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On Control Systems of the Brain: A Study of Their Connections, Activations, and Interactions

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On Control Systems of the Brain: A Study of Their Connections, Activations, and Interactions

by
Haoxin Sun

A dissertation presented to
the Graduate School
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To my parents, who did not let me play video games

ABSTRACT OF THE DISSERTATION

On Control Systems of the Brain:
A Study of Their Connections, Activations, and Interactions

by

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Professor Steven E. Petersen, Chair

Implementation of daily functions in humans crucially relies on both the bottom-up moment-to- moment processing of relevant input and output information as well as the top-down controls that instantiate and regulate goal-directed strategies. The current dissertation focuses on different systems of brain regions related to task control. We are interested in investigating, in detail, some of the basic activity patterns that different control systems carry during simple tasks, and how differences in activity patterns may shed new insight onto the distinctions among the systems' functional roles. In addition, carefully coordinated interactions between brain regions specialized for control-related activity and regions specialized for bottom-up information processing are essential for humans to adeptly undertake various goal-directed tasks. Hence, another goal is to explore how the relationships among regions related to control and regions related to processing will change as result of top-down control signals during tasks.

In Chapter 2, we applied the graph theory method of link communities onto the brain's resting-state intrinsic connectivity structure to identify possible points of interactions among the previously defined functional systems, including various control systems. In Chapter 3, we conducted a meta-analysis of tasks to examine the distinct functional characteristics of control systems in task activation. Using a data-driven clustering analysis, we identified two distinct trial-related response profiles that divided the regions of control systems into a right frontoparietal and cinguloopercular cluster, which may be engaged in fine-tuning task parameters and evaluating performance, and a left frontoparietal and dorsal attention cluster, which may be involved in timely updates of trial-wise parameters as well as information processing. In Chapter 4, we explored the changes in functional relationships among selected systems during individual trials of a goal-direct task and found the presence of complex and dynamic relationships that suggest changes among the various functional systems across a trial reflect both continuous as well as momentary effects of top-down signals. Collectively, the studies presented here both contributed to as well as challenged previous frameworks of task control in an effort to build better understanding of the basic organization and interactions among the brain's functional systems.

CHAPTER 1: INTRODUCTION

Decades of PET and fMRI experiments have observed co-activation in consistent sets of distributed brain regions during certain types of tasks (Pardo, Fox, & Raichle, 1991; Petersen, Fox, Posner, Mintun, & Raichle, 1988; Posner, Petersen, Fox, & Raichle, 1988). Given the evidence gathered from many carefully designed experiments hypothesized to elicit specific types of mental operations, it was suggested that these individual sets of brain regions, or functional systems, may carry different cognitive operations (Corbetta & Shulman, 2002; Dosenbach et al., 2006; Raichle et al., 2001).

However, until the body of work that examined spontaneous fMRI signals, the identities of the functional systems were dependent upon sets of task paradigms, and the early task-based approaches were not sufficient for answering whether the functional systems reflected a fundamental organization of the brain, or whether they were just some transient and specific effects of task. Through the study of spatial pattern within spontaneous fMRI signals, it had been observed that there exist highly correlated spontaneous fluctuations among selected sets of regions of the brain that appear to correspond to task-driven functional systems (Biswal, Yetkin, Haughton, & Hyde, 1995; Dosenbach et al., 2007; Fox, Corbetta, Snyder, Vincent, & Raichle, 2006; Fox et al., 2005; Greicius, Krasnow, Reiss, & Menon, 2003). More recent analyses of the whole-brain spontaneous fluctuations provided further understanding of the intrinsic functional organization of the human brain (Power et al., 2011; Yeo et al., 2011), forming the basis for subsequent investigations regarding the functional roles played by each system as well as the interactions among different systems during task.

The current dissertation focuses on functional systems related to task control. Exercising control is an essential cognitive ability that allows us to navigate flexibly and successfully through everyday tasks. Here we are interested in investigating, in detail, some of the basic activity patterns that different control systems carry during simple tasks, and how differences in activity patterns may shed new insight onto the systems' functional roles. In addition, given the intrinsic functional structure of the brain, we describe how the relationships among regions of different functional systems will change as result of certain control demands during tasks.

I. Resting-State Functional Connectivity and Functional Systems of the Brain

The method of Functional Magnetic Resonance Imaging (fMRI) measures the relative changes in the blood oxygenation level dependent signals (BOLDs) during the performance of a task to infer which areas of the brain are activated. Although the exploration of task-driven activation of the brain has been fruitful, one of the major challenges in neuroimaging is to have the ability to examine the entire set of brain's functional systems without being constrained by an a priori hypothesis. In response to this, resting-state fMRI (rs-fMRI) developed as a valuable adjunct for addressing the challenge.

Rs-fMRI focuses on a spontaneous slow but large amplitude fluctuations occurring in the frequency range of 0.01 to 0.1 Hz. The functional significance of these fluctuations was first revealed in imaging of the brain during rest. In 1995, Biswal and colleague reported that, at rest, the fluctuations in the low frequency BOLD signals are temporally correlated across functionally related areas (Biswal et al., 1995). In this study, during the resting-state acquisitions, subjects were instructed to refrain from any cognitive, language, or motor tasks. Using a seed region in the left somatosensory cortex that was determined by separate acquisitions of task-based fMRI scans in which subjects performed bilateral finger tapping, the authors found, after correlating the time-course of the seed region with the time-courses of other regions of the brain, that the seed region was highly correlated with the homologous area in the contralateral hemisphere. In subsequent studies, the existence of synchronous fluctuations between primary somatosensory areas and other movement related regions, such as in supplementary motor areas, the thalamus, and the cerebellum, were further confirmed, and similar findings were reported in primary and higher-level visual and auditory regions, as well (Cordes et al., 2001; Lowe, Mock, & Sorenson, 1998). The correlation in resting-state BOLD fluctuations is referred to as "functional connectivity".

Over the years, studies using rs-fMRI has made significant progress on identifying several intrinsic functional systems in the human brain. It has been found that regions of higher-level cortical areas that often activate or deactivate together during tasks also showed greater correlated functional connectivity. For example, one of the principal higher-level functional systems is the default-mode system, first identified by Raichle and colleagues using PET (Raichle et al., 2001). Its regions (e.g. posterior cingulate and ventral anterior cingulate cortex) are deactivated during performance of cognitive tasks. More importantly, similar to the visual and motor systems, default-mode regions display selective synchronization during resting-state, suggesting, among them, an intrinsic cohesiveness (Greicius et al., 2003). Subsequent systems of higher function that were identified by resting-state fMRI include attention systems (Fox et al., 2006) and executive control systems (Dosenbach et al., 2007).

Large Scale Functional Network

In order to efficiently and comprehensively explore the overall functional architecture of the human brain, a variety of methods (e.g. seed-based analyses, ICA, clustering) have been applied to rs-fMRI data (Beckmann, DeLuca, Devlin, & Smith, 2005; Smith et al., 2009; Yeo et al., 2011). One of the most powerful approaches is the usage of graph theory concepts (Bullmore & Sporns, 2009; Rubinov & Sporns, 2009). Graph theory is the study of networks. It models a complex system as a mathematical object composed of a set of elements (nodes) and the pair-wise relationships between the elements (edges). Many real world networks that have been subjected to the studies of graph theory include the worldwide web, social networks, ecosystems, and airline infrastructure. Given that, at various physiological levels (i.e. neurons, circuits, neural networks, functional areas, and functional systems, (Churchland & Sejnowski, 1991)), the brain can be thought of as an interactive network, graph theory, consequently, seems to be an appropriate tool for exploring the properties of the brain network. Pertinent topics in graph theory range from identification and characterization of substructures to analyses of hubs and critical components within a network.

It is important to note that, for fMRI, its spatial and temporal resolution limit us to the study of brain network only at the level of function areas and systems. To appropriately model the brain network using rs-fMRI data, putative functional brain areas, which can be defined by either functional connectivity boundary maps (Cohen et al., 2008; Gordon et al., 2014), or battery of fMRI activation studies (Dosenbach et al., 2007), or a conjunction of both, are depicted as nodes while the measured functional connectivity between the areas are depicted as edges (Power et al., 2011).

As mentioned before, much like the person-person interactions of a social network that results in formations of groups and organizations, distributed sets of brain regions harmonize and correlate among themselves as systems (e.g. visual, motor, and default mode system) of a bigger network to support specialized functions. Groupings of close-knit nodes in a network are called communities. Communities are often considered as having rather dense internal relationships but few between group connections, and there is a family of methods (community detection algorithms) that utilize this characteristic to optimize the search for sub-structure within a large network, such as the brain (Fortunato, 2010). For example, Infomap is a community detection method that applies the general concepts of coding theory to explore the regularities in a given network (Rosvall & Bergstrom, 2007). This method seeks a way to encode how information flows through the network by simulating the path of a random walker. A group of highly connected nodes will likely trap the random walker since they allow quick and easy flow among themselves. This scenario can be contrasted with regions that are between two modules: these regions likely have less interconnected edges resulting in fleeting visits from the random walker. Thus, Infomap uses the trajectory of a random walker to detect distinct communities. This method computes the fraction of time that a random walker dwells in a certain place by observing how often the walker visits each individual location. After a few iterations, possible partitions result from the frequency of visits. Overall, the algorithm derived brain communities are attractive because they appeal to the initial challenge in neuroimaging as they allow for fairly comprehensive identification of substructures within the functional organization of the brain without a priori hypotheses.

Power and colleagues sought whole-brain systems by applying Infomap on two types of brain-wide graphs: one composed of 264 putative functional areas and the other a modified voxelwise network that eliminated the potentially noisy short-distance relationships between neighboring voxels. Overall, the two graphs revealed similar substructures within the brain network that resembled well-known functional systems based on previous fMRI studies. These include the visual, motor, auditory, frontoparietal, cinguloopercular, salience, dorsal attention, ventral attention, and the default mode system. Other substructures (e.g. sets of memory related regions) lack established descriptions, but they are corroborated by subsequent analyses of existing task-based fMRI studies (Gilmore, Nelson, & McDermott, 2015; Nelson, Cohen, et al., 2010). Beyond determining the identity of different functional systems, Power et al. also used graph theory measures (i.e. participation coefficient, local efficiency, and motifs) to suggest possible functional characteristics for each system. For example, control systems always held a central position within the brain network such that they are much more integrated with each other and with other processing systems (e.g. visual and auditory). This may reflect the idea that control systems must maintain a diverse set of relationships with the processing systems in order to operate efficiently during tasks. On the other hand, processing systems are more internally connected such that they have more dense connections within the systems than between the systems, suggesting that they are involved in somewhat isolated and compartmentalized functions. Other novel observations include the default mode system showing similar degree of compartmentalization as other processing systems. Although the functional roles of the default system is still an area of debate, the graph analyses indicate the default mode system may act more as a processing system than a control system.

Continuing Explorations

Combining graph theory and rs-fMRI data provided many novel perspectives on the functional structure of the brain and inspired many more new avenues for future explorations.

For one, similar to various real-world systems, the brain is a complex network, and substructures within the network interact with each other and may even overlap (Yeo et al., 2014). Most of the current community detection algorithms assume communities are neatly divisible. Evans and Lambiotte devised a method of partitioning the edges of a network in order to observe the possible overlapping structures of complex networks (Evans & Lambiotte, 2010). Ahn et al. also applied the same concept to several real-world social networks, metabolic networks, and word association networks. They were able to identify relevant sets of relationships that reveal additional interactions within the networks (Ahn, Bagrow, & Lehmann, 2010).

In Chapter 2, we applied the idea of edge-based communities to rs-fMRI data in attempt to observe possible interactions among the previously defined functional systems. With this method, we observed not only networks with strong resemblance with previously known functional systems but also several notable distributed regions of the brain that might be significant to the integrity of inter-community connections. Furthermore, through quantifying the extent of overlaps, the results provided insight onto the level of association between different functional systems, an aspect that is not easily appreciated from conventional methods.

Further, the network-based framework of the brain can be especially useful because it allows for quantitative descriptions that comprehensively characterize the overall network, portions of the network, and individual nodes of the network. A growing number of studies have used these characterizations at different physiological levels to explore changes in the brain's functional structure due to pathological conditions or over the course of development (Chen et al., 2011; Church et al., 2009; Greene et al., 2014; Lerman-Sinkoff & Barch, 2016; William W. Seeley, Crawford, Zhou, Miller, & Greicius, 2009).

II. Task Control and Control Systems

From complex tasks to simple errands, timely and accurate performance requires collaborative interactions of many brain regions. Several of the resting-state functional systems introduced in the previous section are thought of as the source of control signals. These signals may be related to top-down configurations as well as performance reporting and feedback processes. Together, they presumably allow humans to initiate, retain, and adjust configurations needed for satisfactory task implementations.

General Concepts of Control

Seminal psychological theories for mechanisms that account for the selection and implementation of appropriate mental operations distinguish subordinate moment-to-moment processes that can be configured and reconfigured to carry out infinite sets of tasks, through control processes that "program" the moment-to-moment processes. Therefore, as we enter distinct tasks, depending on task instructions, the moment-to-moment processes will operate on incoming input (e.g. sensory information) and transformations of the input to output, while the control processes will regulate the order of operations that moment-to-moment processes need to carry out in service of the task demands.

As the advent of noninvasive neuroimaging techniques using PET and fMRI revealed sets of anatomical areas that appear to be common across task performance, Petersen and Posner outlined the anatomical basis of control processes. Although the original framework has been elaborated and expanded in the years following the initial publication, the three fundamental principles that they first identified continue to help navigate behavioral, systems, cellular and molecular approaches to common exploration of attention research. The first basic concept of systems related to control processes is that they should be anatomically separate from systems related to "data processing " (i.e. regions that involved specific moment-to-moment transformation of information stages of a task) such as sensory and motor regions. Second, control processes are carried out by a network of anatomical areas. Partly drawn from lesion studies of Mesulam 1981, no single region is responsible for control processes, neither is the entire brain. Third, distinct systems of control carry out different cognitive operations in context of attention or executive function. As a consequence of this proposed anatomical configuration, systems of control processes can maintain their own functional identity while directing the moment-to-moment flow of information carried out by data processing systems.

The original and updated framework of Petersen and Posner described systems of control processes and their corresponding cognitive operations under three attention-related domains: alerting, orienting, and detecting (executive control, Petersen and Posner 2012). Particularly, accounts of orienting and executive systems have become the one of the major foci of the current thesis.

Orienting, at least in the visual system, refers to the ability to prioritize sensory input by biasing attention to the location of the target. A behavioral effect of orienting is the improvement in efficiency of subjects' responses to events occurred at the attended location while a physiological effect is the increased discharge rate in neuron's responses when subject attends to the location within the neuron's receptive field than when subject attends elsewhere.

Executive control, originally outlined primary as function of target detecting, refers to control (e.g. initiating, maintaining, and adjusting) of cognitive processing. Previous studies with complex fMRI designs have identified (at least) four distinct types of control signals at both the task set level as well as the trial level (Donaldson, Petersen, Ollinger, & Buckner, 2001; Logan & Gordon, 2001; Meiran, 1996). The task set level control signals include (1) start-cue signals, which may be related to the initial loading of the task parameters, and (2) sustained signals, which may be related to stable maintenance of established parameters across portions or trials of a task. The trial level control signals include (3) trial-wise cueing signals, which may be related to moment-to-moment update of trial-related parameters, and (4) performance-related signals, which maybe related to performance reporting and feedback (e.g. signals affected by errors, ambiguity, conflict, etc.). Under the previously mentioned framework of control systems, these signals should characterize the functional role of control regions across a wide variety of tasks.

Characterization of Orienting Systems

Related to orienting, Corbetta and Shulman identified two independent control systems: the dorsal and ventral attention systems of parietal and frontal regions (Corbetta & Shulman, 2002). The dorsal attention system (DAN) is composed primarily of the intraparietal cortex (IPS) and frontal eye fields (FEF), and it plays a crucial role in voluntary maintenance of spatial attention and has been implicated in preparatory as well as in action selection, or response, aspects of visual attention tasks. Traditionally, the ventral attention system (VAN) is primarily composed of right lateralized temporal parietal junction (TPJ) and ventral frontal cortex (VFC). It is thought to have functions for reorientation of attention and detection of task-relevant stimuli occurring at unexpected locations. For example, regions in the ventral attention system showed greater evoked responses during target periods of invalid trials than during target periods of valid trials during a Posner task (Corbetta, 1998). Moreover, due to its weak evoked responses during cue, the ventral attention system is typically described as not involved in generation or maintenance of top-down attentions but in bottom-up disengagement of attention (Power &

Petersen, 2013). In addition, Fox et al. 2006 used resting-state seedmaps of four regions in IPS, FEF, TPJ, and VFC and demonstrated that the anatomical distinctions between dorsal and ventral attention systems persist in the absence of external task.

Characterization of Executive Control Systems

Using a meta-analysis of 10-task fMRI dataset, Dosenbach and colleagues looked for regions of the brain that carried the start-cue, sustained, and error-related executive control signals. Although the tasks in the dataset differed in their input as well as their output modalities, and they required a variety of task demands and moment-to-moment operations, the control signals that were present across them could not be modality or task specific. Overall, 39 regions of interest that responded to either one or more control signals were identified. Specifically, regions in the dorsal anterior cingulate (dACC)/medial superior frontal cortex (mdFC) and anterior insula (aI)/frontal operculum (fO) demonstrated all three controls signals and were considered as the core system for task implementation. Another set of regions that include the dorsal lateral prefrontal cortex (dlPFC), intraparietal sulcus (IPS), and inferior parietal lobule (IPL) showed start-cue and error signals but lacked sustained signals. Hence, they were set apart from the core regions and were thought to play a more transient role that support the instantiation of task set parameters.

To find the underlying organization to these 39 regions, in a follow-up study, Dosenbach and colleague employed resting-state functional connectivity. As mentioned in the previous section, resting-state functional connectivity (RSFC) has shown to be able to reveal systems of highly related regions without the need of overt tasks. In addition, to test the possibility of multiple systems against the previously proposed “core” system of control (Dosenbach et al., 2006; Duncan, 2001), graph theory approaches were applied by modeling the connectivity of the

39 regions as a network composed of nodes (the regions) and edges (pairwise connections). As a result, it was discovered that the control regions appeared to organize into two distinct systems. One system, the cinguloopercular system (CO), primarily consisted of dACC/msFC and aI/fO. Similar to the "core" regions, CO displayed start-cue and error signals in addition to sustained activity. The other system, the frontoparietal system (FP), contained mostly regions in the frontal and parietal cortex (e.g. dlPFC, mCC, and IPS), and it exhibited only start-cue and error signals. It is important to note that these two systems may operate at different time-scales, with CO showing more sustained activity related to maintenance of task set over longer period of time and FP showing more transient activity related to the loading/adapting the of task set parameters.

As the distinctness of CO and FP has been bolstered by other resting-state as well as lesion studies (Nomura et al., 2010; W. W. Seeley et al., 2007; Vincent et al., 2007), extant characterizations of these two control systems have expanded by more recent studies of CO and FP activation across a variety of tasks. A re-analysis of tasks included in the original Dosenbach meta-analysis revealed that tasks driven mainly by perceptual information do not elicit sustained activity in CO regions (Neta et al., 2015). Follow-up experiments revealed that sustained signals are not driven by task difficulty (perceptual difficulty does not drive sustained activity; Dubis, 2015). Rather, tasks that require top-down information related the overall task set, such as the need of abstracted representations beyond perceptual information (e.g. extraction of semantic information from living/nonliving judgment) and tasks that require maintenance of sequential operations seem to fulfill the criteria for recruitment of sustained activity. Hence, this finding refined the functional role of CO in subset of tasks. Furthermore, besides the sustained signal, CO responds separately to various performance-related signals (e.g. conflict and ambiguity in addition to error), suggesting additional role in task feedback when adjustments in performances are required. Moreover, while CO and FP both show error-related and cue-related responses, they are characterize by different error response time scales and cue types (Neta et al., 2015; Wallis, Stokes, Cousijn, Woolrich, & Nobre, 2015), which imply dissociable implementations of these events.

Continuing Explorations

While most distinctions of different control systems uphold their unique functional identities that involve initiating, maintaining, and/or assessing a set of “task rules” that direct the moment-to-moment operations carried out by data-processing systems, there is also support for trial-level processes that does not fit the identified control signals (Gratton et al., 2016; Nelson, Dosenbach, et al., 2010). In a meta-analysis of decisions-making tasks, Gratton et al. 2016 showed that right FP, left FP, and CO regions displayed separate functions in relation to moment-to-moment decisions-making. Particularly, the left FP displayed an “accumulator-like” response that suggest a role more related to information processing rather than control. Hence, in an effort to explore how these trial-related activation contribute to top-down control, Chapter 3 focus on a meta-analysis of goal-direct tasks that allows for observation of the interplay among different control regions in the context of both control and ongoing information processing.

III. Task-State Functional Connectivity

As control systems act as the source of multiple control signals that direct each moment-to-moment process during task, successful instantiation and implementation of goal-directed behaviors rely on the careful orchestration and coordination of both top-down control systems and bottom-up processing systems. Past electrophysiology as well as fMRI research has shown, especially in the field of visual spatial attention, modifications of neural processing in visual cortex due to spatially oriented attention (likely originated from control-related regions). However, the relative timing as well as the likely durations of the interactions, during task, between control and processing systems remain unclear.

Modulations in Visual Processing Due to Attention

Convergent evidence from nonhuman primate electrophysiology and human functional imaging studies has indicated that attention affects neural processing in the visual cortex. In single cell recording studies, animals might alternate between covertly (without explicit eye movements) directing its attention to a stimulus within a visual neuron's receptive field versus directing attention to elsewhere, away from the receptive field. It has been demonstrated that neural responses to an attended object within the receptive field are enhanced compared to the alternative when animal attends to outside of the receptive field. Such phenomenon is present for neurons in V1, V2, as well as in ventral extrastriated area V4 (Connor, Gallant, Preddie, & VanEssen, 1996; Luck, Chelazzi, Hillyard, & Desimone, 1997; Motter, 1993), and the effect increases with task difficulty (Spitzer, Desimone, & Moran, 1988), suggesting that increased attention increases the responsiveness of the neuron towards processing an attended stimuli.

Additionally, fMRI studies from Kastner and colleagues revealed response differences in visual cortex related to attention directed to multiple competing stimuli versus noncompeting stimuli (Kastner, De Weerd, Desimone, & Ungerleider, 1998). The experimental design included four complex images that were presented in nearby locations. The stimuli were presented under two different conditions: sequentially or simultaneously. In addition, two attentional conditions were also examined: during the attended condition, subjects were instructed to attend to a specific stimulus and to count its number of occurrences while in the unattended condition subjects' attention was directed away from the stimuli. The results showed that while the same areas of the visual cortex were activated under both the attended and unattended condition, the attended condition evoked more activated volumes in V4, TEO, and MT. Furthermore, in single-cell recordings, it has been demonstrated than when two competing stimuli were simultaneously presented within a neuron's receptive field, the magnitude of the neuronal response is a weighted average of the responses to the individual stimuli when presented alone. This suggested a possible mutual suppressive influence of the stimuli. However, when attention was directed towards one of the two stimuli, the neural response was as large as when the stimulus was presented by itself (Moran & Desimone, 1985; Reynolds, Chelazzi, & Desimone, 1999). Here, under the attended condition, the directed attention led to greater activation to simultaneously presented stimuli than for sequentially presented stimuli, indicating that attention enhances the processing of the attended stimuli and filters out competing but unwanted information.

Furthermore, the effects of attention do not depend on the presence or absence of exogenous stimulation. Luck et al., demonstrated when the animal was cued to covertly attend to a location within the neuron's receptive field, before any stimulus was presented, the spontaneous firing rate of the neuron increased 30% - 40%. This has been interpreted as the effect of top-down signals from high-order areas (Luck et al., 1997). However, what is the mechanism for which the top-down signals bias the relevant information and suppress other superfluous information?

Modulations in Task-based Functional Connectivity

Al-Aidroos and colleague proposed such strengthening in representation of prioritized data is through enhancing functional connectivity, the correlation of the spontaneous BOLD signals, between the relevant brains regions (Al-Aidroos, Said, & Turk-Browne, 2012). Past studies have primarily observed the correlations in BOLD signals during resting-state, when subjects are not actively engaged by external stimulation. If two regions show highly correlated fluctuation in BOLD signals, they are presumed to be more related to each other in function than if their BOLD signal fluctuations were not correlated. To interpret BOLDs correlations between two regions when the subject is actively engaged in attention related tasks is complicated by any evoked responses as result of stimulus presentation. Any regions whose responses are time-locked to the presentation of stimuli will correlate highly together, but this stimulus-driven correlation does not inform us about the relatedness of the regions. Hence, to observe functional connectivity during task, first-order stimulus-evoked BOLD activity need be removed from the task-runs. Since spontaneous and task evoke BOLDs are linearly superimposed, it is possible to use general liner model (GLM) to regress out evoked activity from task time-series (Fair et al., 2007) and to extract the spontaneous BOLD signals.

By regressing out task evoked activity, Al-Aidroos et al. showed that extrastriate visual area V4 and ventro-temporal visual association regions (i.e., the fusiform face area and parahippocampal place area) will flexibly increase their BOLD correlations based on the task at hand (e.g., attend to faces or attend to scenes). This perhaps demonstrates that attention may increase functional relationship, at least between higher and lower areas of the visual cortex, in service of prioritizing goal-directed information. In addition, it has been shown that long-range modulation between control-related regions (e.g., prefrontal cortex, intraparietal sulcus) and processing related regions (e.g. visual association regions) can be enhanced or suppressed based on concurrent attentional goals as well (Chadick & Gazzaley, 2011; Gazzaley et al., 2007; Spadone et al., 2015), providing added evidence that control related regions may be the source of modulatory attentional signals.

However, these past studies leave open the exact timing for how control and processing regions interact, and it remains unknown whether control systems maintain the enhance connection with processing systems throughout the whole task, or just during preparatory periods when task goals are specified. Hence in Chapter 4, we test these two hypotheses using a standard Posner task with cue-target paradigm that temporally separate the preparatory portion of each trial from the target execution portion. In attempt to understand the dynamic interactions between control and processing regions, we will directly compare the region-to-region correlations between control and processing systems during preparatory portion to those during the target execution portion.

IV. General Summary

This thesis describes the contributions of different control systems to different types of top-down trial-level control signals (i.e. trial-wise preparatory and response-related control signals) in the contexts of activation response profiles as well as task-based connectivity changes. Complementary to the system classification in the works of Power et al. 2011 and Gordon et al. 2015, we begin by detailing a study that explores the resting-state connectivity of control systems as part of a whole-brain network. In Chapter 2, we applied the concept of link communities, which allowed the description of overlapping functional systems, and compared the results from link communities to previous results from conventional methods. The link-based scheme suggests that regions in control-related systems, such as the frontoparietal, cinguloopercular, and dorsal attention systems, have multiple assignments that are widely distributed among a diverse set of networks while sensory-related networks show restricted overlaps. In Chapter 3, we conducted a meta-analysis of three distinct goal-directed tasks with trial-wise implementations to examine whether distinct systems show separable response patterns that reflect unique functional roles at trial-level. We identified two distinct trial-related response profiles that divided the regions of control systems into a right frontoparietal and cinguloopercular cluster and a left frontoparietal and dorsal attention cluster. Further analyses of the controls regions' response characteristics presented new insight onto their unique roles regarding to trial-wise controls as well as implementations during goal-directed tasks. Finally, in Chapter 4, we use a Posner paradigm to compare cue- and target-related changes in functional connectivity between control (e.g., frontoparietal and dorsal attention) and processing (e.g. visual and motor regions) systems. This study is complementary to both Chapter 2 and Chapter 3 in that it brings together the task-evoked as well as the intrinsic aspects of control systems. Overall, the study reveals the presence of complex dynamics among the functional systems as a result of signals related to goal-directed attention and control. Together, the studies presented in the current dissertation demonstrate that the control systems of the brain maintain their own identities during rest and assume primarily distinct functional roles during task, and they interact with other processing systems in service of goal-directed tasks.

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CHAPTER 2: OVERLAPPING FUNCTIONAL SYSTEMS ORGANIZATION IDENTIFIES INTER-COMMUNITY RELATIONSHIP

I. Abstract

The brain can be thought of as a large interactive network of distributed functional areas. Recent studies using resting state fMRI data and graph theory methods have identified various functional systems of the brain. However, although we know that the brain is a complex network and that functional systems interact, current network-based methods for studying the brain lack description of inter-systems connections and assume that functional systems are neatly separable. Here we applied the concept of link communities to detect functional systems with regions that potentially participate in multiple systems. By comparing the results from link communities with previous results using conventional node-based methods, we observed several notable interactions among the functional systems. The link-based scheme suggests that regions in control-related systems, such as the frontoparietal, cinguloopercular, and dorsal attention systems, have multiple assignments that are widely distributed among a diverse set of networks while sensory-related networks show restricted overlaps. By assessing regions of system-overlaps using other graph theoretical measures, we found that these regions converge with regions that may be significant to the integrity of inter-community connections. Finally, our results provided insight onto the level of association between two functional systems by

quantifying the extent of overlap between them and providing a more detailed representation of the relationship between different systems.

II. Introduction

The brain can be studied as an interactive network of functional areas.

At the systems level, the brain can be thought of as a large interactive network of distributed functional areas. Much like the person-person interactions of a social network that results in formations of communities and organizations, distributed sets of brain regions harmonize and correlate among themselves as sub-systems of a bigger network to support specialized higher level functions (Goldman-Rakic, 1988; M.-M. Mesulam, 1981; Power et al., 2011; Yeo et al., 2011). Hence, an appropriate tool for studying interactive networks of all scales-- graph theory-- has recently gained popularity in the field of neuroscience, and it has been used extensively to explore the properties of the brain network and the identities of its functional sub-systems (Bullmore & Sporns, 2009; Meunier, Lambiotte, & Bullmore, 2010; Power et al., 2011; Rubinov & Sporns, 2009; Sporns, 2013; Wig, Schlaggar, & Petersen, 2011).

Previous works have described a whole-brain network using resting-state functional Magnetic Resonance Imaging (rs-fMRI) data and modeled either individual voxels or putative functional areas of the brain as the units or *nodes* of the network. The nodes' pair-wise relationships, which can be measured by correlations in the blood oxygen level dependent (BOLD) fMRI signals, are modeled as the *edges or links* of the network (Buckner et al., 2009; He et al., 2009; Meunier, Lambiotte, Fornito, Ersche, & Bullmore, 2009; Power et al., 2011; van den Heuvel, Stam, Boersma, & Hulshoff Pol, 2008). Systems of the brain are then identified through the usage of data-driven community detection algorithms (Fortunato, 2010; Newman,

2006) that look for communities of nodes that are significantly correlated with each other. Examples of detected functional sub-systems include sensorimotor systems (e.g., the visual system, the motor system), control systems (e.g., frontoparietal and cinguloopercular systems, dorsal and ventral attention systems), and the default mode system (Corbetta & Shulman, 2002; Dosenbach et al., 2007; Greicius, Krasnow, Reiss, & Menon, 2003; Power et al., 2011; M E Raichle & Snyder, 2007; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008).

