Relating Variations in Network Connectivity to Cognitive Function

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Introduction

Cognitive science is evolving from a focus on discrete brain areas towards an emphasis on distributed models of brain function. In the latter, cognition emerges from the complex interaction of widespread brain areas. To examine interregional interactions, early neuroimaging studies used positron emission tomography (PET) to correlate activity patterns in different brain areas across subjects (Clark et al., 1984; Horwitz et al., 1984; Metter et al., 1984). By contrasting one group of subjects with another, group differences in brain function could then be related to interactions between brain areas (Horwitz et al., 1998). However, the study of individual differences in connectivity patterns with PET was typically not feasible because limited temporal resolution prevented the assessment of connectivity in each subject (although an exception can be found in the work of Glaubus et al., 2003).

The ability to assess network connectivity patterns for each individual subject was one of the exciting advances made possible by the improved temporal resolution of functional magnetic resonance imaging (fMRI). This capability has enabled researchers to examine relationships between individuals' cognitive function and their network connectivity, which has proven to be a powerful approach for studying the neural basis of individual differences. For example, an early study we conducted revealed robust correlations in a relatively limited sample size between reading skills and connectivity between brain areas in the reading circuitry (Hampson et al., 2006a). More recently, studies relating cognitive variables to network connectivity have become popular in cognitive neuroscience. This research has tended to highlight the role of two specific networks in human cognition: the cognitive control network and the default mode network, which are discussed in more detail below.

Cognitive Control or "Task-Positive" Network

Neuroimaging studies have identified a set of frontal and parietal brain regions that appear to be important in human intelligence (Jung and Haier, 2007). In particular, activation-based functional imaging studies have reported increased activity in many brain regions: dorsolateral and ventrolateral prefrontal cortices, premotor areas, dorsomedial prefrontal cortex, anterior insula, the intraparietal sulcus, and portions of the inferior parietal lobule. This activity is seen during a range of working memory and attention/executive function tasks (Cabeza and Nyberg, 2000; Corbetta and Shulman, 2002; Owen et al., 2005). These cognitive control areas have been shown to fluctuate together in the resting state (Fox et al., 2005; Seeley et al., 2007), suggesting that they form an intrinsic brain network. Adopting the terminology of Fox et al. (2005), we refer to these cognitive control regions as "task-positive" areas.

The strength of functional connectivity between task-positive brain areas in the resting state has proven relevant to cognitive function. For example, Seeley and colleagues identified this network via independent components analysis. They reported that the strength of the intraparietal sulcus within the extracted component was correlated with performance on the Trail Making Test, a measure of executive function (Seeley et al., 2007). Another study, by Song et al., identified many functional connections between the dorsolateral prefrontal cortex and other task-positive brain areas that were correlated with intelligence scores on the Wexler Adult Intelligence Scale (Song et al., 2008). Thus, functional connectivity within the task-positive network appears to play a role in individual differences in cognitive ability.

Default Mode or "Task-Negative" Network

Another set of regions that appear to be relevant to cognitive function are the default-mode regions. This set of brain areas includes the ventromedial prefrontal cortex, a region of the posterior cingulate cortex extending into the precuneus, and lateral parietal regions, all of which have been found in meta-analyses to have decreased blood flow during a variety of tasks (Shulman et al., 1997; Mazoyer et al., 2001). These regions were also shown to fluctuate together at rest, supporting the view that they form a well-integrated network (Greicius et al., 2003). This network has been hypothesized to perform the default mental processes subjects engage in when their attention is not focused on a specific task—hence the term "default mode" network (Raichle et al., 2001).

According to the default mode theory, task engagement suspends default mode processing, resulting in decreased activity in these regions. However, it is important to note that a decrease in blood flow can be associated with an increase in information processing and engagement and does not necessarily imply suspension of processing. For example, a region that shifts from random baseline firing to phase-locking with other regions at a lower firing rate may decrease its net activity level (resulting

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in decreased local blood flow) when it becomes more engaged in information processing. Because of the implications inherent in the term "default mode," we prefer the term "task-negative," introduced by Fox et al. (2005). This term accounts for the fact that these brain areas decrease their signal during task performance in neuroimaging studies but does not imply that they are engaged in critical information processing only during the resting (or default) mental state.

