On the neural basis of individual differences in executive function: A series of studies of the “resting” brain

by

Andrew E. Reineberg

B.Phil., University of Pittsburgh, 2009

M.A., University of Colorado Boulder, 2013

A thesis submitted to the
Faculty of the Graduate School of the
University of Colorado in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
Department of Psychlogy & Neuroscience
2016

This thesis entitled:
On the neural basis of individual differences in executive function: A series of studies of the "resting" brain
written by Andrew E. Reineberg
has been approved for the Department of Psychlogy & Neuroscience

Prof. Marie T. Banich

Prof. Christine Brennan

Prof. McKell Carter

Prof. Tim Curran

Prof. Naomi Friedman

Date ____________________

The final copy of this thesis has been examined by the signatories, and we find that both the content and the form meet acceptable presentation standards of scholarly work in the above mentioned discipline.

Reineberg, Andrew E. (Ph.D., Cognitive Neuroscience)

On the neural basis of individual differences in executive function: A series of studies of the "resting" brain

Thesis directed by Prof. Marie T. Banich

Executive functions (EFs) are a thoroughly characterized set of high-level cognitive abilities that contribute to a person's ability to pursue, maintain, and modify goals. A popular theoretical model of EFs - the unity and diversity model - describes the variety of laboratory tasks used to measure EF as having shared components (unity) and components specific to subsets of tasks (diversity). A fundamental question in the field of cognitive neuroscience is what brain characteristics underlie the wide array of high-level cognitive skills and abilities, like the unity and diversity aspects of EF, that vary across the population but are stable within an individual. The development of methodologies such as functional magnetic resonance imaging (fMRI) has contributed to a surge in interest in this fundamental question. Resting-state fMRI, in particular, characterizes the stable oscillatory behavior of the blood oxygen level dependent signal when individuals are not directed overtly to perform a particular task. As such, resting-state fMRI is a non-invasive and minimally-demanding protocol offering the potential to make predictions about individual differences in cognitive functioning. We present results from several resting-state analyses of two large data sets (n = 91 and 251). Participants in each sample were scanned without being overtly directed toward a particular mental task set and administered a battery of EF tasks that measured three EF constructs from the unity and diversity model - the general ability to maintain goals and task sets (common EF), abilities related to fluidly shifting between task sets (shifting-specific EF), and the ability to add to or delete from the contents of working memory (updating-specific EF). The resting-state analyses used here quantify the dynamics of the resting brain at two complementary spatial scales - at the level of networks and individual regions. Taking the results of these network and regional connectivity analyses together, we provide a new perspective on the neural bases of EFs that complements our understanding of the mechanisms of cognitive control (as assessed using the computational modeling approach) and the areas implicated in online cognitive control (as assessed by the brain mapping approach via fMRI studies of demanding versus non-demanding conditions). First, individual differences in common EF were associated with the intensity of the frontoparietal network at rest and connectivity among networks of regions implicated in high level cognition (both “task-positive” and “task-negative” networks). Because common EF captures variance in a wide array of cognitive tasks, these features perhaps underlie the unity of the neural basis of EFs. The diversity aspects from the unity and diversity model of EF are also associated with variation in separable neural substrates as assessed by resting-state connectivity. Individual differences in shifting-specific EF were associated with a more spatially distributed set of resting-state connectivity measures than task-based neuroimaging studies may lead one to believe, for example, the spatial extent of a network of regions implicated in top-down biasing and the diversity of connections in sensorimotor cortex. Individual differences in updating-specific EF are not supported by variation in resting-state networks in the way common EF and shifting-specific EF are but rather by variation in a limited set of graph theoretic properties of individual regions. Some results for updating-specific EF are novel, such as a less integrated frontal pole being associated with higher updating-specific EF ability, while others are in agreement with findings from the computation modeling literature which suggests updating depends upon connectivity of dorsolateral prefrontal cortex. Our work builds upon those findings by showing that not only do the mechanisms of working memory updating depend upon a certain type of connectivity, but variation in the degree to which individuals can update is associated with how connected dorsolateral prefrontal cortex is to a diverse set of other brain areas. The results of this dissertation are evidence that assessment of brain connectivity during the resting state may be a very lucrative avenue for a more thorough understanding of individual differences in ability.

Dedication

This project is dedicated to my family and friends.

Acknowledgements

I would like to thank Marie Banich for all the guidance and support over the course of my graduate school career. Her persistence in encouraging me to “always state the baseline when using comparators” perhaps helped foster my interest in the baseline itself. I would also like to thank past and present members of the Banich Lab who assisted with various aspects of these projects and my training over the last several years: Jessica Andrews-Hanna, Chelsie Benca, Brendan Depue, Dan Leopold, Joe Orr, Kathy Pearson, Luca Ruzic, Harry Smolker, Amy Turner, and Alejandro de la Vega. I would also like to thank members of the Determinants of Executive Function and Dysfunction working group (an NIMH-funded Interdisciplinary Behavioral Science Center supported by grant P50MH079485) who created an environment that supported exploratory research of the neural bases of executive functions. Thank you to the members of this and previous committees who guided my research at CU Boulder: Christine Brennan, McKell Carter, Tim Curran, Naomi Friedman, and Randy O’Reilly. Finally, thank you to Naomi Friedman, her lab, and the Institute for Behavioral Genetics for providing access to and analysis of data from the Colorado Longitudinal Twin Study.

Contents

Chapter

Appendix

Tables

Table

Figures

Figure

Chapter 1

Introduction

Summary

The neurobiological etiology of high-level cognitive functions is not well understood. Most studies of the neural basis of executive functions focus on the online activations and roles of a variety of frontal and parietal cortical areas. But there almost certainly exists distinct differences in the brains of high versus low functioning individuals when those individuals are not actively engaged in high-level cognition. Resting-state fMRI is a methodology used to study correlated hemodynamic response across the whole cortex while individuals are not engaged in an experimentally-directed task set. This measured “functional connectivity” is reliable, reflects actual correlated neural activity across the brain, has been useful in the clinical realm to differentiate affected individuals from controls, and complements measures of individual differences in brain anatomy (e.g., cortical thickness, folding) and anatomical connectivity (e.g., diffusion tractography). Because functional connectivity offers many high quality measures of individual differences in functional brain organization, it is a good candidate for studying how individuals with high versus low executive function ability differ from one another. In this chapter we describe the motivation for three related and complementary analyses to determine how variation in resting-state network and subcomponents of those networks is associated with individual differences in executive functions.

1.1 A Review of the Neural Basis of Executive Functions According to Task-based Neuroimaging

Executive functions (EF) are a set of abilities that allow for the directed pursuit, maintenance, and modification of goals (Banich, 2009). Executive functions are implicated is a wide range of everyday behaviors (e.g., overriding habits or dealing with novelty) and are altered in a large number of psychiatric and neurological disorders (e.g., Barkley (1997); Nieuwenstein et al. (2001)

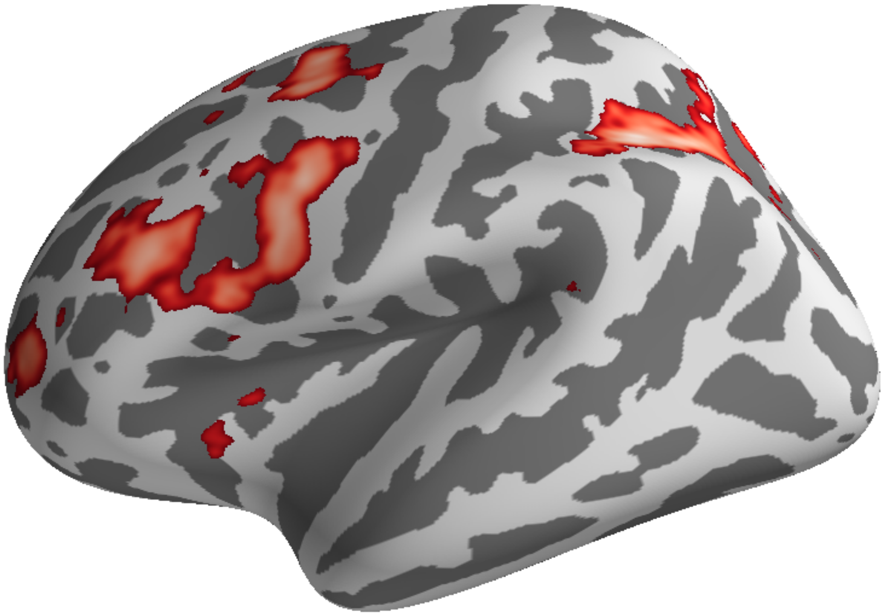
and for a recent comprehensive review see Snyder et al. (2015)). Based on both the observation of individuals whose EFs are compromised as a result of localized brain damage (Alvarez and Emory, 2006; Stuss and Alexander, 2000) and on neuroimaging studies that use univariate approaches to identify those brain regions whose activation increases when EF demands are increased (e.g., Banich et al. (2000a)), it is generally agreed upon that EF abilities rely preferentially on frontal cortex. But these observational and group average neuroimaging studies provide an incomplete view of the neural basis of EFs because they have been interested in the areas and neural functions necessary for EF but have placed less emphasis on determining how variation in neural processes is related to how individuals differ from one another in EF ability. Importantly, regions implicated in group average fMRI studies as compared to studies of individual differences need not be the same; Yarkoni and Braver (2010)). The purpose of this dissertation is to build upon years of neuroimaging work investigating the neural basis of EFs by proposing a set of novel brain features that capture some of the inter-individual variation in EFs.

One notable aspect of EF is that it is known to vary substantially across individuals (Miyake and Friedman (2012) and for a more recent review see Friedman and Miyake (2016)). Research on individual differences, including studies utilizing behavioral genetics techniques, has provided a theoretical framework from which to consider how individuals differ in their EF abilities. One prominent theory, the unity and diversity model, derived from intercorrelated patterns of performance across individuals on multiple measures of EF, posits that EF can be well characterized as consisting of at least three latent factors (Miyake et al., 2000; Miyake and Friedman, 2012). The first factor is a common EF, representing the *unity* aspect of the model, on which all EF tasks load. This factor is thought to represent the general capacity to actively maintain a task goal or attentional set. The second two orthogonal factors represent the *diversity* aspect of the model and are more specific processes above and beyond common EF. Statistically speaking, these factors are residuals of the EF abilities once common EF has been taken into account. One factor, the shifting-specific factor (shifting), reflects abilities relating to flexibly shifting between different tasks or mental sets, while the other factor, the updating-specific factor (updating) indexes the process of rapidly adding or deleting information from the current contents of working memory. The lack of an inhibition-specific factor reflects a recent update to the unity and diversity framework that highlighted the complete overlap of common EF and inhibition-specific variance in behavioral tasks in several samples of adults and adolescents (Miyake & Friedman, 2012). Another goal of the work highlighted in this dissertation is the determine whether or not the neural underpinnings of EF have unity and diversity as well - that is, is inter-individual variation in common EF, shifting-specific EF, and updating-specific explained by the same or distinct neural features.

Neuroimaging studies examining brain activation while performing a variety of EF tasks suggest that these three EF factors are likely to be supported by overlapping yet somewhat distinct brain systems. One of the most dominant findings across many studies of distinct EF tasks in an fMRI or PET context is the presence of a core network of regions that are more active in demanding versus less-demanding EF conditions. This network of regions is referred to as the frontoparietal network throughout this manuscript because the primary regions within this network are lateral frontal (e.g., dorsolateral prefrontal cortex (DLPFC), inferior frontal gyrus (IFG), etc.) and lateral parietal regions. This same network has several alternative names in different niches within cognitive neuroscience: frontoparietal control network (the "control" added to signify the organizational role the network plays as a "controller"), frontocinguloparietal network (noting frequently overlooked insular coactivation), task control network, task positive network, executive control network, cognitive control network, among others. The impression that the three EF factors of the unity and diversity model rely on overlapping brain regions was supported by a positron emission tomography (PET) study performed by Collette et al. (2005), who directly investigated which brain regions consistently activate across all subjects for a variety of EF tasks similar to those typically employed by Miyake, Friedman, and colleagues. Collette et al. (2005) observed that on average across all individuals the left superior parietal gyrus and the right intraparietal sulcus, and to a lesser degree, mid- and inferior prefrontal regions activated for all EF tasks. Others have noted the domain general activation of the frontoparietal network in detailed metaanalyses of imaged cognitive control tasks (Niendam et al., 2012; Fedorenko et al., 2013). Modern neuroimaging tools, such as the metaanalysis platform Neurosynth, allow a systematic review of the recent neuroimaging literature. Figure 1.1 shows a metaanalytic coactivation network of frontal and parietal regions (as well as some insular areas) that emerges from a metaanalysis of 485 EF-related studies. This map was automatically generated by Neurosynth after a 200 dimensionality topic analysis was performed on the database of 11,406 studies. This particular topic (topic 22 from the 200 topic analysis) included terms such as “executive”, “working”, “memory”, “load”, “maintenance”, and many others. One important and central question after reviewing the abundance of neuroimaging studies touting the importance of the frontoparietal network is whether or not the degree to which individuals vary in the integrity of the frontoparietal network is related to their ability on EF tasks.

Although the frontoparietal network emerges as the key set of regions necessary for EF, there are also theorized specialized roles for individual regions within the network. These roles may be common to all EF tasks (e.g., maintaining goals or rules of a certain task) or specific to a subset of EF tasks (e.g., only ones involving updating of working memory). The ability to actively maintain a task goal is thought to rely on areas of lateral prefrontal cortex extending from BA 10 through mid-dorsolateral prefrontal cortex (Banich, 2009; Braver, 2012; Herd, Banich, & O’Reilly, 2006b; Sakai, 2008), potentially including the anterior cingulate and frontal operculum as well (Dosenbach et al., 2008). Set shifting, which requires adapting to changes in task, appears to engage more posterior regions of dorsolateral prefrontal cortex (e.g., inferior frontal junction) as well as parietal regions (e.g., intraparietal sulcus; Derrfuss, Brass, Neumann, & von Cramon, 2005; Wager, Jonides, & Reading, 2004). Working memory updating has been suggested to involve fronto-striatal connections and requires input from the basal ganglia (Braver et al., 1997; McNab & Klingberg, 2008; O’Reilly & Frank, 2006). The work of Collette et al. (2005) also supports the notion that these three EF constructs are supported by some distinct neural activations. They found left frontopolar cortex (BA 10) activity was specifically associated with tasks designed to assess updating-specific EF, while activity of the left intraparietal sulcus was associated with tasks designed to assess shifting-specific EF. Although no unified theory of the neural mechanisms and activations that support EF currently exists, there are theoretical models in development. For example, one model

Figure 1.1: **Meta-analytic Frontoparietal Network**. Figure shows a left lateral projection of cortical surface with superimposed metaanalytic frontoparietal network - the output from a mataanalysis of 485 studies (as generated by Neurosynth; Yarkoni et al. (2011)) whose content and psychological constructs of interest fell within the realm of executive function and other high level cognitive abilities.



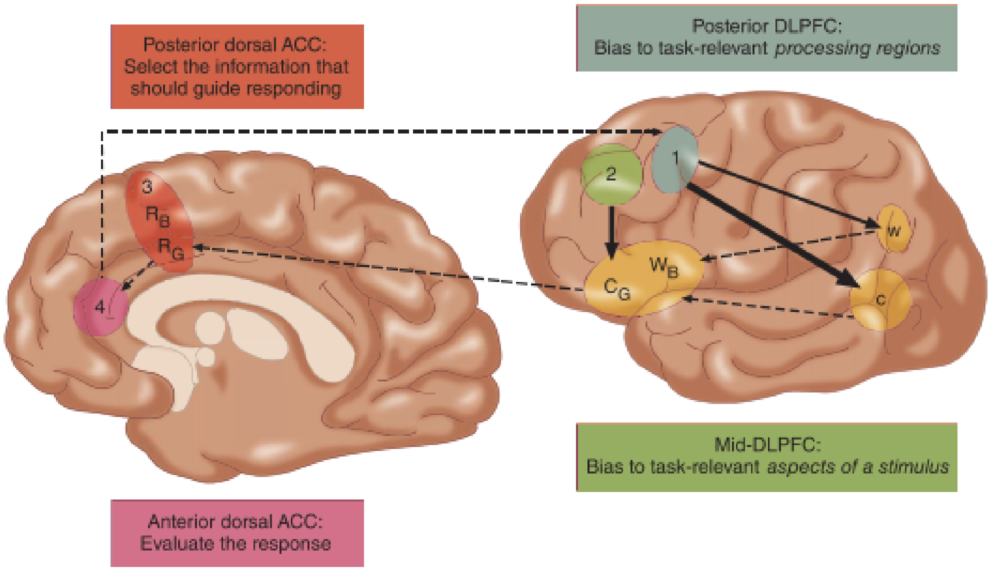
is shown in Figure 1.2 (Banich, 2009). Taken together, these studies demonstrate the variety of cortical and subcortical regions implicated in these different aspects of EF. Moreover, they provide information on the brain regions that are likely to act as key nodes in the brain for each of these distinct EF factors, and across them more generally. The above studies support the idea that different EF constructs may preferentially depend upon the integrity of different subcomponents of the frontoparietal network or possibly other brain regions - an idea we investigate with the studies presented in Chapters 2 and 3.

Studies of task-related activation have provided us with a firm understanding on the neural machinery required to perform EF tasks, but they do not always comment on how individuals vary from one another in EF ability. One thing to consider is that the importance of specific networks and regions in group average neuroimaging studies does not mean those same regions are equally important for differentiating higher versus lower performing individuals from one another (Yarkoni and Braver, 2010). Moreover, studies of task-related activation do not comment on how the brain's intrinsic structure, connectivity, and function supports EF or variation in EF ability. This is a central question that is addressed in this dissertation. A review by Braver et al. (2010) highlights several experimental design goals for cognitive neuroscience approaches to studying individual differences. One technique that would satisfy most of these requirements is a large study of individual differences in intrinsic brain connectivity as those differences relate to variation in stable behavioral measures of EF ability (assessed using the unity and diversity constructs discussed previously). We pursued this idea by performing a series of studies using resting-state functional magnetic resonance imaging to investigate how individual differences in brain organization and connectivity support EF.

1.2 Using Resting-state fMRI to Better Understand Cognition

Resting-state functional magnetic resonance imaging (rs-fMRI) is a tool to that can be used to index the functional dynamics between brain regions while participants are not engaged in a particular task. One new and potentially powerful use of rs-fMRI is to investigate how this intrinsic

Figure 1.2: **Theoretical Model of Roles for Components of Frontoparietal Network**. Sample model presented to show proposed specific roles for regions within the frontoparietal network in the context of the Stroop task (i.e., cognitive control over representations of color (c) and word processing (w)). Although the model, as presented, highlights the roles of lateral frontal and anterior cingulate cortex, the importance of lateral parietal cortical areas as lower-level centers of cognitive control is tacitly endorsed. This model was used as an example with permission. More details can be found in Banich (2009).



activity in the brain is related to the diversity of an individual's cognitive skills/abilities. A broad review of 125 studies by Vaidya and Gordon (2013) showed rs-fMRI is related to variation in cognition, perception, motor skills, personality, language, impulsivity, and decision making within the neurologically normal population. Before discussion of the cognitive-relevance of rs-fMRI, a thorough discussion of the methodology itself is needed.

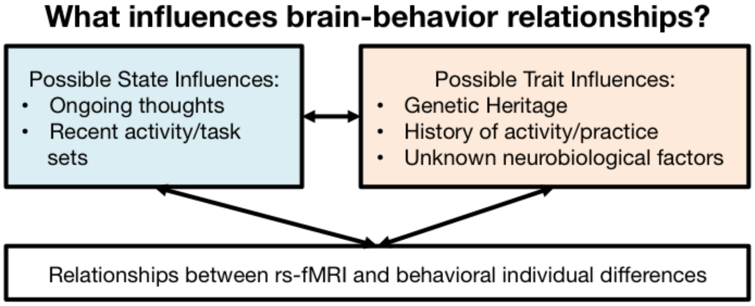
Since the inception of fMRI, a prominent usage of the methodology has been the investigation of a psychological state of interest controlling for response in a baseline condition (i.e., a subtraction design (Donders, 1969) (Donders, 1969); neuroimaging implementation, (Petersen et al., 1988)). One popular baseline condition is the viewing of a simple fixation cross as a low-level visual control condition. Early interest in what is now referred to as the resting state arose from several fMRI and PET studies in which activations were noticed while participants were viewing this fixation cross (Buckner et al., 1996; 1995).

> "Although the fixation task was intended as a low-level control task, it nevertheless may require distinct processing resources" -Buckner et al. (1995)

When individuals are instructed to passively view a fixation cross, distinct networks of widely separated brain regions can be identified as sharing similar temporal patterns of functional activity (Fox and Raichle, 2007; Raichle et al., 2001) - a phenomenon often referred to as resting-state functional connectivity. Regions that are functionally connected at rest show strong correspondence with regions that tend to co-activate during performance of tasks (Smith et al., 2009). Resting-state networks are often grouped into families such as "task positive" networks like the frontoparietal resting-state network - a network of lateral frontal and parietal regions which coactivate together at rest and typically increase in activation during difficult, externally-directed cognitive control tasks compared to baseline - or "task negative" networks like the default network - a network of regions which coactivate at rest and typically decrease in activation during demanding, externally-directed cognitive control tasks compared to baseline. The similarity between resting-state networks and statistical maps from task-based fMRI studies suggests one of several possibilities: 1. functional connectivity is the result of a history of coactivation while performing certain mental operations,

2. functional connectivity is the result of ongoing processing (i.e., processing related to ongoing thoughts and/or internally directed task sets), 3. functional connectivity is the result of carryover effects from recent activity (i.e., task set inertia), or 4. functional connectivity at rest emerges from some combination or interaction of the above. We provide a model of influences on relationships between rs-fMRI and behavior in Figure 1.3. While only preliminary work has investigated the actual neural mechanisms underlying resting-state functional connectivity (i.e., globally propagated calcium signal waves; Matsui et al. (2016)), strong test-retest reliability, usefulness in differentiating clinical from non-clinical participants, and a diverse set of potential analyses has pushed the field toward the unofficial consensus that rs-fMRI likely represents some intrinsic aspect of a individual that may have utility in differentiating among individuals on a variety of dimensions (psychopathology, high versus low ability, etc.).

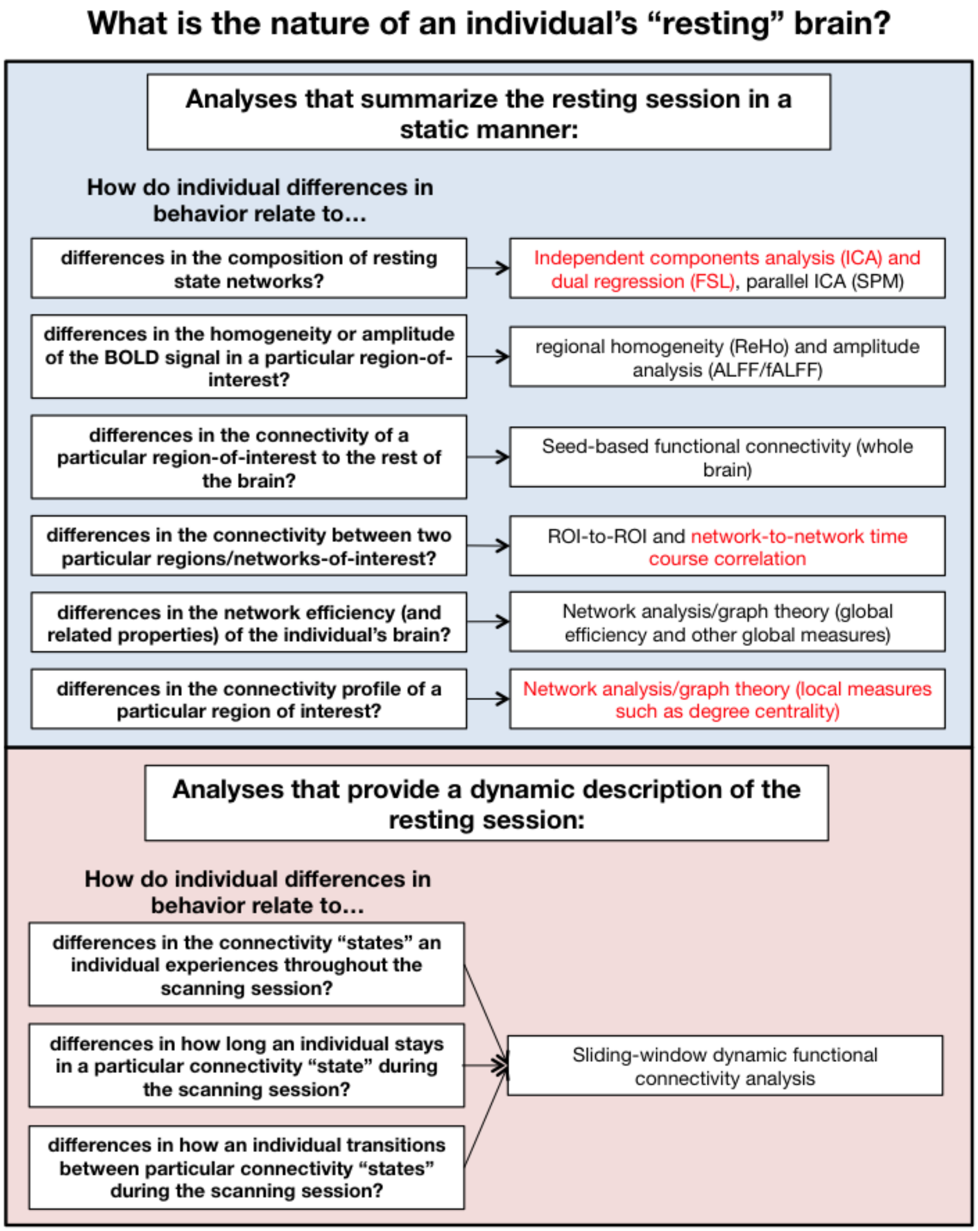
Figure 1.3: **Proposed Model of Influences on rs-fMRI**.



