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The developmental cognitive neuroscience of functional connectivity

Michael C. Stevens *

Olin Neuropsychiatry Research Center, The Institute of Living/Hartford Hospital, 200 Retreat Avenue, Whitehall Building, Hartford, CT 06106, United States
Department of Psychiatry, Yale University School of Medicine, 34 Park Street, New Haven, CT 06510, United States

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ABSTRACT

Developmental cognitive neuroscience is a rapidly growing field that examines the relationships between biological development and cognitive ability. In the past decade, there has been ongoing refinement of concepts and methodology related to the study of 'functional connectivity' among distributed brain regions believed to underlie cognition and behavioral control. Due to the recent availability of relatively easy-to-use tools for functional connectivity analysis, there has been a sharp upsurge of studies that seek to characterize normal and psychopathologically abnormal brain functional integration. However, relatively few studies have applied functional and effective connectivity analysis techniques to developmental cognitive neuroscience. Functional and effective connectivity analysis methods are ideally suited to advance our understanding of the neural substrates of cognitive development, particularly in understanding how and why changes in the functional 'wiring' of neural networks promotes optimal cognitive control throughout development. The purpose of this review is to summarize the central concepts, methods, and findings of functional integration neuroimaging research to discuss key questions in the field of developmental cognitive neuroscience. These ideas will be presented within a context that merges relevant concepts and proposals from different developmental theorists. The review will outline a few general predictions about likely relationships between typical 'executive' cognitive maturation and changes in brain network functional integration during adolescence. Although not exhaustive, this conceptual review also will showcase some of recent findings that have emerged to support these predictions.

1. Organization of review

Developmental cognitive neuroscience is a rapidly growing field that examines the relationships between biological development and cognitive ability. Although the field is derived most directly from theoretical models of cognitive development informed by biological studies of brain maturation, it also draws upon many concepts taken from psychology, neuroscience, social science, and genetics in an effort to better describe specific mechanisms that influence developmental changes in cognition. The purpose of this review is to describe how functional and effective connectivity neuroimaging methods have been valuable tools in understanding the neurobiological basis of cognitive development. The first section will outline the conceptual and methodological issues relevant to this review. The second section will discuss theoretical aspects of neural organization and brain development that are related to the study of functional connectivity. In particular, it will argue that by including concepts of network functional integration into current neuroscience theories, these theories more aptly explain executive cognitive development. The third section will describe several basic predictions for how development might affect neural system operation. This section also will review recent studies of functional and effective connectivity that directly support hypotheses about the neural circuits underlying executive cognitive development. This will include research from this laboratory that has sought to further develop neural network connectivity theories. Finally, there will be a summary and discussion of future directions and yet-to-be-addressed questions in this field of research.

2. Conceptual and methodological overview of functional integration

2.1. The limitations of functional specialization

As a result of the widespread use of functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and electrophysiological recordings (EEG) over the past several decades, there is now a considerable scientific literature to draw upon for understanding the neural basis of cognitive development (see recent reviews by Casey, Galvan, & Hare, 2005; Casey & Munakata, 2002; Diamond & Amso, 2008; Durston & Casey, 2006; Durston et al., 2006; Johnson, 2001, 2005; Kuhn, 2006; Luna & Sweeney,

* Olin Neuropsychiatry Research Center, The Institute of Living/Hartford Hospital, 200 Retreat Avenue, Whitehall Building, Hartford, CT 06106, United States. Fax: +1 860 545 7997.
E-mail address: msteven@harthosp.org.

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2004; Luna et al., 2001; Munakata, Casey, & Diamond, 2004; Westermann, Sirois, Shultz, & Mareschal, 2006). A key foundation of these functional neuroimaging studies is the concept that brain regions are 'functionally specialized' for certain cognitive operations. This understanding follows a long history stretching back over a century to work begun by Broca and Wernicke that includes literally hundreds of neuropsychological lesion studies. This extensive body of research clearly demonstrates that damage to specific brain regions is directly associated with impairment of specific motor, language, or other cognitive abilities. Functional specialization can therefore be defined as the degree of processing specificity of a given brain region for a particular cognitive ability or facet of cognitive operations (Friston, 2002; Johnson, 2005). From this perspective, there is a reasonable presumption that abnormal neural activity or structural characteristic of any given brain region could affect the operation of cognitive processes that engage that region.

The concept of functional specialization (sometimes termed 'functional segregation') has led to great advances in understanding differences among brain regions. However, this perspective is limited in its ability to explain how the entire brain works to enable thinking and behavior. For instance, characterizing brain activity in terms of functionally segregated regions does not reveal anything about how different brain regions communicate with each other, or how such inter-communication among a handful of brain regions could influence neural activity in each local region. The slowness of the fMRI hemodynamic response and the nature of PET metabolic data averaged over minutes make these imaging approaches unable to characterize many types of millisecond changes. As a result, many functional neuroimaging analysis methods often discount, or correct for, signal variability in order to optimize the ability to detect signal change in a particular brain region (i.e., 'activation'). Even at coarse timescales fMRI and PET data contain meaningful information that can inform us about possible coactivation of distal brain regions. This information can be used by suitable analytic approaches to quantify the degree of activation similarity among different brain regions.