To investigate how engagement of the task-negative network relates to cognitive function, we examined functional connectivity between two key regions in this network (the medial prefrontal and posterior cingulate regions), both at rest and during performance of a demanding cognitive task (Hampson et al., 2006b). Furthermore, we correlated the strength of this connection with task performance. We found that these two task-negative regions significantly correlated with each other, both at rest and during task performance, and did not find a significant change in the strength of that connection across conditions (note, however, that this null finding across conditions may have been the result of limited power) (Fransson, 2006). Significantly, the strength of connectivity between the medial prefrontal and posterior cingulate regions in the task-negative network, whether assessed at rest or during task performance, positively related to task performance. In contrast to the default mode theory, our data suggest that these regions work together to facilitate cognitive processing rather than being suspended during cognitive tasks.

A variety of more recent studies have also supported the viewpoint that the task-negative network facilitates cognition. An examination of resting state network properties in the task-negative network and their relationship to intelligence scores reported that individuals with high intelligence quotients (IQs) display greater efficiency in this network (Song et al., 2009). Furthermore, several functional connections between task-negative regions, including the connection between medial frontal and posterior cingulate regions, were related to IQ. Another study reported that episodic memory performance is correlated with the strength of resting state functional connectivity between the posterior cingulate cortex and the hippocampus (Wang et al., 2010b). The hippocampus is generally considered a "default mode" or task-negative region (Greicius and Menon, 2004), although it is likely not a central node in the network (Song et al., 2009). Finally, a study examining network properties in the resting brain reported that the global connectivity efficiency of several task-negative regions is correlated with IQ (van den Heuvel et al., 2009).

Analyses of network properties in the brain, based on both structural connectivity and resting state functional connectivity, have reported that the task-negative regions are hubs, that is, areas of very high global connectivity (Hagmann et al., 2008; Buckner et al., 2009). This centrality may account for their ubiquitous importance across a range of cognitive tasks. It is interesting to note that the same study reporting correlations between the global connectivity efficiency of task-negative regions and IQ also reported that whole-brain efficiency is highly correlated with IQ (van den Heuvel et al., 2009). These data, taken together, suggest that integrity of the task-negative network plays a critical role in the whole-brain dynamics associated with higher level cognition.

Interactions Between Task-Positive and Task-Negative Networks

The task-positive and task-negative networks have been shown to fluctuate in antiphase in the resting brain (Greicius et al., 2003; Fox et al., 2005; Fransson, 2005); however, their antiphase relationship may be an artifact of a commonly used analysis step known as "global regression" (Murphy et al., 2008). Regardless, the strength of the functional connection between task-positive and task-negative regions at rest appears to be related to cognitive function. In one study using global regression, the strength of the anticorrelation between task-positive and task-negative networks was inversely related to intra-individual variability in response time, a measure inversely related to cognitive function (Kelly et al., 2008). In another study, the connectivity between dorsolateral prefrontal cortex (a key task-positive region) and medial prefrontal cortex (a key task-negative region) negatively correlated with the percentage of correct answers on a working memory task (Hampson et al., 2010) when the data were analyzed both with and without global regression. Thus, in all cases, better cognitive function was associated with smaller or more negative correlations between task-positive and task-negative brain areas.

In summary, connectivity both within and between the task-positive and task-negative networks is associated with individual differences in cognitive ability. According to recent analyses of resting state functional connectivity data, task-positive (as well as task-negative) regions act as network hubs in the brain (Cole et al., 2010). Thus, efficient communication between hub regions of

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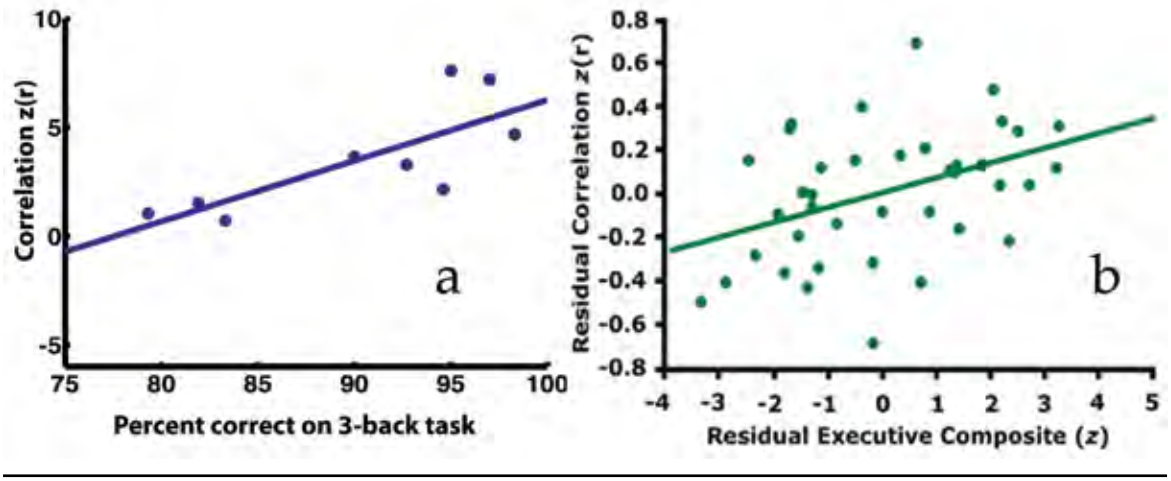