Resting-state fMRI has become the topic of considerable interest for a variety of reasons. First, it is possible to analyze rs-fMRI data in a number of ways that can provide diverse insight into the disorder or behavior of interest. The broadest distinction that can be made between rs-fMRI analysis techniques is between analyses that summarize the resting session in a static manner and those that provide a dynamic description of the scanning session. Development of the latter techniques is so recent that no study has investigated the relationship between dynamic connectivity and individual differences in behavior; thus, all manuscripts discussed in the current review are static in nature. Some of these studies probe functional connectivity of a single *a priori* region of interest to the rest of the brain (i.e., seed-based, whole brain functional connectivity) while others investigate functional connectivity of a set of brain networks (e.g., as assessed by independent components analysis; see Margulies et al. (2010) for review of the many techniques). Additionally, a growing number of studies have adopted a graph theoretic perspective, which summarizes the connectivity profile of regions in ways similar to the means of describing the nodes of a social network. Each technique allows one to ask a very specific question about the nature and function of the resting brain, and the choice of using one or multiple techniques depends on how one thinks the particular behavior-of-interest may manifest, over time, in the resting-state functional connectivity. See Figure 1.4 for a brief review of each technique.

A second reason for the considerable interest in rs-fMRI is the demonstration of reliability within an individual across multiple time points. Test-retest reliability of a neuroimaging measure is an essential component of the ideal design goals set for studies investigating individual differences according to Braver et al. (2010). Here we review the reliability literature with a focus on the distinction between network/whole brain reliability and individual region reliability. It should be noted that not all rs-fMRI analyses discussed in the main review of this manuscript have been subjected to test-retest reliability analysis at this point. Zuo et al. (2010) were among the first to look at within-individual test-retest reliability of rs-fMRI, specifically the stability of resting-state networks derived from a group level independent components analysis (ICA). They found that resting-state network reliability was moderate-to-high at both short (45 minute) and long (5-16 months) retest intervals. Moreover, networks of interest to cognitive neuroscientists, such as fronto-parietal and default networks, were among those with the highest reliability. This work was replicated by Choe et al. (2015) who found high test-retest reliability in the frontoparietal network over a large 3.5 year testing window. Another group found, in a group of older adults, that resting-state networks had moderate one year test-retest reliability (ICC > 0.4 for all networks, Guo et al. (2012)). Wang et al. (2011a) found local graph theory measures (i.e., measures that summarize the connectivity characteristics of a single region) are more reliable than global measures (i.e., those measures that summarize the connectivity characteristics of those whole brain; Wang et al., 2011),

Figure 1.4: **Possible questions to ask of rs-fMRI data in a cognitive context**. Resting-state methods used in the following chapters of this dissertation are highlighted in red text. Methods used to investigate individual differences can also be used in a clinical context to differentiate affected from unaffected individuals or to predict symptom severity.



suggesting the connectivity profile of individual regions is rather stable while summary measures of whole brain connectivity may be prone to larger changes over time. Another group found reliability of graph theory metrics ranged from minimally reliable to strong reliability (ICC up to 0.763) with dependency on the chosen band pass filter, certain preprocessing steps, and the metric of interest suggesting, like many fMRI analyses, the results are sensitive to the chosen preprocessing strategy (Braun et al., 2012). Cao et al. (2013) found a variety of common graph theoretic measure had moderate to high 2-week test-retest reliability and that their reliability was higher than those same measures calculated on data from task-based fMRI paradigms. In summary, because network-based and individual region analyses of rs-fMRI data are moderately to highly reliable within an individual at short and long retest intervals, they are best suited for analyses that test the relationship between rs-fMRI and behavior. Special care should be taken when dealing with global graph theory measures of rs-fMRI data as only a single study has probed test-retest reliability of these measures.

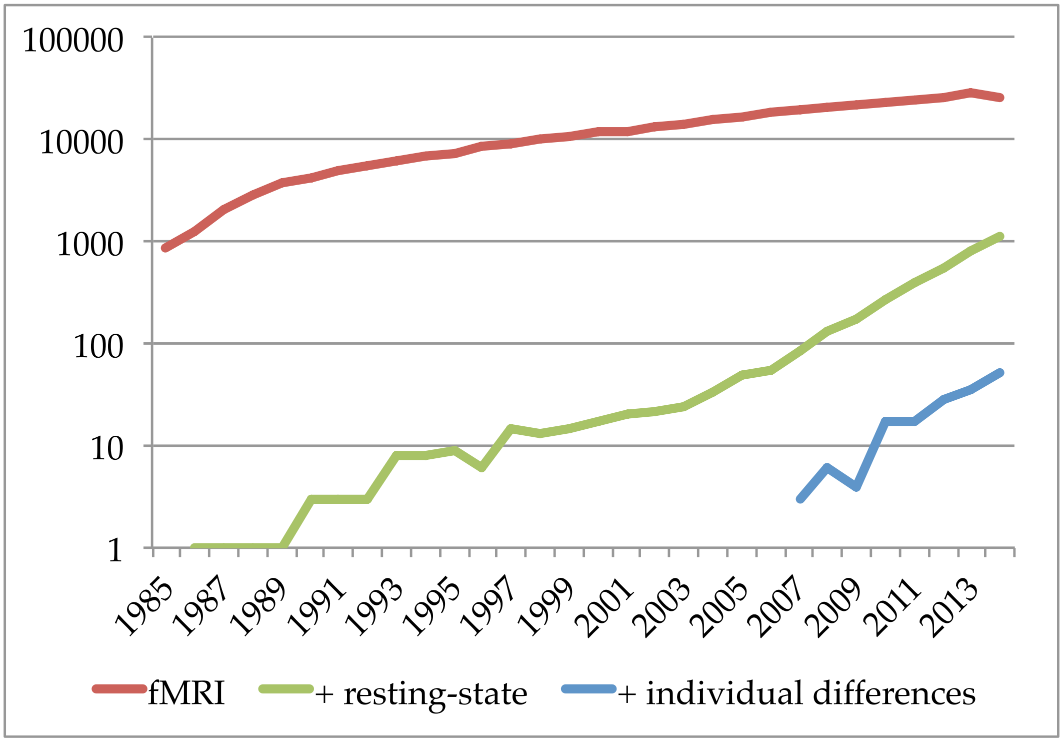
Finally, there is large body of literature indicating RSNs are altered across a plethora of neurological and clinical populations, including Alzheimer's disease, schizophrenia, depression, attention deficit hyperactivity disorder, and others (for reviews see Greicius (2008); Zhang and Raichle (2010)). This characteristic of resting-state networks provides the possibility that a relatively short fMRI scan might be helpful either with regards to diagnosis (i.e., distinguishing affected from unaffected individuals) or prognosis (i.e., clinical severity) of certain clinical disorders. A thorough meta-/re-analysis of the clinical resting-state literature, as performed by Castellanos et al. (2013), showed that predictive modeling using resting scans is highly accurate in differentiating affected from unaffected individuals in many of the previously mentioned clinical conditions.

All this being said, the number of studies that use rs-fMRI to better understand individual differences in cognition in a normal population is only a small portion of all resting-state fMRI studies (see Figure 1.5). To better understand the features that might be most related to individual differences in EF, we searched PubMed for publications that used rs-fMRI as a predictor of higher level cognitive functions, in general, such as working memory, planning, attention tasks, inhibitory control tasks such as Stroop and Stop Signal task, and intelligence. We limited our literature review to studies of neurologically normal populations which yielded a total of 20 studies. We excluded some search results such as studies of creativity and lower-level cognitive processes such as navigation ability. Additionally, only studies of adults (average age in sample > 18) were included as any study conducted at CU Boulder would likely include only adults. This literature review served the purpose of illuminating possible resting-state features of interest that are above and beyond our clear interest in examining both the integrity of the frontoparietal network as a whole and also the constituent parts of the frontoparietal network individually. Perhaps there are overlooked resting-state features that could underly individual differences in either many or a single specific cognitive domain (i.e., could inform predictions about the unity and diversity of the neural basis of EF).

1.3 Synthesis of Review of Resting-state and Individual Differences Literature

For the sake of brevity, we've removed the full discussion of each reviewed study from the main text of this document. In **Appendix 1**, we fully discuss studies in chronological order but grouped by laboratory when one group has performed multiple studies. Additionally, we discuss studies of single behavioral variables before studies that used composites, factors scores, or latent variable type measures. In summary, for each of the cognitive abilities reviewed, we found converging evidence from multiple studies for neural mechanisms that may underlie inter-individual differences. First, for attention processing, we found higher ability is associated with increased integrity of the executive control network and competition between resting-state networks. For inhibitory control, individual differences in ability manifest in the homogeneity of frontoparietal and default network regions. For task set shifting, there was no convergence in methods or specific regions; however, both of the historical studies reviewed showed altered parietal connectivity in individuals with high shifting ability. For working memory updating, individual differences in ability manifest in within-default-network connectivity and default-to-task positive network connectivity. Finally, several

Figure 1.5: **Results of 3 PubMed queries for “fMRI”, “resting-state fMRI”, and “resting-state fMRI individual differences”**.



of the reviewed studies showed evidence of altered DLPFC connectivity in individuals of varying intelligence.

Importantly, one connectivity feature emerged as important across multiple behaviors. Within the domains of attention (Seeley et al., 2007; Kelly et al., 2008; Mennes et al., 2010), inhibitory control (Tian et al., 2013), and working memory (Sala-Llonch et al., 2011; Keller et al., 2015), increased negative connectivity between task-positive and default networks was predictive of higher ability. These networks are logical entities to investigate given their role in online processing during these tasks (as assessed by task fMRI). Task positive networks such as frontoparietal control network, cingulo-opercular network, dorsal attention network, and ventral attention networks are implicated in the various levels of control needed to perform directed tasks. One may think about the task positive networks as organized hierarchically with the dorsal and ventral attention networks being responsible for top-down biasing and interfacing with higher-level networks such as the frontoparietal network (dorsal attention) and bottom up attentional processes such as reorienting or filtering (ventral attention; Vossel et al. (2014)). The frontoparietal and cingulo-opercular networks are implicated in higher-level functions such as biasing of attention towards task relevant information and maintenance of goals, respectively (Dosenbach et al., 2008). The exact role of each task-positive network is still debated. The unifying feature of task positive networks is their increase in BOLD signal during performance of externally directed and demanding cognitive tasks. Concurrent lines of research have proposed two theories of default network function, the sentinel hypothesis and the internal mentation hypothesis. The sentinel hypothesis stems from a line of research showing increased default network activity while participants are passively monitoring for infrequent stimuli (Shulman et al., 1997). The internal mentation hypothesis suggests the default network is implicated in a family of self-related processes such as imagination and reminiscence. The default network is labeled as a task negative network in many studies because of observed decreases in BOLD signal when participants are engaged in demanding cognitive tasks. According to the internal mentation hypothesis, this decrease in BOLD signal would be explained as a decrease focus on the internal world and redirection of attention to the demanding task. It should be noted that task positive and task negative networks are not always in opposition. One example of simultaneous increased in BOLD signal in both the default network and an attention network is during a demanding but internally-directed task (e.g., autobiographical planning; Spreng et al. (2010)). Interestingly, within the rs-fMRI literature, we also found that the connectivity of the regions within the default network to each other was associated with differences in inhibitory control. Tian and colleagues found that higher amplitude signals within the default network were associated with worse stop signal reaction times. This set of results suggests anticorrelation between task positive and negative networks is the most cognitively relevant feature of resting state. It would be prudent to explore this feature further. Additionally, this feature could be a potential target of interventions and real time fMRI protocols. In summary, the observation that default network connectivity predicts variation in cognitive abilities is perhaps the most notable finding of this review. While many studies would agree that a primary predictor of success in high-level cognitive abilities is the ability to upregulate those regions responsible for the specific neural processes involved in that task, these reviewed studies suggest another important factor may be the ability to segregate internally and externally directed processes.

In the studies covered by the literature review, there was a considerable increase in the complexity of resting-state analyses. This complexity increase translates to the ability of cognitive neuroscientists to ask more targeted questions about the relationship between the functional dynamics of the brain at rest and behaviors of interest. For example, early rs-fMRI studies such as Kelly et al. (2008) simply looked at the correlation between time courses for two areas of interest. More recent studies such as Cole et al. (2012) use more advanced graph theory measures to summarize a given regions role in the context of the whole brain. As alluded to in the introduction and Figure 1.4, cutting edge techniques such as dynamic functional connectivity potentially provide the most advanced and thorough summarization of a given rs-fMRI session. These techniques are still in development and have yet to be used to investigate the neural basis of executive functions and other high level cognitive abilities. One general comment after reviewing the wide range of rs-fMRI studies interested in explaining individual differences in cognition is how minimal emphasis is placed in exploration of multiple rs-fMRI measures within the same sample and investigation of how multiple rs-fMRI features can contribute to our understanding of cognition (e.g., do analyses of resting state network composition complement analyses of resting-state graph theory measures?). One strength of the work discussed in this dissertation is application of a variety of analysis techniques to the same data.

1.4 Thesis

The frontoparietal network is implicated in hundreds of neuroimaging studies of EF-related processing. In this dissertation, we conducted a series of analyses to determine if the neural machinery implicated in task-based studies of executive functioning is intrinsically different in high versus low functioning individuals via analysis of rs-fMRI scans. Our approach is among the first to investigate individual differences in this manner and the first to investigate specificity with regard to multiple EF constructs motivated by the unity and diversity model. In **Chapter 2**, we asked **"How does the spatial composition and intensity of the frontoparietal network vary based on inter-individual variation in EF?"**. Also, based on a thorough review of the rs-fMRI literature, we identified a cognitively-relevant feature - the degree to which the frontoparietal network is correlated with the default network at rest. We have a specific hypothesis based on the literature review: High common EF will be associated with increased frontoparietal-to-default connectivity. By isolating time courses for each of these networks, we asked a follow up to question 1, **"How are network-to-network dynamics associated with inter-individual variation in EF?"**. **Chapter 3** was motivated by an abundance of theoretical work that proposes specific roles for smaller subcomponents of the frontoparietal network and even regions outside the frontoparietal network. This historical work implies some regions, for example, dorsolateral prefrontal cortex, might have a distinct connectivity profile at rest based on a specialized role in orchestrating the functions of other brain areas or as a subordinate cognitive control region. In **Chapter 3**, we asked **"How is the connectivity profile of specific regions (as assessed by graph theory measures) related to inter-individual variation in EF?"**. We approached this last question with an exploratory analysis as well in order to address the possibility that the regions most relevant to individual differences in EF are not those usually implicated in group average fMRI studies. For each of these analyses, we first present results from as initial, large study of college-aged students (in some ways considered a “development sample”). We then present results from parallel analyses performed on a much larger sample with a more detailed description of EF behavior. A general discussion along with caveats and future directions is provided in **Chapter 4**. The results of the three analyses proposed here form the foundation of a novel characterization of individual differences in EF and are among the first to suggest high functioning individuals may be characterized by the intrinsic connectivity characteristics of their brains.

Chapter 2

Variation Within and Between Resting-state Networks Associated with Individual Differences in Common and Specific Aspects of Executive Function

Summary

This chapter describes efforts to examine the relationship between resting-state networks and individual differences in three measures of executive function. Resting-state networks are large communities of brain regions that coactivate with each other at rest more than other areas. Resting-state networks are consistent across groups of individuals but there exists some variation on an individual-to-individual basis too (e.g., how expanded a particular network might be in one individual). First, we describe how this variation might be an important indicator of individual differences in the neural circuitry available to do executive function related processing. In a sample of college students we found intensity and spatial variation in right frontoparietal and attention networks was associated with individual differences in common EF and shifting-specific EF, but not updating-specific EF (Reineberg et al., 2015). In a parallel analysis of a sample of older young adults, we did not find these relationships. Second, we examine how the correlation of time courses between different resting-state networks relates to individual differences in executive function. In an analysis of young adults, we found that increased connectivity among task positive networks (left frontoparietal, right frontoparietal, dorsal attention, ventral attention, and cingulo-opercular networks) and between frontoparietal and defaults networks was associated with higher common EF but did not find an association between common EF and attention-to-default network connectivity (another hypothesized relationship). Additionally, we found higher shifting-specific EF was associated with increased connectivity between two predominantly parietal lobe networks - dorsal and ventral attention networks. Taken together, this chapter supports the notion that network structure and interaction is a promising new avenue for exploring individual differences in behavior; however, future work will need to explore why common EF and shifting-specific EF but not updating-specific EF are related to individual differences in connectivity as well as the specificity of the reported relationships with regard to demographics (e.g., age) and other possible confounding individual differences.

2.1 Introductions

When individuals are not engaged in an experimentally-directed task (i.e., are in a resting state), distinct networks of widely separated brain regions can be identified as sharing similar temporal patterns of functional activity (Fox and Raichle, 2007) a phenomenon often referred to as resting state functional connectivity MRI (rs-fcMRI). These resting state networks (RSNs) show strong correspondence with regions that tend to co-activate during performance of a class of tasks (e.g., language processing tasks; Smith et al. (2009) Smith et al., 2009). Moreover, the organization of such RSNs has been found to have behavioral and clinical relevance. A large body of literature indicates that RSNs are altered across a plethora of neurological and clinical populations, including Alzheimer's disease, schizophrenia, depression, attention deficit hyperactivity disorder, and others (for reviews see Greicius (2008); Zhang and Raichle (2010)).

More recently, research has focused on how individual differences in abilities among neurologically normal individuals are related to the organization and extent of networks identified by rs-fcMRI. For example, patterns of rs-MRI are associated with fluid intelligence (Cole et al., 2012), attentional vigilance (Thompson et al., 2012), performance on the trail making test (Seeley et al., 2007), working memory (Hampson et al., 2006; Gordon et al., 2012), and the ability to maintain attentional control in the face of distracting information (Kelly et al., 2008). Additionally, the relationship among RSNs seems to be a domain general predictor of performance attention (Mennes et al., 2010; Tian et al., 2013; Sala-Llonch et al., 2011; Keller et al., 2015). In general, however, there is a paucity of studies that examine the relationship between rs-fcMRI and individual differences in executive function (EF), the ability to engage in and guide goal-oriented behavior. Because EF is a broad umbrella term that encompasses a wide variety of specific functions and component processes (Miyake et al., 2000), our approach in the current study is to examine the relationship between RSNs and individual differences in both general and specific subcomponents of EF in a large sample of participants. Moreover, we take a novel approach of investigating this issue by embedding our research within the framework of a prominent and well-grounded theoretical model of EF, known as the unity and diversity model (for a review, see Miyake and Friedman (2012)). This model, based on intercorrelated patterns of performance across individuals on multiple measures of EF, suggests that many important aspects of EF can be reduced into at least three latent factors. The first is a common EF factor, representing the unity aspect of the model, on which all measured EF tasks load. This factor is thought to represent the general capacity to maintain a task goal, or attentional set, and is thought to be a common feature of all EF tasks. The second two orthogonal factors represent the diversity aspect of the model and are more specific processes above and beyond common EF. Statistically speaking, these factors are residuals of the EF abilities once common EF has been taken into account. One factor, the shifting-specific factor, captures processes relating to flexibly shifting between different task or mental sets, while the other factor, the updating-specific factor, indexes the process of rapidly adding or deleting information from the contents of working memory.

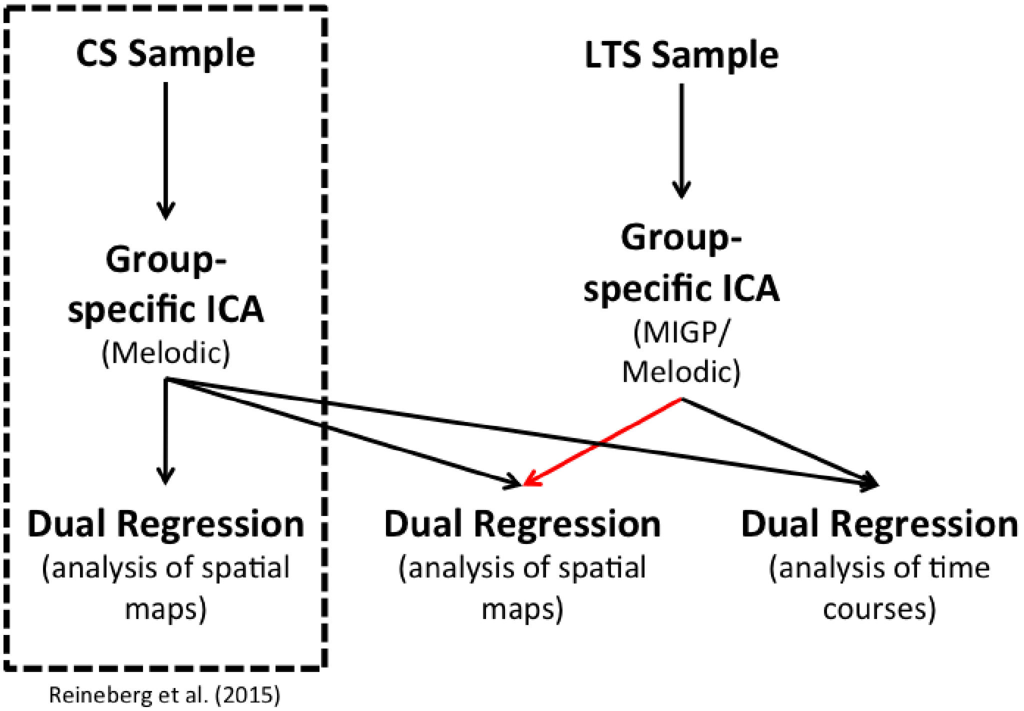
Theoretical considerations, computational modeling, and empirical research by our group and others suggest that these three EF factors are likely to be supported by overlapping yet somewhat distinct brain systems (Miyake and Friedman, 2012; Herd et al., 2014). First, a broad network of lateral frontal, parietal, and insular regions (i.e., the frontoparietal network) activates in a vast array of high-level, demanding cognitive tasks (Fedorenko et al., 2013). The ability to stably maintain a task goal is thought to rely on areas of lateral prefrontal cortex extending from BA 10 through mid-dorsolateral prefrontal cortex (Banich, 2009; Braver, 2012; Herd et al., 2006; Sakai, 2008), potentially including the anterior cingulate and frontal operculum as well (Dosenbach et al., 2008). Set shifting involves changes in the focus of attention and may engage more posterior regions of dorsolateral prefrontal cortex (e.g., inferior frontal junction) as well as parietal regions (e.g., intraparietal sulcus; Wager et al. (2004); Derrfuss et al. (2005)). Working memory updating has been suggested to involve fronto-striatal connections and require input from the basal ganglia (Braver et al., 1997; O'Reilly and Frank, 2006; McNab and Klingberg, 2008). Using task-related PET across multiple EF tasks, Collette et al. (2005) found that regions commonly activated across EF tasks include the left superior parietal gyrus and the right intraparietal sulcus, and to a lesser degree, mid- and inferior prefrontal regions. Moreover, left frontopolar cortex (BA 10) activity was specifically associated with updating-specific EF, while activity of the left intraparietal sulcus was associated with shifting-specific EF. Using these results from task-based neuroimaging as inspiration for investigation of individual differences, we will investigate connectivity of frontoparietal RSN for common EF, connectivity of frontoparietal and attention RSNs with strong parietal representation (dorsal attention, ventral attention) for shifting-specific EF, and connectivity of frontoparietal and subcortical RSNs for updating-specific EF.

Given the relatively limited scope of prior research on rs-fcMRI and EF, the current study had a number of hypotheses. First, we wanted to determine whether patterns of rs-fcMRI are associated with individual differences in both common and specific factors underlying EF. Second, given the research suggesting that these three EF factors may engage somewhat different brain regions, we wanted to ascertain whether different aspects of rs-fcMRI predicted individual differences for each of the three EF factors investigated (i.e., common EF, updating-specific EF, shifting-specific EF) with the hypothesis that they would. Third, we wanted to disentangle whether individual differences in these three aspects of EF are associated with activity in RSNs that are composed of regions commonly activated across individuals when performing EF tasks (e.g., the frontoparietal network), and/or whether they are influenced by activity in RSNs outside those traditionally thought to be engaged in EF (e.g., medial frontal/limbic network). Fourth, we wanted to investigate how individual differences in EF might predict alterations in either the degree to which specific subregions coactivate as part of a particular RSN (e.g., more intense connectivity of DLPFC within the frontoparietal network) or the composition of a particular RSN (e.g., a greater spatial extent of the frontoparietal network). Our hypothesis was that rs-fcMRI would be associated with individual differences in these three aspects of EF. However, based on the paucity of prior research, our investigation was more exploratory with regards to how exactly such individual differences would manifest. Finally, we considered how the temporal correlation between RSNs is related to individual differences in EF. Because network-to-network correlations may reflect a history of coactivation and because the family of “task positive” network is often coactivated together in the effort of demanding cognitive control, we hypothesized that increased correlation among "task positive" networks would be associated with higher common EF. Additionally, we hypothesized increased negative connectivity between frontoparietal and default RSN would be associated with increased common EF due to the small literature suggesting increased negative correlations is a domain general predictor of performance possibly due to negative correlations between network indicating segregation of cognitive functions (Seeley et al., 2007; Kelly et al., 2008; Mennes et al., 2010; Tian et al., 2013; Sala-Llonch et al., 2011; Keller et al., 2015). Two exploratory hypotheses were motivated by our literature review of shifting-specific and updating-specific EFs. First, we hypothesize increased connectivity between parietal attention RSNs (dorsal attention, ventral attention) would be associated with higher shifting-specific EF. Second, increased subcortical to frontoparietal connectivity would be associated with increased updating-specific EF. To investigate all these questions, we utilized dual regression to extract subject-specific spatial maps and time courses for versions of classic RSNs and then performed statistical tests to determine how individual variation in these RSNs predicted EF as characterized by the unity and diversity model.

2.2 Method Overview

Figure 2.1 provides the highest level overview of the analyses discussed in this chapter. This chapter combines one previously published study that utilized a sample of college students (referred to as CS sample throughout the remainder of this document) and a parallel analysis of a sample of older young adults recruited from the Colorado Longitudinal Twin Study (referred to as LTS sample throughout the remainder of this document). The dotted box in **Figure 2.1** shows the analysis of the CS sample performed in Reineberg et al. (2015). The novel parts of this chapter are on the right side of **Figure 2.1**.

Figure 2.1: **Methods overview: A two sample approach**. We follow up an initial analysis of college students with a parallel analysis pipeline in a sample of young adult monozygotic and dizygotic twins. Solid black arrows indicate analyses that were performed and discussed in this manuscript. Solid red arrow indicated an analysis that was not performed.



2.3 Methods: College Student Sample

2.3.1 Participants: College Student Sample

One hundred individuals aged 18 to 34 years ($M_{age} = 21.3$, $SD_{age} = 2.83$) from the University of Colorado Boulder participated for payment over two sessions. Participants were paid $25.00 per hour for the fMRI session and $10.00 per hour for the behavioral session. Session one involved the administration of behavioral tasks that measured EF ability. Session two involved the acquisition of anatomical and functional brain data via magnetic resonance imaging. The two sessions occurred within an average of 31.6 days of each other. Functional brain data from six participants were discarded due to excessive levels of movement during the scanning session (greater than 3mm translation or 3 degrees rotation). Additionally, data from three participants were discarded due to failure to comply with rules on one of more of the behavioral tasks. All presented results are from analyses of data from the remaining 91 participants (48 females).