The functional sub-systems of the brain may not be neatly divisible from each other

However, despite successes in the identification of individual functional sub-systems of the brain, details about the relations between these sub-systems remain uncertain. A major question that the current report explores is whether the brain's functional sub-systems are neatly divisible from one another, or whether some regions effectively belong to more than one system.

In many real-world complex networks, the identities of communities at the node level are not always easily separated (Palla, Barabasi, & Vicsek, 2007; Palla, Derenyi, Farkas, & Vicsek, 2005). For instance, in the context of social networks, a person often belongs to more than one social group, e.g. to a family, a company, and a club. Hence there is overlap in the membership of many communities. More importantly, because of these overlaps in community membership, integration of functions in society can be obtained. The brain may also function as a complex network with overlapping functional sub-systems works. For example, (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006) reported that even though the dorsal and ventral attention networks are considered to be two separate attention-related networks, there are regions in the prefrontal cortex that correlate strongly with both systems. Fox's study provided early evidence that suggests the presence of overlaps in known functional sub-systems. Moreover, the study further speculated that the regions of overlap might serve to mediate interactions between the dorsal and ventral attention systems. A more recent study from (Yeo, Krienen, Eickhoff, et al., 2014) explored possible overlaps in brain systems by applying Independent Component Analysis (ICA) and Latent Dirichlet allocation, which permit a brain region to belong to multiple systems but require a priori estimates of number of systems. The study found that several notable association regions (e.g. lateral temporal cortex, medial prefrontal cortex, and posterior parietal cortex) belong to at least two functional systems and might serve as points of interactions. Hence, understanding how sub-systems are interconnected with each other provides insight into the cooperation and mediation among functional sub-systems.

While past investigations into functional brain organization using various methods (e.g. seed-based correlation and ICA) suggest the presence of overlaps among functional systems (Fox et al., 2006; Yeo, Krienen, Eickhoff, et al., 2014), network-based exploration of overlapping functional systems of the brain has been limited. The network-based framework can be especially useful because it allows for quantitative descriptions that comprehensively characterize the overall network, portions of the network, and individual nodes of the network. However, many current graph-based community detection algorithms are restricted by their underlying assumptions that are tailored to identify only separable communities. In other words, many of the most effective algorithms are unsuitable for the task of observing communities with overlapping regions as they only permit nodes to belong to a single community. As a result, while sub-systems like the default mode, frontoparietal, and ventral attention systems have been highlighted by current community detection algorithms as separate entities, their intercommunity relationships in the context the brain network remain murky.

Use link communities to explore the brain's overlapping functional sub-systems

The current work models the brain's large-scale functional networks as comprised of overlapping sub-systems by adopting a new approach proposed by (Evans & Lambiotte, 2009) and (Ahn, Bagrow, & Lehmann, 2010) called link communities. In the example we introduced before of a social network, an individual (modeled as a node) can belong to multiple communities: school, family, karate clubs, etc. However, Ahn et al. observed that connections (modeled as links) between individuals from each of these groups usually exist for one specific reason (i.e. family ties, coworkers, classmates, etc.). This specificity makes network links more separable into communities than network nodes. Thus, within this framework, unique social relationships are embodied by groups of links that are organized into communities, and communities based on links show lower overlap compared with communities based on nodes. Hence, discrete communities like the link communities are more compatible for many of the current community detection algorithms. More importantly, this method allows a node to participate in more than one community, as determined by the communities assigned to its connected links.

A previous study by (de Reus, Saenger, Kahn, & van den Heuvel, 2014) explored the overlapping community structure of structural connections in the human brain based on a link community analysis of diffusion tensor imaging data. Here, we propose to introduce the link community method to analyze functional data and to observe overlapping functional systems of the brain based on fMRI data from a large sample of healthy individuals. Furthermore, we use node-based brain networks generated from Power et al. 2011 for direct comparison with our link-based brain networks. Since the two methods provide two different perspectives on the same network, this allows us to ask how the identified functional sub-systems compare. Our results show that, although the identities of the functional sub-systems are similar between the two methods, the method of link communities is able to elucidate which members of a functional sub-system are closely connected to other systems and how interconnected two functional systems are by their amount of shared memberships as a result of network overlaps.

II. Methods

Subjects

120 healthy young adults (60M/60F; 24.7 ± 2.4 years old) were recruited from the Washington University campus and the surrounding community. All subjects were native English speakers, were right-handed, and reported no history of neurological or psychiatric disease, and none were on psychotropic medications. All subjects gave informed consent and were compensated for their participation. All data were acquired with the approval of the Institutional Review Board at Washington University.

Data Acquisition

All subjects were scanned in a Siemens MAGNETOM Trio, a Tim System 3T scanner with a Siemens 12 channel Head Matrix Coil (Erlangen, Germany). A T1-weighted sagittal MP-RAGE was obtained (TE = 3.06 ms, TR partition = 2.4 s, TI = 1000 ms, flip angle = 8°, 127 slices with 1 × 1 × 1 mm voxels). A T2-weighted turbo spin echo structural image (TE = 84 ms, TR = 6.8 s, 32 slices with 2 × 1 × 4 mm voxels) in the same anatomical plane as the BOLD images was also obtained to improve alignment to an atlas. Functional images were obtained using a BOLD contrast sensitive gradient echo echo-planar sequence (TE = 27 ms, flip angle = 90°, in-plane resolution = 4 × 4 mm; volume TR = 2.5 s). Whole brain coverage for the functional data was obtained using 32 contiguous interleaved 4 mm axial slices. The number of volumes obtained in our cohort was 336 ± 121 (range 184–724).

Data Processing

Functional images underwent standard fMRI preprocessing to reduce artifacts. These steps included: (1) sinc interpolation of all slices to the temporal midpoint of the first slice, accounting for differences in the acquisition time of each individual slice; (2) correction for head movement within and across runs; and (3) within-run intensity normalization to a whole brain mode value (across voxels and TRs) of 1,000. Atlas transformation of the functional data was computed for each individual via the MP-RAGE scan. Each run was then resampled in atlas space on an isotropic 3 mm grid combining movement correction and atlas transformation in a single interpolation.

To reduce spurious variance unlikely to reflect neuronal activity, additional preprocessing steps were executed for resting-state data as recommended in (Power, Mitra, et al., 2014). Two iterations of resting-state preprocessing were performed. In addition to demeaning and detrending, the first iteration included a multiple regressions of nuisance variables from the BOLD data and a temporal band-pass filter ($0.009 \text{ Hz} < f < 0.08 \text{ Hz}$). Nuisance variables included (1) whole-brain, ventricular plus white matter signals, and (2) motion parameters derived by Volterra expansion (Friston, Williams, Howard, Frackowiak, & Turner, 1996).

Before the start of the second iteration, temporal masks were created to identify motion-contaminated frames. Head motion can cause spurious yet systematic changes in BOLD correlations that affect group comparisons (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Van Dijk, Sabuncu, & Buckner, 2012). Motion-contaminated volumes were defined as having frame-by-frame displacement (FD, described in (Power, Mitra, et al., 2014)) greater than 0.25 mm. High motion volumes in addition to uncensored segments of data lasting fewer than 5 contiguous volumes were flagged for removal. The procedure retained 1239±403 volumes of usable data per subject for task-residuals and retained 215±37 volumes of usable data per subject for resting-state.

Steps of second iteration of processing were similar to the initial processing stream but incorporated the temporal tasks described previously to censor motion-contaminated data. Finally, the data were interpolated across censored frames using least squares spectral estimation of the values at the censored frames. Finally, data with interpolated frames were passed through a band-pass filter ($0.009\ \text{Hz} < f < 0.08\ \text{Hz}$). However, even following this processing stream, censored frames were still ignored in the time-series used to calculate correlations.

Node definition

Our current brain network is composed of 264 regions of interest (ROIs) that represents the centers of putative functional areas. These ROIs were obtained by meta-analytic ROI definition and by fc-Mapping ROI definition (see Power et al. 2011 for further details). Briefly, for the meta-analytic ROI definition, a set of 151 ROIs were identified by searching from a large fMRI database for brain regions that reliably showed significant activity as result of higher-level task-related operations (e.g. cue and error responses) or expected behavioral responses (e.g. button-press and verb generation). For the fc-Mapping ROI definition, fc-Mapping technique from Cohen et al. 2008 (Cohen et al., 2008) was applied to the entire cortical surfaces of 40 young adults (separate from the 120 cohort), and 193 ROIs were identified. After combining the results from the two methods and eliminating redundant regions, a final set of 264 ROIs is produced, and each of the 264 ROIs is modeled as a sphere with diameter of 10mm around the center of the ROI

Edge definition

For each subject, the averaged resting-stated BOLD time-course in each of the ROIs was extracted, and the pairwise Pearson correlation coefficients between the ROI time-series was calculated to form a 264 by 264 correlation matrix. Short-distance correlations can often be distorted by data processing (e.g., blurring, reslicing) and from head motion (Power, Mitra, et al., 2014) In order to reduce the effects of such distortion on network structure, short-distance correlations (Euclidean distance <20 mm) were excluded.

Node-based Brain Network

A node-based network of the brain was constructed using the node and edge definitions described above; the averaged correlation matrix across all subjects was used for all analyses. Several modifications were made to the correlation matrix to suit graph analyses. First, because negative correlations carry ambiguous meanings for many graph theoretical measures, we only retained positive correlations and set the negatives to zero. Furthermore, correlations close to zero may be either insignificant or dominated by noise; hence, we eliminate them by choosing a positive threshold such that only correlations above the chosen threshold are retained. However, in choosing a threshold, there is not an absolute and correct value. Therefore, multiple thresholds are chosen to generate networks with different percentages of possible positive correlations (edge density). We chose a range of thresholds from $r = 0.18$ to 0.34 to generate the corresponding networks of 10.0 to 2.0 percent edge densities.

Link-base Brain Network

The method of link communities uses a link matrix to describe the relationship one edge has with every other edge of the network. Hence, a link matrix is an edge x edge matrix, with elements equals to the similarity between the two edges, for example, E_{ik}, the edge between node k and node i, and E_{jk}, the edge between node k and node j. Following Ahn et al. 2010, the similarity between E_{ik} and E_{jk} is calculated based on the neighbors of node i and node j, written symbolically as n_i and n_j. For a weighted network such as the brain network, the Tanimoto index (S) can be used as the similarity measure of the two sets of neighbors. The Tanimoto index is used in statistics to compare the similarity between two sample sets by looking at the ratio between the weighted sum of their shared elements and the weighted sum of the combined elements. To compare edges E_{ik} and E_{jk}, the similarity measure, S, is:

$$S(E_{ik}, E_{jk}) = \frac{|n_+(i) \cap n_+(j)|}{|n_+(i) \cup n_+(j)|}$$

This construction of the link matrix is applied to the correlation matrix at each edge density (i.e. 10% to 2%) examined.

Community Detection

Infomap is implemented to detect communities of both node-based and link-based brain networks. For more comprehensive understanding of this method, please see (Rosvall & Bergstrom, 2007). Essentially, Infomap applies the general concepts of coding theory to explore the regularities in a given network; it seeks a way to encode how information flows through the network by simulating the path of a random walker; the way a walker flows through a network should provide information about how the network structure relates to its behavior. A group of highly connected nodes will likely trap the random walker since they allow quick and easy flow among themselves. This scenario can be contrasted with regions that are between two modules: these regions likely have less interconnected edges resulting in fleeting visits from the random walker. Thus, Infomap uses the trajectory of a random walker to detect distinct communities. This method computes the fraction of time that a random walker dwells in a certain place by observing how often the walker visits each individual location. After a few iterations, possible partitions result from the frequency of visits.

For clarity, the term link-based functional sub-system will be used to refer to the communities detected through the link matrix while node-based functional sub-system will be used to refer to the network described by the filtered correlation matrix.

Construction of Consensus

By applying Infomap to our link-based version of the brain network at 9 different edge densities, we are able to observe edge-density dependent changes in the functional sub-systems; however, it is often helpful to obtain a summary for each node’s membership assignment(s) across all edge-densities. Therefore, we constructed a consensus assignment that summarized the most consistently observed link-based communities from all of the analyzed edge densities. Generally, we focused on communities that were observed across 4 or more consecutive thresholds, and assigned community memberships to ROIs that had a particular assignment for 4 or more consecutive thresholds, as well. One exception to this criterion is the ventral somatosensory-motor network (vSM), as it only appeared at the threshold of 2% and 3% edge density. However prior work has demonstrated that this division of the motor system is indeed reasonable (Burton, Sinclair, Wingert, & Dierker, 2008; Power et al., 2011); hence, we included vSM in our consensus.

Graph Theoretical Measures

Modularity

In graph theoretical analyses, the quality of community structure is defined by the Newman modularity measure (Girvan & Newman, 2002). A good community tends to have more intra-community connections than inter-community connections; for a particular partition, the modularity measure compares the ratio of these two types of connections against the case if the network were to be randomly partitioned.

Similarity Measures

A graph theoretic measure of similarity between two sets of network assignments is the normalized mutual information (NMI), which measures the amount of information one set of network assignments shares with another. NMI values range from 0 to 1, where values of 1 indicate identical assignments and values of 0 indicate no shared information. We use NMI to test the stability of our link-based network assignments across different thresholds as well as the similarities in assignments for link-based and node-based brain communities.

Participation and Overlapping Memberships

For node-based, or non-overlapping, communities, the metric for diversity of a node’s intercommunity connections is the participation coefficient. Introduced by Guimera et al., 2005 (Guimerà, Mossa, Turtschi, & Amaral, 2005), the participation coefficient evaluates the variety, rather than the mere number, of connections that stem from each node. Specifically, the participation coefficient of a network node spans from 0 to 1, where an index of 0 indicates that all of the node’s connections are within one single community, while and index of 1 indicates that none of the node’s connections are within the same community. For a given node, the participation coefficient is calculated as:

$$P_i = 1 - \sum_{s=1}^{n_s} \left(\frac{K_{is}}{K_i}\right)^2$$

where K_{is} is the number of edges the node i has that connect to nodes in community s, and K_i is the total degree of node i.

For overlapping communities, we use the number of link community memberships as a proxy to evaluate the diversity of a node. However two nodes with the same number of community membership do not necessarily show similar level of diversity. One node with 1 out of 10 edges belonging to another community may play a different role than a node with 5 out 10 edges belonging to another community. Here we adopted a similar calculation as participation coefficient that indicates the link-based diversity of a node: for a given node the link community participation is calculated as:

$$LCP_i = 1 - \sum_{L=1}^{n_L} \left(\frac{K_{iL}}{K_i}\right)^2$$

where K_{iL} is the number of edges of node i that belongs to link community L, and K_i is the total degree of node i.

IV. Results

Figure 2.1 describes the steps of deriving link-based communities from an averaged (120 subjects, 60M/60F, 24.7 ± 2.4 years old) connectivity matrix of 264 ROIs that represent the putative functional areas of the human brain. The current study observes the 264 x 264 connectivity matrix under several edge densities (i.e. we threshold the connectivity matrix so only the top 10% to 2% of the edges remain). For each thresholded connectivity matrix, we convert it to a link matrix, which is an edge x edge matrix with the elements equal to the similarity measures of pairs of edges. Finally, link communities are formed by detecting communities of highly similar edges using the Infomap graph community detection algorithm (see methods). Once the links are sorted into communities, the nodes are sorted into the corresponding communities as well by following the community assignments of the links connected to them. Here, by applying the method of link community to our brain network, we are able to derive communities that resemble various functional systems. These functional systems have overlapping memberships (e.g. many ROIs have memberships from multiple link-based functional systems) and we will explore such overlaps in the following sections. Specifically, we will look at two insights derived from link communities of the brain: (1) link communities provide information about whether a specific ROI shows diverse inter-community connections (e.g. a ROI has multiple community assignments versus singular community assignment), and (2) link communities provide information about whether a system (i.e. the dorsal system) shows high level of self-containment (most of the regions within system have singular membership) or integration (i.e. most of the regions within system have multiple memberships).

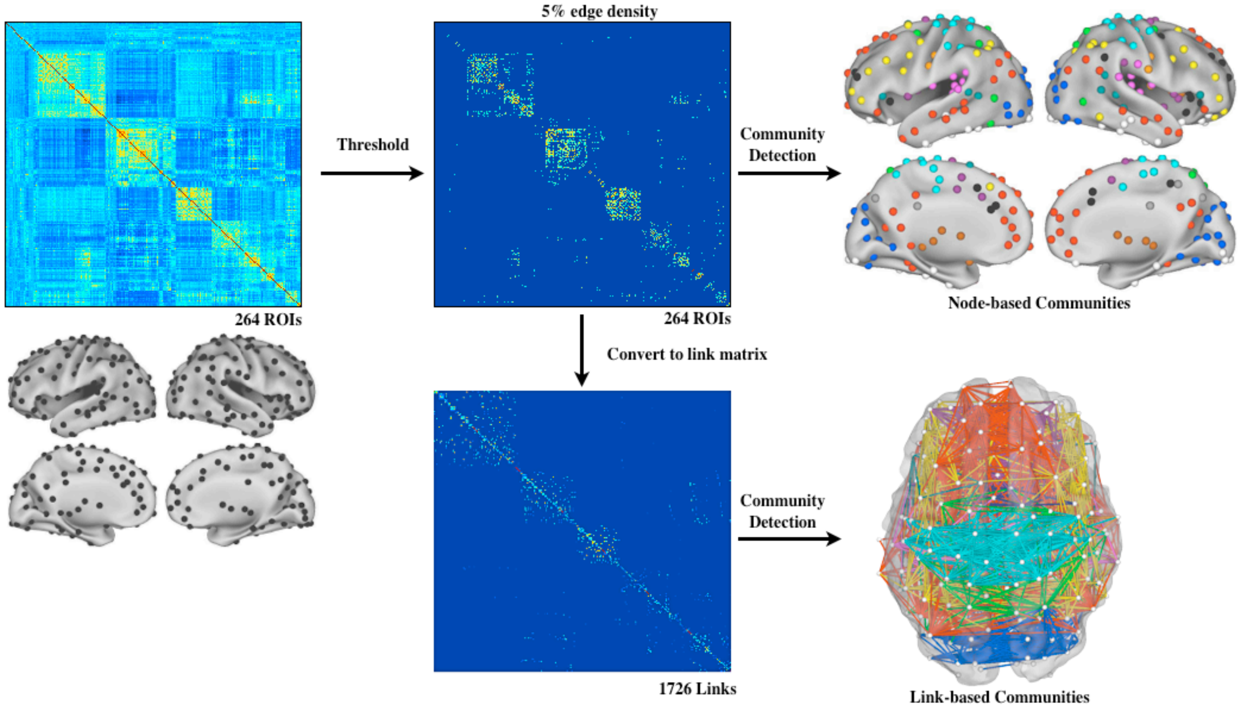

Figure 2.1. Deriving Link-based Communities of the Brain
In deriving link-based communities of the brain, the current study observed the 264x264 connectivity matrix under several edge densities. Here, the 5% edge density is shown as an example. For each thresholded connectivity matrix, we fist convert it into a link matrix, which is an edge x edge matrix with the elements equal to the similarity measures of the corresponding pairs of edges. Link communities are then formed by using the Infomap graph community detection algorithm to detect communities of highly similar edges. Once the links are sorted in communities, the nodes are sorted in to the corresponding communities as well by following the community assignments of the links connected to them.

Link-based communities are well-clustered and robust communities

The strength of the network's division into communities is evaluated through the modularity measure. For our averaged network of 120 subjects, link communities derived from 2% to 10% edge density correlation matrices have high modularity measures ranging from 0.627 to 0.745. This is comparable to the node-base communities derived from the same edge densities. The modularity measures for node-based communities ranged from 0.59 to 0.72.

Repeatability of results suggests stability. We compared link community assignments between two sub-groups of 60 subjects. At each edge density, we took the links that two groups have in common and calculated the normalized mutual information (NMI) of those links' community assignments. The average NMI between the two groups across all edge densities is 0.787±0.0235, **Supplemental Figure 2.2.**

Link-based functional systems

In order to observe consistently detected communities and their overlapping regions, we used a consensus community assignment that summarized the results across all analyzed thresholds (see Methods). The communities roughly fall into two categories, those that resemble control systems and those that resemble sensory systems. The control-like communities detected include a frontoparietal network (regions in middle frontal gyrus and inferior parietal lobule), a dorsal attention network (DAN, regions in the frontal eye field and posterior parietal cortex), and a ventral attention network (VAN, regions in the temporal parietal junction and ventral frontal cortex). Two distinct cinguloopercular (CO) networks were found: one spans the regions of anterior insula and dorsal anterior cingulate while the other spans regions in the posterior insula and mid-cingulate. The sensorimotor communities identified include a visual (VS), an auditory network, and two networks in somatosensory and motor (SM) regions. Other communities include a subcortical/thalamic network, a cerebellar network, and the default mode network. **Figure 2.2** provides visualization of the nodes within each link-based network; for visualization of the edges of link-based networks, see **Supplemental Figure 2.1**.

Through inspection, we see that our link-based brain network resulted in similar communities as that of the node-based brain network ((Power et al., 2011); **Figure 2.3**). **Figure 2.4** shows the NMI values between the link-based and node-based consensus communities. The two versions of DMN, visual, auditory, as well as FP, VAN showed especially good correspondence.

Despite the overall similarities, there are notable differences between link-based and node-based communities. For example, rather than having distinct divisions among the dorsal SM, ventral SM, and posterior insula regions that previously corresponded to hand/body SM, mouth/face SM, and auditory node-based networks (Power et al., 2011; Yeo et al., 2011), the link community approach is able to highlight both the separable as well as the overlapping natures of these systems. Three link-based networks were associated with SM and auditory regions: a larger network (light blue) that is composed of dorsal and ventral SM regions, a smaller community (orange) that is composed mostly of ventral SM regions and regions in the posterior insula, and a third network (pink) that was composed of auditory regions in the posterior insula. Among these three link-based communities we observed overlap between the SM (blue) and ventral SM (orange) networks and between the ventral SM and auditory (pink) networks. Given the ventral SM roughly corresponds to face/mouth portion of the motor strip, the overlap with the larger SM network suggests an association with other motor regions while overlap with auditory network may be driven by functional relatedness between ventral SM and auditory regions, e.g., by a history of coactivation during aural/oral communication. Instead of forming a distinct node-based community, subcortical regions (composed of regions of basal ganglia and the thalamus) share substantial link-based community assignment with regions in the anterior insula, which also belong to the cinguloopercular system. Previous studies of anatomical and functional connections between subcortical (basal ganglia and thalamus) regions revealed diverse cortical associations (Augustine, 1996; Greene et al., 2014; Riva-Posse et al., 2014). Especially, it has been shown that the cinguloopercular system correlates highly with portions of the putamen and palladium, even after regressing out the signals from cortical regions adjacent to the basal ganglia (Greene et al., 2014). Hence, shared link-based community among the anterior insula and subcortical ROIs may reflect the close relationships and communications between subcortical regions and cortical functional systems.

Two link-based networks (purple and black) were identified that encompass regions in the insula, operculum, and dorsal anterior cingulate. Comparatively, the purple network occupies more anterior regions of the insula and cingulate in addition to regions in the frontal gyrus, while the black sub-graph occupies the posterior portion of the insula and cingulate in addition to parts of the supramarginal gyrus. The purple and black link-based networks collectively resemble the distributed cinguloopercular and the salience systems described by Dosenbach et al., 2007 (Dosenbach et al., 2007), and Seeley et al., 2007 (Seeley et al., 2007) respectively. In addition, these link-based networks are comprised of similar ROIs as the node-based cinguloopercular and salience networks indicated by (Power et al., 2011). However, neither link-based network corresponds precisely with the node-based networks. Here, we tentatively refer to the purple link-based network as the anterior-cinguloopercular and the black link-based network as the posterior-cinguloopercular.

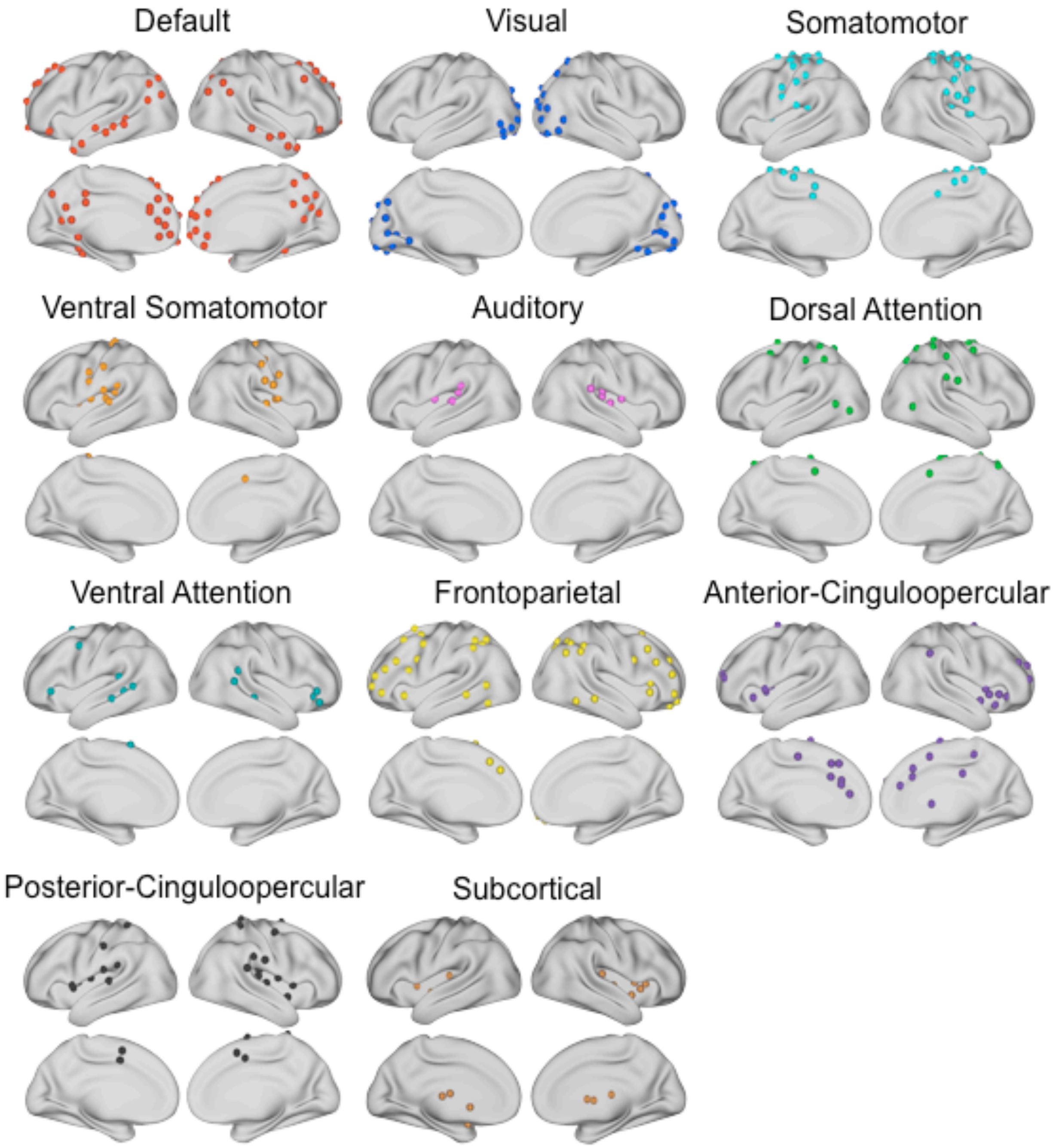

Figure 2.2. Consensus Link-based Communities
Familiar functional systems were detected in the link-based communities. Here, we show a consensus of the most stable link-based networks across all thresholds. Most of the link-based networks were very similar to the node-based networks from Power et al. 2011, shown in **Figure 2.3.** However, some of the familiar networks encompass additional ROIs that have alternative network assignments. For example, the subcortical link-based network is composed of

subcortical regions in addition to regions in the insula that also belong to the cinguloopercular network.

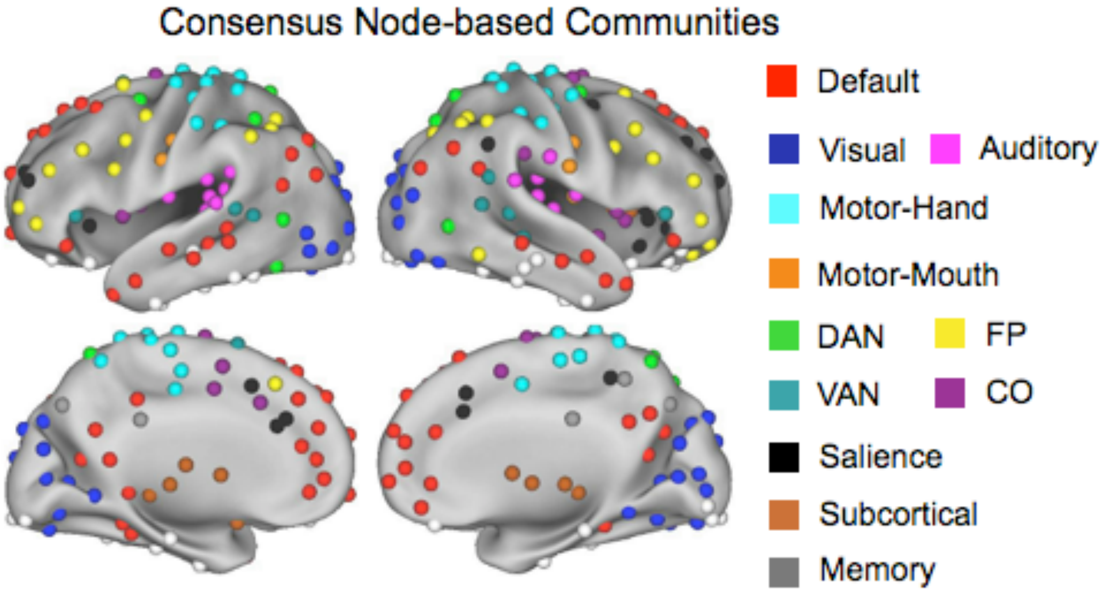

Figure 2.3 Consensus Node-based Communities (Power et al., 2011)

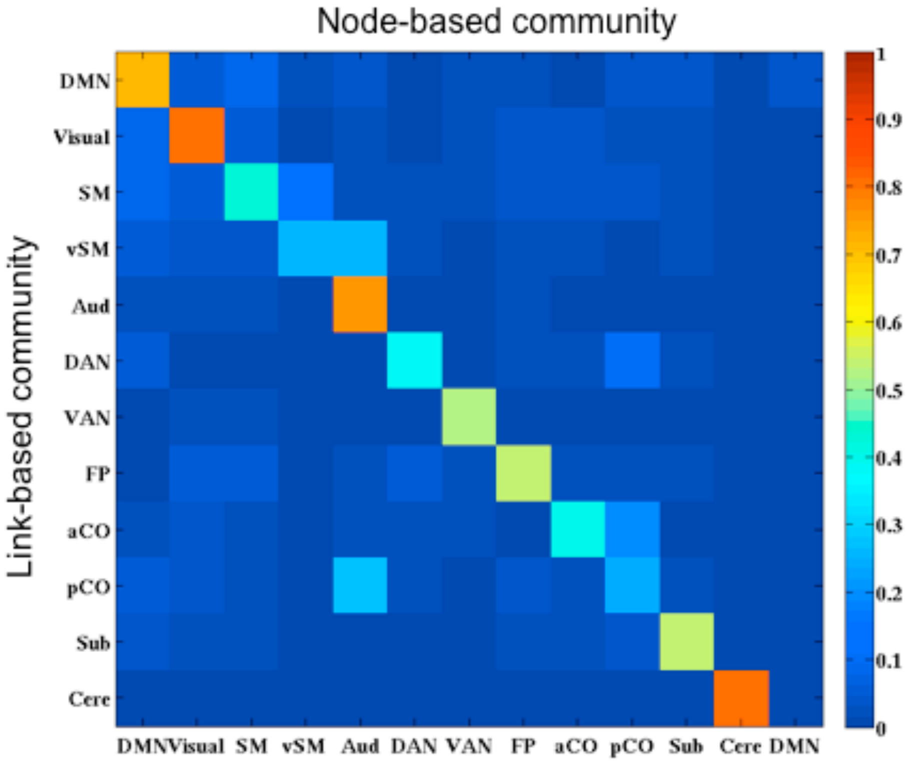

Figure 2.4. Similarity Between Node- and Link-based Communities
The similarity between the node- and link-based communities is quantified here, where it shows the normalized mutual information (NMI) values between sub-graphs from link-based and node-based systems.

