and functional connectivity data. Third, graph-based methods are flexible and general-

izable. Networks can be measured at various temporal scales depending on imaging methodology, at various conditions (during rest or task completion), and can be compared with corresponding networks of structural connectivity or gene co-expression. A graph theoretic approach is therefore well-suited for multimodal investigations linking brain function across temporal scales or examining structural drivers of functional development.

Graph theory techniques for defining network organization

Below we describe 3 broad themes that have emerged with regard to functional (and structural) network analysis in neuroimaging: the brain’s community structure (i.e. the spatial and topological organization of specialized systems), the significance of hub regions that integrate information within and between these systems, and global network properties that facilitate efficient and integrated information transfer.

Community structure

A defining feature of human brain activity is “modularity,” which refers to an unexpectedly high level of within-RSN FC relative to between-RSN FC (Lohse et al., 2014). “Community detection” algorithms partition the brain into distinct communities, or modules, by maximizing this modularity quotient. The adult brain has several modules at the coarsest level that are remarkably reproducible despite slight methodological differences across studies (Doucet et al., 2011; Gordon et al., 2016; Power et al., 2011; Yeo et al., 2011). These modules include (1) segregated, non-distributed modules for sensory/motor activity, such as in early visual cortex and in somatomotor cortex, (2) the default-mode network (DMN), comprising the medial prefrontal, posterior cingulate/precuneus, angular gyrus, and medial temporal cortex; the DMN is considered “task-negative” as it has been linked to internal mentation and is known to deactivate during processing of external stimuli (Buckner et al., 2008), and (3) three large, distributed modules for task-positive cognition: (a) dorsal attention, involved in eye movements and attentional orienting, (b) the cingulo-opercular salience module, involved primarily in attentional maintenance, and (c) the frontoparietal executive module, important for task-switching. At finer resolutions, several other modules can be identified (Doucet et al., 2011; Gordon et al., 2016; Power et al., 2011; Yeo et al., 2011), including hierarchical visual subdivisions, topographical somatomotor subdivisions, an auditory module, a limbic module, a ventral attention module, and other smaller subdivisions of the executive, salience, and default-mode modules. See Fig. 1A and B for a graphical summary.

The brain’s modular composition is believed to help segregate information processing between distinct sensory modalities or cognitive architectures. It remains a fundamental challenge to understand what other network properties help integrate disparate data streams in order to meet complex task demands (Cohen and D’Esposito, 2016; Petersen and Sporns, 2015). As discussed throughout this review, the themes of segregation and integration are core concepts in understanding the brain’s maturational processes. Thus, further analytic exploration is needed to isolate the critical network components that facilitate segregation, integration, or efficiency. Below we briefly describe some local network measures toward this end.

Node measures

The most straightforward nodal description is its *strength* (Rubinov and Sporns, 2010), defined as the sum of a node’s connection weights. Other *centrality* measures quantify higher order measures of influence. For instance, *betweenness centrality* (Rubinov and Sporns, 2010) computes the frequency with which a node lies on the shortest paths that connect any other nodes, a property that theoretically enables

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