2.3.2 Procedures: College Student Sample

In session one, three behavioral tasks were administered from the battery of nine tasks typically used in studies that have provided evidence for the unity and diversity model of EF (see Miyake et al. (2000); updated in Miyake and Friedman (2012)): antisaccade, category switching, and keep track. These three tasks were chosen because they load most highly on common EF, switching-specific, and updating-specific factors, respectively, in a prior large scale study in which the full battery of EF tasks was administered (Friedman et al., 2012). A variety of self-report questionnaires (e.g., emotion regulation style, trait rumination, worry, distractibility) and genetic data were acquired during session 1. Analyses of questionnaire data are outside the scope of the current study. Analyses of genetic data were not performed.

In session two, participants were scanned in a Siemens Tim Trio 3T scanner. During a 5.5 minute resting state scan, participants were instructed to relax and close their eyes.

2.3.3 Session 1: Behavioral Tasks in the College Student Sample

Antisaccade task (adapted from Roberts et al. (1994). This task measures a person's ability to inhibit an automatic process (an eye movement). Participants were instructed to focus on a centrally located fixation cross (lasting 1.5-3.5 sec). When the fixation cross disappeared, an initial box cue flashed 10 cm either to the right or to the left of fixation. The cue disappeared after a fixed interval (233, 200, or 183 ms), after which the target (a digit, 1 through 9) appeared for 150ms before being masked with gray cross-hatching. Participants named the number they saw aloud and the experimenter typed in their response, triggering the next trial to begin. For some trials, the cue was helpful in that it indicated the location at which the target appeared (prosaccade trials). In other trials antisaccade trials the cue appeared on the opposite side of the screen as the target. The task began with a block of 18 prosaccade trials in which the cue disappeared after 183 ms to establish that participants could perform the easy prosaccade trials within the most stringent time demands. Participants were then given three blocks of 36 antisaccade trials (with 233, 200, or 183 ms cue durations, respectively). Participants typically vary in their ability to identify the target on antisaccade trials because it is difficult to inhibit the automatic tendency to look towards an object, in this case the cue. The dependent measure was average accuracy for the three blocks of antisaccade trials.

Category Switch task (adapted from Mayr and Kliegl (2000)). This task measures a person's ability to quickly and accurately switch between different modes of categorization. Participants were asked to categorize words (e.g., alligator, knob, coat, lion) either with regards to animacy (living/non-living) or size (smaller/larger than a soccer ball) depending on a cue that appeared above the word (heart or crossed arrows). After two pure blocks of 32 trials each that involved categorizing items along a single dimensions (e.g., just on animacy), participants completed two blocks of 64 trials each that contained a mixture of trials in which some trials required judgments regarding animacy and others required judgments regarding size. The trials in these blocks were presented in a fixed pseudorandom order such that the subtasks occurred equally often, and 50%

of the trials involved a switch from one subtask to the other. Participants were given unlimited time to respond on each trial, but were instructed to respond as swiftly and accurately as possible. The dependent measure was the switch cost: the difference between average reaction time for correct switch trials and correct repeat trials during the mixed blocks for each subject. Trials following errors were eliminated because it was not clear that the correct set was achieved (precluding categorization of whether the subsequent trial was either a switch or repeat trial). Reaction times identified as within-subject outliers by the Wilcox-Kessleman trimming procedure (Wilcox and Keselman, 2003) were also removed before averaging.

Keep Track task (adapted from Yntema (1963)). This task measures the ability to update working memory. A stream of words is presented, one at a time. The words belong to six categories: relatives, countries, colors, animals, metals, and distances, with six words in each category. Participants were asked to keep track of the most recently presented words from two to five given categories and report them verbally at the end of the trial. Sixteen trials were administered, with each trial containing a stream of 15-25 words. After two practice trials with two categories to remember, there were four blocks, each with one two-, three-, four-, and five-category trial, for a total of 16 trials. The order of the trials within each block was fixed in a pseudorandom order. Each trial began with the list of categories, which remained at the bottom of the screen until the final recall. Each word appeared for 2000ms, followed by the next word. The dependent measure was each participant's accuracy in recalling the target words.

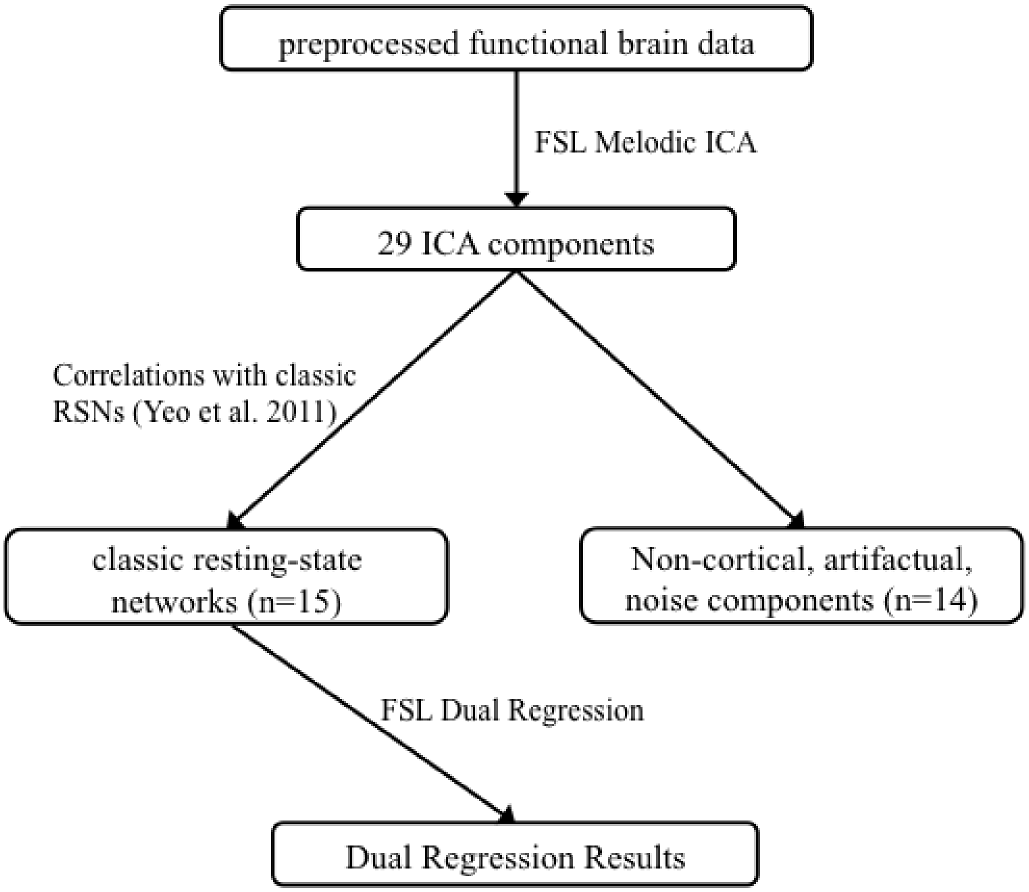
EF scores. We extracted three factors common EF, shifting-specific, and updating-specific in accordance with prior research. Common EF was calculated by taking the average of each subject's three tasks converted to a Z-value (across the group of 91 participants). Shifting-specific was the residual variance in the category switch task, regressing out common EF. Updating-specific was the residual variance in the keep track task, regressing out common EF. This procedure left shifting- and updating-specific orthogonal to Common EF; however, the shifting- and updating-specific residuals were significantly negatively correlated ($r = -.61$, $p < 0.05$). This method of calculating EF component scores is similar to that performed in a recent related study from our laboratory demonstrating that individual differences in these EF component scores predict individual differences in grey matter volume and gyrification index of prefrontal regions as well as fractional anisotropy of specific neural tracts that connect prefrontal regions with posterior brain areas (Smolker, Depue, et al., 2014). Shapiro-Wilks tests confirmed that all three EF measures were normally distributed. Higher scores on three composite measures correspond to greater ability in that construct (i.e. - maintain a goal, shift between task/mental sets, or update working memory).

2.3.4 Session 2: Brain Imaging in the College Student Sample

Neuroanatomical data were acquired with a T1-weighted MP RAGE sequence (acquisition parameters: repetition time (TR) = 2,530ms, echo time (TE) = 1.64, matrix size = 256 x 256 x 192, flip angle (FA) = 7 deg., slice thickness = 1mm). Resting state data was acquired with a T2*-weighted echo-planar functional scan (acquisition parameters: number of volumes = 165, TR = 2,000ms, TE = 29ms, matrix size = 64 x 64 x 33, FA = 75 deg., slice thickness = 3.5mm, field of view (FOV) = 240mm).

Analysis of brain data was performed via a multi-step process (see **Figure 2.2** for summary). First, independent components analysis (ICA) was used to identify networks of brain regions whose activity was correlated across the group of participants. From these so-identified ICA components, we selected those that were significantly correlated with those of a reference study with a larger number of individuals (Yeo et al., 2011) and discarded those that are were irrelevant to the current investigation (e.g., atypical RSNs and artifactual components; see below for procedure). For the relevant RSNs, dual regression was used to derive subject-specific maps of the group-identified RSNs. Finally, statistical analyses were performed to identify differences in the subject-specific RSN maps that predicted EF ability.

Figure 2.2: **Neuroimaging Data Processing Pipeline in the CS Sample**. The processing stream for LTS sample is extremely similar with the addition of an incremental principal components analysis step prior to independent components analysis to remove a computationally burdensome aspect of the analysis (i.e., high RAM demand).



2.4 Methods: LTS Sample

2.4.1 Critical Differences Between College Student Sample and LTS Sample

Although we attempted to keep many aspects of the CS sample and LTS sample consistent, there were some critical differences:

- CS Sample ($M_{age} = 21.3$, $SD_{age} = 2.83$) is younger, on average, but more variable in age than LTS sample ($M_{age} = 28.7$ years, $SD_{age} = 0.57$ years)
- Participants in the LTS sample are twin pairs while the CS sample participants are unrelated
- EF measures in LTS sample are available from data collection at ages 17, 23, and 29
- Testing of the CS sample occurred over two sessions versus a single session in the LTS sample
- EF measures derived from combined performance of three (CS sample) versus nine (LTS sample at ages 17 and 23) or 6 (LTS sample at ages 29) behavioral tasks
- Single- (CS sample) versus multi-band (LTS sample) image acquisition
- Eyes-open (CS sample) versus eyes-closed (LTS sample) resting-state scan
- A native ICA solution was generated for only the CS sample resting-state data

2.4.2 Participants: LTS Sample

The participants in the final analysis of the LTS sample were 251 individuals ($M_{age} = 28.7$ years, $SD_{age} = 0.57$ years; 97 males) after participants were removed due to excessive levels of movement during the scanning session based on the criteria of greater than 2mm translation (motion in X, Y, or Z plane) or 2 degrees rotation (roll, pitch, or yaw motion) ($n = 14$), and failure of the presentation computer to display a fixation cross during the resting scan ($n = 1$). Of the 251 individuals, there were 54 pairs of monozygotic twins (i.e., identical), 45 pairs of dizygotic twins (i.e., fraternal), 24 monozygotic twin singltons, and 28 dizygotic twin singletons. Singletons are members of twin pairs whose cotwin either did not participate or were excluded from analysis. All participants were recruited from the Colorado Longitudinal Twin Study which recruited from the Colorado Twin Registry based on birth records. Additional information about these samples can be found in Rhea et al. (2006, 2013). Comparisons with normative data on several measures suggests that the sample is cognitively, academically, and demographically representative of the state of Colorado. Participants were paid $150 for participation in the study or $25 per half hour for those who did not finish the entire three-hour session. The study session involved the administration of behavioral tasks that measured EF ability as well as acquisition of anatomical and functional brain data via magnetic resonance imaging.

2.4.3 Procedures: LTS Sample

Testing took place in a single three-hour session. Following review and obtainment of informed consent, participants were familiarized with the imaging procedures. If both twins of a pair participated on the same day, one twin then completed behavioral testing with a research assistant while the second twin was administered the functional, structural, and resting-state imaging portions. Twins then switched settings. Separate examiners assessed the twins in order to reduce any method effects directly related to the examiner.

Overall testing procedures for earlier waves of the LTS are described in detail in previous papers (Rhea et al., 2006, 2013). Briefly, at each wave the twins completed a battery of measures in an individual testing session. All study procedures were fully approved by the Institutional Review Board of the University of Colorado Boulder. All participants read and agreed to the informed consent document prior to their initial enrollment in the study and at each follow-up assessment.

2.4.4 Behavioral Tasks: LTS Sample

One strength of the LTS sample is a more detailed characterization of EF ability. Specifically, rather than using surrogate measures for common EF, shifting-specific EF, and updating-specific created using z-score averaging and residualization on data from only three tasks, we utilized approximations of EF factors calculated from many behavioral data obtained on the day of the scan and at earlier time points. These factor scores were created using a battery of six or nine EF tasks as highlighted in Miyake et al. (2000). Common EF, shifting-specific EF, and updating-specific EF were calculated for the age 17 wave using data from nine tasks that fall into three families: Inhibitory control tasks (antisaccade task, stop signal task, and stroop task), updating tasks (keep track task, letter memory task, and spatial 2-back task), and shifting tasks (number-letter task, color shape task, and category switching task). Detailed descriptions of these tasks can be found in Friedman et al. (2008). Common EF, shifting-specific ER, and updating-specific EF were calculated for the age 23 wave using data from the same nine tasks used in the age 17 wave. Common EF, shifting-specific EF, and updating-specific EF were calculated for age 29 wave (time of scanning session) using data acquired both behaviorally and while being imaged. The six tasks used were antisaccade task (inhibitory control), stroop task (inhibitory control), keep track task (working memory), letter memory task (working memory), number-letter task (switching), and category switching task (switching). The keep track task, number-letter task, and antisaccade tasks were acquired during functional fMRI scans. The remaining three tasks were acquired in a purely behavioral experimental setting.

2.4.5 Brain Imaging: LTS Sample

Participants were scanned in a Siemens Tim Trio 3T scanner. Neuroanatomical data were acquired with T1-weighted MP-RAGE sequence (acquisition parameters: repetition time (TR) = 2400 ms, echo time (TE) = 2.07, matrix size = 320 x 320 x 224, voxel size = 0.80mm x 0.80mm x 0.80mm, flip angle (FA) = 8.00 deg., slice thickness = 0.80mm). Resting state data was acquired with a T2*-weighted echo-planar functional scan (acquisition parameters: number of volumes = 816, TR = 460ms, TE = 27.2ms, matrix size = 82 x 82 x 56, voxel size = 3.02mm x 3.02mm x 3.00mm, FA = 44.0 deg., slice thickness = 3.00mm, field of view (FOV) = 248mm). During the resting-state scan, participants were instructed to relax and stare at a fixation cross while blinking as they normally would.

2.5 Methods: Unified Imaging Data Processing Pipeline

2.5.1 Preprocessing

All processing of brain data was performed in a standard install of FSL build 5.06 (Jenkinson et al., 2012). To account for signal stabilization, the first four or ten volumes of each individual functional scan (for CS sample and LTS sample, respectively) were removed, yielding 161 or 806 volumes per subject for additional analysis (again, for CS sample and LTS sample, respectively). The functional scans were corrected for head motion using MCFLIRT, FSL's motion correction tool. Brain extraction (BET) was used to remove signal associated with non-brain material (e.g., skull, sinuses, etc.). FSL's FLIRT utility was used to perform a boundary-based registration of each participant's functional scan to his or her anatomical volume and a 6 degree of freedom affine registration to MNI152 standard space. Finally, the scans were converted to 4mm voxel size, smoothed (5mm FWHM), and high-pass filtered (.01 Hz threshold).

2.5.2 Independent Components Analysis

To decompose the functional brain data into various independent spatiotemporal components, Independent Components Analysis (ICA) was performed on the preprocessed functional scans using Melodic ICA version 3.14 (Beckmann and Smith, 2004). For the CS sample, a dimensionality estimation using the Laplace approximation to the Bayesian evidence of the model order was performed (Beckmann and Smith, 2004). This procedure yielded 29 spatiotemporal components. While one common approach for identifying classical RSNs from a pool of ICA components is to have an expert subjectively label ICA components as signal (e.g., right frontoparietal RSN, default RSN, etc.) or noise (edge effects, movement, etc.), we opted to use a different RSN identification procedure to select RSNs for further analysis. We statistically compared the spatial map of each ICA component to a set of 7 popular RSNs from analysis of resting-state data from approximately 1000 participants (Yeo et al., 2011). We used FLS's "fslcc" tool to calculate Pearson's r for each pairwise relationship and kept only those ICA components that yielded a significant spatial correlation (Pearson's r $>$ .207) with one of the RSNs from Yeo et al. (2011). This procedure identified and helped label 15 RSNs, and identified 14 ICA components that did not significantly correlate with a reference network. ICA components that did not significantly correlate with a reference network were eliminated from further analysis. Further inspection confirmed that the eliminated components were likely artifactual (e.g., edge effects) or were predominantly high frequency signal according to a power frequency distribution curve (i.e., physiological noise such as heartbeat-induced movement). *The 29 network solution derived from group ICA plus automatic dimensionality estimation of the CS sample is referred to as the "CS-derived" networks or solution throughout the rest of this manuscript.*

We were unsure how well the group-specific ICA component maps generated in the CS sample would fit LTS sample, so we performed an additional group-specific ICA analysis on the functional scans from LTS sample. The standard ICA implementation in FSL's Melodic was unable to perform this analysis due to the large file size associated with multiband acquisition in the LTS sample and a single step of the ICA process that requires the entire data set be stored in RAM. We used a new tool, Melodic's Incremental Group-PCA (MIGP; Smith et al. (2014)), to bypass the memory-demanding step and Melodic to identify group-level components. One caveat of this new approach is an inability to perform automatic dimensionality estimation in the LTS sample. Whereas the process described in the previous paragraph utilizes a Bayesian estimation of number of ICA components, we were forced to specify a certain number of ICA components in the analysis of the LTS sample. We specified 29 components to be consistent with the analysis of CS sample. *The 29 network solution derived from the MIGP plus group ICA analysis of the LTS sample is referred to as* *the "LTS-derived" networks or solution throughout the rest of this manuscript.* Future work should implement an automatic dimensionality estimation to determine the best possible group-level ICA components in the LTS sample. This could be accomplished by using an updated version of FSL in which the MIGP software is more mature and perhaps more compatible with CU Boulder's computing infrastructure. From the 29 components identified in the group-ICA we ran "fslcc" again to match output in the LTS sample with output from the analysis of CS sample. We also performed a matching analysis between ICA components from the LTS sample and a set of group-specific ICA components from a large study of adolescents at CU Boulder (results reported in **Appendix B**). This analysis was performed solely to determine how similar or dissimilar different sets of ICA components are from one another. The group-level ICA components from CS and LTS samples were more similar to one another than the ICA components from the LTS sample and adolescent sample suggesting either set of components may be reasonable choices for describing the network structure of the CS and LTS samples. We followed up the correlational observations with a series of one sample t-tests to quantify how well the group-level ICA components represented network structure of the LTS sample (see **Dual Regression - Analysis of Spatial Maps**).

2.5.3 Dual Regression

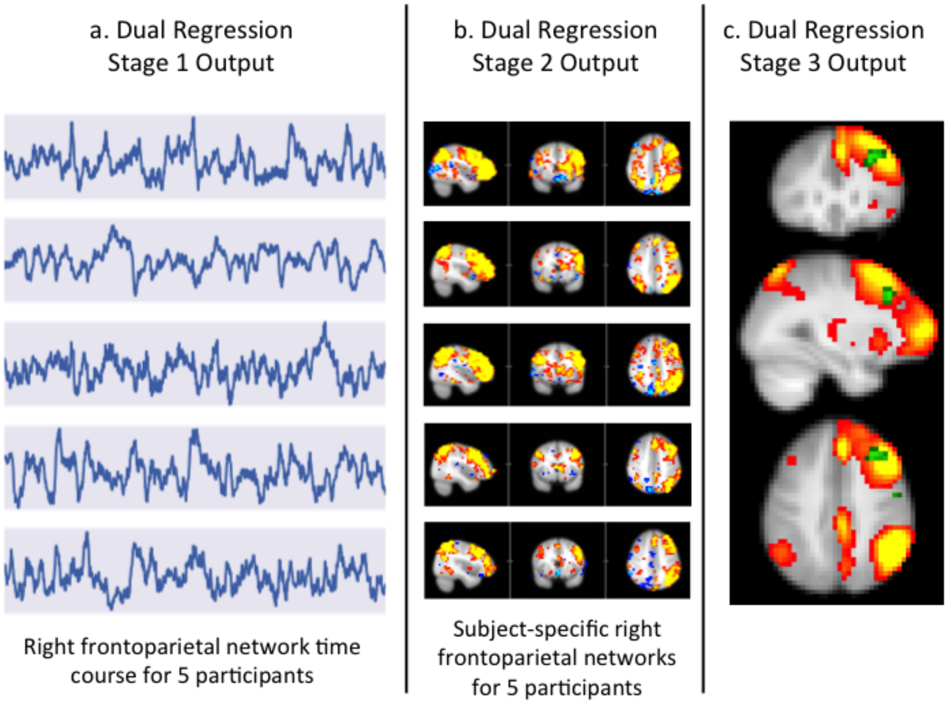
Dual regression is a method that uses unthresholded group-level independent component maps to generate both subject-specific component time courses and subject-specific spatial maps as output (Beckmann et al., 2009). Dual regression can be broken down into two steps: First, for each subject, the group-average set of spatial maps is regressed (as spatial regressors in a multiple regression) on the subject's 4D spatio-temporal dataset (i.e., brain volumes across time). This process results in a set of subject-specific time series, one per group-level component (as shown in **Figure 2.3a**). Next, those time series are regressed (as temporal regressors, again in a multiple regression) into the same 4D dataset, resulting in a set of subject-specific components, one per group-level component (as shown in **Figure 2.3b**). Subject-specific components are whole brain images. Some subjects express a given RSN that is very similar to the group level RSN while others have variations of the group level RSN (e.g., have an expanded RSN or high connectivity of a particular regions of a given RSN). Statistical analyses (discussed below) are performed on these whole brain subject-specific RSNs to determine areas that covary with behavioral covariates of interest, in our case, level of EF (sample outcome of these statistical analyses is shown in **Figure 2.3c**).

In the present study, the associations between EF measures and subject-specific RSNs were analyzed using Randomise, FSL's nonparametric permutation testing tool (Winkler et al., 2014), with 5,000 (CS sample) or 10,000 (LTS sample) permutations, threshold free cluster enhancement (TFCE), and family-wise error rate correction to correct for multiple comparisons. Permutation testing was performed while controlling for between-subject differences in transient movement throughout the scanning session in accordance with Van Dijk et al. (2012). Two summary motion regressors were created for each subject and entered into Randomise as control variables: average motion in the x, y, and z planes (mean translation) and average roll, pitch, and yaw (mean rotation) across the resting state run. The permutation testing procedure was run for each set of subject-specific RSNs (one for each group-level RSN of interest), thus the resulting statistical images reveal how variation in RSNs predict differences in EF. For example, the permutation testing procedure could reveal that individuals with an expanded RSN (i.e., expanded to areas outside the areas included in the group-level RSN) have greater EF.

For the CS sample, to account for the possibility that performance of EF tasks in session one could affect resting-state functional connectivity in session two, we performed an additional series of dual regression analyses adding time between session one and two as a covariate in addition to EF and motion variables. We found no difference in the observed effects of EF after the addition of this covariate and no main effects of time between sessions. For the sake of simplicity, only results from models that included EF, mean translation, and mean rotation are reported below.

In the final analysis, we used the time courses generated by the dual regression procedure to determine whether or not individual differences in network-to-network connectivity are associated with variation in EF ability. We calculated network-to-network connectivity as Fisher's z corrected

Figure 2.3: **Dual Regression Example**. This figure shows a simplified example of dual regression analyses. In part a, the output of dual regression stage 1 is displayed for five sample participants. This output is a subject-specific time course for the right frontoparietal group ICA components. In part b, the output of dual regression stage 2 is displayed for five sample participants. This output is a subject-specific spatial map for the right frontoparietal network. Part c shows the output from dual regression stage 3 which is statistical output after regressing a behavioral index (e.g., common EF) on the spatial regressors shown in part b - essentially performing a simple linear regression at each voxel of the brain maps. The resulting statistical map shows areas that covary with the behavioral index of interest.



Pearson's r values for all pairwise relationships between RSNs of interest. We then performed a multiple regression analysis predicting EF from network-to-network connectivity and several confounding variables - mean translation and rotation movement during the resting-state scan as well as age. In order to take the non-independence of twin pairs into account, relationships between network-to-network connectivity and EF were re-estimated using the complex modeling feature of the Mplus statistical software package (Muthen & Muthen, 2012). This procedure models the fact that twins were nested within family units, and thus estimates the degree of similarity within each twin pair and adjusts the parameter and standard error estimates accordingly. The relevant measures were treated as approximately continuous variables using the robust maximum likelihood estimator (MLR).

2.6 Results

2.6.1 Behavioral Data

We performed checks on the CS sample behavioral data to ensure the data was suitable for the proposed analyses. As anticipated, there were no floor or ceiling effects and scores varied considerably across the group of participants. To ensure the CS sample behavioral data was comparable to the behavioral data collected in the LTS sample, we directly compared performance on the three tasks administered in the CS sample. For comparison of behavioral data, we used the full LTS sample (n = 735+) collected at age 23 (rather than the smaller subset of participants with behavioral and neuroimaging data). Although the average age in the LTS sample was slightly higher (mean age of 22.8 compared to 20.8 in the current study), average results on measures of interest were slightly higher in the CS sample than in the LTS behavioral sample. The mean antisaccade accuracy was 75.5% (SD = 31.4), the mean category-switch switch cost was 174.3 ms (SD = 123.9 ms), and the mean keep-track accuracy was 76.1% (SD = 8.33).

Regarding behavior in the LTS sample, **Tables 2.1, 2.2, and 2.3** show the longitudinal correlation of common EF, shifting-specific EF, and updating-specific EF factor scores, respectively across three waves of behavioral data collection at ages 17, 23, and 29. As one might expect, for all three EFs, correlations were higher for more temporally proximal waves of data collection (i.e., EF at ages 17/23 and 23/29 were more strongly correlated than EF at ages 17/29). Regarding magnitude, within each EF, all three waves were strongly correlated (r > 0.5) but not perfectly so, suggesting EF could be represented in statistical models both as each wave individually or as a composite average that is highly correlated to data from each individual wave. For all analyses that utilized the three waves of EF data in the LTS sample, we first present the relationship between rs-fMRI and EF at the time of scan (the most recent wave of behavioral data) to be most in line with our previous work. We then present regression models using EF at earlier waves.