Link communities provide information about whether a specific ROI show diverse inter-community connections

The consensus community assignment shows that a large majority of regions (175/264 ROIs) have singular membership while 89 ROIs have two or more memberships. We believe that the overlapping regions identified by link communities indicate that these regions may be areas of inter-systems communication. To identify ROIs with diverse inter-system connections based on link-based community assignments, we calculated the average link community participation index for each node (see methods) across a number of thresholds (2%-10% edge density). In **Figure 2.5A (left)**, increasingly warm colors indicate ROIs with more diverse overlapping memberships. As can be seen, ROIs in the anterior insula, mid-cingulate, and dorsal parietal regions have high diversity of community memberships while ROIs in the precuneous, supramarginal gyrus, and calcarine sulcus regions have low diversity of community memberships. ROIs with diverse memberships tend to belong to control related systems such as the cinguloopercular, frontoparietal, and dorsal attention systems, and ROIs with more uniform and low diversity memberships tend to belong to the default-mode and visual systems.

We also compared the ROIs' link community participation indices with their participation coefficients derived from node-based communities. In **Figure 2.5A (right)**, warmer colors indicate high average participation coefficients. Overall, ROIs' link community participation indices correlate with their node-based participation coefficients, see **Figure 2.5B.** The Spearman's rank correlation coefficient between the averaged (across different edge densities) participation coefficients and averaged link community participation indices is high (rho = 0.719, p<0.001). To highlight regions with particularly diverse connections, **Figure 2.5C** shows twenty ROIs with the both high link community participation indices and high participation coefficients. These ROIs are contrasted with twenty regions with low link community participation indices and participation coefficients.

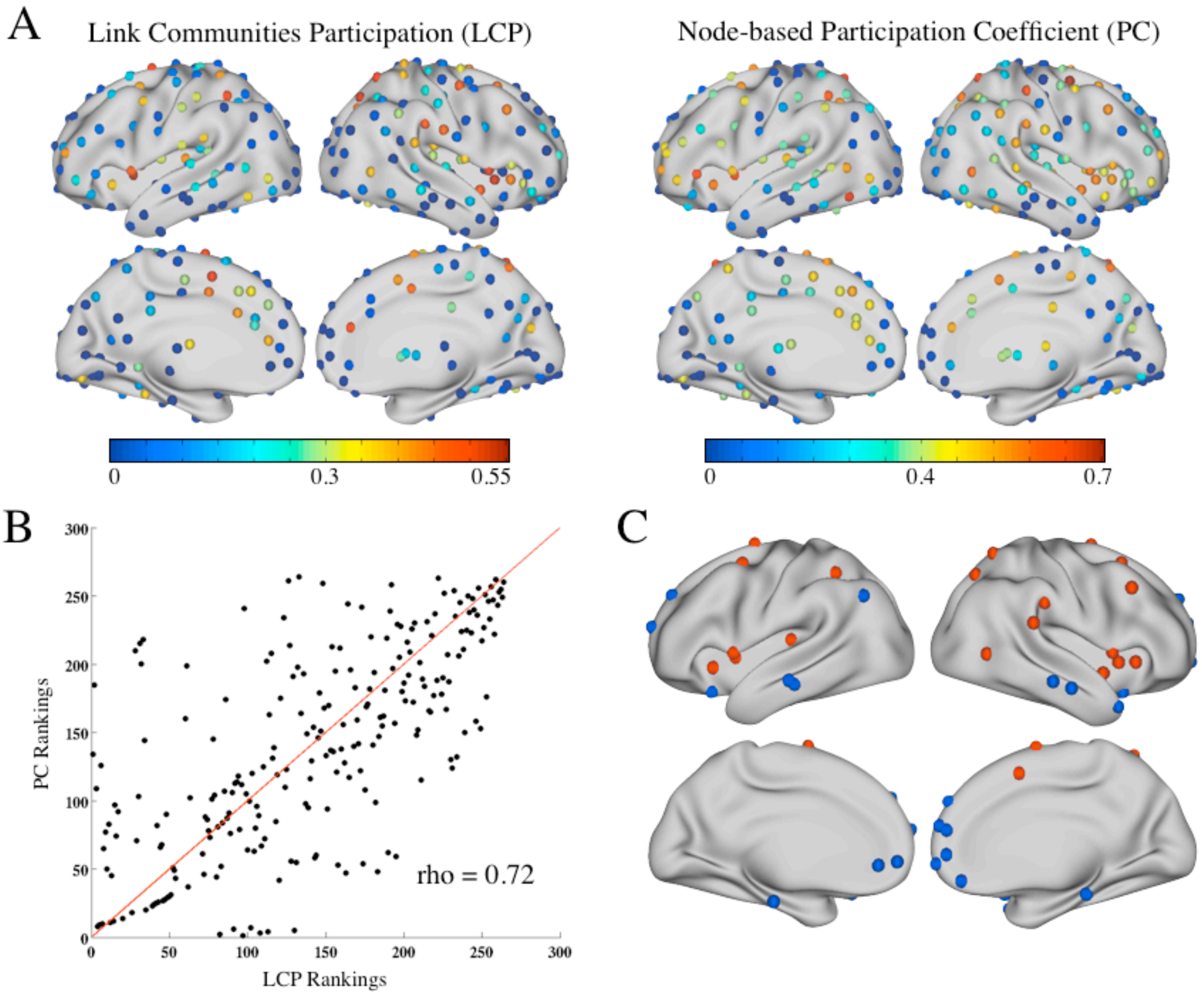

Figure 2.5. Node- and Link-based Participation Measures
The link community participation of an ROI is correlated with its participation coefficient from the node-based communities. (a) The cool to warm colors indicate the spectrum of low to high values of link community participation (LCP) and participation coefficients (PC). (b) The scatter plot illustrates the Spearman's rank correlation between the averaged LCP and PC across 9 thresholds. Each point in the scatter plot corresponds to an ROI. The Spearman rank correlation coefficient is high (rho = 0.72). The line indicates the theoretical scenario if PC and LCP

rankings were the same and provides comparison for our result. (c) Illustrates the 20 ROIs (red) with highest combined PC and LCP values and the 20 ROIs (blue) with the lowest combined PC and LCP values. For coordinates and the network assignment(s) for these ROIs, see **Supplementary Table 2.1**.

Link communities provide information about functional systems' levels of interconnectedness with each other

Link-based communities allow us to directly assess the diversity of connections for a functional network. In particular, with link communities we can assess (1) the distribution of single-membership ROIs versus multi-membership ROIs within a link-based community (e.g. how many ROIs assigned to FP network only have one community assignment versus how many have two or more community assignments), and (2) the diversity of memberships that exist within a particular link-based community (e.g. what are the other community memberships assigned to the ROIs in FP network).

Figure 2.6 illustrates the distribution of single-membership ROIs versus multi-membership ROIs among the consensus link-based communities. In the DMN, visual, cerebellum, as well as the VAN, the majority of their ROIs have only one membership, indicating that the majority of ROIs in these systems are more likely to communicate with each other than members of another system. On the other hand, the FP, DAN, aCO, pCO, and ventral SM have most of their members shared with 2 or more other communities. Having a higher amount of multi-memberships ROIs suggest that these systems may play more interactive roles with other systems.

Figure 2.7 details the identities of the other networks each link-based network overlaps with. In **Figure 2.7** the extent of pair-wise overlap between systems is displayed as a percentage of the (row) community's size. For example, the majority of ROIs in DMN (73.6%) only have one community membership. The other 26.4% of ROIs in DMN are distributed among several other functional systems: 12.5% are shared with the link-based FP system while 5.6% are shared with the link-based CO system. Less than 5.0% of ROIs in DMN overlap with link-based VAN and visual network. The majority of its ROIs (86.90%) in link-based DAN network, on the other hand, participate in other link-based communities. Specifically, DAN ROIs share their memberships strongly with the link-based SM (39.1%), FP (21.7%), and pCO (34.5%), and weakly with visual (17.4%) and aCO (13.0%). Overall, link community descriptions provide information regarding not only whether a community is interconnected with others but also the extent of such interconnections between two communities, an aspect that is not readily provided by previous node-based methods.

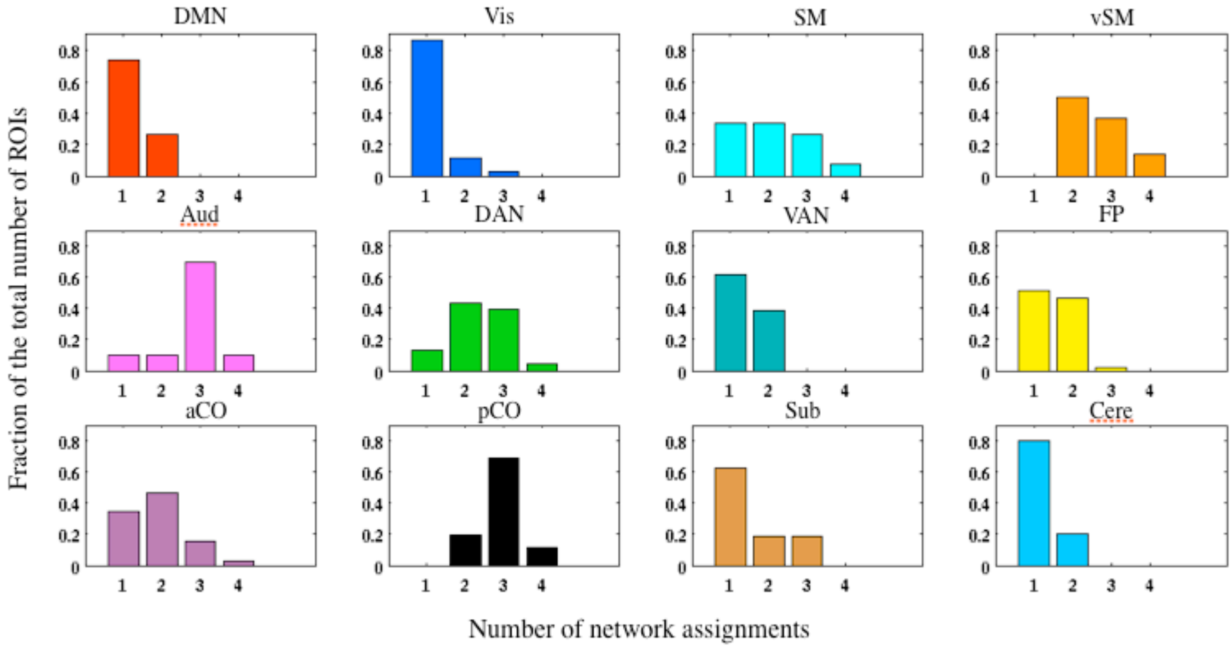

Figure 2.6. Distribution of Number of Network Assignments
Link community reveals how networks are interconnected with each other. Here, we assess the network interconnectedness as the distribution of single-membership ROIs versus multi-

membership ROIs within a link-based network. Specifically, this reveals that ROIs in networks, such the default (DMN) and the visual (Vis) network, are generally localized within single networks, but ROIs in the dorsal attention network (DAN) show more distributed assignments.

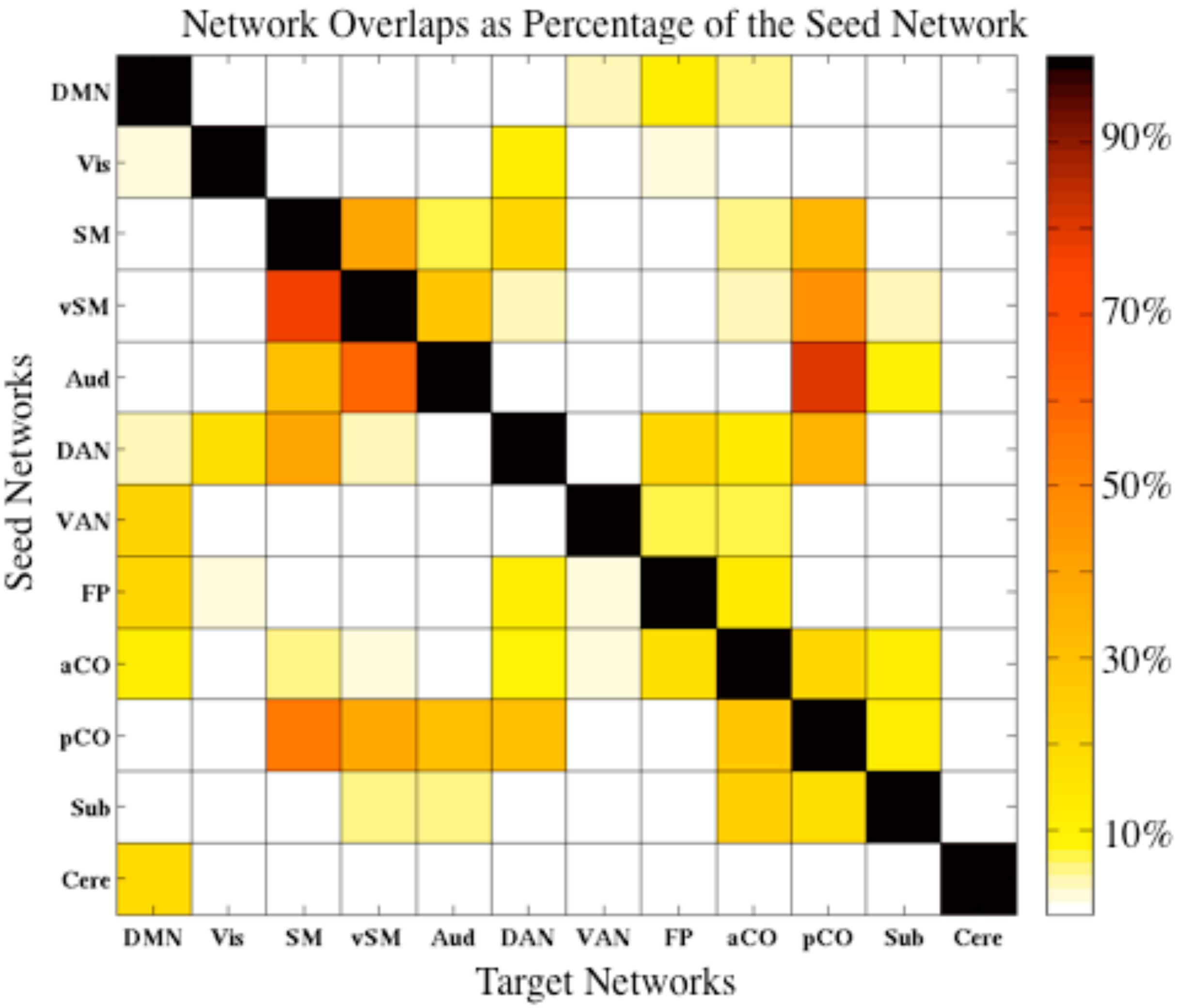

Figure 2.7 Network Overlaps

Each row is the seed network of focus, and the columns are the other networks with which the seed network might overlap. The elements of the matrix indicate the percentage of ROIs in the primary network that share network assignment with the secondary network. The matrix is not symmetrical because the same number of shared ROIs can constitute different percentages from different communities. The percentage of each row adds up to be more than a hundred percent because some of the ROIs in are shared amongst more than two networks. Combined with

Figure 2.6, the amount of overlap between to networks may provide insight into the degree of their interconnectedness.

V. Discussion

Current network-based methods for studying the brain do not allow regions to participate in more that one system, despite the knowledge that the brain is a complex network and that functional systems interact. Hence, the currently study used the concept of link communities to detect regions that participate in multiple functional systems. By comparing the results of link communities with results of conventional node-based methods, we gained new insights onto the intercommunity relationships among the various functional systems of the brain.

Link communities provide an overlapping view of the functional systems

Our link-based functional sub-systems show high convergence with the node-based network identities described in previous work (Power et al., 2011). The majority of regions that grouped together with traditional node-based methods were also grouped together by the method of link communities. When we map link communities onto the brain, **Figure 2.2A**, we see networks resembling the default network (red), frontoparietal network (yellow), cinguloopercular network (purple), and dorsal and ventral attention networks (lime green and teal) that have been introduced and identified in previous functional MRI studies (Corbetta & Shulman, 2002; Dosenbach et al., 2007; Greicius et al., 2003; Power et al., 2011; M. E. Raichle et al., 2001; Vincent et al., 2008; Yeo et al., 2011). The similarity is not only confirmation that the link community approach identifies biologically plausible systems (i.e., see Power et al., 2011 (Power et al., 2011)), but also provides converging evidence for the identity of the brain's major functional networks. Of note, however, there are several differences between the node-based and link-based description of the functional networks. For example, our link-based description includes an additional cinguloopercular network (black) that encompasses posterior insula regions in addition to some canonical cinguloperacular regions in the anterior insula and mid-cingulate. Overall, the differences between node-based and link-based network descriptions warrant further investigation.

Importantly, link communities improve upon the current network-based methods by allowing us to observe overlapping functional systems of the brain. A recent study from Yeo et al., 2014 (Yeo, Krienen, Chee, & Buckner, 2014) explored similar ideas. However, instead of a network approach, they used latent Dirichlet allocation and Independent Component Analysis to find overlapping clusters of voxels that represent functional systems. Similar to the results from Yeo et al. 2014, we observed that overlaps in functional systems occurred mostly in the association cortex such that systems associated with control and attention (e.g. dorsal attention system) often participated in multiple systems. A critical difference between Yeo et al. 2014 and the current study is that instead of using voxels as units of brain organization, we used a previously derived set of ROIs to represent our best estimates of the functional units of the brain (see Methods). This discrepancy may contribute to observations of different functional systems and levels of overlaps. For example, we did not detect addition divisions within the default mode system that contributed to its regions participating in multiple systems. A result, we concluded, in contrast with Yeo et al. 2014, that the default mode system is self-contained with most of its regions localized within the system. Nonetheless, we find that a major strength of our study is that, under the network framework, we are able to use other graph-theoretical measures, such as the participation coefficients, to provide additional quantitative descriptions to regions of overlaps (see following discussions).

Participation coefficient and link community membership

Previous studies emphasized a combination of measures such as centrality and multi-network participation to indicate a region's functional significance (Albert, Jeong, & Barabasi, 2000; Jeong, Mason, Barabasi, & Oltvai, 2001; Jeong, Tombor, Albert, Oltvai, & Barabasi, 2000; Power, Schlaggar, & Petersen, 2014). The link-community approach provides new utilities to evaluate the role of nodes within the network. Both participation coefficient and link community participation provide information regarding the diversity of a node's connections in the graph. For our brain network, information derived from participation coefficients of the node-based scheme and link community participation indices of the link-based scheme converged: there was high correlation between an ROI's participation coefficient and link community participation, which suggests that having regions with multiple community memberships is not simply a byproduct of the link community method, but rather is a reflection of the underlying network structure. Together, these measures identify locations where the functional border between two or more functional systems is blurred, and a point of articulation and integration among these systems may occur (Power, Schlaggar, Lessov-Schlaggar, & Petersen, 2013). These regions may be particularly significant for the flow of information that is crucial to the functional integrity of the brain. **Figure 2.4** shows 20 regions with both high participation coefficients and link community participations. Examples include bilateral anterior insula (aI), posterior parietal cortex (PPC), and posterior middle frontal gyrus (pMFG). Recent evidence demonstrates that focal brain lesions to some of these regions produced severe impairments in a wide range of cognitive domains (Warren et al., 2014) and to measures of functional networks (Gratton, Nomura, Perez, & D'Esposito, 2012), compared with lesions to regions that have low participation in multiple networks, such as anterior medial frontal cortex (amPFC). Such variation in level of impairments suggests the possible importance of these regions' functional role in multi-system communications.

Although the number of overlapping memberships correlates with participation coefficient, it does not simply replicate the information provided by participation coefficients. The aIns, pMFG, and PPC all have high participation coefficient, but link community assignment also indicates that aIns participates with the FP and CO executive control systems, and occasionally, the DMN (at some network thresholds). The PPC has high correlations with nodes in the FP, DAN, and visual systems, while pMFP participates with FP and DAN. Overall, the link community method provides additional insight into high participation ROIs and their functions by describing how these regions are related to a set of joined functional systems. For a comprehensive list of the overlapping network assignments of these regions, see **Supplemental Table 2.1**.

Network Overlap

Understanding the interactions between functional systems is important to studies of cognition and behavior (Akam & Kullmann, 2010; Buschman, Denovellis, Diogo, Bullock, & Miller, 2012; de Pasquale et al., 2012; Fornito, Harrison, Zalesky, & Simons, 2012; Spreng, Sepulcre, Turner, Stevens, & Schacter, 2013; Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010; Yeo, Krienen, Eickhoff, et al., 2014). The link community approach adopted here provides information regarding how different functional systems interact with each other (see Figure 4). The link-based scheme suggests that the majority of ROIs in control-related systems, such as the frontoparietal, cinguloopercular, and dorsal attention systems, have multiple assignments that are widely distributed among a diverse set of networks. As an example, 80% of the dorsal attention network members overlapped with both other control-related networks (i.e.

the cinguloopercular and the frontoparietal networks) as well as sensory-related networks as well (i.e. SM and visual networks). This is consistent with previous evidence that regions in the dorsal attention system, such as the intraparietal sulcus, post parietal sulcus, and frontal eye fields, serve as critical points for integration of information (Goldman-Rakic, 1988; M. M. Mesulam, 1998; Petersen & Posner, 2012). Sensory-related networks, instead, show multiple profiles: some, such as the visual network, only participate in single networks, while others, such as auditory and ventral SM networks, participate in a few. The overlaps in sensory-related networks are generally not as diverse as overlaps in control-related networks, and most of the overlaps with somatomotor-related networks are confined to the SM network that corresponds to hand/body, the ventral SM network that corresponds to face/mouth, and the auditory network. This is partially consistent with the idea that sensory-related regions preferentially participate in local networks (Power et al., 2011; Sepulcre et al., 2010; Yeo, Krienen, Eickhoff, et al., 2014), but networks with high likelihood of co-activation (i.e. aural/oral communication) may have substantial link-based overlaps.

Furthermore, link communities allow us to quantify the level of association between two functional systems (an aspect that is not easily appreciated from node-based communities) by calculating the extent of overlap between them. The quantification of network overlaps may be a particularly interesting feature because it may indicate functional relatedness and the likelihood of co-activation during task. In the previous example of ventral SM network, more than 70% of ROIs in ventral SM network share network assignment with the SM network, suggesting ventral SM is more closely associated with the rest of SM regions than with the auditory network. Other examples of specific overlaps between two networks indicated by link-based networks include, (a) between the frontoparietal and cinguloopercular networks, and (b) between the dorsal attention network and motor and visual networks, see **Supplemental Figure 2.3.** Previous literature has pointed to close functional relationships among these networks, such as the frontoparietal and cinguloopercular systems are associated with various executive control signals, and they work in tandem in control of working memory (Church, Bunge, Petersen, & Schlaggar, 2016; Dosenbach et al., 2006; Dubis, Siegel, Visscher, & Petersen, 2014; Gratton et al., 2016; Ihnen, Petersen, & Schlaggar, 2015; Neta et al., 2015; Wallis, Stokes, Cousijn, Woolrich, & Nobre, 2015). Our results noted that several regions, especially in the bilateral anterior insula and medial frontal cortex, overlapped the two systems, providing possible candidate regions for allowing between-system interactions. Additionally, although regions in the visual and motor systems tend to be more localized within their respective systems, they do show overlaps with the dorsal attention system, for example in regions of MT, posterior parietal cortex, and premotor cortex. Similar findings were reported in Yeo et al. 2014 (Yeo, Krienen, Chee, et al., 2014), and such overlaps among visual, motor, and dorsal attention systems may perhaps be involved in the transformation of visual information from primary visual cortex to the configuration of decisions in regions of premotor cortex. Additionally, the link-based frontoparietal network indicates substantial (>20%) overlap with the default mode network. Previous literature has pointed to a close association (although the nature of such relationships are mostly negative) between the frontoparietal and default mode systems during task (Fox et al., 2005; Spreng et al., 2010; Zalesky, Fornito, & Bullmore, 2012). Here, our current result provides additional evidence for interaction between the two systems and suggests that particular interactions might take place near regions in the superior frontal gyrus and temporal cortex that have been implicated in memory retrieval (Nelson et al., 2010). Other theories suggest that these regions are more likely to be involved in cognitive control operations that orient the focus of attention between internal and external environment (Spreng et al., 2013). Overall, a link community description provides a comprehensive and a quantitative view of system overlaps; however, future research is needed to elucidate further the functional nature of these overlaps.

VI. Conclusions and Future Direction

The link community method allows us to view the brain as an integrative network of overlapping functional systems. The link-based approach groups of region-to-region connections that are similar to each other, and through these networks of links we are able to observe several interesting qualities about functional network organization on both the regional level and system level. However, future work is needed to clarify the functional significance of the overlaps and how they are manifested during tasks.