2.2. Functional and effective connectivity

Numerous data analysis techniques have been developed to quantify the inter-relationships of signal changes in distal brain regions. 'Functional connectivity' is a term that is often used to refer to statistical associations between remote neurophysiological events (Friston, 2002). When distributed brain regions display strongly correlated patterns of neural activity change, it is taken as evidence that those regions are functionally connected, likely via reciprocal excitatory neurotransmission through long distance white matter pathways (Bressler & Kelso, 2001; Fingelkurts & Kahkonen, 2005; Tononi, Edelman, & Sporns, 1998). 'Effective connectivity' can be thought of as a special case of functional connectivity, in which inferences can be made about the cognitive relevance of regional brain function from the presence or strength of statistically-determined 'causal' influences among various regions (Buchel, 2004; Friston, 2002; Friston & Price, 2001). This provides a means to empirically determine whether activity in one brain region has downstream linear or nonlinear effects on others (Friston, 2002). More simply put, functional connectivity analyses can identify functionally-integrated networks, while effective connectivity can measure how brain regions within those networks interact to mediate cognitive demands. Although these two terms have become somewhat well-established, there remains a need for further conceptual refinement of these terms as we learn more about the exact neural mechanisms that establish and maintain connectivity (Horwitz, 2003, 2004). In this review, we use the term 'functional integration' to refer to the product of effective and functional connectivity statistical methods used with functional neuroimaging data. Functional integration generically refers to empirical evidence that neural activity in spatially-remote brain regions is associated. It also is taken to reflect the strength among nodes of a biologically-integrated network that are engaged in a coordinated manner or influence each other in meaningful ways.

2.3. Methods to quantify functional integration

Early functional integration research focused on EEG studies of the relationships among neuron spike trains and helped lay the conceptual groundwork for the study of brain functional connectivity. Indeed, topographical analysis of EEG frequency spectra remains a useful and informative technique for understanding the neural basis of executive and other cognitive functions (Babiloni et al., 2004; Laufs et al., 2003; Makarov, Panetsos, & de Feo, 2005). Neurophysiological studies will continue to be necessary for full understanding of the neural basis of functional connectivity (Fingelkurts & Kahkonen, 2005; Nunez, 2000). However, the availability of neuroimaging techniques like fMRI or PET that provide accurate spatial resolution of neural activity offer opportunities address new and different questions about network structure and function.

The ongoing development of statistical techniques to quantify different types of functional integration has made it relatively easy to measure types of connectivity in fMRI and PET datasets. In most instances, such techniques can be applied directly to data collected for other experimental purposes. This has led to a sharp increase in the number of functional and effective connectivity studies published in recent years. A search of the scientific literature found 249 studies published between 1987 and 2007 that used brain activity data from fMRI, EEG or PET to explore the strength or types of relationships among two or more brain regions. These studies were identified by searching Medline and PsycInfo using terms like "functional connectivity," "functional integration," or "effective connectivity." By early December 2008, 207 more functional integration studies already have been published. This suggests that the final 2008 tally may triple the number of functional integration neuroimaging studies published in 2007, and be five times greater than the number published in 2006 (Fig. 1).

Several reviews of functional integration and available connectivity analytic methods are available, including those with concise evaluations of the relative advantages or limitations of various techniques (Bowman, Guo, & Derado, 2007; Penny, Stephan, Mechelli, & Friston, 2004; Ramnani, Behrens, Penny, & Matthews, 2004; Rogers, Morgan, Newton, & Gore, 2007; Rykhlevskaia, Gratton, &

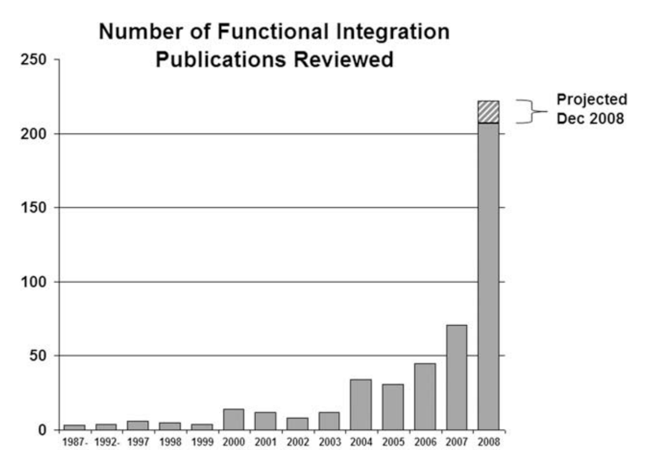

Fig. 1. Illustration of the number of scientific reports on functional and effective connectivity since 1987.