Table 2.1: **Longitudinal Correlation of Common EF in LTS Sample**. Table shows Pearson's *r* values for pairwise relationships between each wave of behavioral data and mean common EF across all three waves of behavioral data collection.

Common EF	Age 17	Age 23	Age 29	Average
Age 17	1.00			
Age 23	0.67	1.00		
Age 29	0.67	0.77	1.00	
Average	0.88	0.91	0.90	1.00

p < .001 for all relationships

Table 2.2: **Longitudinal Correlation of Shifting-specific EF in LTS Sample**. Table shows Pearson's *r* values for pairwise relationships between each wave of behavioral data and mean shifting-specific EF across all three waves of behavioral data collection.

Shifting-specific EF	Age 17	Age 23	Age 29	Average
Age 17	1.00			
Age 23	0.66	1.00		
Age 29	0.56	0.63	1.00	
Average	0.86	0.89	0.84	1.00

p < .001 for all relationships

2.6.2 Independent Components Analysis

The 15 signal RSNs from the CS-derived ICA networks were, with one exception, more fine-grained versions of the large seven major RSNs identified by Yeo et al. (2011): visual, somatomotor,

Table 2.3: **Longitudinal Correlation of Updating-specific in LTS Sample**. Table shows Pearson's r values for pairwise relationships between each wave of behavioral data and mean updating-specific EF across all three waves of behavioral data collection.

Updating-specific EF	Age 17	Age 23	Age 29	Average
Age 17	1.00			
Age 23	0.56	1.00		
Age 29	0.50	0.61	1.00	
Average	0.81	0.86	0.84	1.00

$p < .001$ for all relationships

dorsal attention, limbic, ventral attention, default, and frontoparietal RSNs (see **Figure 2.4**). For all but Yeo's ventral attention and limbic RSN, there was more than a single RSN that correlated significantly with the masks from Yeo et al. (2011). Additionally, five of the 15 RSNs from the current study significantly correlated with more than one RSN (e.g., to both the ventral attention RSN and the frontoparietal RSN of Yeo et al. (2011). In **Figure 2.4**, we show the independent component (IC) numbers from our Melodic output under the label of the reference networks from Yeo et al. (2011). In **Figure 2.4**, our independent components are thresholded at a level consistent with previous research ($z = 5$, compared to $3 < z < 9$ (Rytty et al., 2013), 4 standard deviations above the mean (Allen et al., 2011), and p (signal > noise) > .5 (FSL default)). This threshold was also used for determining the parent RSN of any region later identified in the Dual Regression analyses. Any IC that significantly correlated with more than one reference network is grouped in **Figure 2.4** with the reference network with which it is most strongly correlated. The three RSNs that correlated with Yeo's visual network were composed of regions extending from occipital pole through cuneal cortex and lingual gyrus (ICs 1, 12, and 18). The three RSNs that correlated with Yeo's somatomotor network were composed of the superior pre- and post-central gyrus (IC 6), primary auditory cortex and superior temporal gyrus (IC 11), and post-central gyrus (IC 24). There was a single RSN that extended through orbitofrontal and ventromedial prefrontal cortex that correlated with Yeo's limbic network (IC 28). The three RSNs that correlated with the Yeo's dorsal attention network were composed of dorsolateral frontal, parietal, and occipital regions (ICs 14, 17 and 26). The single RSNs that correlated with Yeo's ventral attention network was composed of a conglomerate of medial and lateral frontal regions (IC 4). The two RSNs that correlated with Yeo's default network were composed of medial prefrontal cortex, posterior cingulate cortex, and precuneus (ICs 10 and 15). Finally, there were two RSNs that correlated with Yeo's frontoparietal networks: classic right and left frontoparietal RSNs (ICs 5 and 9, respectively). In **Figure 2.5**, we show ICs from the current study (plotted in multiple colors) next to reference networks of Yeo et al. (2011) (plotted in red).

To determine how closely the analysis of the LTS sample could be to the analysis of the CS sample, we performed an additional group ICA on data from the LTS sample. We then compared the resulting group-level components from each sample to one another. **Figures 2.6, 2.7, 2.8, and 2.9** show comparisons of select RSNs from the group ICA results of the CS and LTS samples. We chose to show CS/LTS sample comparisons for the task-positive and task-negative reference networks: left and right frontoparietal, dorsal and ventral attention RSN, cingulo-opercular RSN (not discussed in the Yeo et al. parcellation), and default networks. We also included a comparison of the sensory-somatomotor RSN because of our prior work showing variation in a similar network was associated with individual differences in EF Reineberg et al. (2015). For the sake of visual comparison, the output of FSL's Melodic program was thresholded at the same value for each set of results ($z > 3.5$) although for numerical comparison, unthresholded whole brain group-level components were correlated.

Overall, group-level ICA components were similar in each sample. The average of pairwise spatial correlations between the 8 RSNs listed in the paragraph above was high (Pearson's $r = 0.76$). In this paragraph we will present Pearson's r correlation values for the spatial correlation of one canonical RSN in the CS sample to the matched RSN in the LTS sample. These correlations were performed using an FSL tool (fslcc) that collapses the voxels of each RSN to a vector (within a whole brain mask) and performs a standard correlation. There were some notable differences between the ICA components of the two samples. First, both left and right frontoparietal RSNs are larger in the LTS sample (Pearson's $r_{\text{left frontoparietal}} = 0.78$, Pearson's $r_{\text{right frontoparietal}} = 0.87$, **Figure 2.6**). The main areas of extension are inferior frontal lobe and caudal middle frontal

Figure 2.4: **Resting-state Networks in CS Sample**. Spatial maps for resting-state networks thresholded at z > 5 (colors range from orange (z ≈ 5) to yellow (z ≈ 10)). The RSNs are grouped into seven categories based on relation to reference networks visual, somatomotor, limbic, dorsal attention, ventral attention, default, and frontoparietal. Independent components that significantly overlapped with more than one reference are grouped with the reference they correlate most strongly. In addition to the pictured groupings, independent components 11 and 14 significantly overlapped with the ventral attention reference network; independent component 9 also significantly overlapped with the default reference network; and independent components 4 and 26 significantly overlapped with the frontoparietal reference network.

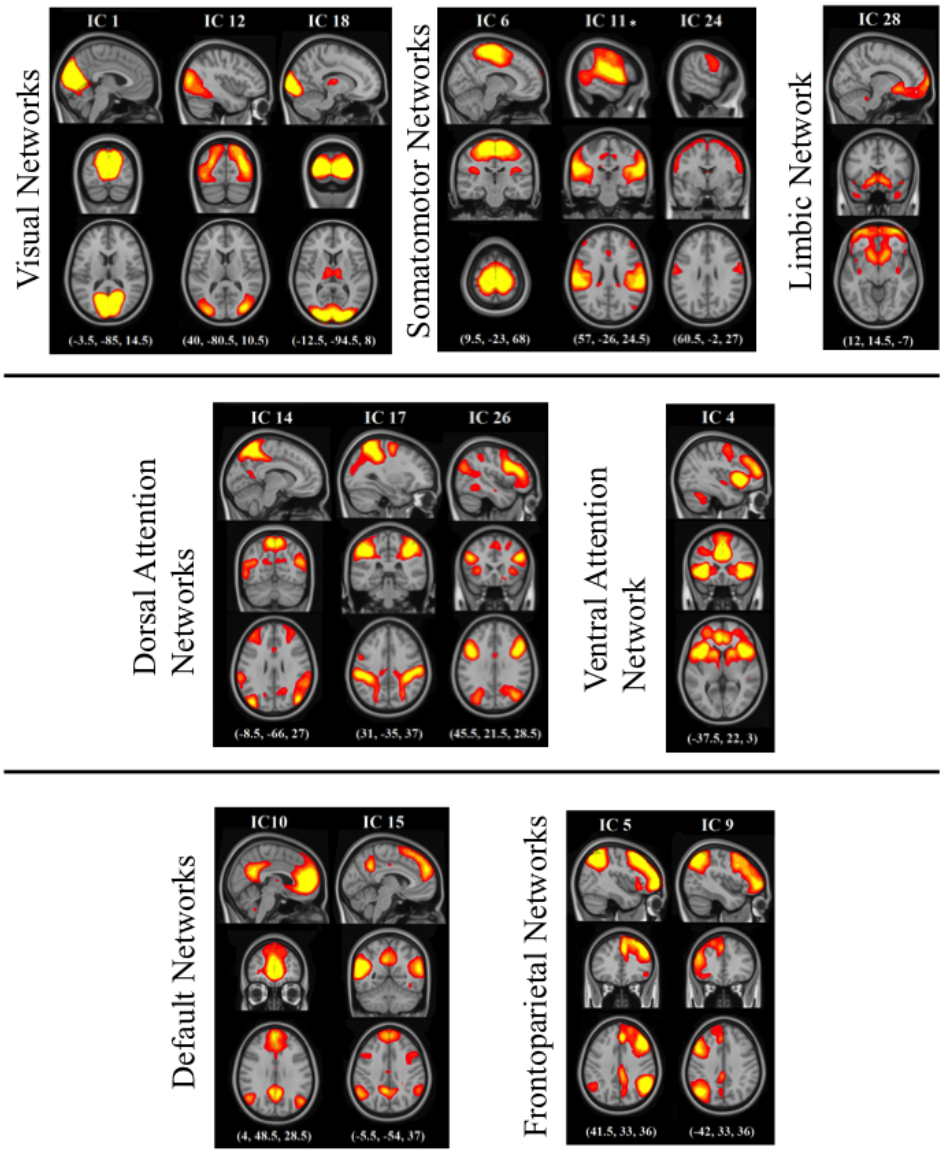
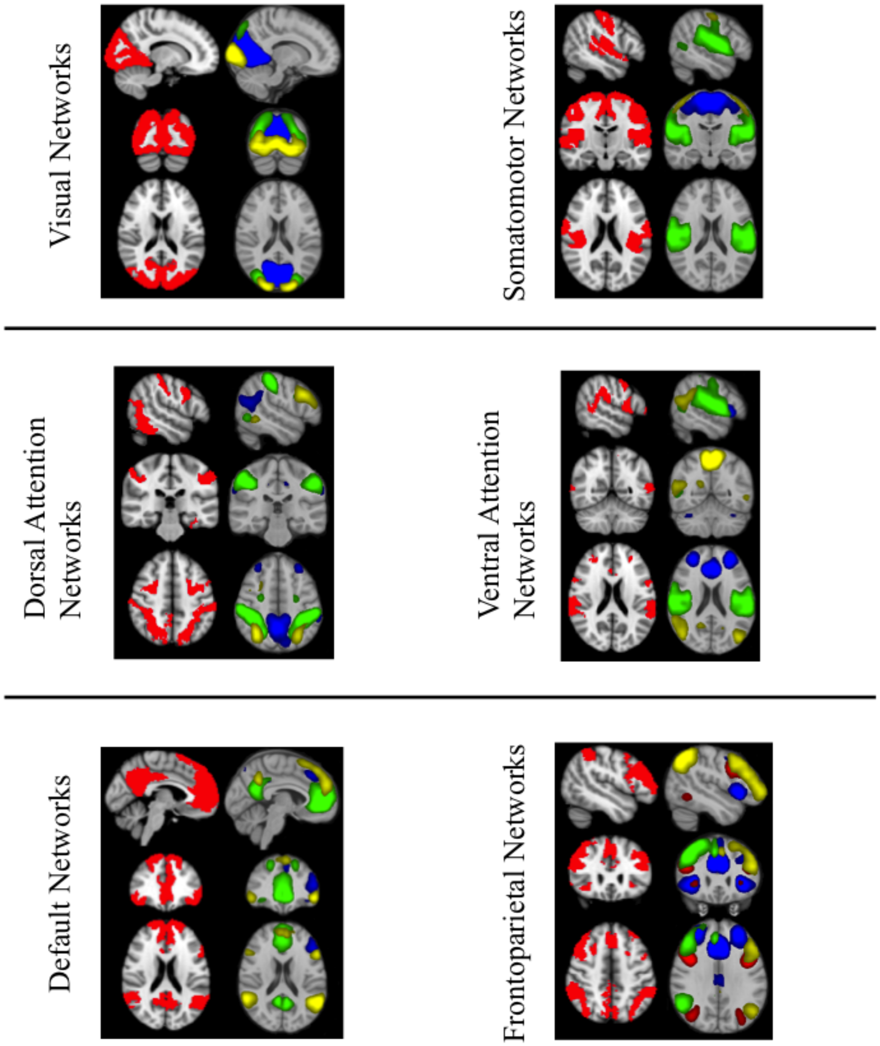


Figure 2.5: **CS Sample Resting-state Networks Compared to Reference Networks**. Reference networks are plotted on the left in red. RSNs from CS sample were spatially combined into a single image and plotted in contrasting colors. Resting state networks provided by Yeo et al. (2011).



gyrus. Dorsal attention RSN was larger in the LTS sample as well with extended inferior parietal activation (Pearson's $r = 0.72$, **Figure 2.7a**). There were large differences in ventral attention RSN as well (Pearson's $r = 0.68$, **Figure 2.7b**). This particular RSN in the CS sample was correlated with multiple reference networks - ventral attention RSN and sensory-somatomotor RSNs (see Reineberg et al. (2015) for prior characterization of this anomaly) - while in the LTS sample it more closely resembled the reference ventral attention RSN, particularly in cingulate activation (Yeo et al., 2011). In the LTS sample, the hubs of the default RSN - medial prefrontal cortex and posterior cingulate cortex - parceled into multiple ICA components while, in the CS sample, those hubs were part of the same RSN (Pearson's $r = 0.66$ between dual hub RSN from the CS sample and anterior single hub RSN from the LTS sample, **Figure 2.8a**). The middle temporal lobe subsystem of the default RSN was similar in both samples (Pearson's $r = 0.78$, **Figure 2.8b**). The sensory-somatomotor RSN was also simialr in both samples with the RSN in the LTS sample more tightly tracking the superior aspects of sensory and motor strips (Pearson's $r = 0.78$, **Figure 2.9a**). Finally, there were some differences in the cingulo-opercular RSN such that this RSN in the CS sample included more posterior cingulate activation (Pearson's $r = 0.81$, **Figure 2.9b**). In summary, the networks that were most similar across the two ICA solutions (Pearson's r $>$ 0.78) were left and right frontoparietal, middle temporal lobe subsystem of the default network, sensory-somatomotor, and cingulo-opercular RSNs. Larger differences were noted for the dorsal attention RSN, ventral attention RSN, and hubs of the default network.

2.6.3 Dual Regression - Analysis of Spatial Maps

To determine how well the CS-derived and LTS-derived group ICA components represent the network structure of the LTS sample as a whole, we performed one sample t-tests using the subject-specific RSNs generated from dual regression run using the networks from both group ICA solutions as a seed. The range of t-statistics and associated p-values is presented in **Table 2.4**. The range of t-statistics shows that, for every group ICA component and from each ICA solution, there was strong fit (). Both ICA solutions fit the LTS sample as a whole, so either could be used

Figure 2.6: **Comparison of Resting-state Networks from 2 Samples: Frontoparietal Networks**. Component maps thresholded at z > 3.5.

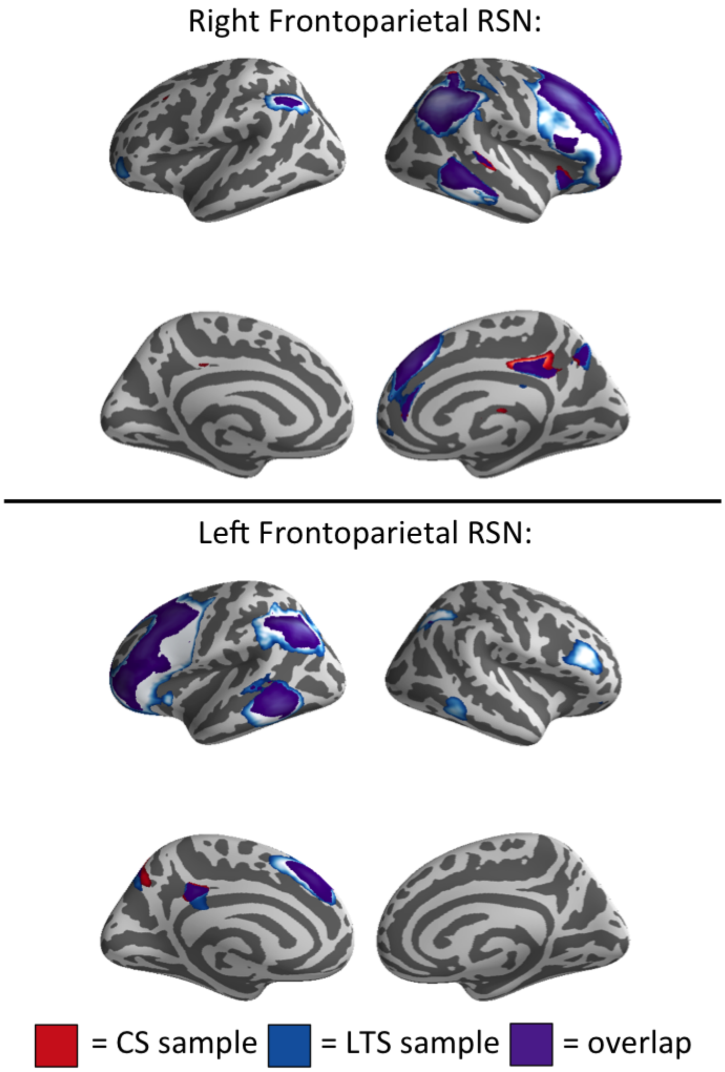


Figure 2.7: **Comparison of Resting-state Networks from 2 Samples: Attention Networks**. Component maps thresholded at z > 3.5.

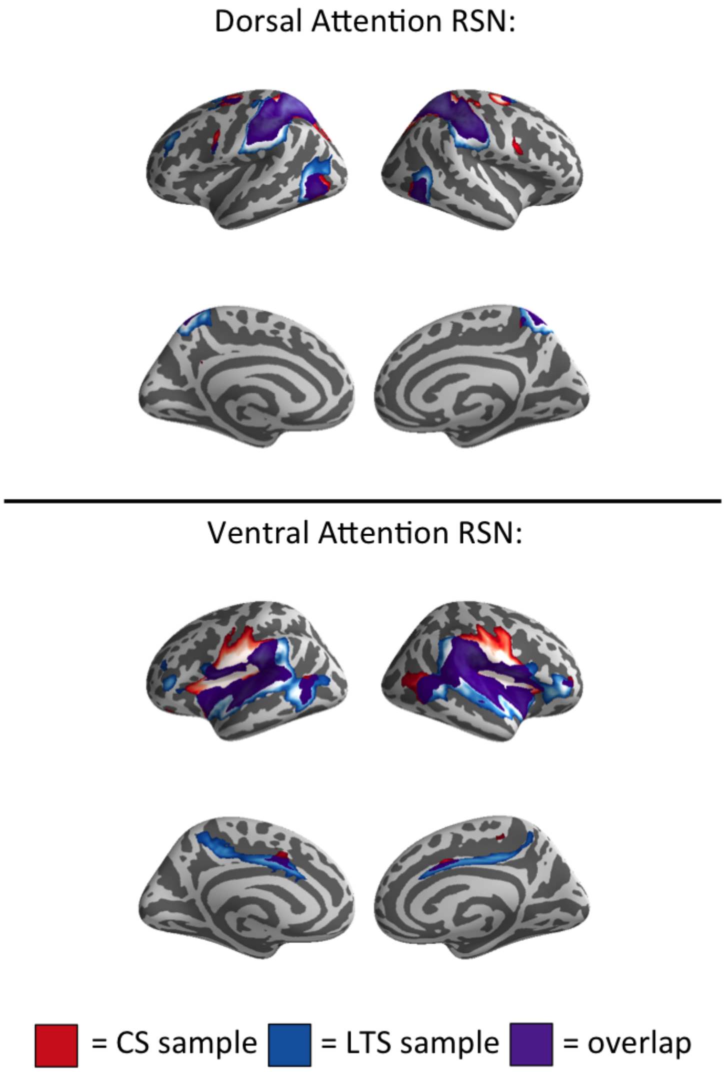


Figure 2.8: **Comparison of Resting-state Networks from 2 Samples: Default Networks**. Component maps thresholded at z > 3.5.

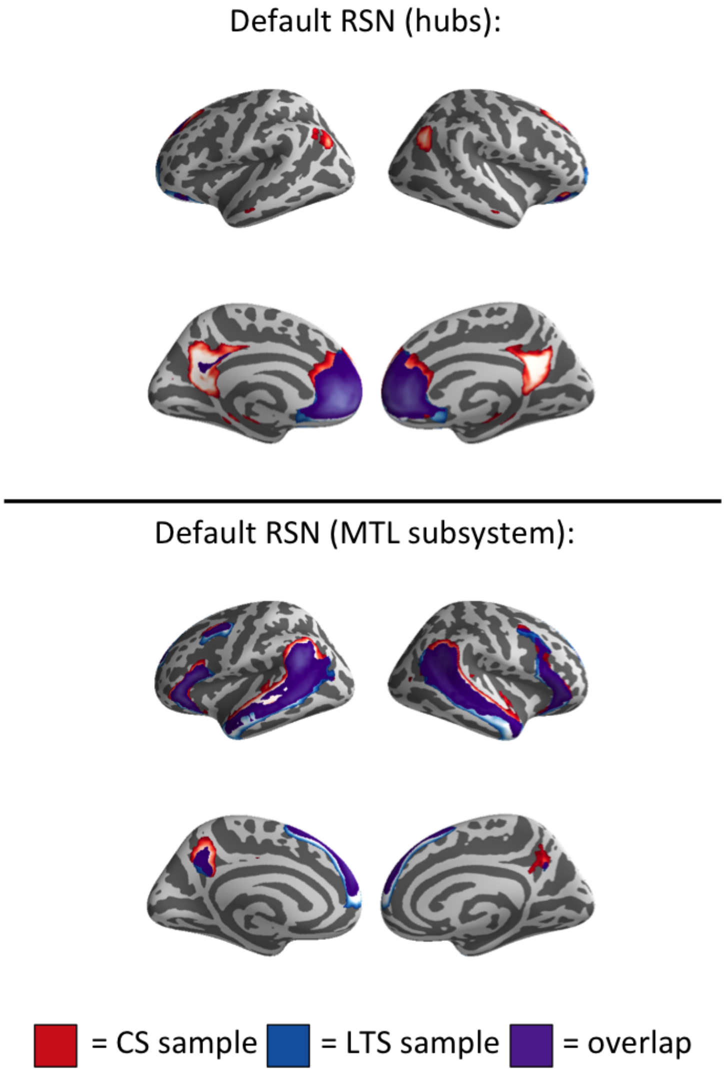
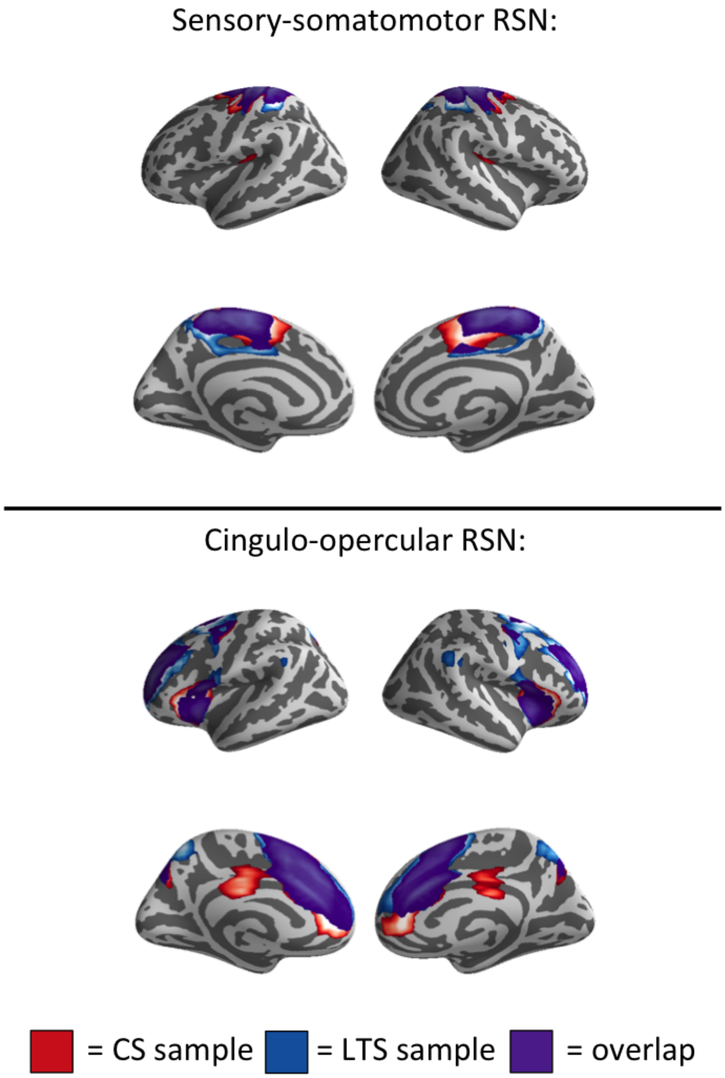


Figure 2.9: **Comparison of Resting-state Networks from 2 Samples: Sensory-somatomotor and Cingulo-opercular Networks**. Component maps thresholded at z > 3.5.



for follow up analyses of individual differences in network structure. It should be noted that both sets of ICA components seem to fit the LTS sample worse than the CS-derived ICA solution fits the CS sample, as evinced by the fact that one sample *t*-tests in the CS sample fit the data extremely well ($p_{\text{FWE-corrected})} < 0.001$, which is the lowest *p*-value FSL will output).

2.6.3.1 Common EF - CS Sample with CS-derived ICA networks

Individual differences in common EF were associated with variation in two RSNs. First, we observed that increased connectivity of Crus I and II of the cerebellum within the right frontoparietal RSN (IC 5) was associated with greater common EF ability (**Figure 2.10a**; $\text{p}_{(\text{corrected})} = 0.037$). Second, we observed that expansion of IC14, a dorsal attentional RSN, to two regions – left frontopolar cortex (**Figure 2.10b**; $\text{p}_{(\text{corrected})} = 0.028$) and right cerebellar regions (**Figure 2.10c**; $\text{p}_{(\text{corrected})} = 0.035$) - was associated with greater common EF. The frontopolar region is part of ICs 4 and 9. Information about the size and location of all reported statistical clusters can be found in **Table 2.5**.