Figure 1. Functional connectivity between ventromedial prefrontal cortex and posterior cingulate/precuneus is plotted against measures of cognitive function for adults aged 28-45 in panel ***a*** and for older adults aged 60-93 (after adjusting for age) in panel ***b***. The relationships are significant for both populations. Data from panel ***a*** were reported in Hampson et al., 2006b; panel ***b*** is from Andrews-Hanna et al., 2007, their Figure 8B, reproduced with permission. Units of functional connectivity on the *y*-axis are not comparable across studies owing to differences in normalization applied.

the brain may be a critical variable for determining cognitive ability.

Clinical Applications

Connectivity within the task-negative network has become a recent focus in aging research. As shown in Figure 1, our finding that cognitive function is related to connectivity between medial areas of the task-negative network was extended to healthy older populations (Andrews-Hanna et al., 2007; Sambataro et al., 2010). In addition, these studies reported that, relative to younger adults, older adults had decreased connectivity in the default mode network. These findings suggest a mechanism for the decrease in cognitive function associated with healthy aging. Other studies have reported altered network connectivity in older adults (Achard and Bullmore, 2007; Gong, 2009; Wang et al., 2010a) but have not correlated these changes with cognitive measures.

Similarly, a variety of studies have reported disrupted network connectivity in Alzheimer's disease (Greicius et al., 2004; Supekar et al., 2008; Wang et al., 2006, 2007) but have not directly correlated network measures with cognitive variables in this group. Interestingly, a growing literature has implicated the disruption of the default mode network in the pathophysiology of Alzheimer's disease, as well as in healthy aging. Decreased connectivity within the default mode network has been reported in patients with Alzheimer's disease (Greicius et al., 2004; Wang et al., 2006), and the default mode regions have been found to overlap with areas showing amyloid-α deposition, a characteristic feature of the disorder (Buckner et al., 2005). Furthermore, two recent studies have reported a relationship between amyloid-α deposition and connectivity in the default mode network (Hedden et al., 2009; Sheline et al., 2010). Finally, genetic predisposition to Alzheimer's disease has been associated with decreased coactivation of default mode regions in healthy young adults (Filippini et al., 2009).

Studies have examined connectivity changes in other clinical populations and related those connectivity changes to cognitive function. For example, aberrant connectivity has been related to disturbed cognitive function in schizophrenics (Camchong et al., 2009; Meda et al., 2009; Whitfield-Gabrieli et al., 2009; Wolf et al., 2009) and in children born preterm (Myers et al., 2010). Such studies have the potential to reveal the dysfunctional network interactions that underlie the cognitive impairments associated with various clinical conditions.

Future Directions

In cognitive neuroscience, interest has shifted from regional activation to connectivity patterns, moving the field towards a more network-oriented perspective. However, for the most part, this trend has not progressed beyond the examination of pairwise connectivity measures. More distributed measures of network properties are just beginning to be explored (Buckner et al., 2009; Bullmore and Sporns, 2009; Song et al., 2009; van den Heuvel

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et al., 2009). These new measures have great potential to summarize the complex patterns of network connectivity that determine brain function, and as such, to provide promising new tools for cognitive neuroscientists.

As more is learned regarding the network properties underlying individual differences in cognition, a critical challenge will be to modulate these patterns in order to improve cognitive function. Along these lines, a recent study explored the relationship between cardiovascular fitness, functional connectivity, and cognition (Voss et al., 2010). Its findings point to the importance of physical exercise as a potential intervention for improving cognitive networks in older adults and the need for more longitudinal studies. Another study involving a paradigm for visual perceptual learning reported significant changes in functional connectivity associated with the degree of learning (Lewis et al., 2009), illustrating our capacity for modulating network dynamics and thereby improving cognitive function. In our lab, a particularly interesting new form of intervention is biofeedback of real-time fMRI, which has been shown effective in modulating pain perception (deCharms et al., 2005) and in facilitating linguistic processing (Rota et al., 2009). Studies examining the relationship between changes in network properties during such interventions, and coincident changes in cognitive function, are likely to yield new insights into the brain organization underlying cognition and its plasticity.

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