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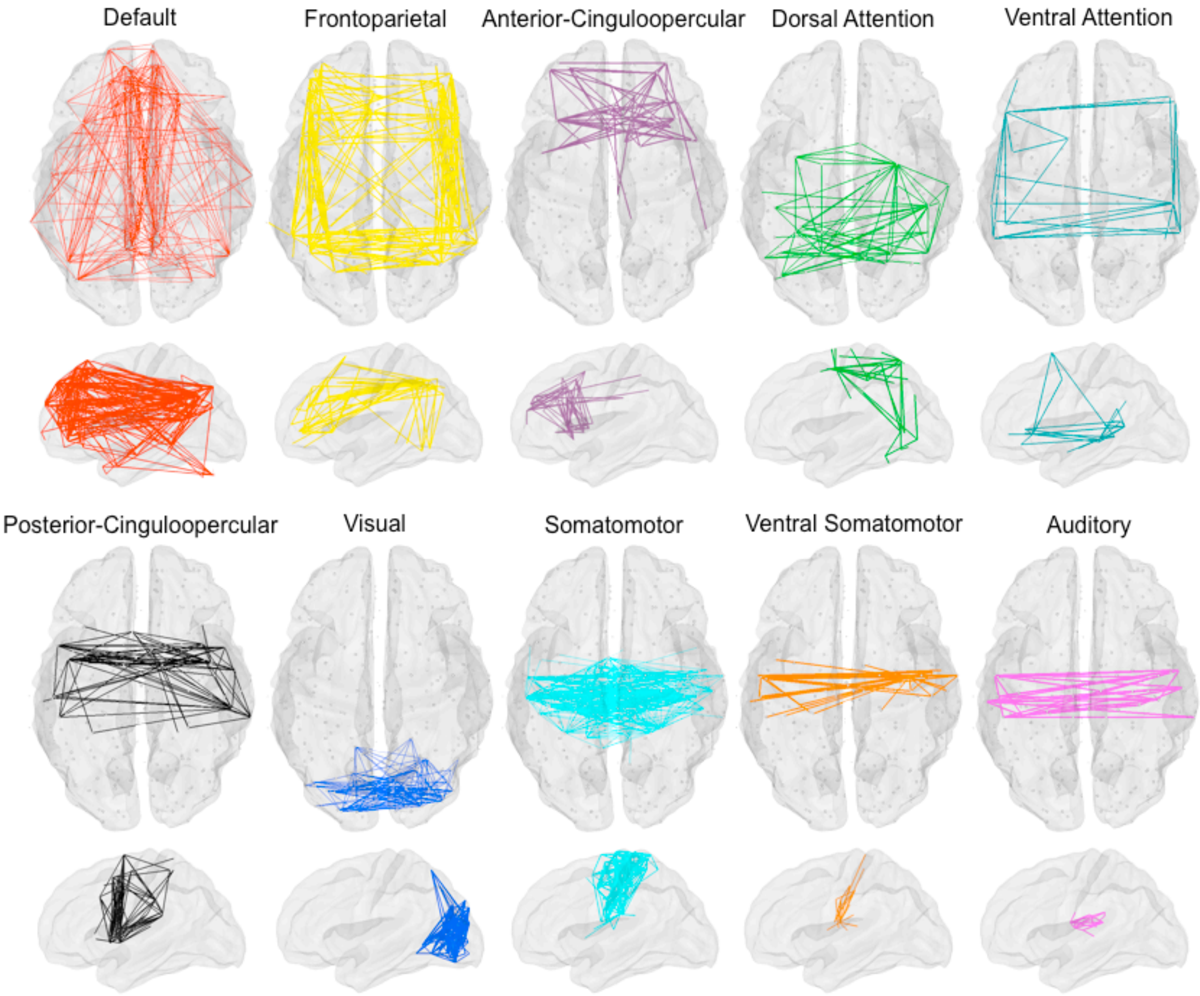
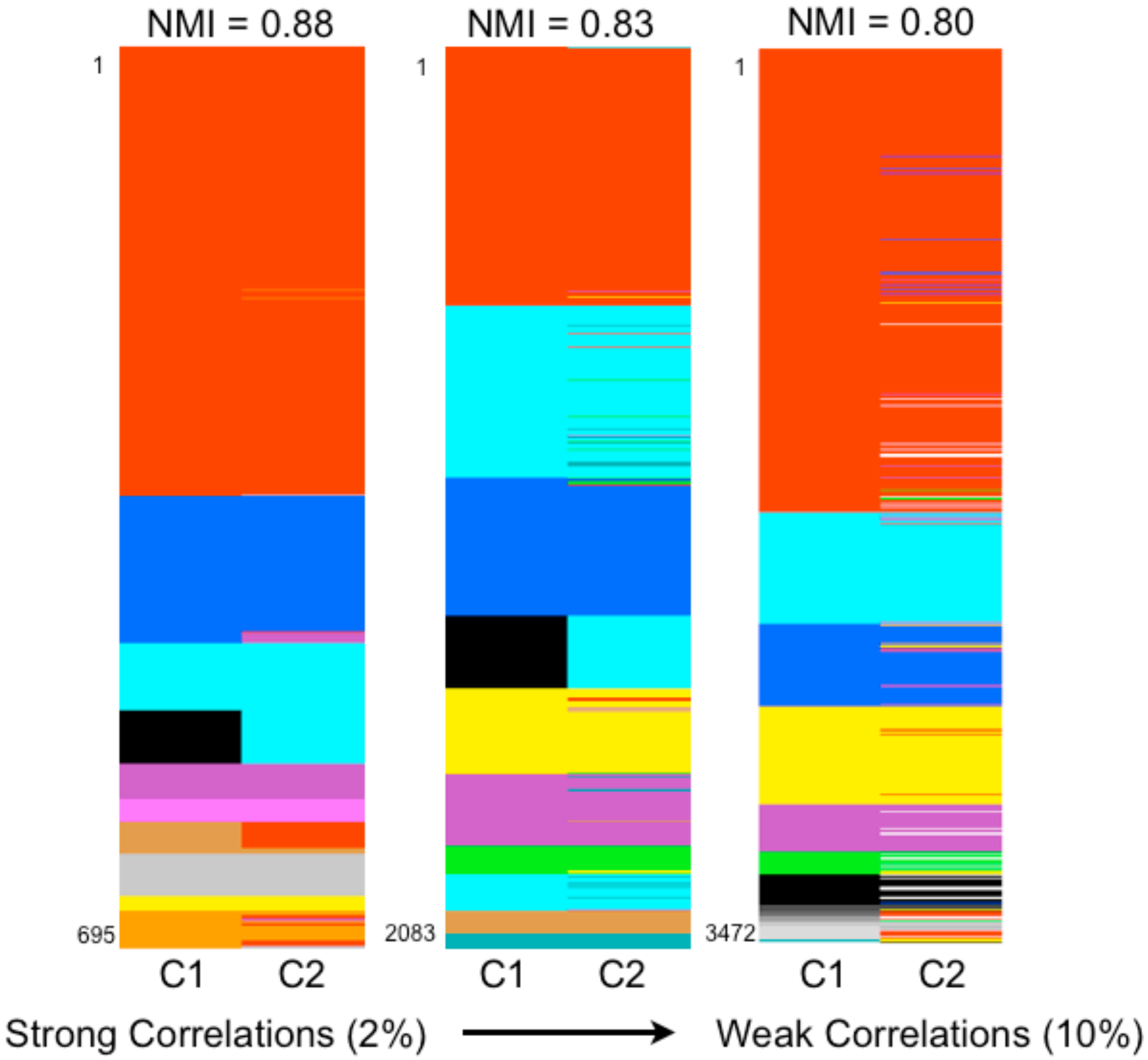
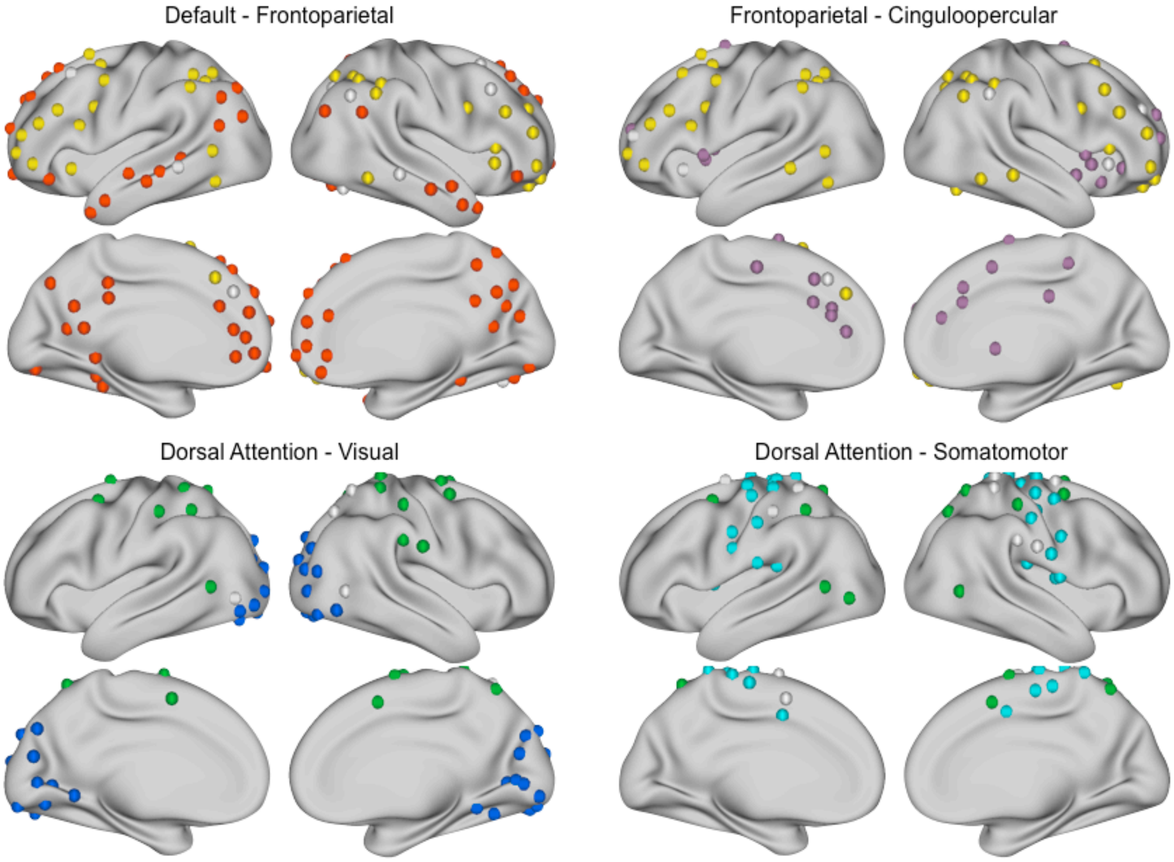
IX. Supporting Information



Supplemental Figure 2.1: A Visualization of the Edges of Link-based Networks
A visualization of the edges of link-based networks derived from our consensus. The link-base networks are colored and label similarly to **Fig 2**, which provides visualization of the nodes within each network.



Supplemental Figure 2.2: Reliability of Link-based Communities
In order to test for repeatability of the link-based communities, we compared the link communities' assignments between two groups of 60 subjects, cohort 1 (C1) and cohort 2 (C2). Links assignments from three thresholded connectivity matrices (10%, 6%, and 2% edge densities) are shown. The ordering of the links is identical for the comparisons. Normalized mutual information (NMI) indicates highly similar patterns across the cohorts (NMI = 1: identical information; NMI = 0: no shared information)



Supplemental Figure 2.3: Examples of Network Overlaps
Examples of specific overlaps between two networks indicated by the method of link communities. Networks are color-coded according to **Supplemental Figure 2.1**

Regions with the highest combined measures:

	X	Y	Z	Assignments
1	-16	-5	71	SSM, aCO, DAN
2	54	-28	34	SSM, DAN, pCO
3	65	-33	20	pCO, Aud
4	-30	-27	12	Subcortical, vSSM
5	13	-1	70	aCO, DAN, pCO
6	49	8	-1	aCO, pCO
7	-51	8	-2	aCO, pCO
8	7	8	51	aCO, DAN, pCO
9	37	1	-4	aCO, pCO, Subcortical
10	46	-59	4	Visual, DAN
11	40	18	40	Default, aCO
12	-34	3	4	Default, FP
13	36	10	1	aCO, pCO, Subcortical
14	-35	20	0	FP, aCO
15	36	22	3	FP, aCO
16	25	-58	60	Visual, DAN
17	22	-65	48	Visual, FP, DAN
18	32	14	56	Default, FP
19	-33	-46	47	FP, DAN
20	-32	-1	54	FP, DAN

Regions with the lowest combined measures:

X	Y	Z	Assignments
8	48	-15	Default
65	-12	-19	Default
6	54	16	Default
6	64	22	Default
-7	51	-1	Default
9	54	3	Default
-3	44	-9	Default
-44	-65	35	Default
13	55	38	Default
-20	45	39	Default
-20	64	19	Default
6	67	-4	Default
46	16	-30	Default
-21	-22	-20	Unassigned
65	-24	-19	Unassigned
-68	-23	-16	Default
-58	-26	-15	Unassigned
17	-28	-17	Unassigned
27	16	-17	Unassigned
-31	19	-19	Unassigned

Supplemental Table 2.1: List of Regions with Highest and Lowest Participation Measures Lists of regions of interest (ROIs) that have the highest and lowest combined measures of participation coefficient and link community participation measures. Link communities provide additional insight into ROIs by describing how the regions are related to a set of joined functional systems. For ROIs with high combined measures, they generally participate in multiple control systems. On the other hand, for ROIs with low combined measures, they mostly only belong to the default system.

CHAPTER 3: DISTINCT RESPONSE PATTERNS IN FUNCTIONAL SYSTEMS DURING GOAL-DIRECTED TASKS

I. Abstract

The executive control systems of the human brain are presumably sources of signals that allow for the implementation of daily tasks. Previous task-based as well as resting-state studies have identified distinct types of control signals (on both task set-level as well as trial-level) and multiple systems of brain regions that are involved in expressing such signals. Although extant characterizations of control systems have indicated separable roles for distinct control systems at task set-level, the contributions of control systems to different types of trial-level signals (i.e. trial-wise preparatory and response-related control signals) have not been extensively explored. Hence, we conducted a meta-analysis of three cue-target tasks that exhibit various trial-wise control and moment-to-moment processing signals to examine whether distinct systems show separable response patterns that reflect unique functional roles at trial-level. Overall, we identified two distinct trial-related response profiles that divided the regions of control systems into a cluster of right frontoparietal (FP) and cinguloopercular (CO) region and a left FP and dorsal attention system (DAN) cluster. The right FP/CO regions show late cue onset and strong error responses, suggesting roles in fine-tuning of task parameters and re-evaluation of performance. The left FP/DAN regions, instead, had early cue onset and strong activity for target

execution, suggesting that they are engaged in moment-to-moment updates of trial-related parameters and also possibly in moment-to-moment target processing itself. These heterogeneous but compact profiles provide evidence for separable contributions, and interplay, of different control systems during trial-wise, goal-directed, tasks.

II. Introduction

The executive control systems of the human brain are sources of control signals that allow for the implementation of daily goals and tasks (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Dosenbach et al., 2007; Power & Petersen, 2013; Shulman & Corbetta, 2011]. Previous task- and rest-based fMRI research has suggested that multiple systems of distributed brain regions are involved in expressing various control signals at both the task set level (i.e. establishment and maintenance of task parameters) as well as the trial level (i.e. moment-to-moment update of trial-related parameters and performance reporting) (Donaldson, Petersen, & Buckner, 2001; Logan & Gordon, 2001; Meiran, 1996]. Included in these systems is a cinguloopercular (CO) system, composed, in main, part of dorsal and anterior cingulate cortex/medial superior frontal cortex (dACC/msFC) and bilateral anterior insula/frontal operculum (aI/fO). Another is a frontoparietal (FP) system, composed of large portions in the dorsal lateral prefrontal cortex (dlPFC), midcingulate cortex (mCC), and intraparietal sulcus (IPS) (Dosenbach et al., 2008; Dosenbach et al., 2007; Dosenbach et al., 2006; Wallis, Stokes, Cousijn, Woolrich, & Nobre, 2015]. Other systems also likely contribute to executive control, including dorsal and ventral attention systems (DAN, VAN; (Corbetta & Shulman, 2002)), and a separate salience system (Seeley et al., 2007]. These control systems are thought to be distinct from “data-processing systems” (i.e. regions exhibiting activity that involves specific moment-to-moment transformation of information across stages of a task), which include sensory, perceptual, premotor and motor regions, as well as more complex systems (e.g. a set of memory-related regions in parietal cortex) (Gilmore, Nelson, & McDermott, 2015; Petersen & Posner, 2012; Posner & Petersen, 1990].

Extant characterizations of control systems have generally argued for different control systems maintaining their own functional identity that involves initiating, maintaining, and/or assessing a set of “task rules” that direct the moment-to-moment flow of information carried out by data-processing systems. For example, the CO system is thought to emphasize stable set maintenance activity across an entire task epoch, while the FP system supports more transient and adaptive cueing activity related to loading of preparatory parameters at the beginning of a task (Dosenbach et al., 2007; Dubis, Siegel, Visscher, & Petersen, 2014; Sadaghiani & D'Esposito, 2015; Sestieri, Corbetta, Spadone, Romani, & Shulman, 2014]. Additionally, the DAN system has been implicated in controlling spatial attention and biasing of pertinent sensory stimuli while the VAN system seems specialized for the reorienting of attention when unexpected but relevant stimuli appear (Corbetta & Shulman, 2002]. Moreover, these control systems consistently segregate during rest (Dosenbach et al., 2008; Power et al., 2011; Seeley et al., 2007; Yeo et al., 2011] and they show relevant and independent effects to focal lesions (Nomura et al., 2010; Shulman & Corbetta, 2011], further supporting the control systems’ distinct functional identities.

Besides evidence for control systems making separate contributions to overall task set control, there is also support for dissociation at the trial-level. Previous analyses of control regions’ blood oxygen level dependent (BOLD) signal time-course profiles indicated that regions across CO and FP showed dissociable response patterns in moment-to-moment decision-making and error-related activity (Gratton et al., 2016; Neta et al., 2015]. Overall, regions from different control systems are consistently active across trials of many tasks (Nelson, Dosenbach, et al., 2010), but how do these trial-specific activations relate to different types of top-down control? Complex fMRI designs have identified several trial-related control signals, which include, (1) trial-wise preparatory signals that set up trial parameters (e.g., cues), and (2) trial-wise response-related control signals (e.g., errors) that reflect performance reporting and feedback processes (Church, Bunge, Petersen, & Schlaggar, 2016; Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Donaldson et al., 2001; Hopfinger, Buonocore, & Mangun, 2000; Neta et al., 2015; Neta, Schlaggar, & Petersen, 2014]. However, in contrast with task set level signals, the contributions of separate control systems to different types of trial-level control signals have not been extensively explored. Hence, unlike previous studies, in which only isolated processes were examined (i.e. error and moment-to-moment processing related to decision making; (Gratton et al., 2016; Neta et al., 2015]), here we use data from three separate goal-directed tasks to contrast the systems' roles in aspects of preparatory- and response-related control (i.e. error) in combination with trial-wise processing.

We focused on goal-directed tasks with a cue-target paradigm because this paradigm temporally dissociates the trials into cue periods, which include the trial-wise preparatory signal (trial-wise control signal 1), and target implementation periods, which include activity related to correct target execution (trial-wise processing), as well as error signals (trial-wise control signal 2) (Hopfinger et al., 2000; Kastner, De Weerd, Desimone, & Ungerleider, 1998; Ollinger, Corbetta, & Shulman, 2001]. We used a meta-analytic approach to identify regions of the brain that are active across three separate cue-target tasks with varying input and output modalities. We then analyzed the regions' activity associated primarily with trial-wise cueing, correct target processing, and error-related feedback during incorrect target response to test whether regions within separate control systems show distinct neural responses to various trial-wise signals.

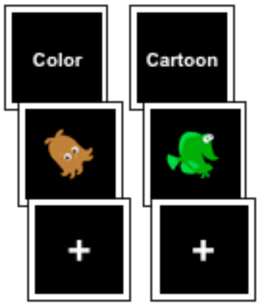
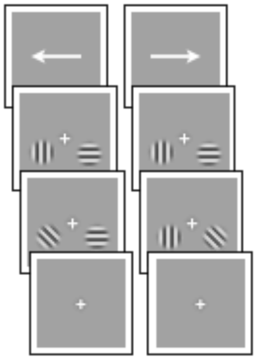
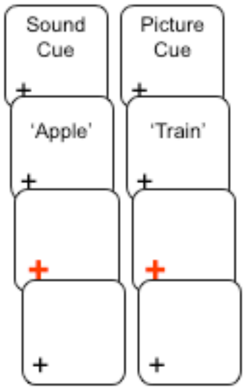
	Task 1	Task 2	Task 3
Task Condition			
Original Publication	Church et al. (2016)	N/A	Wheeler et al. (2006)
Stimuli	Words (cue), Images (target)	Images (cue), Images (target)	Tones (cue), Words (target)
Input Modality	Visual	Visual	Auditory
Output Modality	Button	Button	Button
No. of Subjects	30	30	23
TR (s)	2.0	2.5	2.36
No. of Trials	282	192	240
Scanner	3.0T	3.0T	1.5T
Design Type	Event-related	Event-related	Event-related

Figure 3.1: The Three Task Conditions Used in the Meta-analysis
Three task conditions are used in the meta-analysis. Task 1 is a switching 2-choice task where subjects are asked to identify either the color or the identity of the cartoon character. Task 2 is a Posner cueing task where subjects are asked to perform target detection. Task 3 is a memory retrieval task. Subjects are asked to member whether an item had been previously studied with a picture or a sound. Notably, unlike stimuli in Task 1 and Task 2, the stimuli used for Task 3 are auditory instead of visual. Subjects responded for all three tasks by pushing a button.

III. Methods

Task Descriptions

The meta-analysis utilized 3 separate cohorts of subjects; each cohort performed a different cue-target task, see **Figure 3.1**. The goal here was not to focus on how regions of the brain are activated specifically to a particular task. Instead, the purpose of the current study is to examine regions' response across several tasks and to determine how their patterns of activity inform us of their functional roles in relation to trial-related control and processing.

Task 1 consisted of a cue-switching 2-choice paradigm (Church et al., 2016]. Thirty adults between the ages of 21 to 30 years (12 females, average age is 25.6) participated in the experiment. Subjects performed 6 runs of the task that asked them to identify either the color or the identity of the cartoon characters. The 6 runs were grouped into 3 sets of 2, and for each task pair, the subject learned 2-button choice mappings for a pair of colors and cartoon characters. Subjects were instructed on a trial-by-trial basis to use one of two visually presented task cues (the word "COLOR" or "CARTOON") to make the appropriate response to the following target stimulus (a colorful cartoon figure) using the button choices learned previously. Trials were arranged for analysis in a rapid event-related design where cues were presented for one TR, and targets were presented in the subsequent TR. Inter-trial intervals were randomly distributed between 0, 1, and 2 TRs. In addition, approximately 21% of the trails had only a cue and no target to allow separation of the cue signals from the target signals (i.e., catch trials). For these trials, the subjects were instructed to forget the cue and wait for the next trial.

Task 2 was a visual attention task that resembled the Posner cueing paradigm. Thirty-five adults between the ages of 21 and 30 years (16 females, average age is 24.32) were asked to perform target detection via button press. The target was presented as a set of Gabor patches. A preparatory visual cue in the form of an arrow indicating the likely location of the target was presented at the beginning of each trial; however, only 80% of these cues correctly predicted the location of the target. At 800 or 1600ms post stimulus onset, one of the patches would shift orientation to which the subject would be required to respond. Trials were arranged for analysis in a rapid event-related design where cues were presented for 1 TR, and targets were presented in the subsequent TR. Inter-trial intervals were randomly distributed between 1, 2, and 3 TRs. Approximately 20% of the trials had only cues and no targets (i.e., catch trials).

Task 3 was a memory retrieval task that entailed a study phase and a retrieval phase. Subjects were scanned only at the retrieval phase (Wheeler et al., 2006]. Twenty-three subjects between the ages of 18 and 32 years (14 females, average age is 23.6) were instructed to study 240 auditory words that were paired with either pictures (color or grey-scaled) or sounds (long or short duration) during the study phase. The next day, subjects performed a memory task in the scanner. Subjects were asked to remember if the memory probe (word) had been paired with a color or grey-scale picture, or with a long or short sound. Trials were arranged for analysis in a rapid event-related design. A preparatory auditory cue, indicating whether the memory probe had been studied with a picture or a sound, was presented at the beginning of each trial, prior to the memory probe; however, only 75% of these preparatory cues correctly predicted the modality of the probe. In addition, 20% of the trials had only a preparatory cue and no subsequent memory probe (i.e., catch trials). Inter-trial intervals were randomly distributed between 1, 2, and 3 TRs.

Data Acquisition

For Tasks 1 and 2, data were acquired on a Siemens MAGNETOM Tim Trio 3.0T Scanner with a Siemens 12-channel Head Matrix Coil (Erlangen, Germany). Head movements were limited by using a thermoplastic mask fitted to individual subject's head at each entry into the scanner. For Task 3, data were acquired on a Siemens 1.5T Vision System (Erlangen, Germany). Head movements were restricted for each subject using foam pillows and thermoplastic facemasks. For all 3 tasks, a T1 sagittal MP-RAGE structural image was acquired for each subject. Both Task 1 and Task 2 used the following parameters: TE = 3.06ms, TR-partition = 2.4s, TI = 1000ms, flip angle = 8°, 176 slices with 1x1x1mm voxels. Task 3 used TE = 4.0ms, TR = 9.7ms, TI = 300ms, and flip angle = 12° (Wheeler et al., 2006). In addition, Task 1 and Task 2 also acquired a T2-weighted turbo spin-echo structural image (TE = 84ms, TR = 6.8s, 32 slices with 2 x 1 x 4 mm voxels) in the same anatomical plane as the BOLD images to improve alignment to an atlas.

Functional images for Tasks 1 and 2 were collected using a BOLD contrast sensitive gradient echo echo-planar sequence (volume TR = 2.0s for Task 1 and volume TR = 2.5s for Task 2, TE = 27 ms, flip angle = 90, in-plane resolution = 4x4 mm, 32 contiguous interleaved 4mm axial slices). In Task 1, each task run comprised 144 volumes (288.0 s), and in Task 2, each task run comprised 217 volumes (542.5 s). For both, the first 4 frames were dropped at the beginning to allow for signal intensity acclimation. Functional images for Task 3 were obtained using an asymmetric spin-echo echo-planar sequence sensitive to BOLD contrast (T2*, volume TR = 2.36s, TE = 37ms, in plane resolution 3.75 x 3.75 mm, 16 contiguous interleaved 8 mm axial slices). Each run comprised 167 volumes (394.1s), and the first 4 frames were dropped at the beginning of each run.

Preprocessing

Functional images were first processed to correct for (1) odd versus even slice intensity differences introduced by the acquisition of interleaved slices, (2) head motion within- and across-run using a rigid body rotation and translation algorithm (Snyder, 1996], and (3) within-run intensity normalization to a whole-brain mode-voxel value of 1000 to facilitate across subject comparison (Ojemann et al., 1997]. For all tasks, each subject's data was resampled into 2mm isotropic voxels and transformed into the stereotactic space of Talairach & Tournoux (1988). In both Tasks 1 and 2, atlas transformation of the functional data was computed for each individual via the MP-RAGE scan. In Task 3, the participants' data were resampled and transformed into stereotaxic atlas space via the T1-weighted images (Talairach & Tournoux, 1988].

Moreover, for Tasks 1 and 2, root-mean-square realignment estimates (RMS movements), were calculated from realignment parameters (rotational estimates converted to translational at radius of 50mm). Subjects with more than 3 runs with RMS movement above 1.0mm were excluded. All subjects from Task 1 met processing criteria, and 5 subjects from Task 2 were excluded, resulting in a final set of 30 subjects (15 females) for Task 2. For Task 3, from the 23 subjects, a total of five runs of MRI data with excessive movements were discarded from four participants, one run was discarded for three of the participants, and two runs for one participants, for more detailed description, see Wheeler, 2006.

Using the GLM

Preprocessed data from all 3 tasks were combined and further analyzed (through FIDL, in-house software written in IDL) at the voxel level. A general linear model (GLM) approach was used to model the BOLD response in each subject for each event of each task. Mainly, the trial-wise cues, correct target implementations, and incorrect target implementations were coded according to the same principles across all task conditions. The 3 types of event-related signals were modeled using delta functions immediately following the onset of each event. The use of both cue-only trials and random inter-trial interval durations allowed for sufficient number of independent linear equations to separately estimate the BOLD response for both cue and target events. Overall, this particular approach made no assumption about the shape of the BOLD response but did assume that all events included in a category were associated with the same BOLD response. The shape the BOLD response for each event was estimated from 9 time-points included in the design matrix of the GLM (Miezin, Maccotta, Ollinger, Petersen, & Buckner, 2000]. These 9 time-points denoted the magnitude of each event's response waveforms at 9 successive frames (TRs). In addition, for each BOLD run, the baseline (modeled as a constant) and trend-effects (modeled to account for the linear change in signals across a run) were included in the GLM. Event-related effects were described in terms of percent signal change, which was defined by signal magnitude divided by the constant term.

Cue and target main effect of time were computed from the GLM using voxel-wise repeated measures ANOVA. This approach produced a statistical (z-score) image indicating voxels whose hemodynamic responses deviated from flat across the modeled 9 time-points. In other words, through the statistical map of main effect of time, we can identify voxels that showed significant activity during cue or target. In addition, an accuracy x time repeated measure ANOVA was performed to produced a statistical (z-score) image highlighting voxels whose time-courses for incorrect targets differed significantly from the time-courses of correct targets. Brain surface visualizations were created using the Connectome Workbench software and the Conte69 surface-based atlas (Marcus et al., 2011; Van Essen, Glasser, Dierker, Harwell, & Coalson, 2012].

Regions of Interest

To obtain regions of interest (ROIs) that demonstrated a variety of signals, we selected cortical and subcortical regions that independently demonstrated significant activity regarding to cue, correct target implementations, or error (error activity is determined by contrasting activity of incorrect and correct targets).

We defined cue- and target-related ROIs from peak voxels in the cue and target main effect of time map, respectively, corrected for multiple comparison correction using Monte Carlo simulation and a score of $z > 3.5$. We defined error-related ROIs from peak voxels in the target accuracy x time interaction map, also corrected for multiple comparison correction using Monte Carlo simulation and $z > 3.5$. Functional regions of interest volumes were then defined by growing spheres (10mm-diameter) around these peak voxels using algorithms developed by Abraham Snyder (Wheeler et al., 2006]. This procedure resulted in 56 cue ROIs, 80 target ROIs, and 39 error ROIs. However, a straightforward combination of these 175 ROIs resulted in many that were close together or overlapping. In order to eliminate repeated regions in future analyses, for any pair of ROIs that were within 10 mm of each other, we randomly selected one and deleted the other to form our final set of 98 ROIs.

Hierarchical Clustering

There are many ways in which a region can respond to cue, target, and error. Hence, a second level of analysis was conducted to determine possible groups of ROIs with distinct response shapes and patterns. We used a hierarchical clustering analysis (Cordes, Haughton, Carew, Arfanakis, & Maravilla, 2002; Dosenbach et al., 2007 2015; Salvador et al., 2005] to objectively detect groups of ROIs that had similar response profiles with regard to trial-wise cue, correct target, and error responses.

To do this, for a single ROI, three time-courses were extracted by averaging the time-courses of all the voxels in the ROI. The time-courses were: (1) the trial-wise cue response, (2) the correct target response, and (3) the error response, which was defined as the incorrect target response minus the correct target response. Each time-course consisted of 9 time-points. The three time-courses were then concatenated to form one 1 x 27 vector. These vectors were combined for each of the 98 ROIs in a 98 x 27 matrix. From this matrix, Pearson's correlation coefficients (r) were calculated for all pairs of ROI time-courses, and we generated a 98 x 98 correlation matrix where each column represented the similarities between a particular region's time-courses and all the other regions' time-courses. A "1-r" calculation was then performed on the correlation matrix to generate a distance matrix used for the hierarchical clustering. The hierarchical clustering method iteratively grouped similar sets of data points together based on their distance measures. A dendrogram was then made to visualize the resulted clustering of the ROIs. The algorithm used to build the dendrogram was the unweighted paired group method with an arithmetic mean (UPGMA; (Handl, Knowles, & Kell, 2005; Ploran et al., 2007]), which is included in the Statistics and Bioinfomatics Toolbox available in MATLAB 7.2 (MathWorks). This algorithm defined the distance between two clusters as the mean distance of all possible pairs of data points between the two clusters. To validate our results, we used the cophenetic coefficient as a measurement of correlation between the original distance of two observations and their intergroup distance once they are clustered together (Handl et al., 2005]. Finally, to objectively cut the dendrogram into distinct clusters, we calculated the modularity measure (Q, (Newman, 2006]) for structures that contained anywhere from 1 to 30 total clusters, and the final set of 5 clusters comes from the structure that had the highest Q coefficient.