2.6.3.2 Shifting-specific - CS Sample with CS-derived ICA networks

Greater shifting-specific EF was associated with increased coupling of the left angular gyrus with IC 11, a RSN that correlated significantly with both the somatomotor and ventral attention reference networks. (**Figure 2.10d**; $\text{p}_{(\text{corrected})} = 0.007$). Left angular gyrus is not part of IC 11 from the group level ICA analysis. Information about the size and location of all reported statistical clusters can be found in **Table 2.5**.

2.6.3.3 Updating-specific - CS Sample with CS-derived ICA networks

We found no relationship between the intensity of spatial variation in RSNs and updating-specific EF.

Table 2.4: **Results of One Sample t-tests of RSNs in the LTS Sample**

	CS-derived Group ICA Components				**LTS-derived Group ICA components**			
RSN	$t_{\min}$	$t_{\max}$	Max 1 - p (FWE-corrected)	Max 1- p (uncorrected)	$t_{\min}$	$t_{\max}$	Max 1 - p (FWE-corrected)	Max 1 - p (uncorrected)
Visual A	-4.321312	4.424177	0.942	> 0.999	-4.041251	4.164498	0.988	> 0.999
Cingulo-opercular	-4.192441	4.179454	0.605	> 0.999	-4.061097	4.491586	0.98	> 0.999
Right FPN	-4.573084	3.924655	0.285	> 0.999	-3.821764	3.804973	0.693	> 0.999
SSM A	-4.918931	4.297837	0.681	> 0.999	-4.013468	4.037445	0.886	> 0.999
Left FPN	-3.895601	3.895669	0.815	> 0.999	-4.088006	3.773106	0.798	> 0.999
Default (anterior hub)	-4.399625	4.013601	0.488	> 0.999	-4.03588	4.206484	0.85	> 0.999
VAN	-3.677933	4.283189	0.853	> 0.999	-3.997222	3.801683	0.492	> 0.999
Visual B	-3.98383	4.412307	0.982	> 0.999	-4.434639	4.132876	0.997	> 0.999
Default (MTL subsystem)	-3.791281	4.799391	0.984	> 0.999	-4.261672	4.021281	0.722	> 0.999
DAN	-4.293513	3.964528	0.719	> 0.999	-4.4144	3.781754	0.059	> 0.999
Limbic	-3.967587	4.557539	0.888	> 0.999	-4.260438	5.115931	> 0.999	> 0.999

Figure 2.10: **Dual Regression Results in CS Sample**. Dual regression analyses reveal RSNs vary with common and switching-specific components of EF. The input RSN for dual regression is plotted in warm colors as background image. The dual regression result is plotted as an overlay in blue. Blue regions are regions that covary with individual differences in EF. For all results within the input RSN (a), increased intensity of the highlighted region (thresholded at p(FWE-corrected) $< .05$) corresponds to higher EF construct scores. For outside-group-network results (b, c, d), expansion of the input RSN to the highlighted region corresponds to higher EF construct scores. Next to each dual regression result is a scatter plot of parameter estimates extracted from the voxels identified in the dual regression analysis for each participant's independent component plotted against each participant's EF score. For size of significant clusters identified in the dual regression analysis, see **Table 2.5**.

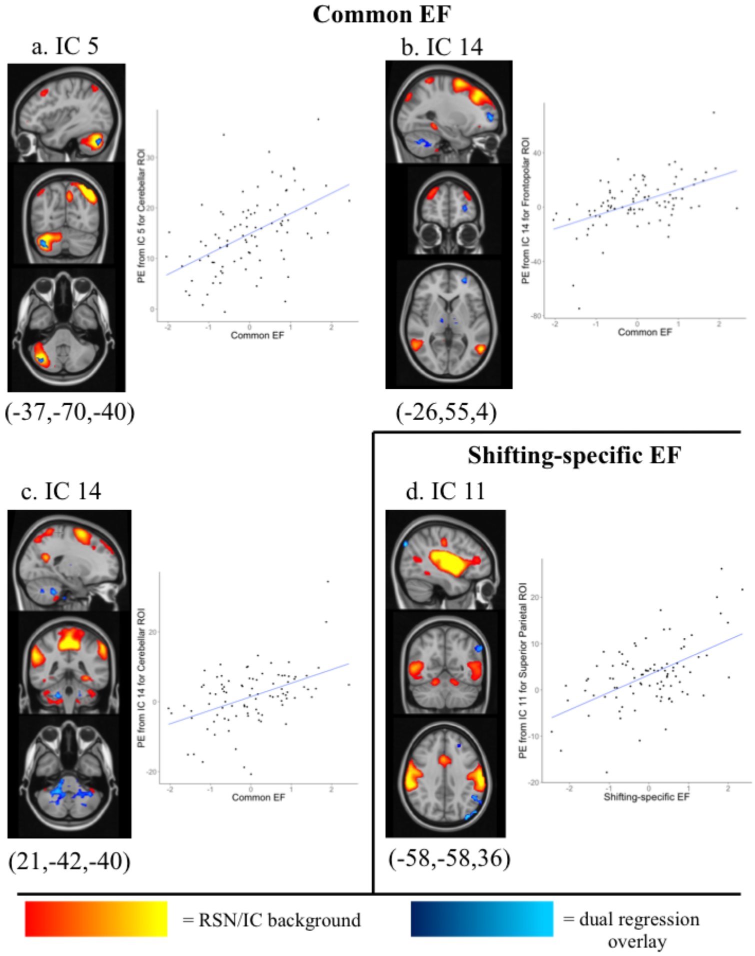


Table 2.5: **Dual Regression Results in CS Sample**. TFCE = threshold-free cluster enhancement. IC = Independent Component.

		Center of mass			p-Value	Cluster size
Executive function	IC	X	Y	Z	(TFCE-corrected)	4mm^3 (2mm^3)
Common EF	5	37	70	40	0.037	3 (24)
Common EF	14	26	55	4	0.028	3 (24)
Common EF	14	21	42	40	0.035	3 (24)
Shifting-specific	11	58	58	36	0.007	31 (248)

2.6.4 Dual Regression - Analysis of CS-derived Networks in LTS Sample

The most parallel analysis in the LTS sample is to extract parameter estimates from the statistical clusters (blue portions of **Figure 2.10**) with subject-specific RSNs of the LTS sample. To be clear, this section discusses analyses seeded by the CS sample's group ICA components in an effort to be most congruent with analysis of the CS sample itself. We extracted parameter estimates from those clusters and entered them into a multiple regression model predicting EF while controlling for movement during the resting-state scan (mean translation and rotation) as was done in Reineberg et al. (2015). We found no statistically significant results suggesting the same network expansions reported above did not hold in the LTS sample (this inconsistency between the two samples is discussed later in **General Discussion** and in **Chapter 4**).

2.6.4.1 Common EF - LTS Sample with CS-derived ICA networks

We followed up the extraction of parameter estimates from the exact clusters reported in Reineberg et al. (2015) with a whole brain analysis to account for the possibility that any variation in the right frontoparietal network, for example, might be associated with individual differences in common EF (as opposed to just the specific cerebellar zone identified in our earlier work and testing in the most direct replication effort). For the analysis of variation in the right frontoparietal RSN that varied as a function of common EF, no statistical clusters across the whole brain passed the conservative parameters set in our earlier work (i.e., threshold-free cluster enhancement with family-wise error rate correction along with 10000 permutations in FSL's Randomise permutation testing tool), but we did notice sizable clusters in TFCE-corrected statistical maps that were not corrected for family-wise error rate but thresholded at a conservative level of *t*-value = 2.75. Three sizable clusters were present: Increased common EF was associated with increased intensity of two clusters within the frontoparietal network, one in right middle frontal gyrus (peak *t*-value = 3.82) and one in midline superior frontal gyrus (peak *t*-value = 3.94). Finally, increased common EF was associated with decreased intensity of a cluster in left superior lateral occipital cortex very close to the border of the parietal lobe (peak *t*-value = -4.24). See **Figure 2.11**.

For the analysis of variation in ventral attention RSN that varied as a function of common EF, no statistical clusters across the whole brain passed the conservative parameters set in our earlier work, but we did notice a single sizable cluster in uncorrected statistical maps thresholded at a *t*-value of 2.75. Individuals with higher common EF had higher intensity of a right middle frontal gyrus cluster (peak *t*-value = 3.15). See **Figure 2.12**.

2.6.4.2 Shifting-specific EF - LTS Sample with CS-derived ICA networks

For the analysis of variation in dorsal attention RSN that varied as a function of shifting-specific EF, no statistical clusters across the whole brain passed the conservative parameters set in our earlier work, but we did notice four sizable clusters in the uncorrected statistical map thresholded at a *t*-value of 2.75. A pair of clusters was bilateral middle frontal gyrus, more posterior and inferior than the previously reported middle frontal gyrus clusters above. Individuals with higher shifting-specific EF have more middle frontal gyrus activation along with the dorsal attention RSN(right middle frontal gyrus: peak *t*-value = 3.52, X = 38, Y = 6, Z = 60; left middle frontal gyrus: peak *t*-value = 3.55, X = -6, Y = 2, Z = 52). Additionally, higher shifting-specific EF was associated with increased intensity of a left superior parietal cluster (peak *t*-value = 3.58). Finally, higher shifting-specific EF was associated with increased intensity of two small clusters, one in left midline posterior cingulate cortex (peak *t*-value = 3.83) and one in right medial supplementary motor area (peak *t*-value = 3.53). See **Figure 2.13**.

Figure 2.11: **Dual Regression Results in LTS Sample: Common EF and Right Frontoparietal Network**. Dual regression analysis reveals parts of RSN that vary with common EF. The input RSN for dual regression is plotted in green as a background image. The dual regression result (i.e., areas that covary with individual differences in EF) is plotted as an overlay in blue-to-red coloring (blue = negative relationship, red = positive relationship).

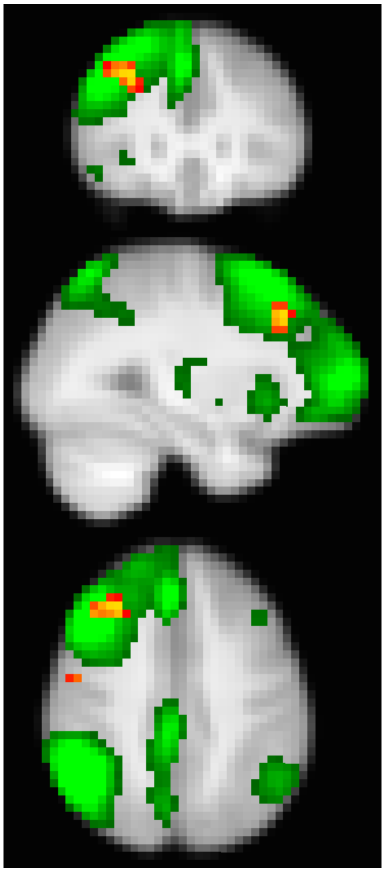


Figure 2.12: **Dual Regression Results in LTS Sample: Common EF and Ventral Attention Network**. Dual regression analysis reveals parts of RSN that vary with common EF. The input RSN for dual regression is plotted in green as a background image. The dual regression result (i.e., areas that covary with individual differences in EF) is plotted as an overlay in blue-to-red coloring (blue = negative relationship, red = positive relationship).

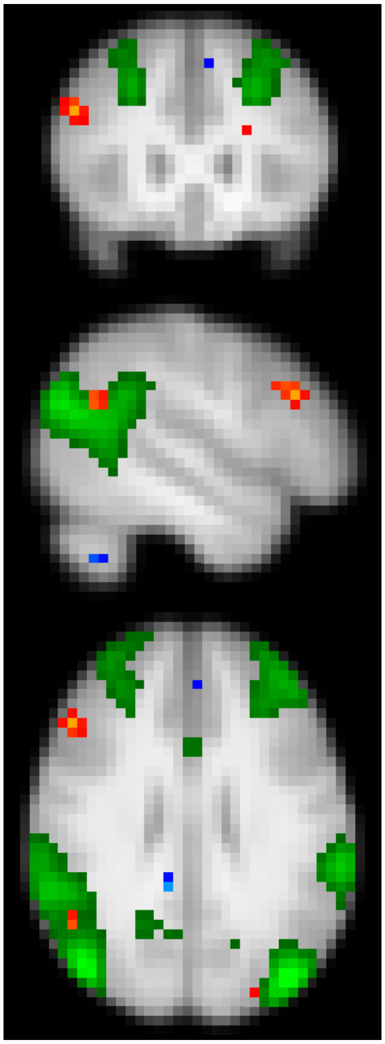
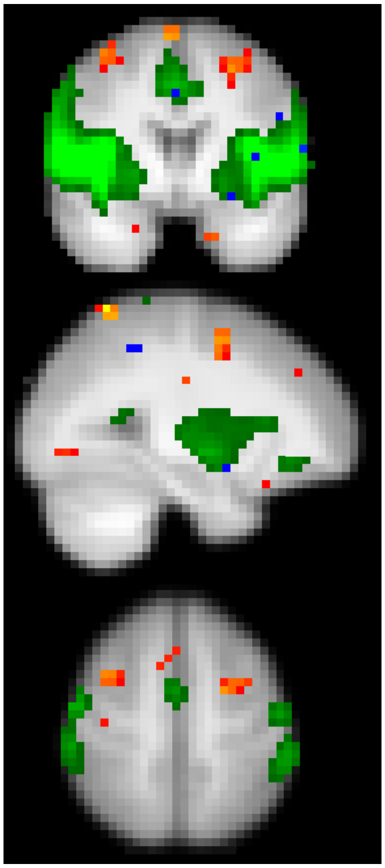


Figure 2.13: **Dual Regression Results in LTS Sample: Shifting-specific EF and Dorsal Attention Network**. Dual regression analysis reveals parts of dorsal attention RSN that vary with shifting-specific EF. The input RSN for dual regression is plotted in green as a background image. The dual regression result (i.e., areas that covary with individual differences in EF) is plotted as an overlay in blue-to-red coloring (blue = negative relationship, red = positive relationship).

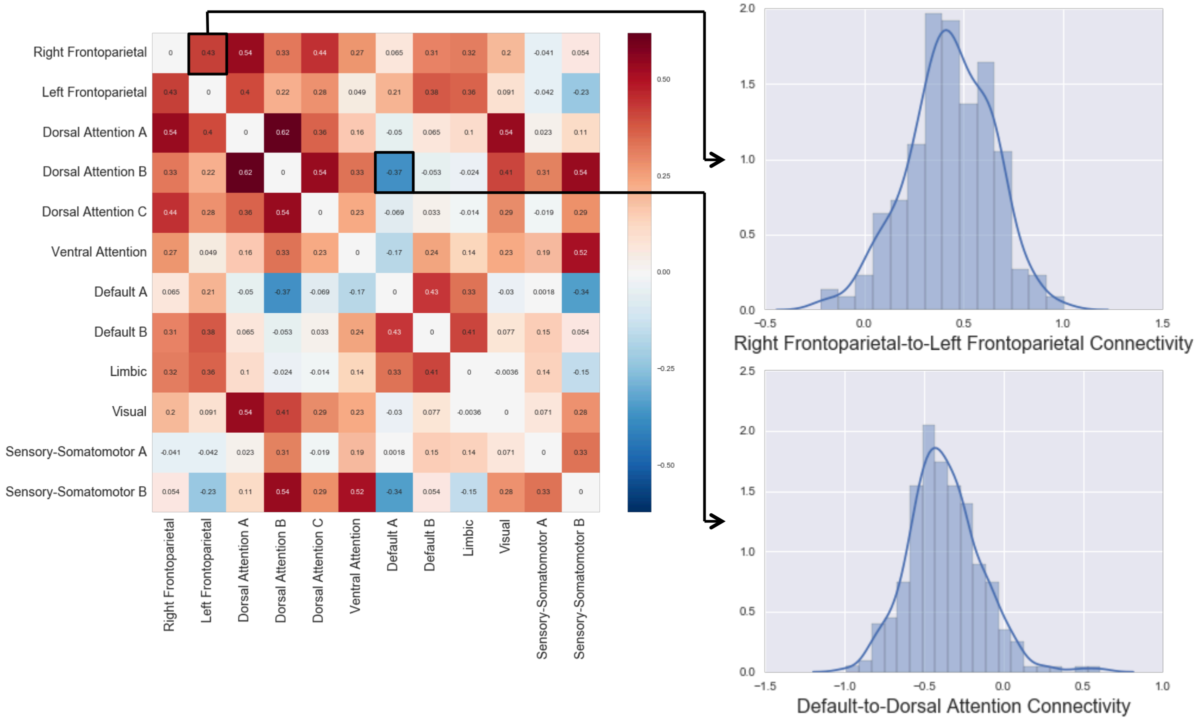


2.6.5 Dual Regression - Analysis of Resting-state Network Time Courses

In this section we report results of analyses investigating how the correlation of RSN time courses is related to individual differences in EF. This analysis was performed in LTS sample participants only and utilizes time courses extracted for each RSN via dual regression using both the CS-derived and LTS-derived ICA solutions. Overall, we found RSNs to be much more positively correlated than expected based on historical studies. Specifically, we expected, at the group level, to find an average negative correlation between "task positive" RSNs and "task negative" RSNs. For the most part we found the opposite - an average positive correlation between frontoparietal and default RSNs. The only notable negative relationship on average was between dorsal attention RSN and one default RSN. The overall lack of many average negative relationships between RSNs is an interesting finding given some past methodological concerns about resting-state preprocessing. Our result possibly speaks to the utility of using a data-driven method to isolate and extract RSN time courses (rather than using ROIs or *a priori* network maps as seeds for time course extraction), but further discussion of this finding is outside the scope of our individual differences studies. Refer to **Figure 2.14** for group average (LTS sample) connectivity between all pairwise relationships of RSNs.

In the following analyses, we performed several variants of multiple regression models. First, at times, we combined several measures of network-to-network connectivity. This procedure was for ease of description of results within the context of task-positive and task-negative RSNs and to reduce number of comparisons. Because there is no consensus on what the term "task positive" specifically represents, we decided to explore how different combinations of networks involved in externally-directed attention correlate. There was high correlation between frontoparietal, dorsal attention, ventral attention, and cingulo-opercular RSNs (average pairwise correlation between all task positive networks: Pearson's $r = 0.31$). When removing relationships between cingulo-opercular network and all others, the average correlation among just frontoparietal, dorsal attention, and ventral attention RSNs increases (average Pearson's $r = 0.35$). Finally, the correlation

Figure 2.14: **LTS Sample Group Average Network-to-Network Connectivity**. **a**. Group average connectivity matrix showing all pairwise relationships between resting-state networks. **b**. Sample of positively correlated resting-state networks across whole sample. Right frontoparietal-to-default network connectivity is positive on average. Figure shows the distribution of Fisher's z adjusted correlation values for 251 participants. **c**. Sample of negatively correlated resting-state networks across whole sample. Default-to-default network connectivity is negative on average. Figure shows the distribution of Fisher's z adjusted correlation values for 251 participants.



	Right Frontoparietal	Left Frontoparietal	Dorsal Attention A	Dorsal Attention B	Dorsal Attention C	Ventral Attention	Default A	Default B	Limbic	Visual	Sensory-Somatomotor A	Sensory-Somatomotor B
Right Frontoparietal	0	0.43	0.54	0.33	0.44	0.27	0.065	0.31	0.32	0.2	-0.041	0.054
Left Frontoparietal	0.43	0	0.4	0.22	0.28	0.049	0.21	0.38	0.36	0.091	-0.042	-0.23
Dorsal Attention A	0.54	0.4	0	0.62	0.36	0.16	-0.05	0.065	0.1	0.54	0.023	0.11
Dorsal Attention B	0.33	0.22	0.62	0	0.54	0.33	-0.37	-0.053	-0.024	0.41	0.31	0.54
Dorsal Attention C	0.44	0.28	0.36	0.54	0	0.23	-0.069	0.033	-0.014	0.29	-0.019	0.29
Ventral Attention	0.27	0.049	0.16	0.33	0.23	0	-0.17	0.24	0.14	0.23	0.19	0.52
Default A	0.065	0.21	-0.05	-0.37	-0.069	-0.17	0	0.43	0.33	-0.03	0.0018	-0.34
Default B	0.31	0.38	0.065	-0.053	0.033	0.24	0.43	0	0.41	0.077	0.15	0.054
Limbic	0.32	0.36	0.1	-0.024	-0.014	0.14	0.33	0.41	0	-0.0036	0.14	-0.15
Visual	0.2	0.091	0.54	0.41	0.29	0.23	-0.03	0.077	-0.0036	0	0.071	0.28
Sensory-Somatomotor A	-0.041	-0.042	0.023	0.31	-0.019	0.19	0.0018	0.15	0.14	0.071	0	0.33
Sensory-Somatomotor B	0.054	-0.23	0.11	0.54	0.29	0.52	-0.34	0.054	-0.15	0.28	0.33	0

among just frontoparietal, dorsal attention, and ventral attention (i.e., removing relationships between ventral attention and all others) was the highest (average Pearson's $r = 0.42$). Given this finding, any reference to "task-positive connectivity" refers to the average of left frontoparietal to right frontoparietal connectivity, left frontoparietal to dorsal attention connectivity, and right frontoparietal to dorsal attention connectivity. It should be noted that we did test the alternative calculations of "task-positive connectivity" within multiple regression models. They were entirely exchangeable with only minor differences in t-statistics and p-values, so we did not report them for the sake of clarity and brevity. Any reference to "frontoparietal to task-negative connectivity" refers to the average pairwise connectivity between frontoparietal and task-negative RSNs: left frontoparietal to default A connectivity, right frontoparietal to default A connectivity, left frontoparietal to default B connectivity, right frontoparietal to default B connectivity. For the sake of transparency, we also report results for individual measures of network-to-network connectivity as well. For tests of specificity, we calculated a measure of "whole brain connectivity" by averaging the upper triangle of each individual's network-to-network connectivity matrix. All multiple regression models included age and movement during the resting-state scan as confound covariates.

Table 2.6 describes results for the analysis of relationships between EF and network-to-network connectivity in the LTS sample using subject-specific time courses extracted from the CS-derived ICA components. For readers with less available time, this table could be utilized to expedite the process of reading all remaining results sections.

2.6.5.1 Common EF - LTS Sample with CS-derived ICA Network Time Courses

Individual differences in common EF were associated with variation in the connectivity of several "task positive" network. A relationship between common EF and task-positive connectivity was observed. Higher common EF (measured at age 29) was associated with higher positive task-positive connectivity ($t = 3.181$, $p = 0.002$) such that a one standard deviation increase in task-positive connectivity was associated with a 0.20 z-score increase in common EF. A similar relationship was found using common EF measured at age 23 ($t = 2.226$, $p = 0.024$) and 17 ($t =$

Table 2.6: **Summary of Network to Network Correlation Analyses in LTS Sample with CS-derived Networks**. cEF = common EF, SHI = shifting-specific EF, UPD = updating-specific EF

DV		**Main effect of:**	
	task-positive connectivity	**frontoparietal-to-default connectivity**	**dorsal-to-ventral attention connectivity**
cEF	yes, positive direction *	yes, positive direction ˆ	not tested
cEF controlling for SHI and UPD	yes, positive direction *	no	no
SHI	not tested	not tested	yes, positive direction ˆ
SHI controlling for cEF and UPD	no	no	no
UPD	not tested	not tested	not tested
UPD controlling for cEF and SHI	no	no	no

* = effect tested for p value inflation due to nonindepenence of twins and is robust

ˆ = effect only marginal after controlling for nonindependence of twins

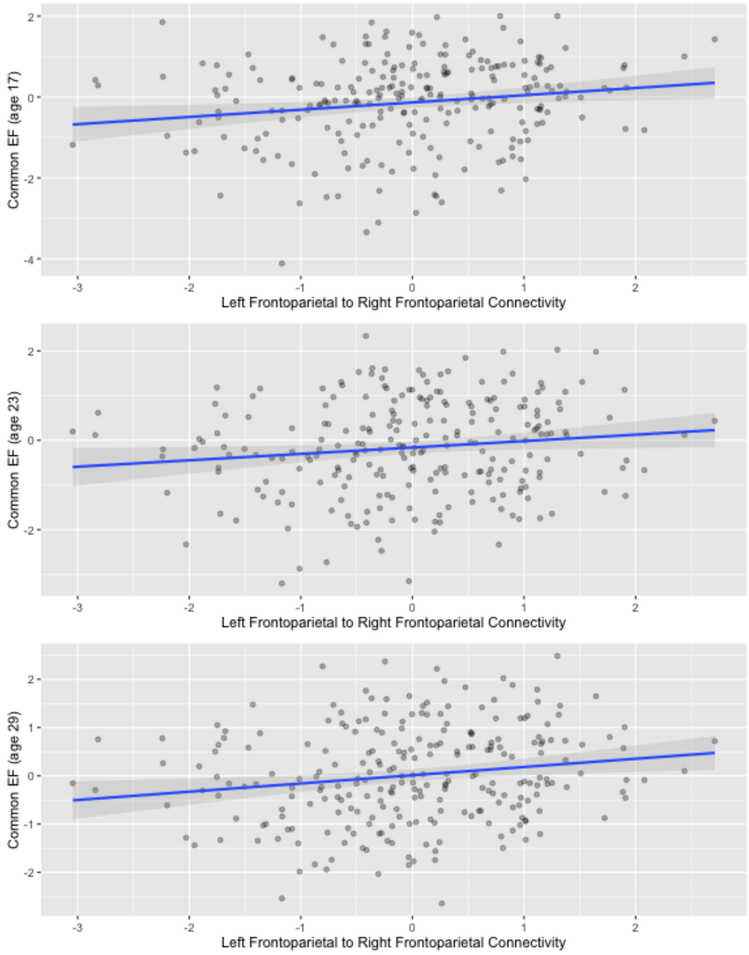
all relationship present after controlling for movement during scan and age

2.990, $p = 0.003$). The relationship between common EF (age 29) and task-positive connectivity remained after controlling for shifting-specific and updating-specific EFs ($t = 2.312$, $p = 0.022$) and after controlling for nonindependence associated with twin pairs. We also observed a similar relationship for specific pairs of task positive network. For example, higher common EF (measured at age 29) was associated with increased positive connectivity between left and right frontoparietal RSN ($t = 2.866$, $p = 0.00452$). A similar relationship was found using common EF measured at age 23 ($t = 2.569$, $p = 0.0108$) and 17 ($t = 2.938$, $p = 0.00363$). See **Figure 2.15** for scatter plots of these relationship. The relationship between common EF (age 29) and left frontoparietal to right frontoparietal RSN connectivity remained after controlling for shifting-specific EF and updating-specific EFs ($t = 2.513$, $p = 0.0126$).

Because the measure of task-positive connectivity contained many pairwise relationships, as a test of specificity, we wanted to ensure common EF wasn't related to how correlated an individual's brain was in general. In a multiple regression model regressing common EF on whole brain connectivity (the average of all network-to-network pairwise relationships), movement, and age, we did find a significant effect of whole brain connectivity ($t = 2.109$, $p = 0.036$). However, when you add task-positive connectivity into this model, there is no longer a main effect of whole brain connectivity. Over and above how correlated an individual's brain was, there is still a positive relationship between common EF and task-positive connectivity ($t = 2.361$, $p = 0.019$).

Individual differences in common EF were also associated with variation in the connectivity between frontoparietal and default RSNs. Individuals with higher common EF (measured at age 29) had more positive frontoparietal to task-negative connectivity ($t = 2.005$, $p = 0.0461$, **Figure 2.16**) such that a one standard deviation increase in frontoparietal to task-negative connectivity was associated with a 0.18 **z**-score increase in common EF. A similar effect was observed when using common EF measured at age 23 ($t = 2.684$, $p = 0.0078$) and marginally so with common EF measured at age 17 ($t = 1.873$, $p = 0.0623$). The relationship between common EF and frontoparietal to task-negative connectivity was strongly trending after controlling for nonindependence associated with twin pairs ($p = 0.57$). The relationship between common EF and frontoparietal to task-

Figure 2.15: **Relationship Between Common EF and Left Frontoparietal to Right Frontoparietal Connectivity**. Higher common EF measured at ages 17, 23, and 29 is associated with increased positive connectivity between left and right frontoparietal networks.

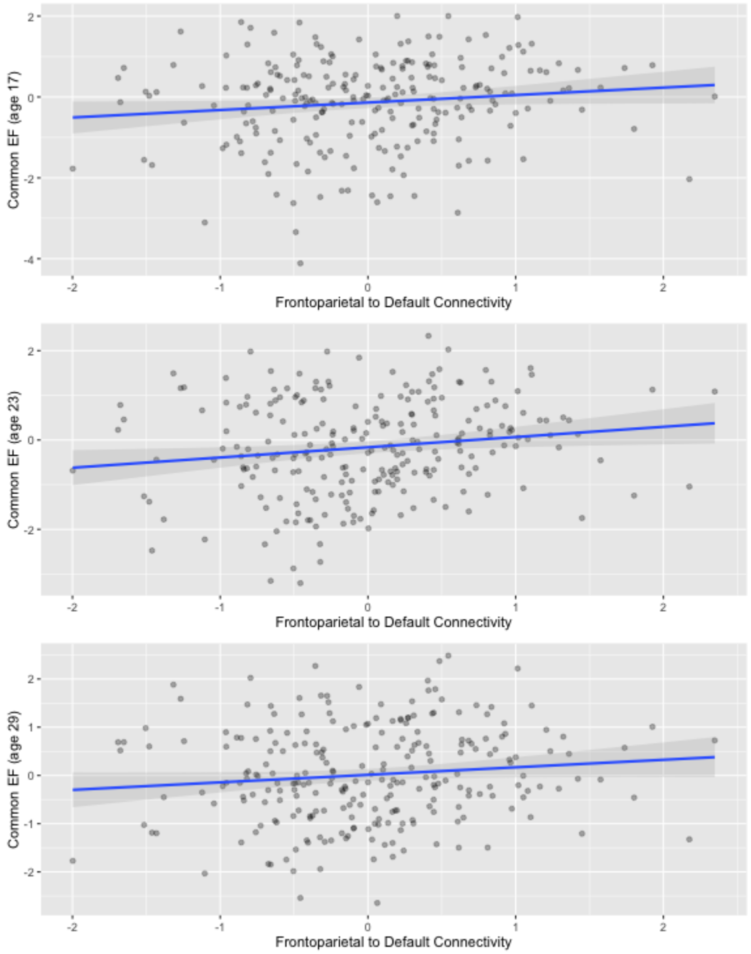


negative connectivity did not remain after controlling for shifting-specific EF and updating-specific EF.

2.6.5.2 Shifting-specific EF - LTS Sample with CS-derived ICA Network Time Courses

We were interested in how the connectivity of parietal lobe containing RSNs was associated with individual differences in shifting-specific EF. First, our earlier analysis of the relationship between task positive network connectivity and common EF controlling for shifting-specific EF were effective tests of relationships between network-to-network connectivity and individual differences in shifting-specific EF. We found no shifting-specific effects in these analyses. One specific network-to-network relationship we had not explicitly tested for common EF was dorsal to ventral attention RSN connectivity, both of which are primarily parietal RSNs. Higher shifting-specific EF (age 29) was associated with increased dorsal attention A to ventral attention RSN connectivity ($t = 2.017$, $p = 0.0447$) such that a one standard deviation increase in dorsal attention A to ventral attention connectivity was associated with a 0.12 z-score increase in shifting-specific EF. Additionally, higher shifting-specific EF (age 29) was associated with increased dorsal attention RSN B to ventral attention RSN connectivity ($t = 2.079$, $p = 0.0387$) such that a one standard deviation increase in dorsal attention A to ventral attention connectivity was associated with a 0.13 z-score increase in shifting-specific EF. Both of these relationships were only marginal ($p = 0.071$ and $p = 0.60$, respectively) after controlling for nonindependence associated with twins. The relationship between shifting-specific EF and connectivity of dorsal attention RSN A to ventral attention RSN was not present with earlier waves of behavioral shifting-specific EF data. The relationship between shifting-specific EF and connectivity of dorsal attention RSN B to ventral attention RSN was marginally significant with shifting-specific EF data collected at age 23 ($t = 1.674$, $p = 0.0954$) and age 17 ($t = 1.911$, $p = 0.0573$). These relationships did not persist when controlling for common EF and updating-specific EF.

Figure 2.16: **Relationship Between Common EF and Frontoparietal to Default Network Connectivity**. Higher common EF measured at ages 17 and 23 (marginally so at age 29) is associated with increased positive connectivity between frontoparietal and default networks.



2.6.5.3 Updating-specific EF - LTS Sample with CS-derived ICA network Time Courses

First, our earlier analyses of common EF or shifting-specific EF controlling for updating-specific EF were effective tests of relationships between network-to-network connectivity and individual differences in updating-specific EF. We did not find any updating-specific effects in these analyses. However, one hypothesized relationship was between updating-specific EF and frontal-to-subcortical connectivity. We tested this hypothesis by regressing updating-specific EF on frontoparietal to limbic RSN (the main subcortical-containing RSN), movement, and age but did not find any significant effects.

2.6.5.4 Analyses Using LTS-derived ICA Network Time Courses

Because it is unclear what the best group ICA solution for the LTS sample is, we tested all the relationships above using time courses extracted from the second set of ICA components (the ICA performed on the LTS sample). Using this alternative set of RSN time courses we found some overlap in the common EF results. First, when combining all the measures of connectivity between frontoparietal and dorsal attention RSNs, we found a similar positive relationship such that individual with higher common EF (measured at age 29) had more connected task positive RSNs ($t = 2.920$, $p = 0.004$). This effeect was present with age 17 common EF ($t = 2.456$, $p = 0.015$) and was trending with age 23 common EF ($t = 1.745$, $p = 0.082$). This effect also remained even in a multiple regression model that included common EF, shifting-specific EF, and updating-specific EF ($t = 2.309$, $p = 0.022$). Interestingly, in multiple regression models that included all three EF measures from earlier time points, the effect of common EF was not present, however there were marginally significant effects of updating-specific EF at age 17 ($t = 1.723$, $p = 0.086$) and 23 ($t = 1.818$, $p = 0.070$). When the composite dependent variable of task-positive connectivity is broken down into individual measures of network-to-network connectivity, higher common EF (measured at age 29) was associated with increased connectivity between left frontoparietal RSN and dorsal attention RSN ($t = 3.084$, $p = 0.002$) and, only to a trend-level, the connectivity between left and right frontoparietal RSNs ($t = 1.805$, $p = 0.072$).

Regarding the relationship between common EF and frontoparietal to task-negative connectivity, we found a relationship very similar to the one reported above. Higher common EF was associated with increased frontoparietal to task-negative connectivity ($t = 2.398$, $p = 0.017$). This effect was present when using common EF data acquired at age 23 ($t = 2.933$, $p = 0.004$) and age 17 ($t = 2.898$, $p = 0.004$). This effect was marginally significant in a multiple regression model that included common EF, shifting-specific EF, and updating-specific EF acquired at age 29 ($t = 1.875$, $p = 0.062$) and significant in similar models that included all three EF acquired at age 23 ($t = 2.659$, $p = 0.008$) or 17 ($t = 2.179$, $p = 0.030$). When the composite dependent variable is broken down into individual measures of network-to-network connectivity, higher common EF (measured at age 29) was most associated with increased connectivity between left frontoparietal RSN and the posterior cingulate cortex hub of the default RSN ($t = 2.773$, $p = 0.006$).

2.7 Discussion

Our findings indicate that aspects of the functional architecture of the resting brain are associated with variation amongst individuals in different aspects of EF. While an abundance of studies have identified sets of regions that consistently coactivate together during periods of rest, we have shown that the composition of these RSNs and their interaction with one another varies based on individual differences in EF. More specifically, higher common EF is associated with intensity differences within the right frontoparietal RSN, expansion of an attention RSN to frontopolar cortex and cerebellum, increased connectivity among task positive RSNs, and increased connectivity between frontoparietal and default RSNs. Better shifting-specific ability was associated with expansion of a somatomotor/attention RSN to angular gyrus and increased connectivity between attention RSNs. No relationships were observed between rs-fcMRI and updating-specific ability. This set of results confirms our general hypotheses. First, we confirmed that rs-fMRI is relevant to individual differences in two of the three EF constructs measured. Second, the features relevant to individual differences in common EF were distinct from those features relevant to individual differences in shifting-specific suggesting some diversity in the neural bases of EFs. Third, although the frontoparietal RSN emerged in a variety of our analyses, other networks, such as the attention and default RSNs, did as well suggesting that areas outside those typically identified by task-based fMRI are important for individual differences in EF. Regarding specific hypotheses, several of our hypotheses were confirmed or partially confirmed. First, we confirmed the hypothesis that connectivity among those networks most strongly implicated in externally-directed cognition (the task positive networks) would be associated with increased common EF. Second, although we found a relationship between common EF and frontoparietal to default connectivity that was robust, it was in the opposite direction of the predicted relationship. Regarding shifting-specific EF, parietal areas emerged as important in both the dual regression analysis and the network-to-network time course correlations. Finally, we did not confirm our hypothesis about the role of subcortical areas for individual differences in updating-specific EF.

2.7.1 Common EF

Higher common EF was associated with differences in the right frontoparietal RSN in the CS sample. Specifically, increased coupling between the right frontoparietal RSN and Crus I and II of the cerebellum predicted higher common EF. Such a result is consistent with task-based research showing that frontal and parietal regions emerge as important in both region-of-interest (Alvarez and Emory, 2006; Buckner, 2013) and network-based analyses (Zhang and Li, 2012) of executive function tasks. This result is also in line with work that shows a strong connection between Crus I/II and frontoparietal regions both functionally (Buckner et al., 2011) and anatomically (Kelly and Strick, 2003). Additionally, Crus I and II have been shown to activate in task-based fMRI studies of working memory and EF, and greater activation and functional connectivity of these regions is associated with better performance (Bernard et al., 2013; Salmi et al., 2010; Stoodley and Schmahmann, 2009). This result supplements these task-based findings by demonstrating that the degree to which Crus I and II couples with the frontoparietal RSN at rest predicts differences in EF. The exact role of cerebellar regions in the service of EF is still debated. Two prominent theories stemming from the motor control literature suggest that cerebellum is crucial for timing of cognitive events and/or provides a means for predicting the outcome of implemented plans (Ivry and Keele, 1989; Ramnani, 2006). While our study cannot speak directly to these theories, we have shown that a key difference between individuals with high versus low Common EF may be the degree to which cerebellum is involved in a network of regions broadly implicated in higher-order cognitive operations.

Additionally, Common EF was associated with variation in a RSN supporting attention to the external environment (IC 14) in the CS sample. Individuals with higher common EF showed increased coupling of a frontopolar region with this attentional RSN, which is composed of lateral frontal and superior parietal/occipital regions. An attention RSN similar to IC 14 has previously been linked to performance on the antisaccade task (Schaeffer et al., 2013), which is a task that loads strongly on the Common EF construct (Miyake & Friedman, 2012). Notably though, the frontopolar region identified in the dual regression analysis has not been characterized as part of the dorsal attention RSN and is not contained within the dorsal attention RSN that was identified at the group level of the current study. Rather, this frontopolar region is part of two frontoparietal RSNs ICs 4 and 9. Importantly, this frontopolar region has previously been linked to maintenance of goals and abstract task sets (Ramnani and Owen, 2004; Vincent et al., 2008; Christoff et al., 2009; Dosenbach et al., 2008; Orr and Banich, 2014). As such, co-activation of regions implicated in the maintenance of abstract representation and/or goals with the attentional machinery to implement those goals, characterizes individuals with high levels of common EF.

Regarding the parallel analysis of the LTS sample. We did not find any of the three common EF effects reported in Reineberg et al. (2015) and described above. This inconsistency is discussed in **General Discussion**. To build upon this work and account for the possibility that network properties of the right frontoparietal and ventral attention network are associated with individual differences in common EF in a way that is different in the second sample, we looked at whole brain maps for each network rather than just within the statistical clusters identified previously.

For both networks we found increased activity within middle frontal gyrus was associated with higher common EF with the caveat that a less conservative correction technique was used for this analysis (no family-wise error rate correction). This result resembles the finding from Reineberg et al. (2015) insomuch as we demonstrated variation within a key part of the frontoparietal network - although there are considerable differences between cerebellum and middle frontal gyrus. While interpreting results as "variation within a key part of the frontoparietal network" is a vague and nonspecific description of the results, there is a historical precedent. One of the only other studies utilizing a dual regression analysis of spatial maps has described network intensity results simply as variation in the whole network rather than providing specific anatomical specificity for their results (Tian et al., 2013). Taking this less specific approach, one could say our our parallel analysis of the LTS sample was congruent with the findings of Reineberg et al. (2015) because both analyses revealed variation within the right frontoparietal network. The finding that increased middle frontal gyrus activity along with the ventral attention network is a novel finding. Together, these new dual regression analysis results suggest the middle frontal gyrus may have a larger role globally (or at least in 2 of the major cognitively-relevant, task-positive, resting-state networks) in higher performing individuals in the LTS sample.

We also extended the dual regression analysis of spatial maps by investigating how network-to-network time course correlations were related to individual differences in EF in the LTS sample. This analysis was motivated by a literature review (summarized in **Chapter 1**) that revealed network-to-network correlations are perhaps the most behaviorally-relevant feature of the resting brain. Because performance in a wide array of behaviors was associated with individual differences in the correlation of frontoparietal and default RSNs, we first sought to investigate how these RSN correlations was related to common EF ability. Individuals with higher common EF had increased positive correlations between frontoparietal and default RSNs. Although no consensus theoretical interpretation of frontoparietal to default correlations exists, some speculate that increased negative correlations between the RSNs enables segregation of functions. This interpretation stems from a wide range of studies showing opposing activation in externally directed cognitive tasks for the frontoparietal and default RSNs, during which functions of the two networks ought to be segregated to prevent interference from the internal mentation functions of the default network. In our study, we found increased positive correlation for high performing individuals implying there is some benefit to a highly correlated frontoparietal and default network. Considering frontoparietal and default functions to be goal maintenance/biasing and internal mentation/autobiographical thinking, respectively, there are perhaps instances in which those functions work in concert. Perhaps individuals with high common EF have a tendency to bootstrap goal maintenance with autobiographical memory or other internal mentation strategies. Future work could investigate the mechanism by which individuals with high common EF develop this intrinsic relationship between the frontoparietal and default networks. One methodological consideration when trying to fit our positive correlation finding into a historical context full of negative correlations is that one should be cautious to attribute a certain functional role to intrinsic network dynamics with no knowledge of the underlying mechanisms. At this time it is still unknown if the neural processes that underly positive RSN correlations are that same or different from the neural processes that underly negative correlations. Considering our lack of understanding of the mechanism underlying correlations of different directionality, future work could also investigate the relationship between common EF and the absolute value of the correlation between frontoparietal and default RSNs (or alternatively explore non-linear relationships).

In the same analysis of network-to-network correlations, we also found increased positive connectivity amongst the task-positive networks was associated with higher common EF. This analysis was motivated by our interest in the family of task-positive networks which often coactivate in the context of externally-directed cognitive tasks. When combining all measures of pairwise connectivity between left frontoparietal, right frontoparietal, and dorsal attention networks, we found a positive relationship between "task positive" connectivity and common EF. This result can be interpreted in the same way as our default network finding - cooperation and historical coactivation of all the networks underlying externally-directed attention may be higher in individuals with higher common EF. The historical coactivation interpretation could even be expanded to propose an intervention study. Because coactivation of task-positive networks is a common state in the laboratory, future studies could investigate how practice or training in this coactivation is associated with gains in cognitive control.

In summary, in the CS sample we found alterations in RSNs associated with high common EF can be characterized as expanded compared to those with low common EF, encompassing both higher-order areas involved in setting abstract goals (i.e., frontopolar cortex) and lower-level regions that could aid in implement those goals more automatically (i.e., cerebellum). We did not find these same expansions in the LTS sample indicating this finding may be sample or context dependent. Our network-to-network correlation analyses within the LTS sample indicated that one property of higher function individuals is a more connected brain. More specifically, we found increased connectivity among networks typically involved in externally-directed attention (e.g., frontoparietal, dorsal attention, ventral attention, cingulo-opercular) was associated with higher common EF.

2.7.2 Shifting-specific

Higher Shifting-specific EF was associated with variation in a somatomotor/attentional RSN (IC 11), suggesting it is involved in sensory aspects of spatial processing. Specifically, individuals with higher EF had greater recruitment of the angular gyrus, which lies outside IC. Lateral parietal regions are frequently implicated in executive processes, and are especially important for shifting-specific aspects of EF (Collette et al., 2005; Esterman et al., 2009), perhaps due to their ability to integrate multimodal information. Additionally, this particular region of the angular gyrus is characterized by a distinct pattern of anatomical connectivity to a variety of regions implicated in higher order cognitive process, such as ventrolateral prefrontal cortex, among others (Uddin et al., 2010). Shifting-specific tasks depends not only on active abilities to move from one task set to the other, but also the passive linking between lower order centers of control and appropriate targets (e.g., motor regions). It may be that individuals with higher shifting-specific EF effectively utilize parietal regions to control the stimulus-response mappings that are required to perform different tasks.

Regarding the parallel analysis of the LTS sample, we did not find the shifting-specific effect reported in Reineberg et al. (2015). This inconsistency is discussed in **General Discussion**. To build upon this work and account for the possibility that network properties of the dorsal attention RSN are associated with individual differences in shifting-specific EF in a way that is different in the second sample, we looked at the whole brain dual regression statistical map for the dorsal attention RSN rather than just within the statistical clusters identified previously. We found four clusters outside the classic ventral attention RSN whose intensity was related to individual differences such that more coupling of these regions along with the rest of the ventral attention RSN was associated with higher shifting-specific EF - bilateral middle frontal gyrus, left superior parietal cortex, and left midline posterior cingulate cortex. This result can broadly be described as an expanded ventral attention RSN being associated with higher functioning. Although we did not find expansion to angular gyrus as in Reineberg et al. (2015), we did find expansion to a nearby parietal area in the same hemisphere. We also found the ventral attention RSN was expanded to middle frontal gyrus which is quite similar to the coupling of middle frontal gyrus and right frontoparietal and ventral attention RSNs in higher common EF individuals reported above although these areas did not overlap at all. This particular part of middle frontal gyrus was more inferior and and posterior than the area reported in the common EF results. Still, finding expansions to nearby middle frontal gyrus regions for both shifting and common EF shows some consistency, perhaps suggesting a similar mechanism in middle frontal gyrus but specialization with regard to the application to particular functions. One study has described middle frontal gyrus (although more anterior and inferior than reported here) as having a unique "global connectivity" to a diverse array of brain areas that underlies that particular area's ability to coordinate many different brain systems, a connectivity that corresponds to middle frontal gyrus' role in fluid intelligence (Cole et al., 2015, 2012).

Building on the dual regression analysis of spatial maps, and, in particular, an inherent interest in how parietal lobe functions contribute to individual differences in shifting-specific EF, we investigated how network-to-network time course correlations were related to individual differences in shifting-specific EF in the LTS sample. Our earlier analyses of common EF in which we controlled for shifting-specific and updating-specific EFs demonstrated a lack of relationship between shifting-specific EF and a number of frontoparietal and default network relationships. One novel analysis performed for shifting-specific EF was to investigated effects of the connectivity of dorsal attention network to ventral attention network. There was a relationship such that the individuals higher in shifting-specific EF had increased connectivity between those networks. Both dorsal and ventral attention networks have a strong parietal presence. The ventral attention network (in which the temporal-parietal junction is a key region) is implicated in bottom up attentional processes such as reorienting or filtering for infrequent stimuli (Vossel et al., 2014). The dorsal attention network's functions are complementary and are involved in top down biasing and interfacing with higher-level, frontal cognitive systems (*ibid.*). Keeping in line with other interpretations, this could indicate individuals with a history of coupling between these two systems are more suited for tasks that involve both top-down biasing and bottom up processes.

2.7.3 Updating-specific

One unexpected aspect of our findings was a lack of a relationship between individual differences in updating-specific ability and any RSN expansion or time course relationship in either the CS or LTS samples. On the basis of both theoretical and empirical findings regarding the neural substrates of updating (Frank et al., 2001), one might have predicted a priori that connectivity between the DLPFC and basal ganglia might influence individual differences in updating ability. However, we did not find such an effect. Our null results may arise because of the qualitative differences between processes supporting updating-specific EF as compared to common EF and shifting-specific EF. Updating requires the contents of working memory to be manipulated, and as such may rely more on a more circumscribed brain region, notably DLPFC, without connectivity to other regions playing as much of a role. In contrast, when switching between tasks, new task sets and stimulus-response mappings need to be loaded to perform the task, and hence switching may rely on a more distributed network (e.g., frontopolar regions for selecting the task set, parietal regions for stimulus-response mappings, etc.). Of course one must be circumspect when discussing potential reasons for a null result.

2.7.4 General Discussion

One notable aspect of our results is that the different EF constructs were supported by distinct sets of resting-state features. Only one aspect of the results was common to multiple EFs - the presence of middle frontal gyrus in both common EF and shifting-specific results in the whole brain analyses of the CS-derived ICA components in LTS sample. But the vast majority of our findings were unique to a particular EF construct. As such, our findings support the idea that EF represents a family of abilities. More importantly, however, it suggests that these different abilities may preferentially recruit distinct neural substrates, at least with respect to individual differences in EF.

The study, and in particular, the analysis of the LTS data, is not without limitations. First, we experienced a technical limitation of not being able to utilize the same ICA algorithm used on the CS sample due to high RAM requirements with a data set as large as the LTS sample. The implementation of the MIGP workaround for RAM requirements, at the current time, is not as fully featured as vanilla Melodic. The main issue caused by the current MIGP implementation is inability to perform automatic dimensionality estimation. Without a means to automatically estimate the number of ICA components that best fits the LTS data, the parallel analysis should be viewed in a somewhat circumspect manner. Although dual regression analysis using the CS sample group ICA as a seed is a valid solution, future work must investigate how variation in a network solution native to the LTS sample is associated with individual differences in EF.

These technical limitation could have contributed to the minimal consistency between the parallel ICA and dual regression (spatial maps analysis) analyses in the CS and LTS samples. Differences in the samples is another likely contributor to our inability to replicate the network expansion findings from the CS study. For example there could be substantial development between age 21 and 29 that contributed to a lack of brain/behavior relationships in the areas we focus on in Reineberg et al. (2015). Given the stability of the EF constructs over time (**Tables 2.1, 2.2, and 2.3**; also see Friedman et al. (2016)), the most likely developmental effects are in the brain. Age-related changes have been documented in a wide array of age ranges and in both anatomical and functional neuroimaging measures including cortical volume (Walhovd et al., 2005; Allen et al., 2005; Jernigan et al., 2001; Walhovd et al., 2011), cortical thickness (Salat et al., 2004; Sowell, 2004; Shaw et al., 2008; Lemaitre et al., 2012), white matter tracts (Asato et al., 2010), functional brain networks (Meunier et al., 2009), and resting-state functional connectivity more generally (Bernard et al., 2013; Hampson et al., 2012; Mowinckel et al., 2012; Yang et al., 2013). Some preliminary work suggests neuroanatomical differences in older age contribute to increased cognitive control abilities. For example, Liston et al. (2006) found decreased radial diffusivity (a measure often associated with demyelination or poor white matter integrity) within a white matter tract connecting frontal lobe to subcortical areas was associated with better performance (decreased reaction times) on a motoric response inhibition task (go/no-go). Taking into account the possibility that age-related differences in our samples contributed to inconsistencies in the parallel analyses, future work might consider collecting a sample with a wider age range than each individual study highlighted in this chapter. Such a study could reveal how age interacts with the relevance of different rs-fMRI features to behavior at different points in developmental trajectories.

2.7.5 Conclusion

In a large group of individuals, we demonstrate that the resting state architecture of the brain is associated with individual differences in different aspects of a theoretically motivated framework of EF the unity and diversity model. The results are notable for providing a fine-grained picture of the relationships with specific regions within and outside of well-known RSNs. In the case of common EF, individuals higher in EF had greater recruitment of cerebellar regions within a group-identified frontoparietal RSN, increased coupling of a frontopolar region to an attention RSN, and increased connectivity among task positive network and between frontoparietal and default networks. Those individuals higher in shifting-specific EF had increased coupling of angular gyrus and a somatomotor/attention RSN as well as increased connectivity between attention RSNs. The current study significantly expands our knowledge of neural influences on EF, showing that variability in EF across individuals man be sculpted by patterns of resting-state functional connectivity within and between large-scale cognitive brain networks. In the next chapter, we will explore how the connectivity of specific regions, rather than that of large scale networks, is also associated with individual differences in EF.