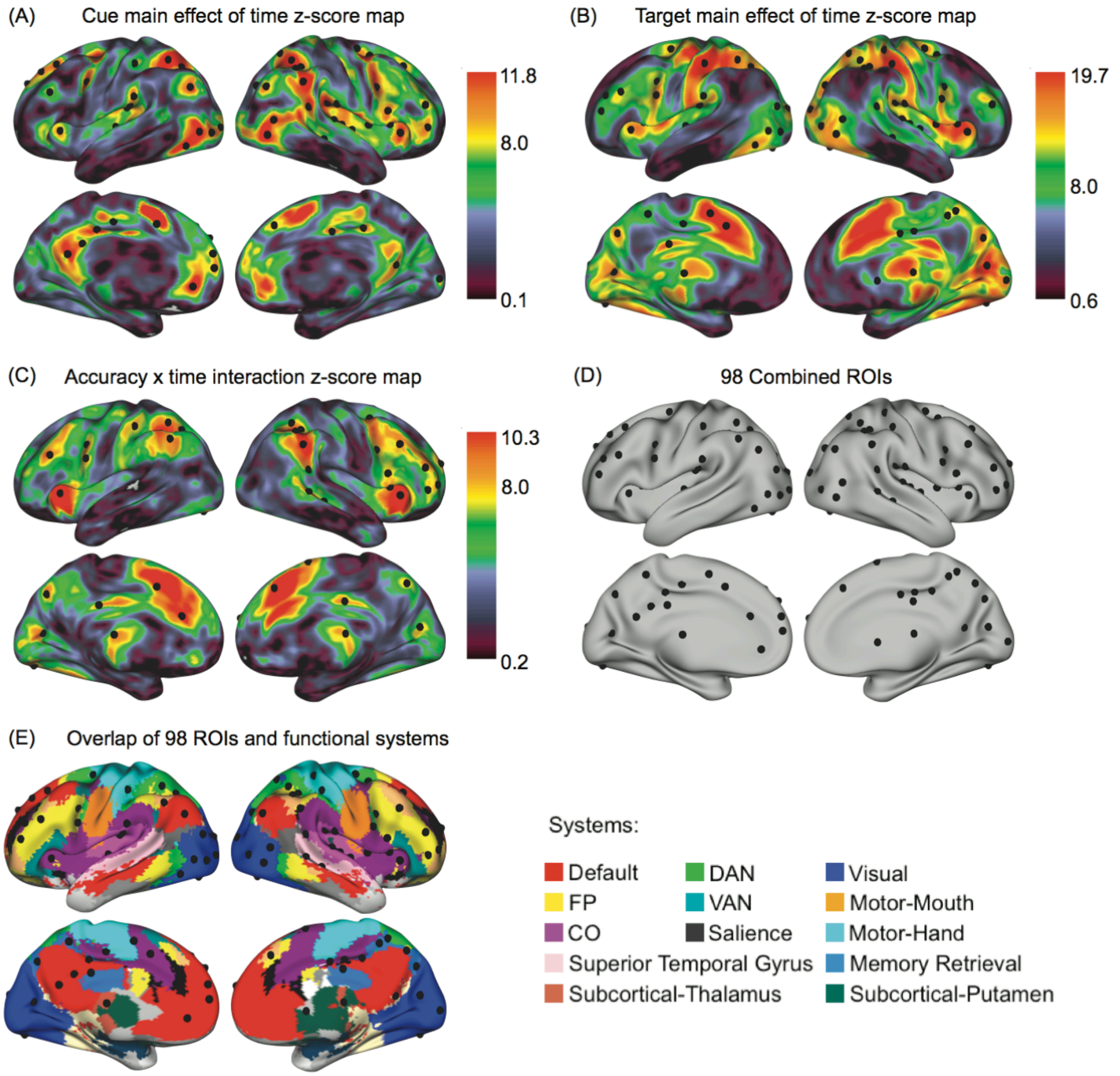


Figure 3.2: Selecting Regions of Interest (ROIs)
Cue main effect of time, correct target main effect of time, and accuracy x time interaction are used to select regions of interest (ROIs). (**A-B**) Z-score maps and peak ROIs for both cue and target main effect of time across all participants and all 3 tasks. (**C**) Z-score map and peak ROIs of accuracy x time interaction. (**D-E**) The final set of ROIs is obtained by combining the peak regions from all three maps, and they are projected onto inflated cortical surfaces to show their anatomical locations as well as their putative functional systems.

IV. Results

The main effect of time for trial-wise cues and correct targets revealed several regions whose activity deviated significantly from zero (see Methods). Regions that showed significant cue activity (cue-related regions) included, but were not limited to, the dorsolateral frontal cortex, intraparietal sulcus (IPS), bilateral anterior insula and frontal operculum (aI/fO), dorsal midcingulate (dmCC), dorsal anterior cingulate (dACC), and right temporal parietal junction (TPJ), see **Figure 3.2a**. Many of these regions, such as the dorsolateral frontal cortex and aI/fO, had been previously associated with start-cue signals (Dosenbach et al., 2006). Regions that showed significant target activity (target-related regions) covered more cortex than cue-related regions. Target-related regions included, but were not limited to, the bilateral IPS, the frontal eye field (FEF), and regions of visual cortex, see **Figure 3.2b.**

For error-related activity, the target accuracy x time repeated measure ANOVA revealed regions whose activity during incorrect and correct target periods differentiated significantly from each other across the 9 time-points. Regions that showed significant error activity (error-related regions) included, but were not limited to, the right TPJ, dACC, aI/fO, IPS, and right DLPFC (see **Figure 3.2c**).

Regions of Interest

Cue and target main effect of time and target accuracy x time interaction produced 56, 80, and 39 peak regions, respectively. We combined these sets of regions and consolidated them (see Methods) to a final group of 98 ROIs that was used in the following hierarchical clustering analysis (**Figure 3.2d).** To show the relationship between these regions and predefined functional networks, **Figure 3.2e** overlays the 98 ROIs onto a brain surface showing functional networks.

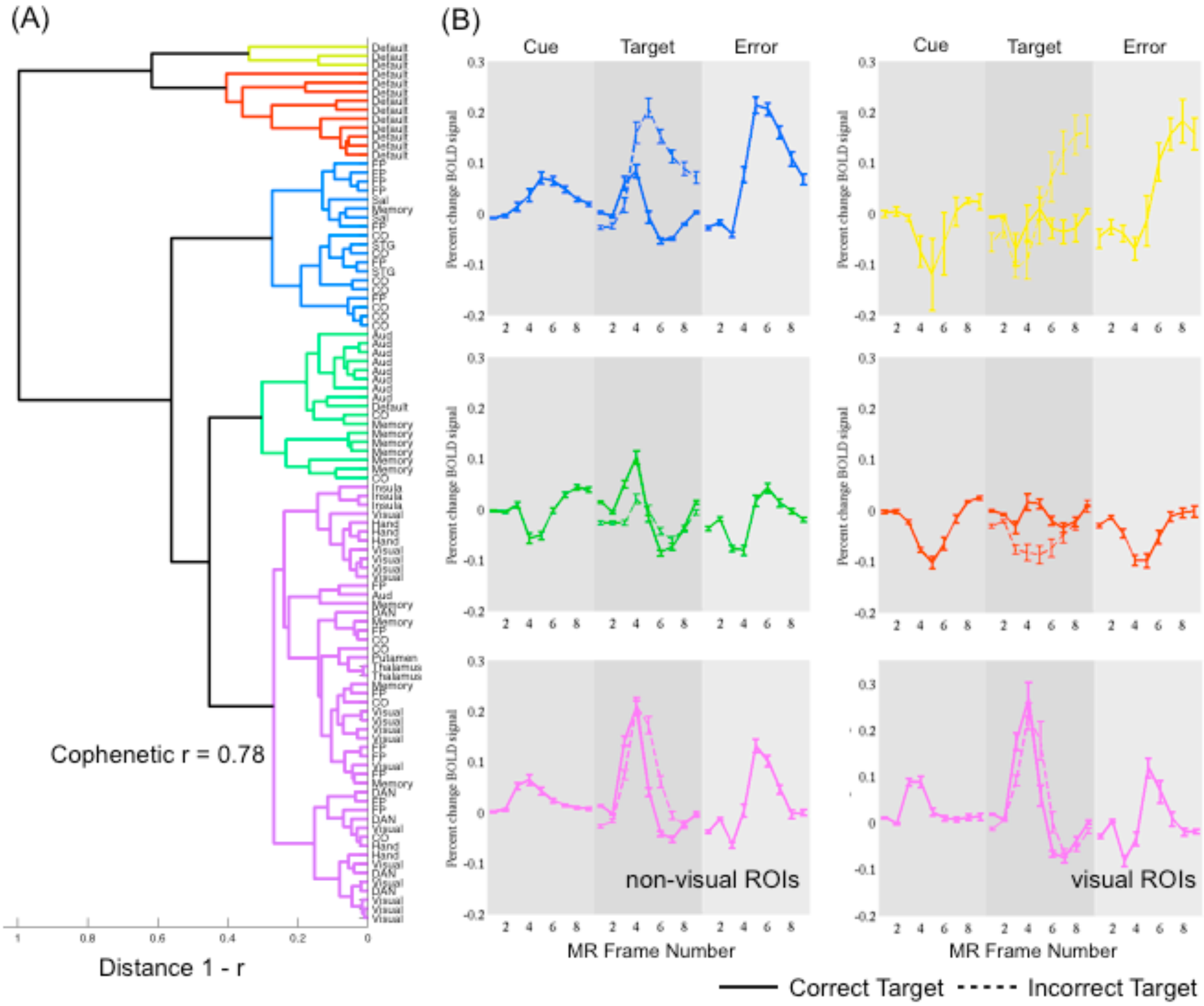


Figure 3.3: Hierarchical Clustering of ROIs
Cue, correct target, and error (incorrect target - correct target) time-courses from 98 ROIs are clustered into separate, as well as overlapping, control- and processing-related regions. (**A**) The dendrogram displays the similarity between time-courses in terms of a distance measure, 1-r, where r is the Pearson correlation coefficient. Pruning the dendrogram at 1-r = 0.4 results in 5 distinct clusters. (**B**) Within each cluster, the ROIs' time-courses are averaged together, and each error bar represents the standard error across ROIs. The panels are color-coded based on the respective clusters in the dendrogram. In the target column, the solid line corresponds to correct target, and the dotted line corresponds to incorrect target. We additionally divided the magenta cluster into visual and non-visual regions (see Discussion for elaboration)

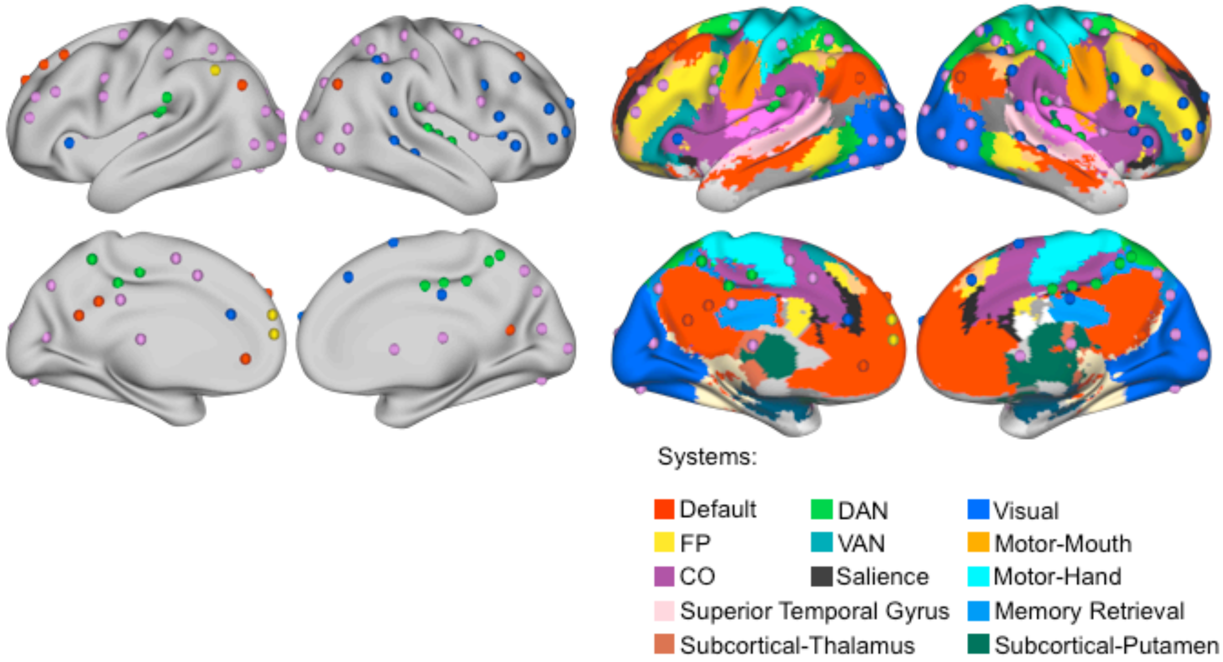


Figure 3.4: Projection of Color-coded ROIs Onto an Inflated Brain
ROIs, color-coded according to their respective clusters, are projected onto an inflated brain to show their anatomical locations and their putative functional systems.

Five distinct sets of time-course profiles showed varying cue, target and error responses

In order to analyze and compare each region's pattern of activity across cue, correct target, and error target responses, we conducted a hierarchical clustering analysis on the concatenated time-courses of our ROIs. We then organized the results from our hierarchical clustering analysis in a dendrogram. From the selected ROIs, regions with more similar time-course patterns were clustered closer together than regions with more divergent patterns. The cophenetic correlation coefficient for the dendrogram was $r = 0.78$, suggesting that the clustering followed hierarchical organization well. Pruning the dendrogram at $1 - r = 0.4$ produced 5 clusters (see Methods section), and the time-course patterns from each cluster were averaged across the ROIs.

Figure 3.3 displays the resultant clusters and their respective time-course profiles. One cluster (blue) had 19 ROIs that were mostly located in parts of the right FP (right frontal cortex and right dACC) and core regions of CO (bilateral aI/fO). Also included in this cluster were part of the salience system (left anterior cingulate) and two regions in the superior temporal gyrus. These ROIs collectively showed a positive cue response, a positive correct target response, and an error response effect (incorrect target - correct target) whose peak had a greater magnitude than that of the correct target. Another cluster (magenta) had 49 ROIs that spanned most of the left FP (left frontal cortex and left middle frontal gyrus), the DAN (bilateral FEF and IPS), a small fraction of the CO (left dorsal midcingulate), and the visual system (occipital cortex). In addition to a very robust target response, this cluster showed a positive cue response and a positive error response whose peak magnitude was less than the peak magnitude of the correct target response. A third cluster (green) had 16 ROIs that were located mostly in the auditory system (bilateral posterior insula) and along the paracentral gyrus. Its averaged time-course profile exhibited a negative response to cue, a positive response to correct targets, and an incorrect target response that was weaker than the corresponding correct target response.

The rest of the ROIs were located within the default mode system and were grouped together at the highest level of the dendrogram. We identified two clusters (10 ROIs in red and 3 ROIs in yellow) that both showed robust deactivation associated with trial-wise cues. The red cluster had a positive but weak correct target response in addition to a negative error response. The yellow cluster had a bimodal and negative (also weak) correct target response with a noisy but overall positive error response.

Time-course profiles in the blue and magenta cluster differ in their onsets and magnitudes

Two clusters (magenta and blue) contained mostly regions in various control systems, and they had similar time-courses in that they both showed a positive cue response, a positive correct target response, and a positive error response. To characterize and contrast the control regions' time-course profiles in a more detailed and quantitative fashion, the data processing-related visual regions were first removed from the magenta regions (see **Figure 3.3**, **Figure 3.4**, and Discussion). Then, the onset time (the time at 50% of the peak magnitude is achieved) and the peak magnitude of the time-courses from the modified magenta cluster and the blue cluster were derived for further analyses. Cluster averages for peak magnitude and onset time were plotted in **Figure 3.5**. For the cue response, there was no significant difference between the peak magnitudes of the magenta and the blue clusters ($t(50) = 0.85$, $p > 0.05$). However, the magenta cluster, on average, seemed to have the fastest onset time, and a t-test indicated that onsets were significantly earlier in magenta cluster than in the blue cluster ($t(50) = 3.09$, $p < 0.01$). For the correct target response, peak magnitudes were significantly higher for the magenta cluster than for the blue cluster ($t(50) = 5.63$ $p < 0.001$). In addition, a t-test showed that these clusters were not significantly different in their target onsets ($t(50) = 1.09$, $p > 0.05$). Finally, for the error response, the magenta cluster had significantly lower peak magnitudes than the blue cluster ($t(50) = 4.73$, $p < 0.001$), but there were no significant differences in the onset times ($t(50) = 0.77$, $p> 0.05$).

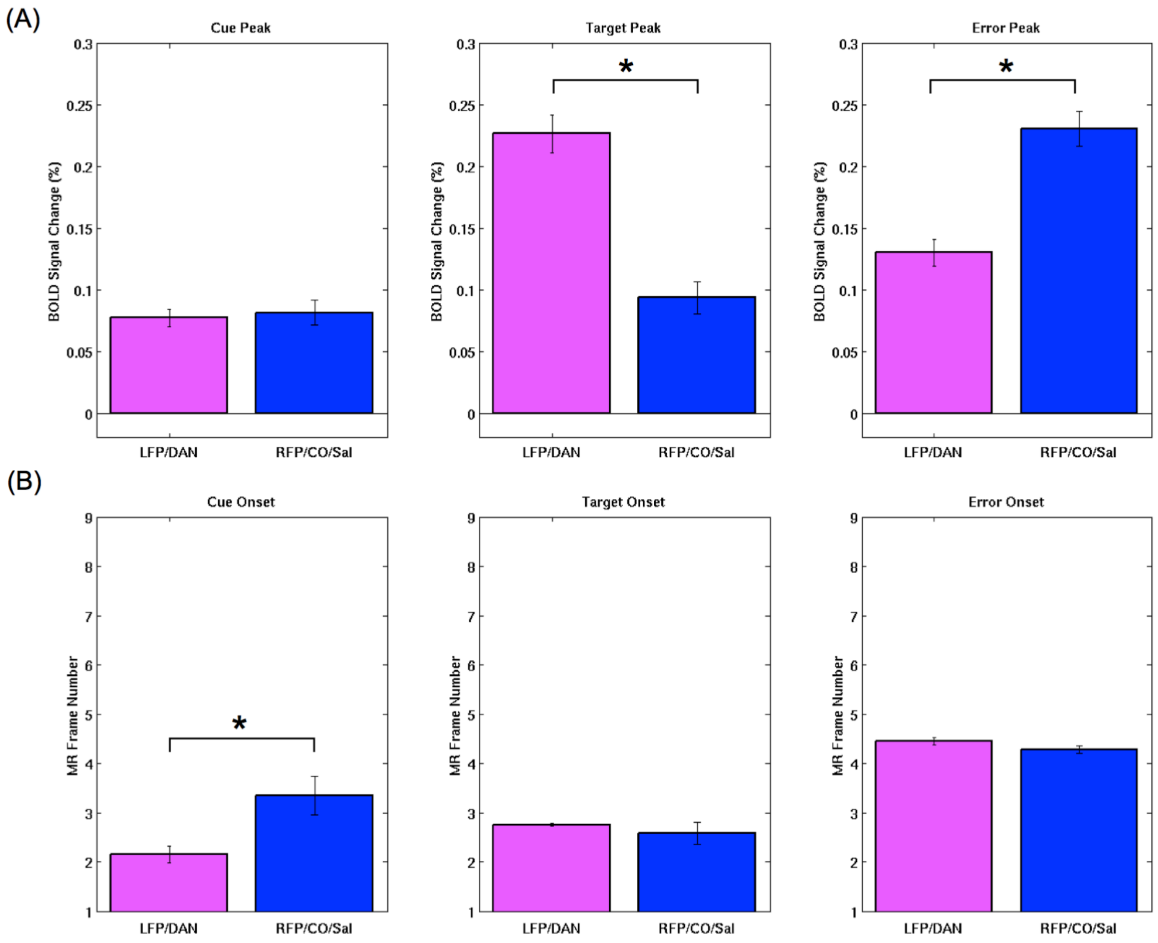


Figure 3.5: Analyses of Control Regions' Time-course Profiles
(**A**) Time-course peak magnitudes and (**B**) onsets are extracted and plotted for the magenta cluster (left FP, DAN and visual ROIs) and the blue cluster (right FP, CO, and salience ROIs). The bars are color-coded according to their respective clusters shown on the dendrogram in **Figure 3.3**. Error bars indicate standard error across ROIs, and asterisks indicate significant t-test differences ($p < 0.05$).

V. Discussion

We conducted a small-scale meta-analysis of 3 fMRI tasks with cue-target paradigms that spanned multiple stimulus modalities. Unlike previous studies that focused primarily on the average magnitude of activation in control systems (Dosenbach et al., 2006; Woolgar, Afshar, Williams, & Rich, 2015; Woolgar, Thompson, Bor, & Duncan, 2011], the current study emphasized the comparison of response shapes associated with cue-, correct target-, and error-related activity under goal-directed attention in an effort to understand how different control systems respond within trials in which there are a combination of preparatory control, responses-related control (i.e. error), and moment-to-moment processing signals.

To examine and characterize the time-courses of control systems during goal-directed tasks, we identified regions that showed reliable activation to cues, errors, and correct targets and objectively defined groups that showed unique response patterns. Overall, we found 5 clusters of regions that had distinct time-course profiles, indicating that they may differentially contribute to processes within a trial. These time-course profiles are largely consistent across tasks. Specifically, two clusters, one with regions in the left FP, DAN, and visual cortex (magenta, **Figure 3.3**) and another with regions in the right FP, bilateral aI/fO of CO, and anterior cingulate of salience system (blue, **Figure 3.3**), showed positive trial-wise cue-, correct target-, and error-related responses. Interestingly, comparison of time-course parameters showed that, relative to the LFP/DAN/visual magenta cluster, the RFP/CO/salience blue cluster had delayed cue onsets, weaker correct target response magnitudes, and stronger error response magnitudes. These patterns suggest dissociable control-related roles, specifically in trial-wise cueing and feedback, for the right FP and CO compared with the left FP, DAN, and visual systems. Instead, the left FP, DAN, and visual systems appear to play a more prominent role in moment-to-moment-target processing (see following discussion for elaboration). A third cluster (green, **Figure 3.3**) with regions in the posterior insula and paracentral gyrus exhibited correct target-related activation and no control signals related to cueing and feedback (error). Finally, two clusters (red and yellow, **Figure 3.3**) were composed of regions in the default mode system. Both clusters showed cue-related deactivation and negligible correct target responses, characteristics that did not clearly fit into control or roles related to moment-to-moment transformation of stimulus information.

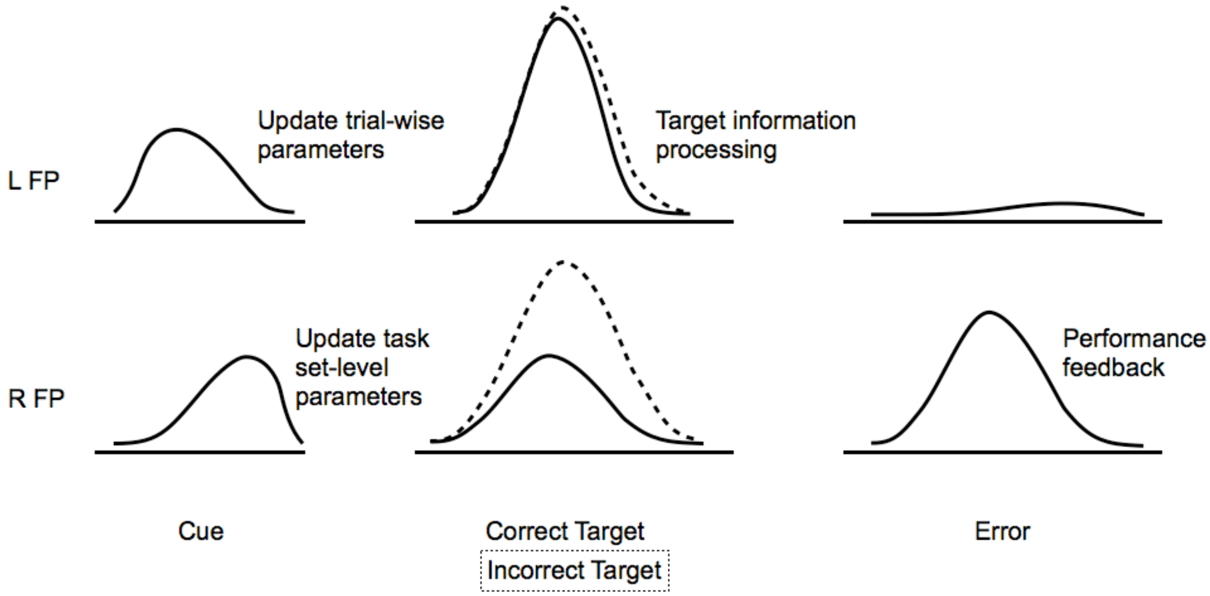


Figure 3.6: Summary of Distinct Functional Roles of Control Systems
Combining information from hierarchical clustering and time-course analysis, the diagram summarizes the hypothesized functional roles of the different control systems during goal-directed tasks. Overall, the FP system is divided such that time-courses from left FP regions were more similar with those in DAN regions while time-courses from the right FP regions were more similar with CO. During the set-up portions of the trial (cue), the left FP and DAN group showed quick onset in contrast with the slow cue onset of the right FP and CO group. Error responses were significantly more prominent in right FP and CO regions; however, left FP and DAN regions showed greater activity for target-related processes.

Dissociable roles of control systems

Largely consistent with the idea that separate control systems make unique contributions to trial-related processes, we identified two distinct trial-related response profiles that divided the regions of control systems into a right FP and CO cluster and a left FP and DAN cluster.

Right FP and CO engaged in fine-tuning task parameters and evaluating performances

The right FP and CO cluster was composed of regions in the right FP (the right frontal cortex and IPS), CO (bilateral aI/fO and IPL), a small portion of the salience system (Sal, anterior cingulate) and regions of superior temporal gyrus (STG). Together, they showed robust activation in response to both cues and errors. The cue response had a later onset compared to other clusters while error-related responses in these regions had among the highest peak magnitudes.

Past evidence has suggested that regions of the CO and FP systems play a critical role in task control. The CO system, especially in its core regions (i.e. dACC and bilateral aI/fO), carries sustained signals, task-initiation signals and various aspects of performance feedback signals pertaining to accuracy, reaction time, and ambiguity (Dehaene, Posner, & Tucker, 1994; Dosenbach et al., 2006; Hester, Fassbender, & Garavan, 2004; Holroyd, Dien, & Coles, 1998; Neta et al., 2015; Neta et al., 2014; Ullsperger, Harsay, Wessel, & Ridderinkhof, 2010]. The FP system, in both right and left hemispheres, also carries task-initiation signals as well as error signals (Carp, Kim, Taylor, Fitzgerald, & Weissman, 2010; Dosenbach et al., 2006; Wessel, 2012]. A meta-analysis of perceptual recognition tasks with a specialized “slow-reveal” paradigm (e.g. stimuli slowly revealed over time to dissociate aspects of the decision-making response) found that CO regions exhibited consistent control-related activity at the moment of decision while right FP regions exhibited activity in post-trial processing associated with performance re-evaluation (Gratton et al., 2016]. Additionally, other behavioral and lesion studies have found that CO (aI/fO) and right FP regions are critical for monitoring and detecting discrepancies between behavioral responses and task instructions, suggesting they help carry out important performance evaluation and task adjustment signals (Stuss & Alexander, 2007; Vallesi, Shallice, & Walsh, 2007].

Other regions clustered with right FP and CO were associated with the salience system (left anterior cingulate) and regions in the superior temporal gyrus (STG). The salience system, although it appears to be dissociable in resting-state (i.e. BOLD signal correlations in the absence of a task), tends to co-activate with executive control systems, especially CO, during tasks (Power et al., 2011; Power & Petersen, 2013; Seeley et al., 2007]. Regions in the STG have high intrinsic functional connectivity with the ventral attention system (VAN). Regions of VAN have been shown to exhibit activity related to monitoring (strong activation in response to unexpected targets), and they are thought to be integral to reorientations of attention (Corbetta et al., 2000; Fox, Corbetta, Snyder, Vincent, & Raichle, 2006; Serences et al., 2005].

Based on the current and past evidence, we propose that, for right FP and CO (along with components of the salience system and STG), the late cue onset and the strong response associated with error suggest possible involvement in the fine-tuning of task set-level parameters (**Figure 3.5**). Here, the delayed signature in cue is similar to right FP's delayed post-decision processing signals shown across 5 perceptual recognition tasks (Gratton et al., 2016], as well as the right FP's prolonged error responses shown across 12 tasks (Neta et al., 2015]. One possibility is that, during cue, rather than processes related to the immediate update of trial-wise parameters (see contrasting fast cue response profile in left FP and DAN), right FP and CO regions might be engaged in incorporating the updated information into the task set-level parameters. Relatedly, significantly greater error-related responses in right FP and CO cluster suggest that these regions are also engaged in performance-related control processes, which may include response evaluation and feedback for improvement of future performance.

Left FP and DAN engaged in updating trial parameters and processing target information

Regions in left FP and DAN were originally grouped with regions of the visual cortex; however, due to visual region's modality-dependent characteristics, we removed them from modality-general characteristics of the left FP and DAN control regions (see discussion on processing regions for more detail). Overall, the time-course profiles of the magenta cluster remained similar in shape and magnitude after the exclusion of visual ROIs. In left FP and DAN, we observed cue responses with early onset, moderate error responses (although the error responses were significantly weaker than those in the right FP/CO/Sal cluster), and strong target responses.

Traditionally, left FP and DAN regions have been considered to be control-related. In previous studies, the left FP has been grouped with its right hemisphere homologues in association with trial-level control, such as start-cue/task-initiation signals and establishment of task-set parameters (Dosenbach et al., 2006; Wallis et al., 2015]. In addition, studies using theta-burst transcranial magnetic stimulation to disrupt functions in regions of left FP (prefrontal cortex) have found decreased tuning of task-relevant representations within extrastriate visual cortex (Lee & D'Esposito, 2012; Miller, Vytlacil, Fegen, Pradhan, & D'Esposito, 2011], indicating a role in "top-down" control of visual processing for left prefrontal cortex. However, left FP regions may have more specialized roles in top-down control that are separate from the right FP. Specifically, lesion patients with localized damage in the left frontal cortex consistently showed more errors related to deficiencies in establishing contingent task-relevant rules than right frontal lobe lesion patients (Stuss & Alexander, 2007]. Relatedly, the DAN is thought to help prioritize, in top-down fashion, sensory inputs relevant to the task at hand (Bressler, Tang, Sylvester, Shulman, & Corbetta, 2008; Corbetta et al., 1998; Thompson, Biscoe, & Sato, 2005;

Vossel, Weidner, Driver, Friston, & Fink, 2012], and disruptions and lesions in DAN regions have been shown to lead to significant modulations of visual cortex activity (Ruff et al., 2008; Ruff et al., 2006; Vuilleumier et al., 2008).

In this study, left FP and DAN regions had dissociable roles from right FP and CO regions related to preparatory (cue) and error-related control. Left FP and DAN regions showed an earlier cue onset. Combined with lesion evidence that indicated left FP's role in setting of task rules (Stuss & Alexander, 2007), this suggests involvement in fast update of trial-wise parameters. Compared to the right FP and CO cluster in which the incorrect-target time-course deviated significantly from the correct-target time-course, the incorrect- and correct-target time-courses in left FP and DAN regions appeared to have similar shapes and magnitude; consequently, the error response (incorrect target > correct target) had a significantly lower magnitude in left FP and DAN than in the right FP and CO regions. Taken together, left FP and DAN regions' time-course characteristics suggest that they may be more associated with loading trial-wise parameters than performance feedback.