Chapter 3

Associations Between Individual Differences in Executive Function and Connectivity Profiles of Individual Brain Regions: Graph Theoretic Analyses

Summary

To complement the previous chapter, we also investigate how the connectivity profile of individual regions might be related to individual differences in executive function. Based on years of task-based neuroimaging of executive function tasks, a number of brain regions stand out as particularly important. Graph theory offers a way of characterizing the importance of individual regions based on the role that region assumes within the context of a mathematical graph. In this chapter, we discuss how to digest and simplify the functional connectivity of each individuals' brains using several graph theoretical measures. We found a complex pattern of brain connectivity measures was associated with individual differences in each of the three EF measures of interest (as reported in Reineberg and Banich (2016)). We found that one of these measures of connectivity - how diverse the connections of dorsolateral prefrontal cortex are - was also associated with individual differences in EF (updating-specific EF) in a separate sample. A variety of other features did not replicate in our second sample indicating some context or sample specificity of the observed results.

3.1 Introductions

The goal of the present study is to examine whether differences in the connectivity profiles of brain regions at rest are associated with differences among individuals in their level of executive functions (EF). Executive functions (EF) are a set of abilities that allow for the directed pursuit, maintenance, and modification of goals (Banich, 2009), and they are altered in a large number of psychiatric and neurological disorders (e.g., Barkley (1997); Nieuwenstein et al. (2001). It is generally agreed that such abilities rely preferentially on frontal cortex, based on both the results of individuals whose EF functions are compromised as a result of localized brain damage (Alvarez and Emory, 2006; Stuss and Alexander, 2000) and on neuroimaging studies that use univariate approaches to identify those brain regions whose activation increases when EF demands are increased (e.g., Banich et al. (2000a)). One of the more prominent theories regarding the neural bases of EF suggests that frontal regions work to modulate the processing in remote target brain regions so as to enable task goals (Miller and Cohen, 2001). Implicit in this theory is the notion that the successful application of executive control requires interaction between brain regions. Empirical evidence supports such an idea as meta-analyses indicate that EF tasks not only activate frontal regions, but a network of brain regions extending to parietal regions and beyond (Jurado and Rosselli, 2007; Wager et al., 2004). Finally, computational models that can successfully mimic performance on EF tasks indicate that network dynamics are critical for such executive control (e.g., Chatham et al. (2011); Herd et al. (2006, 2014)). Given the strong evidence that EF is supported by an interaction between disparate brain networks, it is somewhat surprising that neuroimaging studies have, for the most part, not focused on network properties to better understand individual variation in EF, an issue we address in the current study.

One notable aspect of EF is that it is known to vary substantially across individuals (Miyake and Friedman, 2012). Research on individual differences, including studies utilizing behavioral genetics techniques, has provided a theoretical framework from which to consider how individuals differ in their EF abilities. One prominent theory, the unity and diversity model, derived from intercorrelated patterns of performance across individuals on multiple measures of EF, posits that EF can be well characterized as consisting of at least three latent factors (Miyake and Friedman, 2012) - common EF, shifting-specific EF (shifting), and updating-specific EF (updating) - as described in more detail in the previous chapters. Neuroimaging studies examining brain activation while performing a variety of EF tasks (as reviewed in the Introductions of Chapter 1) provide information on the brain regions that are likely to act as key nodes in brain for each of these distinct EF factors, and across them more generally. Nonetheless, as these studies focus on the average pattern of activation across groups of individuals, they provide no information on how connectivity of such regions might be related to individual differences in EF, an issue we address in the current study.

To examine this issue, we investigate connectivity profiles of specific brain regions during resting-state fMRI (rs-fMRI) because rs-fMRI is purported to reflect stable aspects of brain function for a given individual. More specifically, rs-fMRI has been used to characterize and quantify low frequency fluctuations in the BOLD signal while individuals are not engaged in an experimentally-directed task (hence the name resting state: Fox & Raichle, 2007). A growing number of studies have shown the pattern of this intrinsic oscillatory behavior between regions mimics patterns of co-activation during task-based fMRI studies. Specifically, regions that work in concert during the performance of tasks seem to fluctuate together during resting-state scans (Cole et al., 2014; Smith et al., 2009). Importantly for the purposes of the present study, these patterns of co-activation across regions are consistent within an individual across multiple time points that span months to years (Choe et al., 2015; Shehzad et al., 2009), suggesting that they can serve as a sensitive measure of individual differences. Hence, the present study examines whether graph theoretic measures of such static connectivity patterns, which are intrinsic to an individual, are associated with individual differences in EF. If so, it would suggest that subtle but important individual differences in the organization of brain networks are associated with the ability to exert executive control.

In the current paper we focus on analyzing such rs-fMRI data using graph theoretic measures. Graph theory is used to mathematically characterize the functional architecture of the brain as a set of interconnected nodes (Sporns et al., 2004). Typically in a graph theoretic approach, the connections (edges) between regions (nodes) are Pearson's r-values for each possible pairwise relationship. Summarizing a single node's pattern of edges to the rest of the brain (or to the subset of regions to which it is most highly connected) can provide an abundance of information about the propagation of information through a complex system like the brain, and specifically, what a given region's role might be in the context of a larger system. Local graph theoretic measures can be broadly classified into several groups: measures of integration (including some measures of centrality), segregation, or other measures of centrality that do not necessarily fall into either of the previous categories (Rubinov and Sporns, 2010). Measures of integration, such as betweenness centrality and participation coefficient, assess a region's ability to link disparate parts of the brain (i.e., act as a hub). Measures of segregation, such as clustering coefficient, assess the involvement of a particular region in specialized local processing. Other measures, such as degree centrality and eigenvector centrality, are useful for characterizing the general importance of a given region based on the number of connections to other regions or the number of connections of other important regions, respectively. In Methods we discuss all graph theoretic measures used in the current study in more detail.

Our impetus for examining the relationship between graph theoretic measures of resting-state activation and individual differences in these EF dimensions is motivated by a variety of considerations. First, at least one prior study by Cole et al. (2012) has found that increased global connectivity of a left lateral prefrontal cortex region implicated in cognitive control is associated with an individual-difference measure, fluid intelligence. Those researchers speculated that global connectivity of lateral prefrontal cortex might support the ability of this region to regulate processing in many distinct and disparate brain regions, similar to the role that this region is thought to play in EF. Second, computational modeling of individual differences in EF suggest that connectivity of lateral prefrontal regions may influence both common EF and switching-specific abilities (Herd et al., 2014). Third, at least some aspects of cognitive control may benefit from segregation rather than integration of information. For example, the basal ganglia has been suggested to play a prominent role in working memory updating (Frank, Loughry, & O'Reilly, 2001), and segregation of Go vs. No-Go circuits may support such a role (Hazy et al., 2007). Likewise, during task switching, keeping information about specific stimulus-response mappings for each task separate might be aided by having relevant regions highly connected and irrelevant regions less connected.

In summary, the current study examines whether individual differences in dimensions of EF are related to individual differences in graph theoretic measures of brain organization as derived from resting-state data, which is known to be stable within an individual. The graph theoretic approach taken in the current study is notable for a variety of reasons. First, unlike prior studies that have examined just a single measure of EF (e.g., performance on an N-back working memory task), the current study looks at 3 well-validated dimensions underlying individual differences in EF. Second, the current study uses larger-sized samples than prior studies, carefully examining individual differences in one sample close to 100 individuals and another much larger sample of 251 individuals. Third, brain-EF relationships are examined in an a priori manner and in an unbiased manner. Prior work by our group and others provided a number of a priori regions of interest. For example, an earlier study from our group suggested that individual variation in brain structure including grey matter volume, cortical thickness and cortical folding is related to individual differences in the three EF dimensions we examine here (Smolker et al., 2014). Moreover, in another study we observed that individual differences in brain regions contributing to or composing specific resting-state brain networks as determined by ICA (e.g. frontoparietal network, dorsal attention network) are also related to individual differences in two of these three EF dimensions (Reineberg et al., 2015). While this prior study (Reineberg et al., 2015) examined the strength and composition of more large-scale resting-state networks as a function of EF dimensions in the same group of participants as the present study, the focus here is on connectivity profile of specific nodes (i.e., smaller brain regions). The current study complements these prior anatomical and network-based investigations by asking whether or not regions-of-interest in the frontoparietal network have different graph theoretic properties depending on an individual's level of function for each of these three dimensions of EF. Interestingly, our prior work also revealed that regions outside the classic network of regions commonly implicated in cognitive control, such as ventromedial prefrontal cortex, as associated with dimensions of EF. Taking into account these findings, we also performed an unbiased analysis searching across the whole brain for regions whose connectivity is related to individual differences in each of the three dimensions of EF. By taking such a broad perspective, the current study provides important insights into how individual differences in brain connectivity may be related to individual differences in a notable aspect of cognitive function, namely EF.

3.2 Methods

3.2.1 Information About Two Sample Design

This analysis utilized the same behavioral and brain data as described in **Chapter 2**. Due to the desire to quantify the graph theoretic properties of individual brain areas (as opposed to networks), we utilized a neuroimaging processing pipeline unique to this chapter. The analysis of the CS sample was presented in Reineberg and Banich (2016). Novel to this chapter is a parallel analysis in the LTS sample.

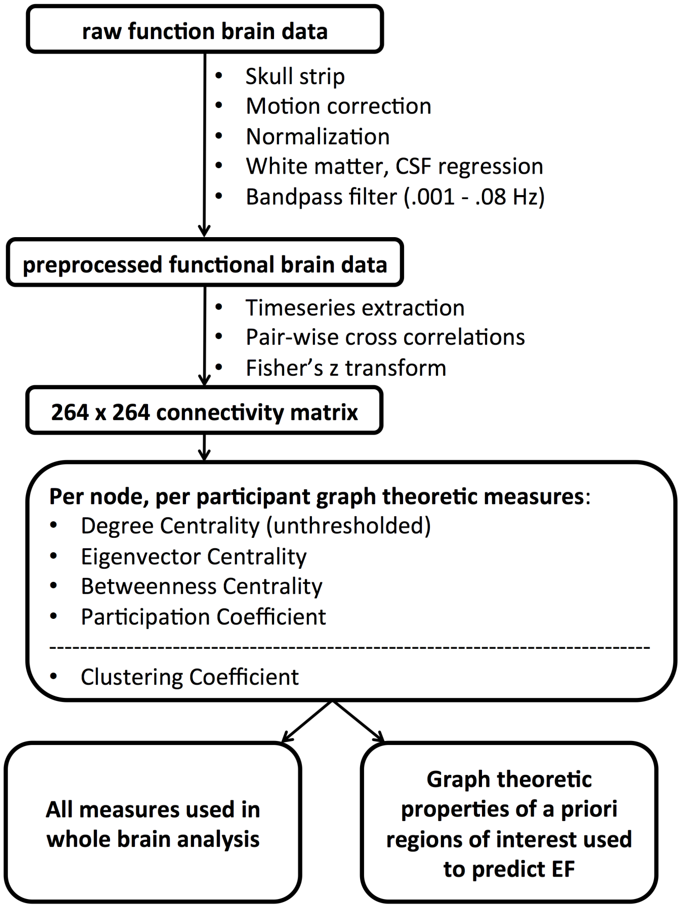
3.2.2 Brain Data

Neuroanatomical and functional brain data acquisition parameters for the CS and LTS samples is described in **Chapter 2, Methods**. Analysis of functional brain data was performed via a multi-step process documented in **Figure 3.1** and in detail below. This pipeline was identical for functional data from each sample.

3.2.3 Preprocessing

Preprocessing of brain data was performed in FSL (build 506; Jenkinsonet al., 2012) and Python. To allow for signal stabilization, the first four or ten volumes of each individual functional scan (for CS sample and LTS sample, respectively) were removed, yielding 161 or 806 volumes per subject for additional analysis (again, for CS sample and LTS sample, respectively). The functional scans were corrected for head motion using MCFLIRT, FSL's motion correction tool. Brain extraction (BET) was used to remove signal associated with non-brain material (e.g., skull, sinuses, etc.). Signal was extracted from masks of the lateral ventricles and white matter and regressed. FSL's FLIRT utility was used to perform a 6 degrees-of-freedom affine registration of each participant's functional scan to their anatomical volume and a 12 degrees-of-freedom affine registration of each participant's anatomical scan to MNI152 standard space. The transformation matrix from the latter registration was applied to each participant's functional scan. Finally, the

Figure 3.1: **Data Processing Pipeline**. An overview of methods for the graph theory analysis.



scans were band-pass filtered (.001 - .08 Hz band).

3.2.4 Network Analyses

For each participant, we extracted the BOLD time series from each of 264, 1cm spherical ROIs, drawn from Power et al. (2011), which serve as the nodes for the present analysis. We used these nodes as they are drawn from a meta-analysis of functional activations and have a community structure that agrees with task-based functional networks (i.e., are organized into networks such as default mode network and frontoparietal task control network). The functional networks in this parcellation structure are very similar to the network discussed in **Chapter 2** with the addition of explicitly labeling a cingulo-opercular network. One centimeter spherical ROIs were chosen as they provide the largest possible size for a given ROI but preclude overlap with neighboring ROIs. Within each participant, all pairwise Pearson's r correlations were calculated, yielding a 264 x 264 correlation matrix. All Pearson's r-values were subjected to the Fisher's z transformation to normalize the variance in correlation values. For each node of each connectivity matrix, four graph theoretic metrics were calculated after a proportional threshold of 0.15 was applied (i.e., only the strongest 15% of positive correlations were maintained): eigenvector centrality, participation coefficient, betweenness centrality, and clustering coefficient. As there is no consensus or strong precedent on which specific sparcity threshold is best, we chose a value in the middle of a range of values commonly used in related work. We feel the selection of this value balances using very sparse graphs (e.g., $<$ 10% sparcity threshold, which has been linked to high test-retest reliability of global graph theory measures (Wang et al., 2011a)) and denser graphs (e.g., $>$ 20% sparcity threshold, which could potentially investigate the cognitive-relevance of weak connections as in Santarnecchi et al. (2014)). Additionally, global connectivity was calculated in an unthresholded manner on positive edge weights within each connectivity matrix. This analysis process yielded 1320 (264 regions x 5 graph theoretic measures) features per participant for use in further analyses. All measures were calculated using NetworkX package for Python (Hagberg et al., 2008).

Our selection of graph theoretic measures was based on the desire to sample a variety of connectivity characteristics while also reducing redundancy between measures (e.g., clustering coefficient and transitivity are both measures of segregation). First, we chose a basic quantification of the connectedness of a region, global connectivity. Global connectivity is the unthresholded, weighted degree centrality, or the average of each row/column of each participant's positive connectivity matrix. Global connectivity has previously been linked to individual differences in intelligence and cognitive control (Cole et al., 2012). Second, we chose a measure that weighs a given region's important connections more heavily than connections to less important regions, eigenvector centrality. Eigenvector centrality is obtained for each participant by calculating an eigenvector for that participant's connectivity matrix such that each component is greater than zero (Newman, 2010). Third, we chose a measure that reflects how important a region is for connecting disparate parts of the brain, betweenness centrality (betweenness). This measure provides an index of how frequently a given region is part of the shortest path between all other pairs of regions in the brain and is one way of measuring the degree to which a region can be considered a connector hub (van den Heuvel and Sporns, 2013). Mathematically, betweenness is the sum of the fraction of all other node pair's shortest paths that pass through the node of interest (Brandes, 2008; as implemented in NetworkX in the current study, the resulting value is scaled by the number of other node pairs in the graph). Fourth, we chose a measure that reflects how diverse a given region's connections are, participation coefficient. For example, one region may have a pattern of connectivity such that it is connected to regions of similar function (i.e., only members of its own community, such as regions within the visual network), while another region may have significant connections to a diverse set of functional communities (e.g., frontoparietal network, dorsal attention network, cingulo-opercular network). Mathematically, participation coefficient measures the diversity of a region's connections to a set of *a priori* defined functional communities such as the visual and frontoparietal resting-state networks (Guimerà and Amaral, 2005). Lesions to regions with a high participation coefficient produce more severe and broad cognitive deficits than lesions to areas with a lower participation coefficient (Warren et al., 2014), suggesting that such regions play a more central role across a variety of processes. Participation coefficient is also of interest to the current study as we have recently found that the dorsal and ventral attention networks of individuals with high EF are expanded to include regions not observed in the networks of individuals with lower EF such as the frontal pole and angular gyrus (Reineberg et al., 2015). In the current study, we measure participation coefficient using the 14 a priori defined functional communities provided by the authors of the reference atlas from which the nodes were obtained (Power et al., 2011). Finally, we chose a measure thought to reflect the degree to which a given region is involved in specialized processing, clustering coefficient. Clustering coefficient is a measure of segregation that could reflect whether or not an area is suitably isolated from the influence of other functional communities. Mathematically, clustering coefficient quantifies the percentage of a region's neighbors that are neighbors of each other (Onnela et al., 2005). We did not calculate any other graph theoretic measures.

Our a priori analyses only involved a select set of nodes located in close proximity to statistical clusters from our prior functional and anatomical studies of individual differences in EF (Reineberg et al., 2015; Smolker et al., 2014) as well as a set of nodes in close proximity to a lateral prefrontal cortex region described in Cole et al. (2012). In all cases, the 1cm spherical nodes that were selected from the reference atlas were either directly overlapping a cluster from prior research or within 1cm of a cluster. All 18 a priori nodes are presented in **Table 3.1**. First, we identified one node that corresponded to frontal polar cortex, two nodes that corresponded to lateral occipital cortex and precuneus, and three nodes that corresponded to cerebellum. These six nodes overlap with brain regions that previously showed a relationship between one of the three EF dimensions and functional connectivity via a complementary network analysis (Reineberg et al., 2015). Specifically, resting state networks such as frontoparietal network were expanded to these areas (to cerebellum, for example) in individuals who showed higher functioning on a given dimension of EF (see **Figure 2.10**). Second, we identified nine anatomically separable regions within the frontal lobe - ventromedial (n = 2), paracingulate (n = 1), orbitofrontal (n = 3), ventrolateral (n = 1), and dorsolateral prefrontal cortex (n = 2) - that were shown to vary (i.e., cortical thickness and local gyrification) with the level of performance on a given dimension of EF (i.e., regions presented in Figures 1, 2, and 3 of Smolker et al. (2014)). Finally, we identified 3 left lateral prefrontal regions in close proximity (< 10mm, average distance = 7mm) to an area that Cole et al. (2012) showed has increased global connectivity in individuals with high fluid intelligence. One of these regions fell within middle frontal gyrus (MFG) and two fell near inferior frontal junction (see Table 1 of Cole et al. (2012)). Throughout the rest of this manuscript, the *a priori* regions will be referred to as "*a priori* Region X". These *a priori* regions should not be confused with our attempts to investigate consistency between the two samples as one could confuse the probing of results from the CS sample in the LTS data as investigating an *a priori* relationship of interest as well.

For each of these 18 a priori regions we calculated each of the 5 graph theoretic measures described above for a total of 90 features. In contrast, the exploratory analysis utilized all 1320 features (264 nodes by 5 measures) to determine which graph theoretic properties of the resting brain were most strongly related to individual differences in each of the three EF dimensions.
Statistics

A priori analysis: For the analysis of a priori regions of interest, we calculated the statistical relationship between each of 18 regions of interest and each other three dimensions of EF - common EF, shifting-specific EF, and updating-specific EF. To do so, we ran linear models regressing each dimension of EF on each graph theoretic feature from the regions of interest (one model per feature) while controlling for age and possible motion-related confounds mean translation (average motion in the x, y, and z plane during the resting-state scan) and mean rotation (average roll, pitch, and yaw movement during the resting-state scan). To account for sampling error, we performed 1000 permutations of each regression model sampling from the 91 participants with replacement. To determine which graph theoretic features had significant linear relationships with each dimension of EF, we calculated a p-value associated with the mean of each feature's bootstrapped t-statistics. We report graph theoretic features with bootstrap p-value < 0.05. Results of these multiple regression models are reported in Results a priori analysis and **Table 3.2**.

Exploratory Analysis. For the exploratory analysis, we calculated the statistical relationship between each graph theoretic feature and each of the three EF dimensions of interest. To do so, we ran linear models regressing each EF dimension on each graph theoretic feature while controlling

Table 3.1: ***a priori* Regions of Interest**. Table lists all *a priori* regions of interest, index number from the current study, index number from the 264 node reference atlas (Power et al. 2011), anatomical label, and MNI coordinates. Regions 1-3 were on interest due to proximity to regions taken from Reineberg et al. (2015). Regions 4-15 were of interest due to proximity to regions from Smolker et al. (2014). Regions 16-18 were of interest due to proximity to regions from Cole et al. (2012). VMPFC = ventromedial prefrontal cortex, VLPFC = ventrolateral prefrontal cortex, DLPFC = dorsolateral prefrontal cortex.

Index	Reference Atlas Index	Label	X	Y	Z
1	197	Frontal Pole	-34	55	4
2	74	Lateral Occipital Cortex	-41	-75	26
3	87	Precuneus	-39	-75	44
4	243	Cerebellum - Lobule VI	-16	-65	-20
5	183	Cerebellum - Crus I/Lobule VI	-18	-76	-24
6	244	Cerebellum - Lobule VI	-32	-55	-25
7	5	VMPFC	8	41	-24
8	76	VMPFC	8	48	-15
9	109	Paracingulate Gyrus	-3	44	-9
10	3	Orbitofrontal Cortex	24	32	-18
11	180	Orbitofrontal Cortex	24	45	-15
12	181	Orbitofrontal Cortex	34	54	-13
13	200	VLPFC	43	49	-2
14	188	DLPFC	-42	38	21
15	220	Frontal Pole	-39	51	17
16	187	Inferior Frontal Junction	-41	6	33
17	201	DLPFC	-42	25	30
18	176	Inferior Frontal Junction	-47	11	23

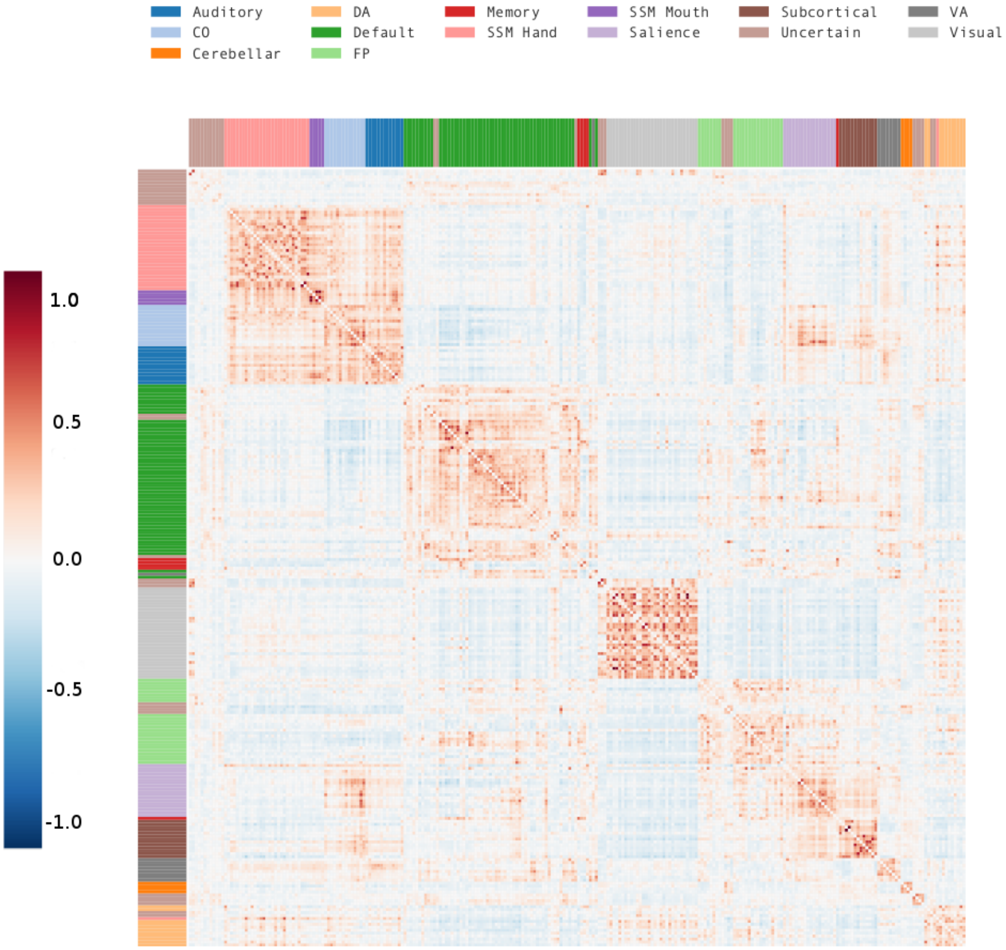
for age and possible motion-related confounds mean translation and mean rotation. To account for sampling error, we performed the same bootstrapping procedure described above. We report graph theoretic features with bootstrap p-value < 0.005 ($p < 0.015/3$, or p corrected for performing three sets of analyses, one for each dependent variable of interest). Results are presented in Results whole brain analysis and **Table 3.3**.

Finally, as an exploration of the amount of variance that might be potentially explained by the full set of features ($N = 1320$) identified in the exploratory analysis, we included all measures for a given EF dimension ($n = 9$ for common EF, $n = 11$ for shifting, $n = 7$ for updating) in a multiple regression model (i.e., one model for each EF dimension). Although these models run the risk of over-fitting the data, they provide a benchmark for comparison in future studies. We compared the percentage of variance explained by the combined set of appropriate features for a given EF measure to a set of graph theoretic features of the same size drawn randomly from all features. We discuss the overall amount of variance explained in each EF measure in Results whole brain results. All statistics were calculated using Scikit-learn (Pedregosa and Varoquaux, 2011) and statsmodels modules for the Python programming language.

3.3 Results - CS Sample

We first performed analyses to ensure that our sample was representative relative to prior studies. As reported previously (Reineberg et al., 2015), behavioral performance for this group of participants on the EF tasks and pairwise correlations between the three EF tasks was in line with previous studies examining individual differences in EF using similar behavioral tasks. We then examined whether the connectivity pattern for the resting-state fMRI data between areas for these 91 participants is in line with prior reports (e.g., Power et al. (2011)). **Figure 3.2** shows the community structure of the group average connectivity matrix across all 91 participants. The modules, positioned along the diagonal of the matrix are qualitatively similar to those found in group connectivity matrices from prior research using the same reference atlas (e.g., when compared to the connectivity matrix provided in Figure 3 of Cole et al. (2014)).

Figure 3.2: **Group Average Connectivity Matrix and Modules in CS Sample**. Group connectivity matrix calculated from the average of 91 participants' individual connectivity matrices. Red indicates positive Pearson's r-values and blue indicates negative Pearson's r-values. CO = cingulo-opercular, DA = dorsal attention, FP = frontoparietal, SSM = sensory/somatomotor, VA = ventral attention.