Additionally, unlike right FP and CO control regions, we also found strong activity in left FP and DAN during correct target implementation. Extensive neurophysiological studies in monkeys and event-related fMRI studies in humans have recorded activity consistent with the left FP and DAN regions (i.e. dlPFC and frontal eye field, FEF) contributing during moment-to-moment processing, such as encoding and maintaining stimulus information during working memory (Chafee & Goldman-Rakic, 1998; Constantinidis, Franowicz, & Goldman-Rakic, 2001; Druzgal & D'Esposito, 2003; Ester, Sprague, & Serences, 2015]. Although, it is difficult to dissociate signals related to control from signals related to stimulus processing during target implementation, previous perceptual decision studies conducted by our lab have shown that as more perceptual information is presented, regions in the left frontal cortex, MFG, and IPS exhibited early onsets and gradual increases that peak at the time of decision, similar to processing-related decision-making neurons (i.e., the gradual integration of processed information towards a decision (Gold & Shadlen, 2007; Gratton et al., 2016; Ploran et al., 2007]). Given that the left FP evidence accumulation regions from Gratton et al., 2016 show close correspondence with the left FP regions in the current study (the mean distance between the accumulator regions from Gratton et al., 2016 and the nearest corresponding left FP regions from current study is 8.80 ± 4.45mm, see **Figure 3.7**), we propose that left FP, together with DAN, are involved in processing of target information (**Figure 3.6**).

However, an alternative is that the correct and incorrect target-related activity present in left FP and DAN regions may also reflect ongoing control-related top-down attention signals that modulate processing to facilitate performance (Curtis & D'Esposito, 2003; Gazzaley et al., 2007; Monosov, Trageser, & Thompson, 2008; Moore & Armstrong, 2003]. For example, left FP regions, specifically the left middle frontal gyrus, demonstrated strengthened interactions with regions of visual association cortex during cognitively demanding visual tasks (Gazzaley et al., 2007]. Relatedly, in primate frontal eye fields (FEF, one of the most widely studied regions in the DAN), sub-threshold stimulations of retinotopically corresponding sites within the FEF have shown to produce enhanced visual responses in area V4 (Moore & Armstrong, 2003]. This evidence suggests a possible role that left FP and DAN regions may play in maintaining goal-directed attention across a trial, and the activity during target implementation in this study could reflect this ongoing trial-level control.

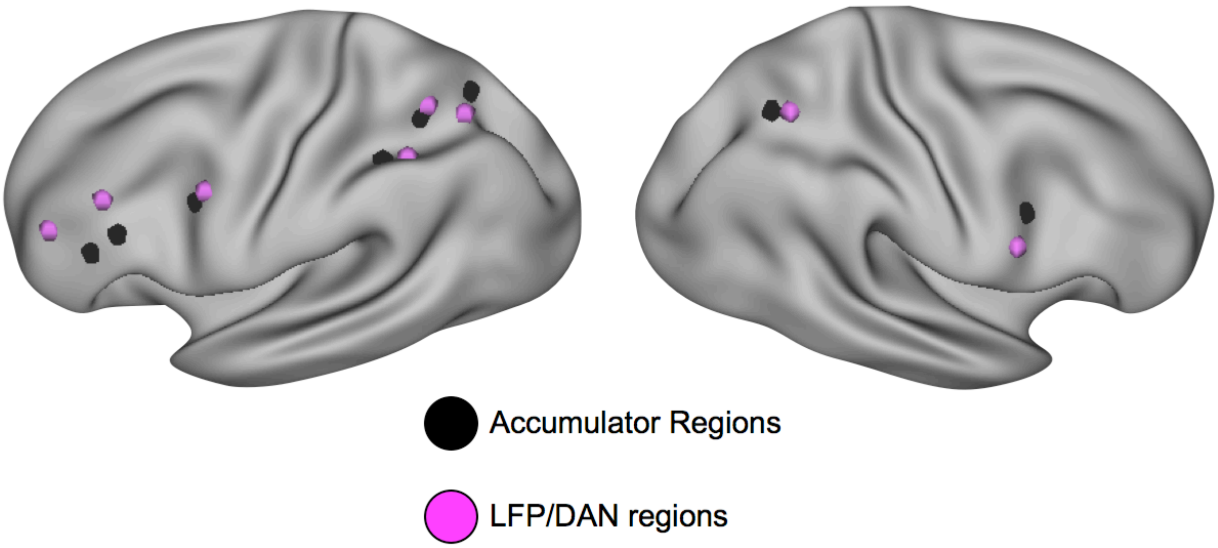


Figure 3.7: Proximity Between Accumulator Regions and LFP/DAN Regions
Accumulator regions from Gratton et al., 2016, and the closest LFP/DAN regions are projected onto inflated cortical surfaces to demonstrate their proximity. The mean distance between each accumulator region and its nearest corresponding left FP region from the current study is 8.80±4.45mm.

Asymmetries in the frontoparietal system reveal functional dissociation

The hierarchical clustering of cue, correct target, and error responses produced two distinct clusters that separated the traditional FP system. The right FP regions' delayed cue, moderate target, and strong error response suggested functional roles in re-evaluation of trial-related parameters and performance feedback. In contrast, the left FP regions' early cue, strong target, and moderate error responses suggested functional roles in update of trial-related parameters and target information processing.

Past research has provided evidence supporting distinct functions in the left and right hemispheres of the FP system. Lesion studies have found laterality effects when examining patients with focal left prefrontal lesions and patients with focal right prefrontal lesions (Stuss &

Alexander, 2007]. Lesions in the left prefrontal cortex were linked with difficulty in discerning target versus non-target events. The increase of false alarm rate in left frontal lesion patients was interpreted as a deficiency in setting up proper task-set parameters. However this could also represent a poor mapping of task rules to data accumulation processes as might be expected in regions with "mixed" processing characteristics. Lesions to the right prefrontal cortex were linked with increased overall task errors including both false positive as well as false negative errors, suggesting that the right prefrontal cortex may play a more critical role in enforcing relevant performance-related rules. From our analysis, we propose that the delayed cue onsets together with the robust error responses in right FP regions are associated with task updating and performance feedback.

In related work, Wang and colleagues recently observed that resting-state connectivity of the left and right hemisphere of the FP system preferentially coupled to different functional systems of the brain. The left hemisphere connected more strongly to the default system while the right hemisphere had stronger coupling with other control systems such as regions of CO (Wang, Buckner, & Liu, 2014]. The latter aspect of this result is consistent with our clustering analysis, which revealed that the right FP regions shared very similar cue, correct target, and error profiles with the core regions of CO (bilateral aI/fO). Other task-related fMRI studies have also demonstrated functional asymmetries within the FP system regarding, for example, error response profiles (Neta et al., 2015], attentional control during reading (Ihnen, Petersen, & Schlaggar, 2015], and trial-wise processes during decision-making (Gratton et al., 2016]. Here, our data provided additional evidence supporting specialized functions in the two hemispheres of the FP system.

Response profiles of data processing systems are distinct from control systems

Regions in the auditory system (posterior insula) and parietal memory system (paracentral gyrus) were clustered together and displayed activity primarily during target implementation. Moreover, these regions showed a slight deactivation during cue, and comparison between correct and incorrect target responses indicated weaker peak magnitude for incorrect target responses, which is not consistent with activity seen for performance feedback. As such, regions of auditory and memory systems seem more processing-related. Furthermore, existing literature has attributed data-processing functions to these regions: the posterior insula is associated with auditory-processing (Bamiou, Musiek, & Luxon, 2003] and the paracentral gyrus is associated with processing during memory encoding and retrieval (Gilmore et al., 2015; Kim, 2013; Nelson, Cohen, et al., 2010; Power et al., 2011; Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012; Yeo et al., 2011].

In our analysis, visual regions did not separate into their own distinct cluster. Instead, they showed robust responses to both cues and targets, grouping with the left FP and DAN regions. Given that some of these regions are in the primary visual cortex, we have good reason to believe that they are purely processing-related regions (Felleman & Van Essen, 1991; Hubel & Wiesel, 1959]. Two of the three tasks (Task 1 and Task 2) used visual cues and targets. Because we combined the tasks in the meta-analysis, even though Task 3 did not use any visual stimuli, the averaged time-course profile from visual regions across all three tasks showed strong activation for both cue and target conditions. In order to confirm that our visual regions were data processing- rather than control-related, we examined time-courses from each individual task. The visual regions showed robust cue and target activation specific to the visual stimuli in

Task 1 and Task 2 and not in Task 3 (where the cues and targets were auditory), corroborating that their activity was stimulus modality-driven.

Regions of the default mode system are in a league of their own

Lastly, the hierarchical clustering analyses produced two clusters (red and yellow in **Figure 3.3**) composed of 13 regions in the default mode system (DMN), including left posterior cingulate cortex, left medial prefrontal cortex, right retrosplenial cortex, bilateral IPL, and bilateral dorsal PFC. These clusters showed a time-course profile distinct from our original hypothesized categories: a robust, negative cue signal along with a much weaker (or negligible) target signal. The DMN has been widely reported to show task-related decreases in activity, especially during cognitively demanding tasks (McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003]. In addition, regions within the DMN are highly intercorrelated both at rest and during tasks, and are negatively correlated with brain regions that show task-related increases in activity (Fox et al., 2005; Greicius, Krasnow, Reiss, & Menon, 2003; Greicius & Menon, 2004]. These findings suggest the presence of an inhibitory interaction, possibly through a third party (e.g. the thalamus), between positively activated regions and regions of DMN (Sherman, 2001]. As such, it is possible that, during task performance, especially during the cue phase, the robust deactivation in these 13 regions was modulated by other more active control-related regions. Future research will be needed to clarify the functional roles of the default system.

VI. Conclusion

Taken together, the current study characterized the relative roles of control systems in preparatory- and error-related control, along with target processing. We found a group of largely right FP and core CO regions that showed late cue onsets and large error responses, reflecting roles in evaluation of trial-wise parameters and trial performance, respectively. Another group composed of left FP and bilateral DAN regions showed a prominent cue response with early onset and strong correct target activity, suggesting roles in establishing trial-wise parameters and information processing. Finally, other processing-related systems (i.e. auditory and memory regions) and the DMN showed unique response profiles separate from the control systems. In conclusion, our results demonstrate a set separable response profiles within various control systems that indicate differential contributions to the implementation of goal-directed tasks.

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CHAPTER 4: COMPLEX AND DYNAMIC SYSTEM INTERACTIONS ACROSS DIFFERENT STAGES OF A GOAL-DIRECTED TRIAL

I. Abstract

Goal-directed attention tasks involve activity of top-down control and bottom-up sensory systems. However, how and when these systems interact remains unclear. Here, we use a Posner-like cued attention paradigm to compare, within a trial, the cue- and target-related changes in functional connectivity (FC) between control (e.g., frontoparietal and dorsal attention) and processing (e.g. visual and motor regions) systems. We specifically ask whether the control systems interact with the processing systems throughout the trial, or just at the preparatory period, i.e. during the cue. Comparisons between resting-state and task-state as well as within task-state (cues versus targets) indicate that FC changed subtly but significantly. Compared to rest, cue-periods were related to enhanced integration of control systems both with sensory systems and with other control systems. While some control systems maintained their strengthened connectivity with processing systems throughout the task, others (i.e. the frontoparietal system) decrease their connectivity with the visual system during target processing. Overall, the results reveal the presence of complex and dynamic relationships that suggest changes among the various functional systems across a trial reflect both continuous as well as momentary effects of top-down signals.

II. Introduction

Humans rely on both bottom-up moment-to-moment processing of relevant input and output information and top-down control to instantiate and regulate goal-directed behavior (Baddeley, 1996; Desimone & Duncan, 1995; Logan & Gordon, 2001; Miller & Cohen, 2001). Successful orchestration of these processing streams is presumed to require carefully coordinated interactions between brain regions specialized for control-related activity and regions specialized for bottom-up information processing.

Early examples of such interactions come from nonhuman primate electrophysiology. Past studies have demonstrated that goal-directed attention from higher-level control regions affects neural processing in the visual cortex. When an animal covertly (without explicit eye movements) directs its attention to a stimulus within a visual neuron's receptive field, the neuron’s responses are enhanced compared to when animal attended elsewhere (Connor, Gallant, Preddie, & VanEssen, 1996; Luck, Chelazzi, Hillyard, & Desimone, 1997; Motter, 1993). This effect increases with task difficulty (Spitzer, Desimone, & Moran, 1988) and persists even in the absence of exogenous stimulations (Luck et al., 1997). Collectively, these findings have led to the proposition that response modulations in lower-level visual cortex is a result of top-down modulations that bias visual processing in favor of attended information (Kastner & Ungerleider, 2000).

An active area of study, then, is to understand how top-down signals interact with processing regions. Some insight into this question has come from using fMRI to examine how correlations in spontaneous blood oxygenation level-dependent signals (BOLDs) measured from different brain regions are influenced by tasks (Al-Aidroos, Said, & Turk-Browne, 2012; Norman-Haignere, McCarthy, Chun, & Turk-Browne, 2012). This method has revealed specific influence of top-down attention on the correlation structure between control and processing regions (Al-Aidroos et al., 2012; Griffis, Elkhetali, Burge, Chen, & Visscher, 2015; Sali, Courtney, & Yantis, 2016; Spadone et al., 2015). For example, Al-Aidroos et al. have shown that extrastriate visual area V4 and ventro-temporal visual association regions (i.e., the fusiform face area and parahippocampal place area) will flexibly increase their BOLD correlations based on the task at hand (e.g., attend to faces or attend to scenes). In addition, long-range modulation between control-related regions (e.g., prefrontal cortex) and processing related regions (e.g. visual association regions) can be enhanced or suppressed based on concurrent attentional goals (Griffis et al., 2015; Spadone et al., 2015). Hence, attentional demands appear to alter the functional coupling between relevant control and processing regions.

However, the dynamic nature of one form of these interactions, reflected by correlation in relevant regions' intrinsic BOLDs fluctuations during a trial of a task, remains unknown. Do higher-level control regions send continuous top-down instructions to lower-level processing regions, or are they the result of a momentary top-down signal that establishes goal-relevant processing? Understanding this timing places important constraints on the mechanisms by which top-down control modifies basic processing.

To address this question, our study first takes a system-level approach. Converging evidence has suggested that multiple functional systems of distributed brain regions act as sources of control signals (Corbetta & Shulman, 2002; Dosenbach et al., 2007; Miller & Cohen, 2001; Petersen & Posner, 2012; Power & Petersen, 2013). Control systems include: (1) the cinguloopercular task maintenance system (***CO***, dorsal and anterior cingulate cortex/medial superior frontal cortex and bilateral anterior insula/frontal operculum), (2) the frontoparietal adaptive control system (***FP***, dorsal lateral prefrontal cortex, medial cingulate cortex, and intraparietal sulcus), (3) the dorsal attention system for top-down attention (***DAN,*** dorsal lateral prefrontal cortex and frontal eye field), and (4) ventral attention system for re-orienting (***VAN***; right lateral ventral frontal cortex and temporoparietal junction). On the other hand, bottom-up processing occurs in systems such as the visual, auditory, and somatomotor systems (Bamiou, Musiek, & Luxon, 2003; Felleman & Van Essen, 1991; Matyas et al., 2010; Penfield & Boldrey, 1937), as well as higher order decision-making regions.

To observe how top-down signals interact with bottom-up processing, we employed a Posner-like cued detection task to investigate how attention changes the intrinsic functional relationships among distributed brain regions. The cue-target paradigm temporally separates the trial into (1) preparatory periods (cues), when trial-wise parameters are delivered for the configuration of top-down attention, and (2) trial implementation periods (targets), when the execution of the trial instructions occur (Hopfinger, Buonocore, & Mangun, 2000; Kastner, De Weerd, Desimone, & Ungerleider, 1998; Ollinger, Corbetta, & Shulman, 2001). Using this task, we can ask how region-to-region correlations evolve over the trial period, compared to a resting state. Furthermore, unlike previous experiments that focused on small sets of regions, the current study uses a system-level approach based on system definitions from a prior whole-brain parcellation (Gordon et al., 2014). Thus, we can directly probe the properties of multiple putative systems related to top-down control and bottom-up processing (*control-to-processing* interactions). Additionally, to get a more complete understanding of the system-level interactions we examine how interactions change among different control systems (control-to-control interactions) and within task-relevant processing systems (within-processing interactions).

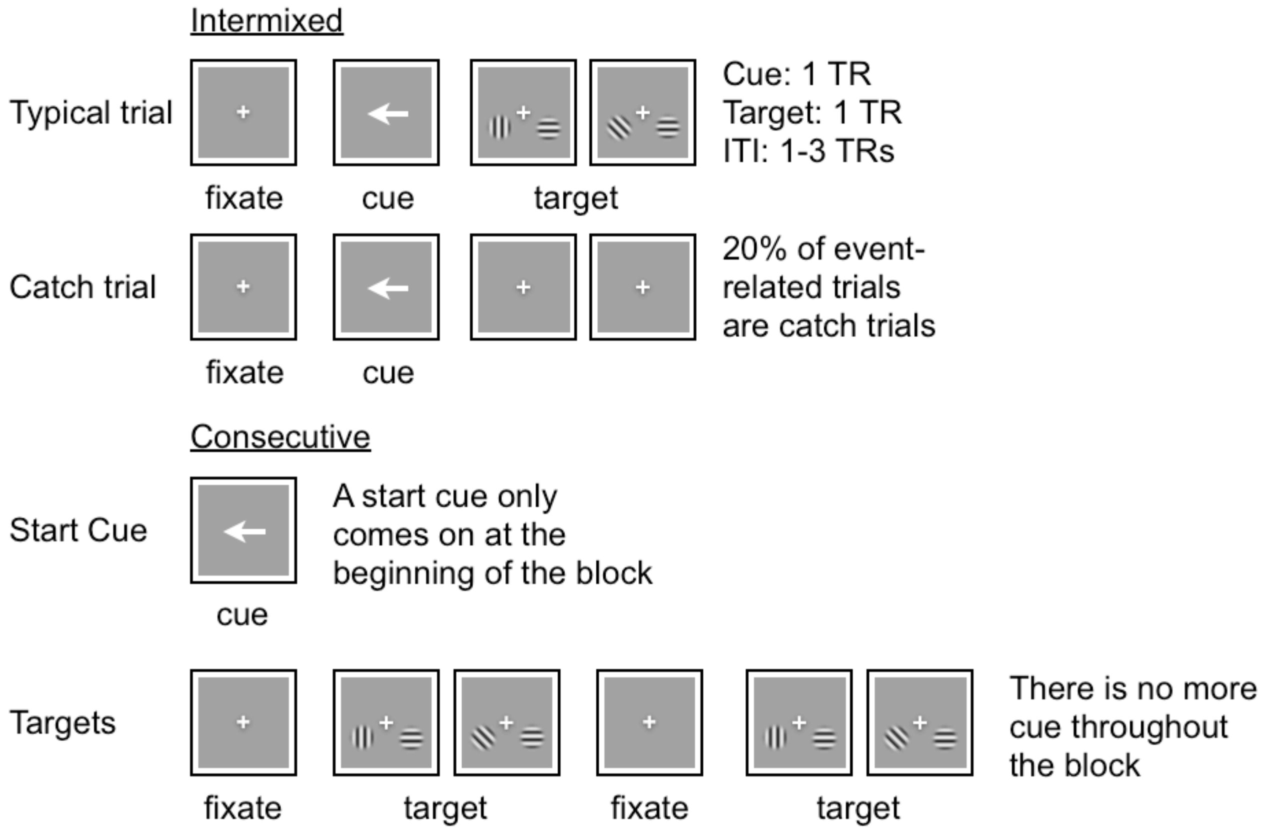

Figure 4.1: Task Paradigm

Subjects were instructed to perform target detection under two different conditions: *intermixed* and *consecutive*. For the *intermixed* condition, a preparatory visual cue in the form of a horizontal arrow was presented at the beginning of each trial. For 80% of the time they correctly predicted the likely location of the following target. From this condition, only catch trials (trials with cues and not target) were analyzed in this study, to allow for isolation of the cue signals from the target signals. Approximately 20% of the trials were catch trials. In the *consecutive* condition, subjects were given similar instructions as in the *intermixed* condition. However, a cue (arrow) was shown only once at the start of the run to indicate the likely location of the following targets. No subsequent trial-wise cue was given, although extra fixation frames were included where the trial-wise cues would have fallen. From this condition, the trials excluding the start cue were analyzed in this study, to allow for isolation of the target signals.

III. Methods

Subjects

Thirty-five healthy adults between the age of 21 and 30 (16 females, average age is 24.32 years) were recruited from Washington University in St. Louis and the surrounding community. All subjects participated for monetary compensation, and prior to scanning, each subject gave informed consent in accordance with the guidelines and approvals of the Washington University Human Study Committee. Subjects with less than 85% accuracy on the task or with excessive movements were excluded. In total, 28 (15 females) out of 35 subjects were retained after implementing the exclusion criteria.

Task design

The experiment was set up using a Posner-like paradigm (**Figure 4.1**). Subjects were instructed to perform target detection. Two cue-target conditions were presented: *intermixed* and *consecutive*. For the *intermixed* condition, a preparatory visual cue in the form of a horizontal arrow was presented at the beginning of each trial to indicate the likely location (80% validity) of the following target. The target display included two Gabor patches, one on the left and one on the right side of the screen. At either 800 or 1600ms post target stimulus onset, one of the patches would rotate. Subjects were then required to respond to the orientation change via pressing a button using their right index finger. Cues were presented for 1 TR, and targets were presented in the subsequent TR. Durations of inter-trial intervals were randomly distributed for 1, 2, or 3 TRs. From this condition, only catch trials -- trials with cues and no target -- were analyzed in this study, to allow for isolation of the cue signals from the target signals. Approximately 20% of the trials were catch trials; on these trials, subjects were instructed to wait for the next trial. In the *consecutive* condition, subjects were given similar instructions as in the intermixed condition. However, a cue (arrow) was shown only once at the start of the condition to indicate the likely location of the following targets. No subsequent trial-wise cues were given, although extra fixation frames were included where the trial-wise cues would have fallen. From this condition, the trials excluding the start cue were analyzed in this study, as they allowed for isolation of the target signals. Overall, this task design allows us to isolate cue and target events for functional connectivity analyses without introducing prolonged delays or unwanted signals between cue- and target-related processes.

Resting State

Resting-state data were obtained from 25 out of 28 subjects during the same session as the task data. During the resting-state scans, subjects lay quietly in the scanner while passively viewing a fixation cross.

Image Acquisition

Data were obtained from a Siemens MAGNETOM Tim Trio 3.0T Scanner with a Siemens 12-channel Head Matrix Coil (Erlangen, Germany). Head movements were limited by using a thermoplastic mask fitted to individual subject's head at each entry into the scanner. Functional images for task and resting-state runs were acquired using a BOLD-contrast sensitive gradient-echo echo-planar sequence with following parameters: TE = 27ms, volume TR = 2.5s, flip angle = 90^o, in-plane resolution = 4x4 mm, and 32 contiguous interleaved 4 mm axial slices. For each subject, six to eight task runs and one to two resting-state runs lasting 217 volumes each were obtained. Additionally, a T1 sagittal MP-RAGE structural image (TE = 3.06ms, TR-partition = 2.4s, TI = 1000ms, flip angle = 8°, 176 slices with 1x1x1mm voxels) and a T2-weighted turbo spin-echo structural image (TE = 84ms, TR = 6.8s, 32 slices with 2 x 1 x 4 mm voxels) were acquired for each subject in the same anatomical plane as the BOLD images to improve alignment to an atlas.

Preprocessing

Both task and resting-state functional images were first processed to reduce artifacts (Miezin, Maccotta, Ollinger, Petersen, & Buckner, 2000). Steps were included to correct for (1) odd versus even slice intensity differences, (2) head motion within- and across-run using a rigid body rotation and translation algorithm (Snyder, 1996), and (3) within-run intensity normalization to a whole-brain mode-voxel value of 1000 to facilitate across subject comparison (Ojemann et al., 1997). Using the MP-RAGE scan, atlas transformation of the functional data was computed for each individual. Each run was then resampled to an isotropic 3-mm grid, combining movement correction and atlas transformation in a single interpolation. For task runs, root-mean-square (RMS) realignment estimates were calculated from the realignment parameters (rotational estimates converted to translational at radius of 50mm), and subjects having more than 4 runs with RMS movement above 1.0mm were first excluded.

Task Residual Calculation

After preprocessing, first-order stimulus-evoked BOLD activity were removed from the task-runs. A general linear model (GLM) approach was applied to model the BOLD signals in each subject using in-house imaging software (FIDL). The GLM included linear and constant terms for each run to remove baseline and drift effects. Additionally, start cues, end cues, trial events by condition types (i.e. cues for the intermixed condition, targets for the intermixed condition, cues for the consecutive condition, and targets for consecutive condition), errors, and sustained task responses were modeled in the GLM. For the trial events, 9 time-points were modeled using delta functions immediately following the onset of each event to capture the full hemodynamic response (Miezin et al., 2000). Overall, this approach makes no assumption about the shape of the hemodynamic response but does assume that all events included in a category were associated with the same response. Sustained responses for both intermixed and consecutive conditions were modeled as a block effect. All subsequent operations were performed on the residual time-series that were extracted by removing task-evoked activity from task time-series using the GLM.

Functional Connectivity Processing

To reduce spurious variance unlikely to reflect neuronal activity, additional preprocessing steps were executed for resting-state and task residual data as recommended in Power et al. 2014. The preprocessing steps include demeaning and detrending, a multiple regression of nuisance variables from the BOLD data, and a temporal band-pass filter ($0.009 \text{ Hz} < f < 0.08 \text{ Hz}$). Nuisance variables included (1) whole-brain, ventricular, and white matter signals, and (2) motion parameters derived by Volterra expansion (Friston, Williams, Howard, Frackowiak, & Turner, 1996).

In addition, temporal masks were created to identify motion-contaminated frames. Head motion can cause spurious yet systematic changes in BOLD correlations that affect group comparisons (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Van Dijk, Sabuncu, & Buckner, 2012). Motion-contaminated volumes were defined as having frame-by-frame displacement (FD, described in Power et al. 2012) greater than 0.25 mm. High motion volumes and uncensored segments of data lasting fewer than 5 contiguous volumes were flagged for removal. The procedure retained 1239±403 volumes (3097±1007 s) of usable data per subject for task-residuals and retained 215±37 volumes (537±92 s) of usable data per subject for resting-state.

After the temporal masks were incorporated into the processing steps to censor motion-contaminated data, data were interpolated across censored frames using least squares spectral estimation of the values at the censored frames. Finally, data with interpolated frames were passed through a band-pass filter (0.009 Hz < f < 0.08 Hz). However, even following this processing stream, censored frames were still ignored in the time-series used to calculate correlations.

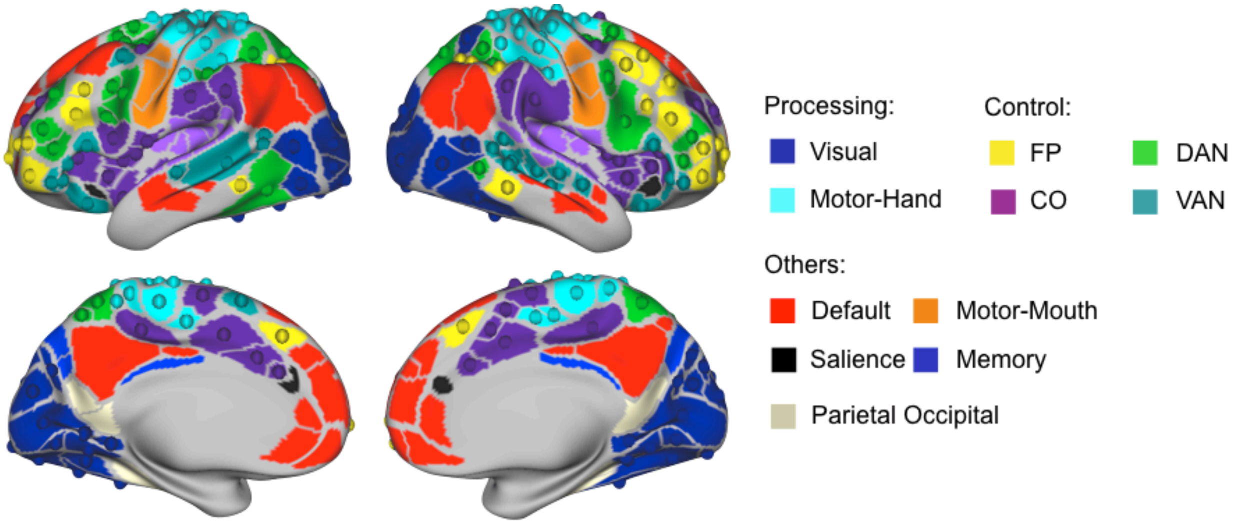

Figure 4.2: Regions of Interest (ROIs)
The 333 parcels from Gordon et al., 2014 are depicted here. The system assignment of each parcel is color-coded. For selecting regions of interest, we focused on previously defined areas in six functional systems. Some of these systems are chosen based on their roles in task control and orientation of attention; they include, frontoparietal, cinguloopercular, dorsal attention, and ventral attention systems. Other systems are chosen because of their relevant processing functions; they include the visual and the somatomotor systems. Regions in the selected systems are also modeled as 10mm-diameter spheres.

ROI Definition and System Assignments

We defined our regions of interest from a prior whole-brain parcellation (Gordon et al., 2014). From Gordon et al. 2015, 333 parcels derived from a group averaged (n = 120) resting-state functional connectivity boundary map that represented putative cortical areas (Gordon et al., 2014). All 333 parcels were assigned to a set of 13 networks that reflect the functional systems of the brain. The current study adopted 196 parcels and their network assignments based on their control- and processing related properties. The networks are: frontoparietal, dorsal attention, ventral attention, cinguloopercular, visual, and somatomotor systems, see **Figure 4.2**. Lastly, the 196 regions of interest (ROIs) were modeled as 10mm-diameter spheres fixed at the parcels' geometric centers.

Functional Connectivity Calculations

To extract signals from cue-related periods, cue-related volumes were taken only from catch-trials within the *intermixed* condition, where no target stimulus appeared in the subsequent four to six TRs following the onset of the cue stimulus. Target-related volumes were taken from trials in the *consecutive* condition, where no trial-wise cue was present.

To construct the rest-, cue-, and target-related correlation matrix for each subject, the averaged task-residual (cue and target) and resting-state BOLD time-series were extracted separately for each of the 196 ROIs. For cues and targets, post-stimulus segments (5 consecutive TRs after cue and target stimulus onset. Similar results were found using 4 consecutive TRs) were concatenated across all catch-cues and targets for each subject. For rest, time-series from resting-state runs were extracted and then matched in frame numbers with each task-related condition. Finally, for cue, target and rest separately, the Pearson correlation coefficients were calculated between the BOLD time-series of all possible pairs of the ROIs, forming 196x196 correlation matrices. All correlation coefficients were normalized using Fisher's r-to-z transform.

Comparing correlation matrices

For statistical comparisons of the subjects' correlation matrices derived from rest, cue and target, a single p-value was calculated to indicate significance of matrix differences using methods from the emerging field of object oriented data analysis (OODA, La Rosa et al., 2012). OODA is a multivariate method capable of finding patterns of differences in correlation matrices. It employs classical statistical approaches (e.g. hypothesis testing) by treating each correlation matrix as a data point. From each sample, the averaged matrix is computed under the assumption that matrices follow the Gibb's distribution. Average matrices from different samples are then compared to each other by taking the Euclidean distance between them. To evaluate the statistical significance for the comparison, the Euclidean distance between the two sample means are compared to a distribution of distances generated by paired permutations (n = 1000) of the original samples. The OODA method reduces the need for substantial data reduction in the correlation matrices, but prevents the loss of power that comes from testing each connection separately.

After the comparisons of whole-brain correlation matrices, additional *post hoc* comparisons of between-system and within-system connectivity were conducted to investigate which specific control-to-processing, control-to-control, and within-processing interactions drove the omnibus effect. For each comparison (i.e. rest versus cue, rest versus target, and target versus cue), subsets of system-to-system correlations (e.g., frontoparietal-to-visual, frontoparietal-to-dorsal attention, and within-visual) were extracted and compared using two approaches. (1) We further applied OODA to each set of within-system and between-system correlations. Individual system-to-system OODA were then subjected to false discovery rate (FDR) correction for multiple comparisons. (2) To identify which within- and between-system relationships changed the most for each comparison, we extracted the mean and standard deviation from the absolute values of the entire difference matrix, as well as from the absolute differences in each system-to-system relationships. Then, we computed standard scores associated with each within- and between-system modulations to indicate their deviations from the average connectivity change. Although this method lacks a measure of statistical significance, its main purpose is to indicate which system-to-system relationships differed the most for each rest versus cue, rest versus target, and target versus cue comparison.

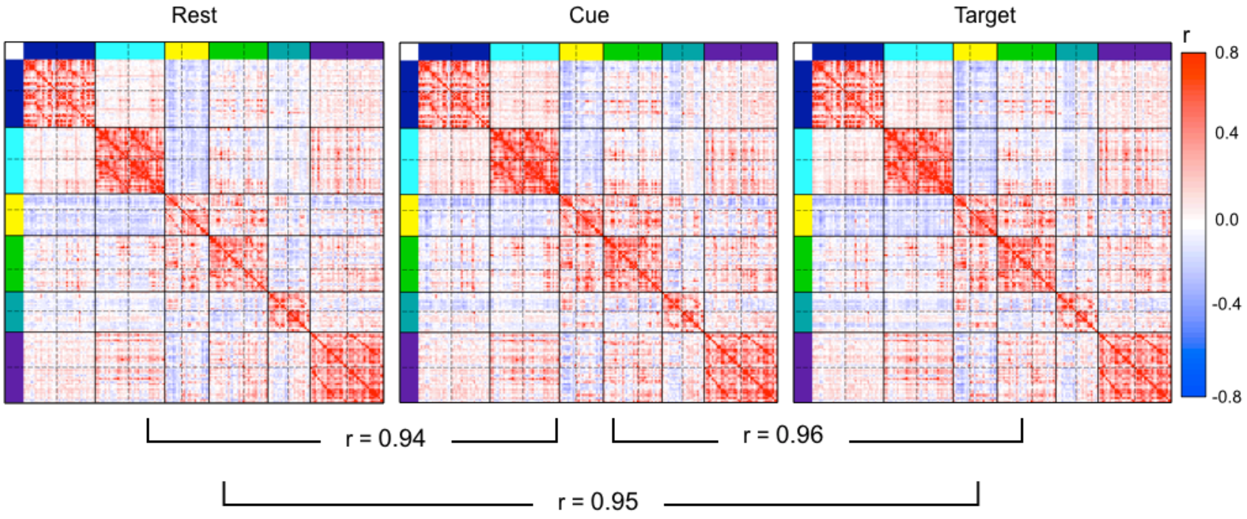

Figure 4.3: Rest-, Cue-, and Target-related Connectivity Organization
The large-scale connectivity organization of the selected functional systems was similar between different trial conditions (cue and target) and resting-state. The Pearson's correlation coefficients r = 0.94, r = 0.95, and r = 0.96 for rest versus cue, rest versus target, and cue versus target, respectively.

IV. Results

Task-state showed similar functional connectivity structure as resting-state

Overall, the large-scale functional network organization of the 196 ROIs was similar between task and resting-state (see **Figure 4.3**). The correlation between averaged cue- and rest-related connectivity matrices is r = 0.90 while the correlation between averaged target- and rest-related connectivity matrices is r = 0.91. Comparing cue and target conditions also indicates a largely similar underlying network organization, with a correlation between the averaged connectivity matrices of r = 0.95.

A

	Cue vs Rest (OODA, uncorrected)						Target vs. Cue (OODA, uncorrected)						Target vs. Rest (OODA, uncorrected)					
196x196 Matrix	p < 0.001						p < 0.05						p < 0.001					
	Visual	Hand	FP	DAN	VAN	CO	Visual	Hand	FP	DAN	VAN	CO	Visual	Hand	FP	DAN	VAN	CO
Visual	0.06	**0.031**	**<0.001**	**<0.001**	**0.009**	0.094	**0.004**	0.371	**0.012**	0.089	0.332	0.412	0.211	**0.031**	**0.003**	**0.001**	**0.021**	**0.055**
Hand		0.239	**0.001**	**0.013**	0.119	**0.01**		0.122	0.06	**0.036**	0.438	0.281		0.097	**0.013**	0.05	0.073	**0.005**
FP			0.075	**<0.001**	**0.031**	**0.015**			**0.003**	0.243	0.084	0.479			0.079	**<0.01**	**0.007**	**0.029**
DAN				**0.001**	**0.006**	**0.004**				**0.021**	0.15	0.345				**<0.001**	**0.005**	**0.002**
VAN					**0.004**	**0.011**					0.131	0.106					**0.002**	**0.019**
CO						**0.003**						0.597						**<0.001**

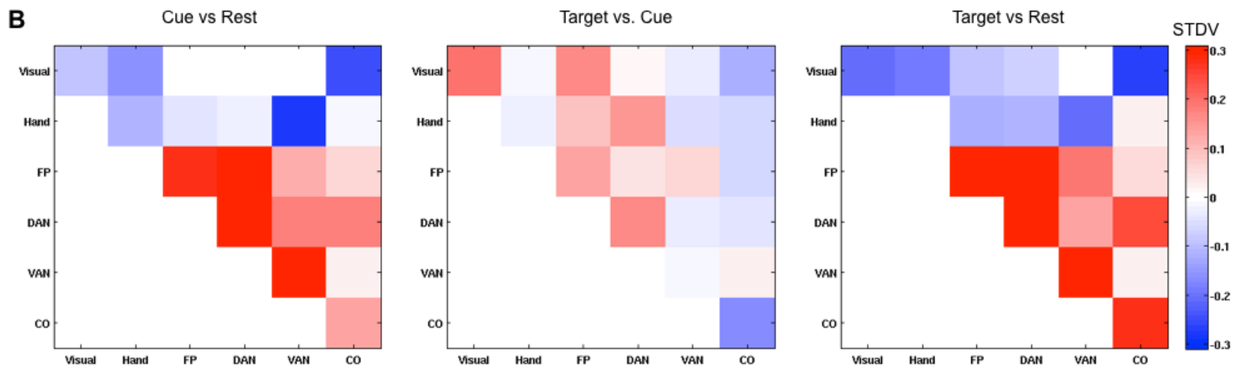

Figure 4.4: Comparisons of Task Conditions
(A) using paired OODA, we found significant differences between cue and rest, target and rest, target and cue. For the full matrix of all selected functional regions, we found significant differences between cue and resting-state ($p < 0.001$), target and cue ($p < 0.05$), and target and resting-state ($p < 0.001$). The resulting p-values (uncorrected) from *post hoc* block-wise paired OODA indicated which system-to-system connectivity are driving the overall effects. (B) For each cue versus rest, target versus cue, and target versus rest comparison, the standard scores associated with individual system-to-system connectivity indicated which ones changed the most compared to the mean absolute change of the full matrix.

Connectivity changes are significant across different conditions

Despite the overall similarity of network organization among cue, target and resting-state, there exist consistent differences between each state (Figure 4). Using object oriented data analyses (OODA, see Methods), we found significant differences ($p < 0.001$) between cue and resting-state connectivity matrices as well as between target and resting-state connectivity matrices. Cue and target-related connectivity matrices also showed significant differences ($p < 0.05$).

Given the significant whole connectivity differences, we next sought to identify which within-system and between-system relationships were driving the overall effects. For each cue versus rest, target vs. rest, and target versus cue comparison, we applied post hoc OODA analyses to sets of system-to-system connectivity and calculated standard scores associated with their mean absolute difference to further characterize changes, especially in control-to-processing, control-to-control, and within-processing interactions, across distinct portions of the trial (see Methods). Additionally, we investigated the changes in interaction as well. **Figure 4.4** shows, for each comparison, the resulting OODA p-values (uncorrected) and standard scores associated with individual system-to-system connectivity. **Supplemental Figure 4.1** shows, for each comparison, the mean absolute correlation change associated with individual system-to-system connectivity. We will further describe these system-to-system changes in the following sections.

Cue vs. Rest

Figure 4.5 shows the difference in cue and resting-state matrices, as well as seedmaps of two example regions: one in a right frontal cortex region of the frontoparietal system (ROI1) and the other in a right posterior parietal region of the dorsal attention system (ROI2). These regions were chosen because, compared to resting-state, they showed some of the highest cue-related changes in connectivity. ROI1 in right frontal cortex showed cue-related increases with not only other regions of frontoparietal system, but also with bilateral superior parietal lobule (SPL) and dorsal lateral prefrontal cortex regions of the dorsal attention system; the bilateral anterior insula and dorsal mid-cingulate regions of the cinguloopercular system; and right superior temporal gyrus and ventral frontal cortex of the ventral attention system. In addition, besides increases with most of the control systems, connectivity between ROI1 and lateral regions of the visual and motor systems also increased. Similarly, ROI2 in the right parietal region also showed largely increased connectivity with other control (e.g. regions in the frontal cortex and IPS of the frontoparietal system, regions in anterior insula and mid-cingulate of the cinguloopercular system) and processing (e.g. lateral visual cortex, motor cortex) regions.

These example patterns of system-to-system modulations in connectivity are representative of the overall changes seen in the comparisons between cue and resting-state. These connectivity changes are consistent across subjects, and they are supported by several comparison approaches. Significant *post hoc* block-wise OODA comparisons were observed in specific control-to-processing and control-to-control relationships. For control-to-processing system interactions, the most significant differences (OODA, $p < 0.001$, FDR corrected) were seen between frontoparietal-to-visual, and dorsal attention-to-visual correlations. These correlation changes were mostly cue-related increases, especially between right-lateralized FP regions and the visual system. Other control-to-processing modulations, such as ventral attention-to-visual, frontoparietal-to-motor, and cinguloopercular-to-motor were significant as well, albeit to a lesser degree (OODA, $p<0.05$, FDR corrected), and they largely showed cue-related connectivity increases, except for connectivity between ventral attention system (especially regions in the left hemisphere) and visual system, which decreased. For control-to-control system interactions, almost all relationships revealed significant differences. These control-to-control modulations were mostly cue-related increases, and, on average, had the highest standard scores, suggesting that they predominantly drove the overall difference between cue and rest connectivity.

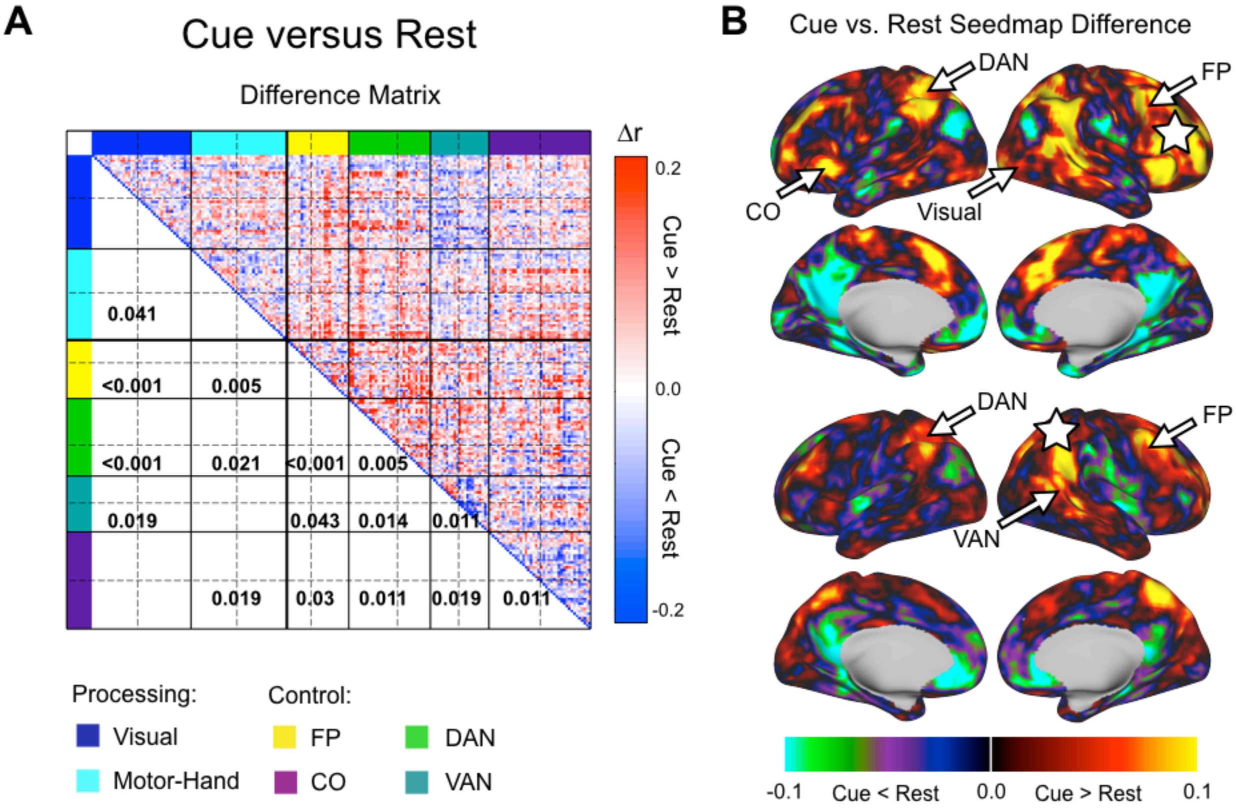

Figure 4.5: Cue Versus Rest Comparison

(A) the cue versus rest difference matrix is indicated by changes in Pearson's correlation coefficient at individual region-to-region connections. The warmer colors indicate connections that are greater during cue than rest, and cooler colors indicate otherwise. The lower triangle shows the p-values of significant system-system blocks indicated by OODA, after FDR correction for multiple comparisons. Additionally, the thicker solid black line divides control-related systems from processing systems to indicate connectivity differences within processing systems, within control systems, and between control and processing systems. The thin solid lines delineate individual systems, and the dashed lines divide regions in the left and right hemispheres. (B) *Top*: the cue versus rest contrast seedmap of an example ROI in the frontoparietal (FP) system. The FP seed revealed cue-related correlation increases with dorsal attention (DAN), ventral attention (VAN), and cinguloopercular control (CO) systems as well as with a few lateral visual regions. *Bottom*: the cue versus rest contrast seedmap of an example ROI in the DAN system. The DAN seed also revealed cue-related correlation increases with regions of FP, VAN, and visual systems.

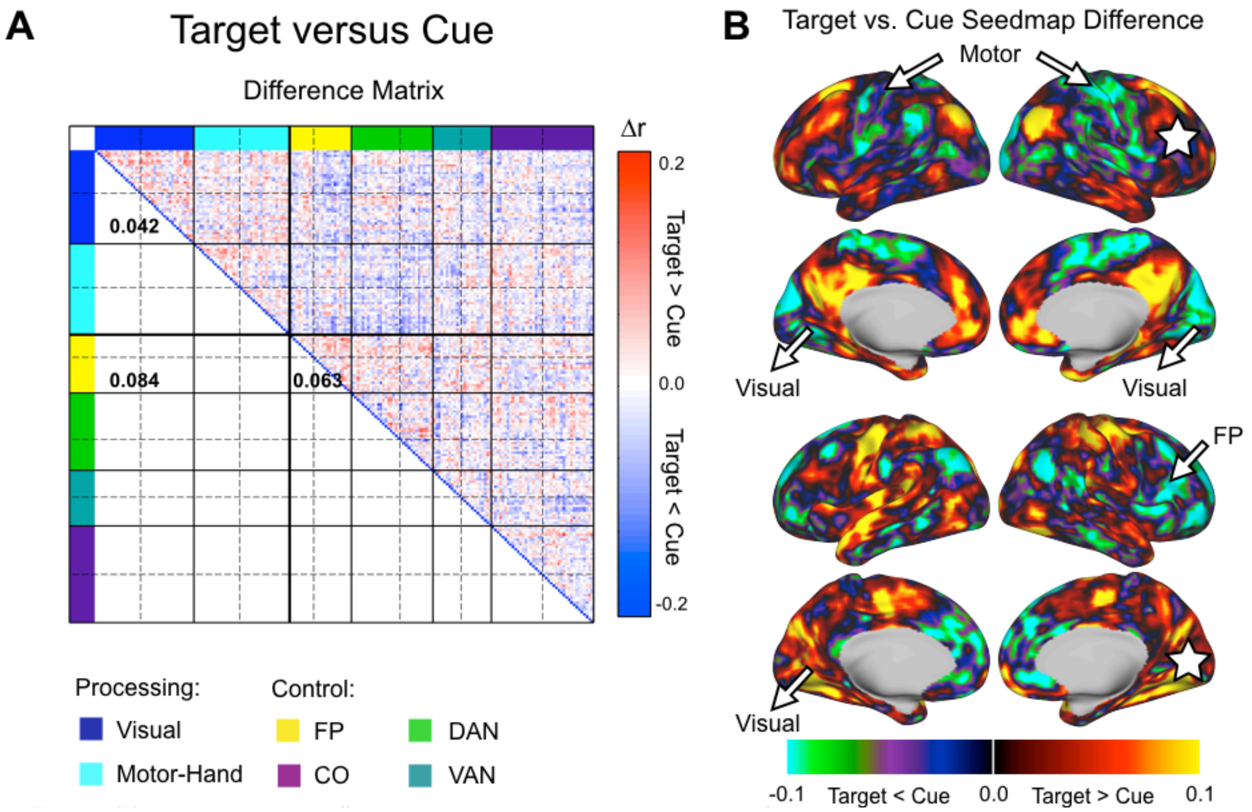

Figure 4.6: Target Versus Cue Comparison

(A) The target versus cue difference matrix is organized in similar fashion as **Figure 4.5**. The warmer colors indicate connections that are greater during target than cue, and cooler colors indicate otherwise. The lower triangle shows the p-values of significant and trend-level system-system blocks indicated by OODA, after FDR correction for multiple comparisons. Specifically, within-visual connectivity showed target-related increase; within-frontoparietal connectivity showed target-related increase; and frontoparietal-visual connectivity showed mixed modulations such that right frontoparietal regions showed more target-related connectivity decreases with the visual regions. (B) *Top*: the target versus cue contrast seedmap of the same example ROI in the right frontoparietal system (FP) as in **Figure 4.5**. The FP seed revealed target-related correlation increases mostly with other regions of FP system. The FP seed also showed target-related decreases with visual and motor regions. *Bottom*: the target versus cue contrast seedmap of a visual seed in the right calcarine sulcus. Congruent with the pattern in the FP seed, here we see the expected target-related connectivity decreases with the right FP regions. In addition, the visual seed also revealed target-related connectivity increase within the visual system.

Target vs. Rest

Modulation of connectivity between target and resting-state showed an overall similar pattern of changes as seen between cue and resting-state (**Supplemental Figure 4.2**). Most notably, control-to-control (e.g. frontoparietal-to-dorsal attention, dorsal attention-to-ventral attention) system changes not only revealed statistically significant differences (OODA, $p < 0.05$, FDR corrected), they had the highest magnitude of target-related changes relative to rest. Additionally, similar control-to-processing changes as those seen in cue versus rest comparison were significant here as well (i.e. frontoparietal-, dorsal attention-, and ventral attention-to-visual).

Cue vs. Target

Despite the largely similar cue- and target- related connectivity modulations relative to resting-state, there were consistent and specific differences between these two portions of the trial. **Figure 4.6** shows the difference between target and cue seedmaps of the aforementioned frontoparietal region in the right frontal cortex (ROI1, see cue vs. rest) and a visual region in the right calcarine sulcus (ROI2). These regions were chosen because they show high absolute changes in connectivity, and they provided insight into both the control and processing systems of the brain. ROI1 in the right frontal cortex showed increases in target-related connectivity with other regions of the frontoparietal system (e.g. dlPFC) and dorsal attention system (e.g. bilateral frontal eye fields). However, ROI1 also showed target-related connectivity decreases with the visual and motor processing systems. Correspondingly, ROI2 in the right calcarine sulcus of the visual system showed primarily strong target-related decreases with a large subset of the frontoparietal regions, especially in the right frontal cortex. Increases in connectivity were also seen between ROI2 and other regions of the visual and motor cortex.

The contrast between target- and cue-related full correlation matrices demonstrated similar patterns of modulations indicated by the examples (**Figure 6**). It is important to note that OODA comparison of the complete connectivity matrices revealed overall significant differences across cue and target portions of the trial. While only the within-visual block-wise OODA comparison passed FDR correction for multiple comparisons (OODA p = 0.042, corrected), frontoparietal-to-visual, and within-frontoparietal connectivity also demonstrated trend-level differences (OODA p = 0.084 corrected; OODA p = 0.063 corrected). On average, these specific system-to-system relationships modulated the most, as the corresponding standard scores suggest. Furthermore, target-related decreases were seen for control-to-processing connectivity, especially between right frontoparietal and visual regions (**Supplemental Figure 2**). Target-related increases were seen within control (i.e. frontoparietal system) and processing (i.e. visual) system connectivity (**Supplemental Figure 2**).

V. Discussion

Top-down attention influences bottom-up processing in regions such as the visual cortex. Supported by evidence from single-cell recordings and neuroimaging studies, influential theories of attention, i.e., the biased competition model and the divisive normalization model, propose that top-down control signals instantiate an environment that allows for selective processing of relevant stimuli, perhaps via shrinking the neuronal receptive fields around the attended stimulus (Moran & Desimone, 1985), enhancing the neuronal response by a gain factor (Spitzer & Richmond, 1991), or increasing the neuron's contrast gain by elevating the baseline activity (Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999; Ress, Backus, & Heeger, 2000). However, each of these models lacks descriptions for the temporal characteristics of top-down control; thus, our analyses hope to shed further insight.

The current study took a system-level approach and examined how the interactions among various control and processing systems differed across separate portions of a trial. By looking at the timing of the changes in functional connectivity and relating the observed changes to cue- and target-related processing, we examined functional connectivity modulations between control and processing systems, between control-related systems (control-to-control), and within processing-related systems (within-processing) to better understand trial-related dynamics among a selected set of functional systems.

Our task used a specialized experimental design that allowed for the separation of cue and target events for connectivity analyses while retaining the respective cognitive aspects of each event. Overall, we found that, similar to the conclusions from previous task-related connectivity studies, connectivity patterns derived from cue and target periods were largely similar to resting-state (Cole, Bassett, Power, Braver, & Petersen, 2014; Yeo et al., 2014). However, across portions of a trial, we observed subtle changes among processing regions, mostly in the visual system, that were accompanied by additional complex and dynamic modulations in their connectivity with distinct control systems. Our results demonstrated a large cue-driven enhancement in control-to-processing as well as control-to-control connectivity that was generally maintained throughout the trial. However, this global increase was further accompanied by more specific target-driven reductions (from cue-related enhancements) in connectivity between some control and processing systems (i.e. frontoparietal to visual connections). Taken together, changes among the various functional systems across a trial reflect effects of top-down signals that are both continuous as well as momentary.

Control-to-processing interactions

From rest to cue: Control systems engage with processing systems during the preparatory phase

In comparison to resting-state, executive control- and attention-related functional systems all demonstrated statistically significant changes in their interactions with processing systems during the cue portion of a goal-directed trial. These specific control-to-processing interactions are likely to reflect the engagement (and in some cases disengagement) of relevant higher- and lower-level brain regions as a result of top-down attention.

In support of this idea, past evidence has suggested that the frontoparietal, cinguloopercular, and dorsal attention systems are sources of top-down control signals. Specifically, the frontoparietal system (dorsal lateral prefrontal cortex, medial cingulate cortex, and intraparietal sulcus) is thought to emphasize initiating and adapting relevant parameters on both a task set level as well as a trial level, while the cinguloopercular system (dorsal and anterior cingulate cortex/medial superior frontal cortex and bilateral anterior insula/frontal operculum) might be engaged in stable maintenance of parameters across the task (Dosenbach et al., 2007; Neta et al., 2015). The dorsal attention system (intraparietal cortex and frontal eye fields) has exhibited activity related to trial preparation as well as action selection in goal-directed tasks. Additionally, the DAN is thought to also play a crucial role in voluntary maintenance of spatial attention (Corbetta & Shulman, 2002).

Recently, regions in the frontoparietal and dorsal attention systems have been implicated in selective attention operations through increasing their connectivity with visual association regions (Bressler, Tang, Sylvester, Shulman, & Corbetta, 2008; Gazzaley et al., 2007; Spadone et al., 2015). Previous studies using combined TMS and fMRI have directly investigated the influence of control regions (e.g., prefrontal cortex, intraparietal sulcus, and frontal eye fields) on lower-level sensory regions (Lee & D'Esposito, 2012; Ruff et al., 2008; Ruff et al., 2006; Vuilleumier et al., 2008). Notably, disruption of PFC function has shown to decrease the tuning of extrastriate cortex responses and cause decrements in task performance (Lee & D'Esposito, 2012). Although the current results also revealed FC enhancements between control and processing regions, here we emphasize the initiation of the top-down effects during the cue preparatory period.

A fourth attention-related network, the ventral attention system (VAN) is specialized for reorientation of attention and detection of task-relevant stimuli occurring at unexpected locations. For example, during a Posner task, ventral attention regions show greater evoked responses during target periods of invalid trials than during target periods of valid trials (Corbetta, 1998). Due to its weak evoked responses during a preparatory cue, the ventral attention system is typically described as not involved in the generation or maintenance of top-down attention, but is instead thought to be modulated by stimulus-driven attentional control (Corbetta & Shulman, 2002; Serences et al., 2005). Although traditionally described as right lateralized, the ventral attention system defined in the current study is composed of bilateral TPJ, superior temporal gyrus, and ventral frontal regions. Our results indicated significant overall decrease in connectivity between VAN and visual regions, especially in the left VAN regions. Perhaps consistent with the traditional descriptions, this initial decreased coupling between VAN and visual system seen in the current study is suggestive of VAN's role outside of preparatory top-down regulation.

From cue to target execution: Some control systems showed target-driven decoupling with processing regions

We observed that the functional connectivity estimated during target implementation was significantly different from the functional connectivity estimated during preparatory portions of the trials, suggesting variations in interactions among the functional systems as result of differences in cue- and target-related processing. One salient set of changes was the decreases in target-related correlation between visual and the right lateralized FP regions, suggesting a relative decoupling of functional connectivity across two systems. In combination with the observed increased connectivity seen from rest to cue, this "integrate then separate" relationship between FP and visual systems is surprising based on the body of literature that demonstrated enhanced long-range modulations between regions of the FP system and regions of processing systems (Gazzaley et al., 2007; Ruff et al., 2006). It is important to note that while our results showed connectivity fluctuations between FP to processing system within different periods of a task, connectivity between these systems was overall stronger during task than rest, which is consistent with previous observations. However, the data further suggest that FP regions do not provide a steady signal to relevant processing regions, such as the visual regions. We speculate that control regions in FP may specifically act to "update" attention bias signals at the beginning of the trial by transiently boosting connectivity with relevant processing regions and then attenuating connectivity to allow visual and motor regions to process target-related information efficiently.

On the other hand, many control regions, especially in the CO system, also maintained relatively steady interactions with the processing systems across the cue and target portions of a trial. How distinct control systems maintain or alter their interactions with processing systems is perhaps indicative of their functional specializations. Extant theoretical models of the task control have delineated dissociable control signals that operate on different time-scales (Dosenbach et al., 2007; Logan & Gordon, 2001). While signals, such as trial-wise cueing, are adapted on trial-by-trial basis, others, such as sustained signals, are maintained across an entire task set (Chawla, Rees, & Friston, 1999; Dosenbach et al., 2007; Dosenbach et al., 2006). Here we show that FP varies its interaction with processing systems based on the concurrent trial-related operations, and perhaps this pattern of function connectivity change contributes to FP's fast and adaptive activity in task control. In contrast, given the lack of significant changes in functional connectivity between cue and target, CO showed relatively steady interactions with the visual system, and we speculate that the continuous enhancement between CO and visual regions reflect the longer acting, across-trial, sustained signals from the CO system.

Within-processing interactions

FC also was modulated among processing regions during different periods of the task. Notably, FC within the visual system showed an initial trend-level decrease during the cue period that then transitioned into a significant increase back to baseline during the target. This effect is partly inconsistent with previous observations, which have reported connectivity decreases within the visual systems during movie viewing and visually cued tasks (Betti et al., 2013; Spadone et al., 2015). However, it is possible that the decrease in within-visual coherence observed here, during cue, and in previous studies reflects the selective effect of top-down attention on subgroups of visual neurons, and the return to baseline coherence during target reflect visual processing of the trial stimuli.

Control-to-control interactions

Control-related systems showed substantial integration during this goal-driven attention task. A comparison with resting-state showed significant connectivity increases between and within almost all control systems, and the increased connectivity was largely maintained throughout both cue and target periods of the task. This finding suggests that control systems become more interconnected in the presence of goal-directed attentional signals. Some of the increased connectivity may be at the service of exchanging executive control signals between frontoparietal and cinguloopercular systems during task implementation, such that the increases may reflect the ongoing communication between parameter updating, monitoring, and performance feedback signals necessary for task performance (Dosenbach et al., 2006; Gratton et al., 2016; Sadaghiani & D'Esposito, 2015; Wallis, Stokes, Cousijn, Woolrich, & Nobre, 2015). Although few studies have specifically examined changes in between-network interactions of control systems during task, studies using graph theory to examine network properties of brain regions have shown a high frequency of hub-like regions in frontoparietal, cinguloopercular, and dorsal attention systems (Power, Schlaggar, Lessov-Schlaggar, & Petersen, 2013; van den Heuvel & Sporns, 2011) These hub-like regions exhibit increased interactions specifically with other control systems during various tasks, and lesions in a hub region can result in disruption of the brain's intrinsic functional organization and detrimental impairments in task performance across many neuropsychological and cognitive domains (Gratton, Nomura, Perez, & D'Esposito, 2012; Warren et al., 2014). Here, we have provided additional evidence for increased connectivity among control systems as a result of both trial-related cueing and target implementation, further supporting the collective roles of the control systems during task performance.

VI. Conclusions

In conclusion, the present study provides new insight into the subtle modulations of the brain's functional structure during the implementation of goal-directed tasks. In particular, we found that trial-wise preparatory signals during cue periods produced enhanced connectivity in control-to-control and control-to-processing relationships. While we did observe substantially maintained changes in network interactions across cue and target processing, some momentary effects were present among various functional systems as well. Most notably, we observed decreases in between-system relationships (e.g. frontoparietal-visual) and increases in within-systems relationships (e.g. frontoparietal, dorsal attention, and visual) during target processing, compared with the cue period. Future research will be needed to explore the association between task-induced alterations in functional structure and performance in order to broaden understandings of the significance and effects of task-based connectivity modulations.

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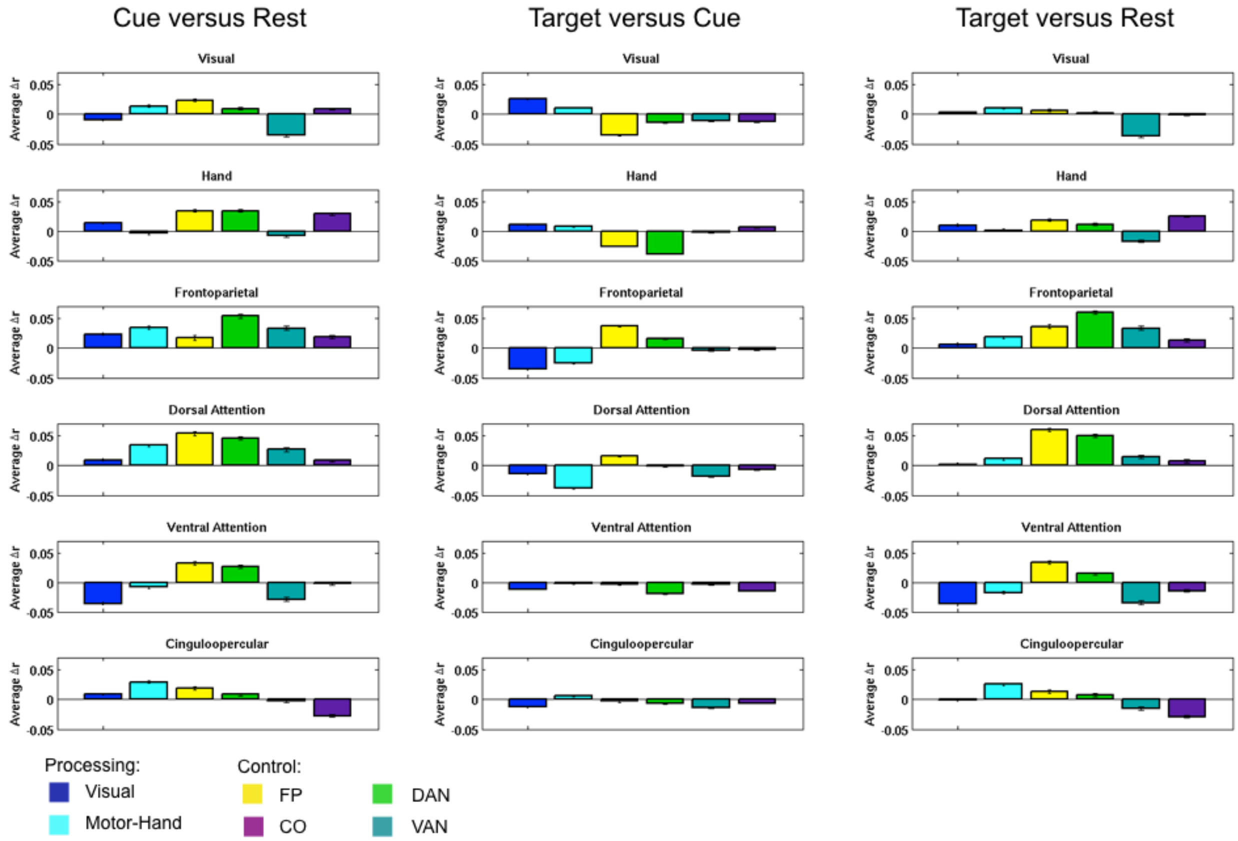
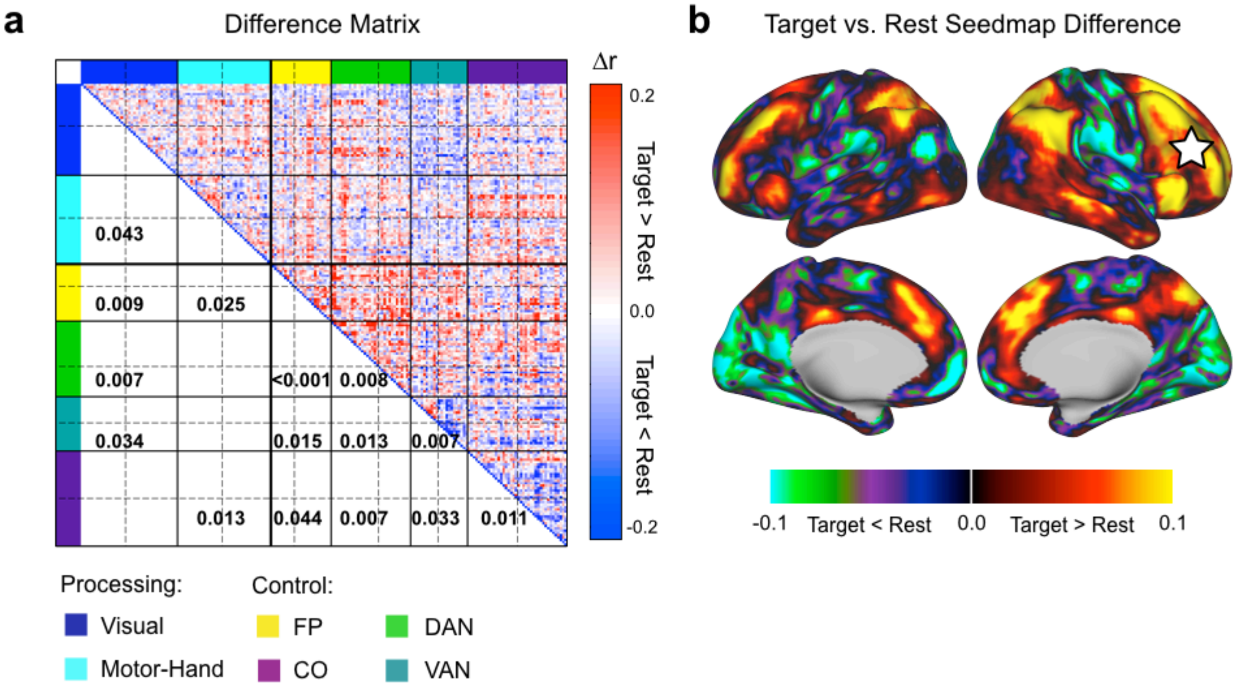
VIII. Supporting Information



Supplementary Figure 4.1: Averaged Connectivity Changes
For each cue versus rest, target versus cue, and target versus rest comparison, to determine whether each between and within system fucntional connectivity increased or decreased, we calculated the mean correlation change within each system-to-system block. For example, under the cue versus rest colunn, the first panel indicates the mean correlation change between visual and every other selected functional system.



Supplementary Figure 4.2: Target Versus Rest Comparison
(a) The target versus rest difference matrix is depicted and organized in similar fashion as Figure 4.5 and Figure 4.6. The warmer colors indicate connections that are greater during target than rest, and the cooler colors indicate otehrwise. The lower triangle shows the p-values of singificant system-system blocks indicated by OODA, after FDR correction for multiple comparisons. Overall the pattern of changes between target and restin-state is similar to that of between cue and resting-state. (b) The target versus contrast seedmap of the same example ROI in the right frontoparietal system (FP) as in Figure 4.5. The FP seed revealed target-related increases in connectivity mostly with other regions of FP, dorsal attention, cinguloopercular, and right ventral attention systems. However, unlike the cue versus resting-state comparison, here we see more target-realted decreases in connectivity between the seed region and medial visual regions as well as motor regions.

CHAPTER 5: CONCLUSIONS

Implementation of daily functions in humans relies on both bottom-up moment-to-moment processing of relevant sensory information and top-down controls that instantiate and regulate goal-directed strategies. Carefully coordinated interactions between brain regions specialized for control-related activity and regions specialized for bottom-up information processing allow humans to adeptly undertake various goal-directed tasks. Past seminal framework that outlined the anatomical basis of task control proposed that, (1) systems related to control processes should be anatomically separate from systems related to "data processing "; (2) control processes are carried out by a network of anatomical areas; and (3) distinct systems of control carry out different cognitive operations in context of attention (Petersen and Posner, 2012). The work contained in this thesis further address these propositions by focusing on characterizing control systems' distinctness in the contexts of resting-state connectivity, task-activation, as well as task-based connectivity.

I. Summary of Results

In Chapter 2, using graph theory methods, we explored the resting-state intrinsic connectivity and system overlaps in various functional systems, including control systems. Specifically, resting-state fMRI studies in the past have modeled the brain as a large interactive network of distributed functional areas and employed complex graph theory methods to identify and characterize the brain's various functional systems (Bullmore & Sporns, 2009; Rubinov &

Sporns, 2009). Despite knowing that the functional structure of the brain is extremely complex and that different systems interact, current graph-based methods used for studying the brain lack description of inter-system connections and assume that functional systems are neatly separable. Here, a major idea that the chapter explores is whether some regions of the brain effectively belong to more than one functional system. Motivated by this, we applied the concept of link communities, which allowed the description of overlapping functional systems, and compared the results from link communities to previous results from conventional methods.

Primarily, the link-based functional systems showed high overall convergence with the traditional node-based network identities. For example, we see networks with strong resemblance with the default mode network, frontoparietal network, cinguloopercular network, and many others, which not only confirm that the resultant link-based communities are biologically plausible systems but provide converging evidence for the identity of the brain's major functional systems. Additionally, we observed several notable interactions among the functional systems as result of the link communities approach. The link-based scheme suggests that regions in control-related systems, such as the frontoparietal, cinguloopercular, and dorsal attention systems, have multiple assignments that are widely distributed among a diverse set of networks while sensory-related networks show more restricted overlaps. The overlapping regions from link communities converge with regions that may be significant to the integrity of inter-community connections, as assessed with other graph theoretical measures, such as participation coeffcient. Recent evidence also revealed that focal lesions to some of these articulation regions result in degradation in resting-state functional structure and also severe impairment in a wide range of neuropsychological domains (Gratton, Nomura, Perez, & D'Esposito, 2012; Warren et al., 2014). Finally, our results provided insight onto the level of association between functional systems. For example, our results noted that 15% of frontoparietal ROIs are shared with the cinguloopercular system. In addition, several regions, especially in the bilateral anterior insula and medial frontal cortex, overlapped the two systems. Taken together, by quantifying the extent of overlap and providing detailed descriptions of the relationship between different systems, link community descriptions provide a more comprehensive and quantitative view of system overlaps, an aspect that is not easily appreciated from node-based communities.

In Chapter 3, we conducted a meta-analysis of tasks to examine the distinct functional characteristics of control systems in task activation. Studies in the past have made significant strides toward identifying and characterizing distinct types of control signals (on both task set-level as well as trial-level) and multiple systems of brain regions involved in expressing such signals (Corbetta & Shulman, 2002; Dosenbach et al., 2007; Dosenbach et al., 2006). Although extant characterizations of control systems have indicated separable roles for distinct control systems at task set-level, the contributions of control systems to different types of top-down trial-level signals (i.e. trial-wise preparatory and response-related control signals) have not been extensively explored. Motivated by this, we conducted a meta-analysis of three distinct goal-directed tasks with trial-wise implementations to examine whether distinct systems show separable response patterns that reflect unique functional roles at the trial-level.

The tasks in the meta-analysis all used a cue-target paradigm, which temporally dissociates each trial into a cue period and a target execution period, each containing distinct set of trial-level signals. Using a data-driven clustering analysis, we identified two distinct trial-related response profiles that divided the regions of control systems into a right frontoparietal and cinguloopercular cluster and a left frontoparietal and dorsal attention cluster. Further analyses of the controls regions' response characteristics presented new insights about their unique roles regarding trial-wise control as well as its implementation during goal-directed tasks. The right frontoparietal and cinguloopercular regions, from their delayed response to cues and robust response to error, are thought to engage in fine-tuning task parameters (potentially for subsequent trials) and evaluating performance. On the other hand, the left frontoparietal and dorsal attention regions, from their early cue onset, were thought to engage in timely updates of trial-wise parameters. In addition, not only did left frontoparietal and dorsal attention regions have weak error signals, they showed strong activity related to correct target implementation. Taken together with previous results that suggested the left frontoparietal regions' involvement in accumulation of perceptual information, an aspect that is not related to task control, we speculate that left frontoparietal and dorsal attention regions are also involved in processing of target information. The combination of our results with previous work provides a more complete description of various control systems' function. Overall, this study delivers important implications for future understanding and characterizations of control systems.

Finally, in Chapter 4, we explored (1) how the functional connectivity of selected systems changes during individual trials of a goal-direct task, and (2) how these connectivity changes further inform the functional roles of these systems. Previous influential theories of attention, such as biased competition theory and divisive normalization model, have proposed that, under interactions of control and processing systems, top-down signals, originating from control systems, may instantiate an environment for the processing systems to selectively process task-relevant stimuli. This is accomplished perhaps via increasing a processing neuron's response by a gain factor (Spitzer, Desimone, & Moran, 1988) or via enhancing a processing neuron's contrast gain by elevating its baseline activity (Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999; Ress, Backus, & Heeger, 2000). However, most of the models lack descriptions for the temporal characteristics of top-down control. Hence, our analyses hope to shed further insight onto how and when control and processing systems interact.

Using a Posner paradigm, we compared cue- and target-related changes in functional connectivity between a set of control and processing systems. By testing whether the control systems interact with the processing systems throughout the task, or just at the preparatory period, i.e. during the cue, the results provided new evidence regarding the subtle modulations of the brain's functional structure during the implementation of goal-directed task. Notably, we found that trial-wise preparatory signals during cue periods produced enhanced connectivity among various control-related systems (e.g. frontoparietal, dorsal attention, and cinguloopercular systems) and between control- and processing-related systems, such as between frontoparietal and visual regions, dorsal attention and motor regions. We speculated that these specific control-to-control and control-to-processing interactions likely reflect the engagement (and in some cases disengagement) of the task-relevant functional systems as a result of top-down attention. Furthermore, as most control systems (cinguloopercular and ventral attention systems) maintained their strengthened connectivity with visual and motor processing systems throughout the trial, the frontoparietal system, on the other hand, weakened its connectivity with the visual system during target processing. Hence, we speculate that the control regions in frontoparietal system may specifically act to "update" attention biasing signals at the beginning of the trial by transiently boosting connectivity with relevant processing regions and then decreasing the connectivity to allow visual and motor regions to process target-related information efficiently. Lastly, the way that, e.g., the frontoparietal system, behaves differently from e.g., the cinguloopercular system, further instantiates their functional specializations. Taken together, the results reveal the presence of complex and dynamic relationships that suggest changes among the various functional systems across a trial reflect both continuous as well as momentary effects of top-down signals.

II. Future Directions

The work described in this dissertation advances the field's understanding of the basic organization and interactions among the brain's functional systems during rest as well as during tasks (although we have only focused on a limited set of tasks). Further work will be required to determine the mechanisms and importance of these interactions, perhaps via (1) perturbing the typical network organization and observing the resulting behavioral correlates, (2) designing experimental manipulations that isolate specific aspects of inter-systems communication, or (3) examining certain developmental changes and corresponding variations in behavior. In this section, we will discuss some possible future experiments/research.

Functional significance of overlapping regions identified by link communities

From current lesion literature, descriptions of focal lesions and the ensuing cognitive and behavioral deficits have provided great advances to our knowledge of localized functions of certain brain regions (i.e., Broca's area). However, in some cases, circumscribed lesions tend to have surprising cognitive effects that are far broader than would be predicted based on the lesions' sizes and locations. This type of lesion has been thought to reflect the presence of interactions (typically through structural connections) between the affected and unaffected regions (Mesulam, 1990).

Recently, the advent of non-invasive neuroimaging methods and graph-based network descriptions of the brain's functional connectivity (such as the study described in Chapter 2) has provided a possible alternative explanation for these unusually damaging focal lesions (Power, Schlaggar, Lessov-Schlaggar, & Petersen, 2013). Previous studies emphasized using a combination of measures such as centrality and degree to indicate a region's functional significance to the overall integration as well as the resilience of the brain network. "Hubs" is a term that describes the nodes of a network that often interact with many parts of the network to facilitate communication; however, when hubs are disrupted, they tend to cripple much of the entire network. In a modular network, like the brain, the measure of participation coefficient allows the assessment of a node's hub-like qualities (Guimerà, Mossa, Turtschi, & Amaral, 2005). Nodes with high participation coefficients have edges that are well distributed among different modules, which suggest integration of functions. Hence, it is possible that a brain region's cross-system participation may help explain the variability in lesion outcomes.

In chapter 2, the link-community approach provided new utilities to evaluate the roles of different nodes within the network. Specifically, we used the number of link community memberships as a proxy to evaluate the diversity of a node and implemented a measure, the link community participation, to indicate the link-based diversity of a node. From our study, information derived from participation coefficients of the node-based scheme and link community participation indices of the link-based scheme converged. Although several studies have examined the network effect as well as neurophysiological effect of lesions to hubs identified by participation coefficient, the results tend to focus more on large-scale perspectives. For example, Warren et al., 2013 found that damage to hub locations produced much greater cognitive impairment, in general, than damage to other locations (Warren et al., 2014). Additionally, Gratton et al., 2012 also observed that hub lesions have a widespread, nonlocal impact on brain network organization as a whole (Gratton et al., 2012). However, one of the potential benefits of link communities is that the method also specifies with which systems a region acts as the point of integration. Hence a testable hypothesis would be that the information from link communities about the effected systems can further predict the magnitude of the network disruption as well as the likely domains of neurological impairments caused by the lesion.

Although 264 regions of interest (ROIs) used in Chapter 2 were obtained through combining the results from a task fMRI meta-analysis and a fc-Mapping technique to represent the putative functional areas of the human brain, their overall coverage, especially of the frontal cortex, is not ideal. Hence, before testing our hypothesis, an alternative link-based representation using a voxel-wise scheme could prove to be helpful either as a source of converging evidence as well as a possible solution to better spatial coverage. We plan to use the edge x edge matrix derived from the modified voxel-wise scheme similar to that described in Power et al., 2011. The modified voxel-wise version eliminates connections between voxels that are less than 20mm apart in hope to minimize the short distance correlations' susceptibility to spurious inflation of magnitude due to motion. In addition, only the top percentages of the strongest voxel-to-voxel correlations are retained for the construction of the link matrix. Here the link matrix will have elements that equal to the similarities between pairs of voxel-to-voxel edges. By applying Infomap on the link matrix, we can detect communities within the link-based network and observe voxels with overlapping community assignments.

To test whether link communities can predict the size of network disruption, we will select regions with consistent system overlaps indicated by converging results from the 264 ROIs as well as the voxel-wise scheme, and observe whether lesions at these regions would produce disruptions to the systems in which the regions partake specifically. Adding to the observations in Nomura et al., 2010, which demonstrated that heterogeneous lesions in either frontoparietal or cinguloopercular system generally produce altered connectivity only within the damaged network while leaving the other network preserved, we speculate that damages to regions, such as the anterior insula, that partake in both frontoparietal and cinguloopercular systems, will produce simultaneous disruptions to both systems. Alternatively, it is also possible that damage to the anterior insula will leave the within-system functional structures intact while disrupting the between-system functional structure of the frontoparietal and cinguloopercular systems.

Extending the example of frontoparietal and cinguloopercular systems, to test whether link communities can predict the domains of neurological impairments of certain lesions, we will compare the behavioral performance of patients with distinct frontoparietal or cinguloopercular focal lesions to patients with lesions at overlapping regions such as the anterior insula. Given what we know about the significance of frontoparietal and cinguloopercular systems, it is possible that patients with within-systems lesions will exhibit deficits pertaining to each system's functional roles while patients with lesion locations that overlap the two systems, such as the anterior insula, will show many combined deficits exhibited by patients with within-system lesions. Furthermore, ideally, with this approach, we can provide confirmation to the functional significance of overlapping regions and gain additional understanding of how parallel systems integrate their activities to carry out complex cognitive processes.

Further inquiries about the left frontoparietal regions

In Chapter 3, we have observed that the left frontoparietal regions showed dissociable roles from the right frontoparietal regions related to target processing. Extensive neurophysiological studies in monkeys and event-related fMRI studies in humans have recorded activity consistent with the left frontoparietal regions' (i.e. dlPFC and frontal eye field, FEF) contributions during moment-to-moment processing, such as encoding and maintaining stimulus information during working memory (Chafee & Goldman-Rakic, 1998; Constantinidis, Franowicz, & Goldman-Rakic, 2001 2001; Druzgal & D'Esposito, 2003; Ester, Sprague, & Serences, 2015 2015) as well as gradual accumulation of evidence during decision making (Gratton et al., 2016) However, due to the possible on-going control signals, such as maintenance and monitoring signals, it is unlikely that activity during target uniquely identifies processing-related operations. Hence, further work is needed to elucidate the nature of the left frontoparietal regions' functions.

One way to see whether some of the left frontoparietal regions are related to data processing is perhaps by comparing their corresponding response patterns to different types of task-relevant sensory information. If these cortical regions encode different features related to the stimuli, then we can design an experiment, very much like early studies in visual cortex, in which we vary the color or location of the stimuli, and see whether there are magnitude or shape differences in a left frontoparietal region's response profile. Previous studies have also used multivoxel pattern analysis of functional imaging data to demonstrate distinctions in the patterns of activation in frontoparietal regions (Woolgar, Afshar, Williams, & Rich, 2015; Woolgar, Thompson, Bor, & Duncan, 2011). It has been found that frontoparietal activity may adjust to various aspects of task information, such as task complexity and task rules. Here additional experiments can be designed to distinguish the patterns of activity in frontoparietal regions regarding the stimuli's sensory information. For example, a cue-target paradigm can be performed, in which only the shape of each cue provides task-relevant information. However, we would vary the color of the cues as well and test whether the left frontoparietal activation patterns show distinctions regarding to similarly shaped cues with different colors. This way, as we experimentally control for the effects of task rules and attentional controls, we can attribute differences in the responses to sensory-related data processing with greater confidence.

However, another manifestation of the left frontoparietal cortical regions' data-processing characteristics could lie in their task-based functional connectivity. Previous connectivity studies that looked at state-based variations in synchronization of blood oxygenation level dependent signals (BOLDs) within and between functional systems have observed reliable system-specific changes. Comparisons of the intrinsic functional structure during resting-state and task-state indicated consistent within-network correlation decreases especially in the visual system and, to a lesser extent, in other sensory systems (somatomotor, somatomotor lateral, and auditory) during different types of tasks. This uniform decrease in within-network correlations seems more specific to processing systems. Additionally, evidence from recent electrophysiology studies has demonstrated that correlated variability in sensory neurons tends to decrease due to increases in their activity, whether it is caused by the onset of a stimulus (Churchland et al., 2010; Huang & Lisberger, 2009; Kohn & Smith, 2005; Smith & Kohn, 2008; Snyder, Morais, Kohn, & Smith, 2014), by directed attention to the receptive field of the neuron (M. R. Cohen & Maunsell, 2009, 2011; Herrero, Gieselmann, Sanayei, & Thiele, 2013; Mitchell, Sundberg, & Reynolds, 2007, 2009; Zenon & Krauzlis, 2012), or by increasing task difficulty (Ruff & Cohen, 2014). Taken together, although at different physiological scales, it is possible that the task-related decreases in within-system connectivity are linked with the findings at the neuronal level, indicating that attention decreases correlations among individual sensory or motor neurons to allow the neurons to partake in more specialized operations. If neurons of left frontoparietal regions are tuned to encoding, maintaining, and accumulating stimulus information, then this processing specialization may be demonstrated by significant task-related decrease in correlations among these frontoparietal regions compared to resting-state. Of course, conclusions from such hypothesis would need to be further supported by evidence that suggest left frontoparietal regions show characteristically different connectivity profile when engaged in operations related to executive control (i.e. during updating of task parameters and reporting of performance errors).

While we have predominantly focused on how left frontoparietal regions exhibited processing-like functions in addition to their traditionally associated control-related roles, these apparent mixed functional characteristics may come from a lack of good anatomical distinctions in these cortical regions. As outlined previously in the Introduction, one of the main concepts from Posner and Petersen reviews is that control-related functions are supposed to be anatomically separate from data processing operations (Petersen & Posner, 2012). It could be that there is a functional distinction within the left frontoparietal cortical regions, where some areas are important for control and others are responsible for data processing. To develop better anatomical description of the left frontoparietal regions (i.e. the frontal cortex and parietal cortex), we could divide left frontoparietal regions into presumptive functional areas, or substructures, by using (1) resting-state functional connectivity boundary mapping (A. L. Cohen, Nelson, Miezin, Schlaggar, & Petersen, 2009; Gordon et al., 2014) or (2) clustering or community detection algorithms. Then, we can further inspect and differentiate what types of operations are performed in these areas/sub-structures by applying them to the tasks used in Chapter 3 and look for control versus data-processing distinctions.

Relating task-based changes in functional connectivity to behavior and development

A limitation in our study of task-based connectivity changes across a goal-directed trial is that the task design only permitted a limited amount of usable data per subject for cue-related analyses. Despite the weakness in data quantity, the experimental paradigm provided a major advantage in that it allowed us to isolate cue and target events for functional connectivity analyses without introducing prolonged delays or unwanted signals between cue- and target-related processes. Taken together, a simple improvement to the experimental design can come from having more catch trials and longer runs, especially in the intermixed condition, so that we can increase the quantity of data for better estimations of cue-related connectivity.

Furthermore, the discussions and interpretations of the results in Chapter 4 are based on extrapolating changes in connectivity within a single trial through comparisons of isolated rest, cue, and target-related activity derived from separate task conditions. Alternatively, it is possible that the observed correlation changes are reflective of differences across the intermixed and consecutive conditions used in the study, and the results reveal distinctions in brain's connectivity due to variations in types of cueing (i.e. trial-wise versus block-wise cueing). Thus, in order to observe connectivity changes related to differences between cue and target processes under the same task condition, a more carefully designed slow event-related cue-target paradigm that combines elements from both intermixed and consecutive conditions (i.e., mini-blocks of target stimuli (~20 seconds) each led by a cue (~ 6 seconds)) may be needed to temporally separate the slow BOLDs response related to cue from that related to target. However, control experiments will also likely be needed to account for any additional signals introduced by the delays and longer intervals.

Chapter 4 presented a study that provided new insight into the subtle modulations of the brain's functional structure during the implementation of goal-directed tasks. In particular, we found that trial-wise preparatory signals during cue periods produced enhanced connectivity in between-system relationships among control systems, as well as between control and processing systems. Some of these changes in network interactions were substantially maintained across cue and target processing while others, most notably connections between frontoparietal and visual systems, showed decreases in between-system relationships during target processing, compared with the cue period. This experiment motivates additional scientific questions relating task-based changes to behavior. Specifically, will changes in functional connectivity track with performance (i.e. reaction time, accuracy)?

At the planning stage of our task-based connectivity study using the Posner paradigm (see Method in Chapter 4), we were aware of the behavioral effects attention has on one's perception and processing of a given stimulus. In the classic experiment, Posner demonstrated that subjects can detect the relevant target faster if it appeared at an overtly as well as covertly attended location than if the target appeared at a non-attended location (Posner, Snyder, & Davidson, 1980). This improvement in the processing speed at the attended location may come from enhanced coupling between attention orienting control regions and visual processing regions, and increasing in coupling between control and processing regions may lead to more efficient and faster target detection. If such relationship exists, then perhaps we would see a strong negative correlation between reaction time and connectivity strength between, for example, dorsal attention and visual systems. Moreover, studying the association between task-based functional connectivity change and task performance may give insight into the coordination and cooperation that various functional systems undergo to achieve satisfactory task implementations. If a positive relationship exists, such that higher frontoparietal-to-cinguloopercular correlation is associated with better task performance (provided that we have accounted for any possibility of third-party modulators), one could argue this as supporting evidence for these systems function in a “closed loop”, in which information may flow between the frontoparietal and cinguloopercular networks, rather than a parallel framework, in which each system operates on separate processing streams (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Dosenbach et al., 2007).

Finally, developmentally, it has been well established that children do not perform as well as adults on multiple cognitive domains and task-control measures. Previous research comparing children to adults has found that children are slower, less flexible during task switching, and have less efficient working memory capabilities (Chatham, Frank, & Munakata, 2009; De Luca et al., 2003; Luna, Garver, Urban, Lazar, & Sweeney, 2004). Physiologically, it has been shown that stronger engagement of anterior cingulate, anterior insula, lateral prefrontal cortex, and the intraparietal sulcus were associated with adjustment of conflict processing in older than in younger subjects (Wilk & Morton, 2012). Relatedly, children exhibit weaker activation related to preparatory control while showing greater activity in target implementation compared to adults (Church, Bunge, Petersen, & Schlaggar, 2016). Hence the overall insufficiencies in children’s task performances are thought of as the consequence of delayed maturation in cognitive control implemented by various control systems.

A complementary line of thoughts to poorer task control in children is that being slower and less efficient may be caused by largely non-optimal cooperation across functional systems during tasks, particularly between various control systems and between control and processing systems. For example, perhaps stronger correlations among anterior cingulate, anterior insula, lateral prefrontal cortex, and the intraparietal sulcus in addition to their strengthened activation in conflict processing contributed to the overall performance improvement in older children. Moreover, in Chapter 4, under the cue-target paradigm, we saw a relative decrease in connectivity strength between control and processing systems following an initial cue-related enhancement. Perhaps the reason children do not switch tasks efficiently could be related to deviation from these control-to-processing dynamics, which could result in (or from) control systems inefficiently disengaging with current processing, thus slowing down other subsequent operations. Overall, careful examination of adult's and children's between-system connectivity strengths associated with control-related systems while engaged in conflict processing or preparatory control may shed insight on the possible age-related shifts in task-based connectivity structure that contribute to improvement in cognitive abilities.

III. Final Thoughts

This thesis has investigated the characteristics of multiple control systems' functional distinctness in the contexts of resting-state connectivity and task-activation. We also ventured into a newly explored territory of task-based functional connectivity to examine how control systems, with distinct functional signatures, cooperate with each other and with processing systems under specific task demands. To comprehend the underlying mechanisms of distributed functional systems allows one to appreciate how humans can adeptly undertake innumerable tasks. Although a great amount of work is still needed in service of this goal, the studies presented here both contributed to as well challenged previous hypotheses in an effort to build better understanding of the basic organization and interactions among the brain's functional systems.

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