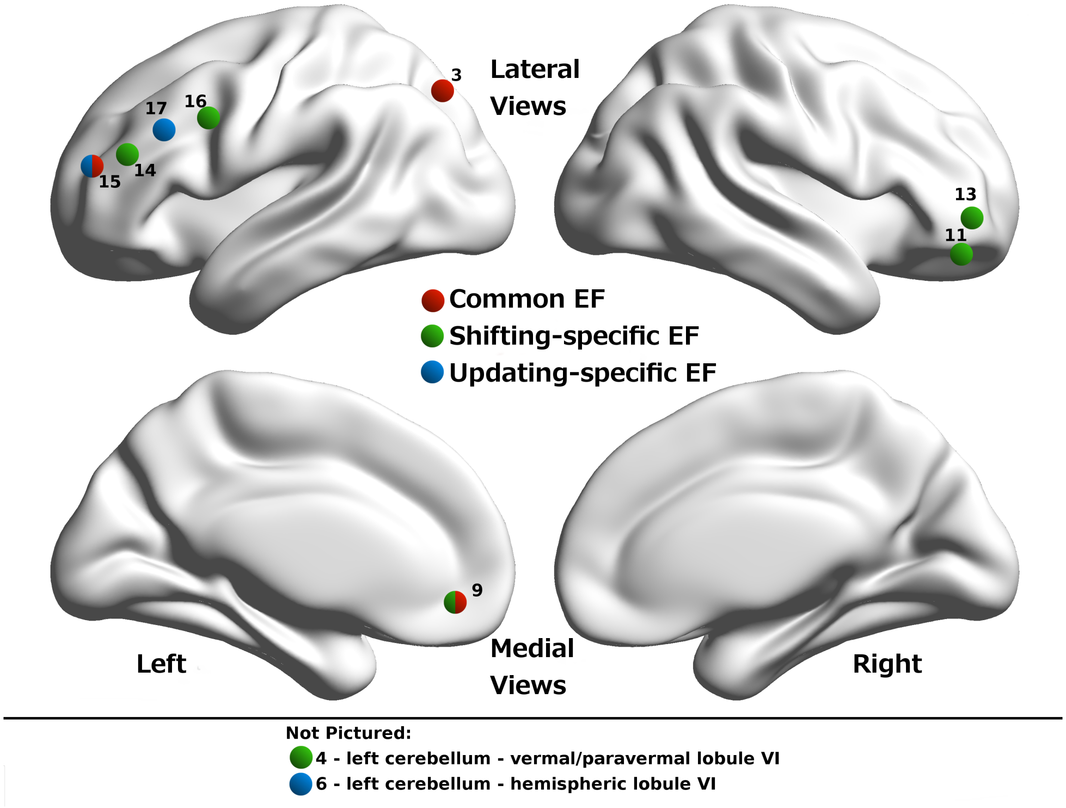
3.3.1 *a priori* ROI Analysis in CS Sample

Individual differences in the three EF dimensions were associated with differences in the graph theoretic properties of 10 of 18 a priori regions-of-interest (See **Figure 3.3** for location of all regions). For relationships between EF dimension and graph theoretic measures, all t-statistics are presented in **Table 3.2** and are the mean t-statistic from 1000 permuted multiple regression models controlling for age and movement during the resting-state scan.

a. Higher common EF was associated with decreased eigenvector centrality and decreased clustering coefficient of a portion of the precuneus (*a priori* Region 3), decreased global connectivity and decreased eigenvector centrality of a pregenual region of the paracingulate gyrus region (*a priori* Region 9), and decreased betweenness centrality of a dorsolateral frontal pole region (*a priori* Region 15). In sum, higher common EF is associated with less hublike and less central regions involved in cognitive control (precuneus, dorsolateral frontal polar regions), and emotion-related prefrontal areas (pregenual cortex).

b. Higher shifting was associated with decreased global connectivity of a region of Lobule VI of the cerebellum (*a priori* Region 4), decreased clustering coefficient of a pregenual region of the paracingulate gyrus region (*a priori* Region 9), decreased global connectivity and decreased eigenvector centrality of an orbitofrontal region of the frontal pole (BA 10/47) (*a priori* Region 11), decreased clustering coefficient of a ventrolateral (i.e. inferior frontal gyrus) frontal pole region (*a priori* Region 13), increased clustering coefficient and decreased participation coefficient of a middorsolateral region (i.e., middle frontal gyrus, MFG; *a priori* Region 14), and increased global connectivity of a posterior MFG region near the inferior frontal junction (*a priori* Region 16). In sum, higher shifting EF is associated with less locally focused connectivity (as represented by a decreased clustering coefficient) in pregenual and ventrolateral region, but increased locally focused connectivity in in midlateral frontal polar regions. It is also associated with less central attributes of orbitofrontal regions, decreased global connectivity of the cerebellum and orbitofrontal regions, and increased global connectivity of the inferior frontal junction.

Figure 3.3: **Results from Analysis of *a priori* Regions of Interest in CS Sample**. Colored spheres indicate the location of a priori regions of interest with significant relationships to one of three EF measures. Red = common EF, green = shifting-specific EF, blue = updating-specific EF, multiple colors = combination of EF measures.



🟥 Common EF
🟩 Shifting-specific EF
🟦 Updating-specific EF

Not Pictured:
🟩 4 - left cerebellum - vermal/paravermal lobule VI
🟦 6 - left cerebellum - hemispheric lobule VI

c. Higher updating was associated with decreased global connectivity of a region of Lobule VI of the cerebellum (*a priori* Region 6), decreased betweenness centrality of dorsolateral frontal pole region (*a priori* Region 15), and decreased participation coefficient of a dorsolateral (MFG) region of prefrontal cortex (*a priori* Region 17). In summary, higher updating is associated with less hublike frontopolar and dorsolateral prefrontal regions, and less global connectivity of the cerebellum.

No relationships were found for *a priori* nodes 1, 2, 5, 7, 8, 10, 12, and 18.

3.3.2 Whole Brain Analysis in CS Sample

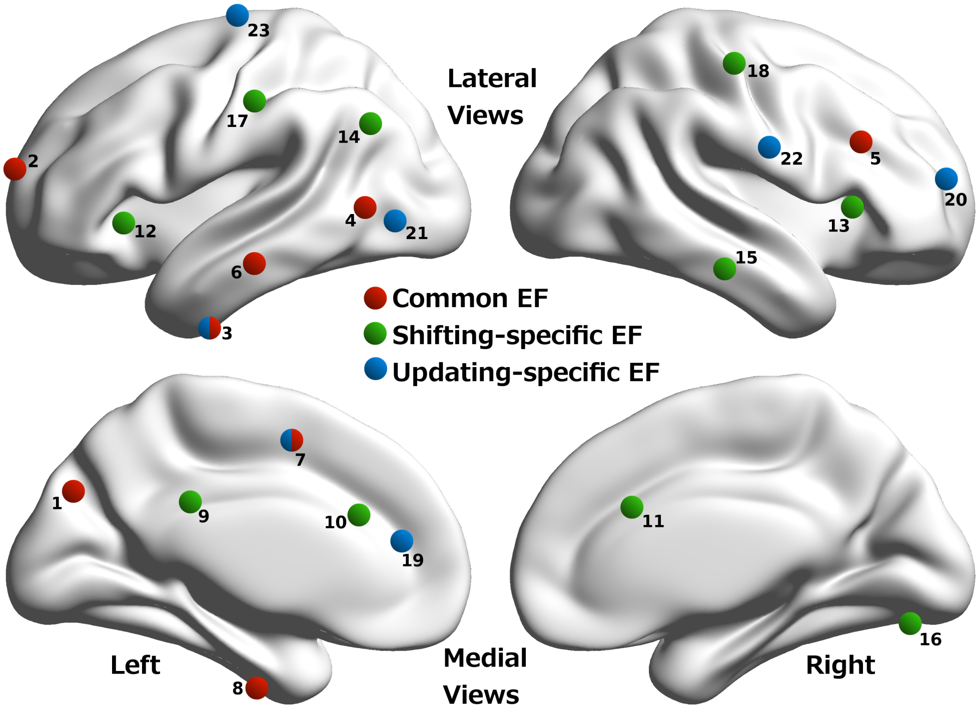
All statistics are presented in **Table 3.3** and are the mean t-statistic from 1000 permuted multiple regression models controlling for age and movement during the resting-state scan. See **Figure 3.4** for location of all regions.

a. The regions associated with higher common EF generally fell into two broad categories: frontoparietal regions, and regions of the left temporal lobe. With regards to the frontoparietal network, results revealed that higher EF was associated with decreased clustering coefficient of a dorsal frontal pole region (Region 2), decreased global connectivity and decreased eigenvector centrality of a dorsolateral prefrontal cortex region (i.e., MFG; Region 5) and increased betweenness centrality of a region of the supplementary motor area (BA 6) (Region 7). In sum, higher common EF was associated with decreased centrality of lateral prefrontal regions and more hublike medial aspects of the frontoparietal network and cuneus. With regards to temporal regions, higher EF was associated with decreased clustering coefficient of a lateral (Region 3) and decreased global connectivity of a medial (Region 8) portion of the anterior inferior temporal gyrus, decreased global connectivity of a middle temporal gyrus region (Region 6), and increased eigenvector centrality of the posterior temporal cortex at its junction with lateral occipital cortex (Region 4). In sum, higher EF is associated with less globally connected left anterior temporal regions and a more hublike left posterior temporal cortex. Additionally, higher common EF was associated with increased betweenness centrality of a portion of the cuneus (Region 1).

Table 3.2: **Results from Analysis of *a priori* Regions of Interest**. VLPFC = ventrolateral prefrontal cortex, DLPFC = dorsolateral prefrontal cortex.

Index	EF	Measure	t-value	p-value	X	Y	Z	Label
3	Common EF	eigenvector centrality	-2.3256	0.0223	-39	-75	44	Precuneus
3	Common EF	clustering coefficient	-2.5386	0.0128	-39	-75	44	Precuneus
9	Common EF	global connectivity	-2.3074	0.0233	-3	44	-9	Paracingulate Gyrus
9	Common EF	eigenvector centrality	-2.1353	0.0355	-3	44	-9	Paracingulate Gyrus
15	Common EF	betweenness centrality	-2.0344	0.0449	-39	51	17	Frontal Pole
4	Shifting	global connectivity	-2.6478	0.0096	-16	-65	-20	Cerebellum - Lobule VI
9	Shifting	clustering coefficient	-2.5633	0.012	-3	44	-9	Paracingulate Gyrus
11	Shifting	global connectivity	-2.3837	0.0192	24	45	-15	Orbitofrontal Cortex
11	Shifting	eigenvector centrality	-2.715	0.0079	24	45	-15	Orbitofrontal Cortex
13	Shifting	clustering coefficient	-2.062	0.0421	43	49	-2	VLPFC
14	Shifting	clustering coefficient	2.2049	0.03	-42	38	21	DLPFC
14	Shifting	participation coefficient	-2.3971	0.0186	-42	38	21	DLPFC
16	Shifting	global connectivity	2.081	0.0403	-41	6	33	Inferior Frontal Junction
6	Updating	global connectivity	-2.0289	0.0454	-32	-55	-25	Cerebellum - Lobule VI
15	Updating	betweenness centrality	-2.0176	0.0466	-39	51	17	Frontal Pole
17	Updating	participation coefficient	-2.5777	0.0116	-42	25	30	DLPFC

Figure 3.4: **Exploratory Results in CS Sample**. Regions from the exploratory Analysis with connectivity profiles related to EF. Colored spheres indicate the location of regions with most significant relationships to each of three EF measures. Red = common EF, green = shifting-specific EF, blue = updating-specific EF, multiple colors = combination of EF measures.



b. Higher shifting specific EF was associated with the connectivity characteristics of sets of bilateral nodes within the cingulo-opercular network as well as some somato-motor areas. In particular, higher shifting specific EF was associated with increased betweenness centrality of cingulo-opercular cortex in the left hemisphere (Region 12), and decreased betweenness centrality of an analogous region in the right hemisphere (Region 13); decreased betweenness centrality of a rostral anterior cingulate gyrus region both in the left hemisphere (Region 10), and the right (Region 11); and an increased participation coefficient in both the left postcentral gyrus region (Region 17) and the right postcentral gyrus region (Region 18). In sum, higher shifting-specific EF was associated with differential hubness of right and left fronto-opercular-insular regions, less hublike rostral anterior cingulate cortex and more hublike postcentral gyrus. In addition, higher shifting specific EF was associated with greater participation coefficient and decreased clustering coefficient of a posterior cingulate gyrus region (Region 9), increased betweenness centrality of a lateral occipital cortex region (Region 14), decreased global connectivity of a middle temporal gyrus region (Region 15), and decreased clustering coefficient of a region of the occipital fusiform gyrus (Region 16).

c. Higher updating was associated with graph theoretic properties of some frontal and parietal nodes, including decreased betweenness centrality of a frontal pole region (Region 20), decreased eigenvector centrality of a ventral postcentral gyrus region (Region 22), decreased betweenness centrality of a dorsal precentral gyrus region (Region 23), decreased clustering coefficient of a supplementary motor area region (Region 7), and decreased betweenness centrality of a supragenual region of the anterior cingulate gyrus (Region 19). In sum, higher updating specific EF was associated with less hublike lateral and medial prefrontal cortex as well as a precentral gyrus region. Higher shifting-specific EF was also associated with decreased clustering coefficient of a lateral occipital cortex region (Region 21) and an inferior temporal gyrus region (Region 3).

To explore the combined ability of each set of exploratory features to explain variance in each of the three EF dimensions, we conducted a multiple regression analysis regressing each of the three EF dimensions on the sets of regressors in the three paragraphs above. For common EF, the 9 exploratory features explained 42.9% of the variance in EF ability ($F_{(9,\ 81)} = 6.77$, $p < 0.001$). We permuted 1000 null models regressing common EF on randomly selected sets of 9 graph theoretic features. On average, these models explained 20.7% of variance in common EF. For shifting-specific EF, the 11 exploratory features explained 54.8% of the variance in EF ability ($F_{(11,\ 79)} = 8.72$, $p < 0.001$). We permuted 1000 null models regressing shifting-specific EF on randomly selected sets of 9 graph theoretic features. On average, these models explained 22.8% of variance in shifting-specific EF. For updating-specific EF, the 7 exploratory features explained 34.1% of the variance in EF ability ($F_{(7,\ 83)} = 6.14$, $p < 0.001$). We permuted 1000 null models regressing updating-specific EF on randomly selected sets of 7 graph theoretic features. On average, these models explained 14.4% of variance in updating-specific EF. Even considering the likely overfitting of these models, the graph theoretic measures of brain systems accounted for a non-trivial amount of variance related to individual differences in each of these aspects of EF.

3.4 Results - LTS Sample

We extracted all the features identified in the analysis of the CS sample and replicated regression models in the LTS sample. The results are largely null. However one feature identified in the exploratory analysis of the CS sample as associated with individual differences in shifting-specific EF was also associated with individual differences in shifting-specific EF in the LTS sample. The same was true for a single feature associated with individual differences in updating-specific EF.

3.4.1 Models Involving *a priori* Regions of Interest from the CS Sample

We tested the five features identified as significantly associated with common EF in the analysis of the CS sample. None of these five features were significantly associated with individual differences in Common EF. This was also true for the eight shifting-specific features. Of the three updating-specific features identified above in the CS sample, one feature exhibited the same relationship in the LTS sample. Higher updating-specific EF (age 29) was associated with decreased participation coefficient in DLPFC (*a priori* Region 17, $t = -2.614$, $p = 0.009$; **Figure 3.5**). This

Table 3.3: **Exploratory analysis results for the CS Sample**. Exploratory relationships between EF and graph metrics. Table lists regions with strongest relationships to each of three EF dimensions, index from current study, anatomical label from a query of the Harvard-Oxford atlas, index from reference atlas (Power et al., 2011), relationship with EF measures, and specific graph theoretic measure.

Index	Reference Index	EF	Measure	t-value	p-value	X	Y	Z	Label
1	166	Common EF	betweenness centrality	2.9155	0.0045	-16	-77	34	Cuneal Cortex
2	114	Common EF	clustering coefficient	-3.242	0.0017	-20	64	19	Frontal Pole
3	250	Common EF	clustering coefficient	-3.078	0.0028	-50	-7	-39	Inferior Temporal Gyrus
4	252	Common EF	eigenvector centrality	4.15	0.0001	-52	-63	5	Lateral Occipital Cortex
5	175	Common EF	eigenvector centrality	-2.9309	0.0043	48	25	27	Middle Frontal Gyrus
5	175	Common EF	global connectivity	-3.3353	0.0012	48	25	27	Middle Frontal Gyrus
6	83	Common EF	global connectivity	-2.9351	0.0042	-68	-23	-16	Middle Temporal Gyrus
7	47	Common EF	betweenness centrality	2.969	0.0038	-3	2	53	Supplementary Motor Area
8	248	Common EF	global connectivity	-3.0872	0.0027	-31	-10	-36	Temporal Fusiform Cortex
9	133	Shifting	clustering coefficient	-3.2772	0.0015	-2	-35	31	Cingulate Gyrus
9	133	Shifting	participation coefficient	2.9554	0.004	-2	-35	31	Cingulate Gyrus
10	212	Shifting	betweenness centrality	-3.4529	0.0008	-11	26	25	Cingulate Gyrus
11	217	Shifting	betweenness centrality	-2.9106	0.0045	10	22	27	Cingulate Gyrus
12	242	Shifting	betweenness centrality	3.1189	0.0024	-49	25	-1	Frontal Operculum Cortex
13	209	Shifting	betweenness centrality	-2.8984	0.0047	36	22	3	Insular Cortex
14	86	Shifting	betweenness centrality	3.5551	0.0006	-44	-65	35	Lateral Occipital Cortex
15	9	Shifting	global connectivity	-2.8956	0.0047	65	-24	-19	Middle Temporal Gyrus
16	165	Shifting	clustering coefficient	-3.1289	0.0024	26	-79	-16	Occipital Fusiform Gyrus
17	20	Shifting	participation coefficient	3.9972	0.0001	-54	-23	43	Postcentral Gyrus
18	36	Shifting	participation coefficient	4.9259	< 0.0001	42	-20	55	Postcentral Gyrus
19	113	Updating	betweenness centrality	-2.9548	0.004	-3	42	16	Cingulate Gyrus
20	218	Updating	betweenness centrality	-2.8861	0.0049	31	56	14	Frontal Pole
3	250	Updating	clustering coefficient	-3.0971	0.0026	-50	-7	-39	Inferior Temporal Gyrus
21	164	Updating	clustering coefficient	-3.2544	0.0016	-42	-74	0	Lateral Occipital Cortex
22	46	Updating	eigenvector centrality	-3.0854	0.0027	66	-8	25	Postcentral Gyrus
23	35	Updating	betweenness centrality	-3.1441	0.0023	-13	-17	75	Precentral Gyrus
7	47	Updating	clustering coefficient	-3.1843	0.002	-3	2	53	Supplementary Motor Area

relationship was present when using a measure of updating-specific EF collected at age 23 (t = -2.389, p = 0.018) but not from age 17.

3.4.2 Models Involving Features from CS Sample Exploratory Analysis

None of the nine common EF features identified in the exploratory analysis of the CS sample were significantly associated with individual differences in common EF in the LTS sample.

One shifting-specific feature identified in the exploratory analysis of the CS sample, the participation coefficient of postcentral gyrus (Region 17) was significantly associated with individual differences in shifting-specific EF in the LTS sample. Individuals with higher shifting-specific EF had decreased participation coefficient in postcentral gyrus (t = -3.118, p = 0.002). This relationship was also observed when using shifting-specific EF data collected at age 23 (t = -2.956, p = 0.003) and age 17 (t = -2.420, p = 0.016) as well.

One updating-specific feature identified in the exploratory analysis of the CS sample, the betweenness centrality of right frontal pole (Region 20) was significantly associated with individual differences in updating-specific EF in the LTS sample. Individuals with higher updating-specific EF had increased betweenness centrality in frontal pole (t = 2.275, p = 0.024). This relationship was non-significant when using updating-specific EF data collected at age 23 and showed a trend in significance when using age 17 data (t = 1.861, p = 0.064).

3.5 Discussion

The main finding of the current study is that individual differences in three different dimensions of EF - common EF, shifting-specific EF, and updating specific EF - are associated with distinct aspects of regional functional connectivity, both with regards to regions involved and the nature of their connectivity as assessed by different graph theoretic measures. While some of the identified regions fall within the frontoparietal network, which is typically conceptualized as a brain network that is critical for EF, other regions fall within networks less typically associated with EF. Importantly, exploratory analyses suggest that the graph theoretic measures identified could ac-

Figure 3.5: **Relationship Between Updating-specific EF and Participation Coefficient of DLPFC in the LTS Sample**. Scatterplot of relationship between individual differences in updating-specific EF and participation coefficient of dorsolateral prefrontal cortex (DLPFC) in the LTS sample.

count for a significant amount of the variance across individuals in each of the different aspects of EF in the CS sample (no equivalent analysis was performed in the LTS sample). A few features identified in these analyses were associated with individual differences in EF in an analysis of a separate sample suggesting some of the features identified in this work could be a more general predictor that is robust to differences in samples such as age and minor variation in behavioral measurement while other features may be specific to the sample or context of the CS sample. Below we discuss the implications of these finding for each of the three EF dimensions.

3.5.1 Common EF

Our results indicated that individual differences in common EF are associated with differential patterns of connectivity for numerous nodes in our analysis of the CS sample. In general, the pattern observed is that individuals with higher common EF have nodes with less central attributes (i.e., lower eigenvector centrality or other measures of relative importance) than individuals with lower common EF. Higher common EF was associated with lower eigenvector centrality, which reflects how much a node connects to other important nodes within the brain, in a priori regions 3 and 9 as well as exploratory region 5 precuneus, paracingulate gyrus and MFG, respectively. Higher common EF was associated with lower global connectivity, which measures connectivity of any strength across the whole brain, in a priori region 9 as well as exploratory regions 8, 6, and 8. Hence, individuals with higher common EF do not appear to have a brain organization in which a portion of the frontoparietal network acts as a highly centralized hub, but instead have a number of widely distributed regions (from a variety of resting-state communities) that play an important role.

This general pattern, and more specifically lower global connectivity in a node within right lateral prefrontal cortex (exploratory region 5) situated squarely within dorsolateral prefrontal cortex (DLPFC), appears to directly conflict with the suggestion of Cole et al. (2012) that high global connectivity of the homologous region in the left hemisphere allows it to flexibly modulate activity across the whole brain. The reason for the discrepancy in these findings is not clear. It may be that these differences reflect aspects of hemispheric asymmetries that are associated with individual differences in common EF. Additionally, this reversal in the direction of this particular relationship could either highlight the utility of our multidimensional approach to EF (i.e., less susceptibility to measurement error) or perhaps suggest that the finding of Cole et al. (2012) is driven by some aspect of intelligence and working memory (the primary measure of their study) that is not captured by our common EF measure.

Regarding how well hubs integrate information across disparate brain regions, as assessed by betweenness centrality, there were some notable findings. In particular, two midline nodes in the frontoparietal network, one in the supplementary motor area and another in the cuneus, showed increased betweenness centrality with higher common EF. In addition, higher common EF was associated with increased eigenvector centrality of a region at the juncture of the occipital and temporal lobes. Notable is the cuneus region because this node is only slightly posterior and inferior to a superior parietal region (-18, -69, 51) that emerged in a task-based positron emission tomography (PET) conjunction analysis of eight EF tasks (Collette et al., 2005) chosen for their correspondence to the three facets of EF used in the current study. Based on the location of this node in superior cuneal cortex and caudal precuneus, this region is likely involved in higher-level attentional processing, which may play a role in supporting common EF.

Regarding measures of segregation, we found higher common EF was associated with decreased clustering coefficient for nodes in the precuneus, frontal pole, and inferior temporal gyrus. This finding suggests that the functioning of these nodes is not as isolated from that of other brain regions for individuals with higher compared to lower common EF. This effect for one of the frontopolar nodes identified in our whole brain analysis (exploratory Node 2) is notable as it is close to the frontal pole region) that emerged in our prior ICA-based analysis as associated with common EF ability (x = -26, y = 55, z = 4; Reineberg et al. (2015)). In particular, in that study we found that individuals with higher common EF had dorsal attention networks that extended to this region. This node falls within regions that have been suggested to enable control at the highest level of abstraction (Badre, 2008; Koechlin et al., 2003), Hence, we would speculate that decreased local processing at this node may enhance the reach or influence of such abstract control in individuals with higher common EF. According to a recent parcellation of the frontal pole performed by our lab (Orr et al., 2015), such frontopolar regions have connections that are mainly limited to prefrontal regions. In addition, our parcellation suggests a gradient of function from monitoring/regulation in more medial aspects to cognitive representations in more lateral aspects. Connectivity also suggests a second gradient representing actions and plans in more dorsal aspects and stimuli/emotions in more ventral aspects. Based on the anatomical connectivity of the frontal pole region identified in the current study, the region we have identified as associated with common EF appears to be involved in cognitive representations of actions and plans.

In our parallel analysis of the LTS sample, we tested all the features identified in the *a priori* and exploratory analysis. We did not find any exact replications for common EF with regard to regional connectivity profiles as assessed by graph theory measures. We discuss this inconsistency in **Comments on Consistency in Parallel Analyses**.

3.5.2 Shifting-specific EF

We found a graph theoretic property of one region was significantly associated with individual differences in shifting-specific EF in both the CS and LTS samples. In the CS sample higher shifting-specific EF was associated with increased participation coefficient in left and right primary sensory cortex (exploratory regions 17 and 18). In the LTS sample, higher shifting-specific EF was associated with decreased participation coefficient in left primary sensory cortex (exploratory region 17). Shifting-specific EF is described as the ability to fluidly transition between different representations of task-set. This ability involves both the mechanism of transitioning between task sets and maintaining representations of task sets that are often multimodal in nature (i.e., may contain a variety of sensory information and also mappings between the sensory stimuli and appropriate motor responses). While parietal regions are often thought of as being involved in shifts of attention, somatosensory regions are more likely to be involved in the stimulus-response mappings that vary among tasks, a more concrete and less abstract level of planning. It may be that increased connectivity in regions associated with stimulus-response mapping allows individual with higher switching-specific EF to link stimuli and responses for a given task more easily or allow for more robust or distinct stimulus-response representations for each task set. A notable inconsistency between the two samples is the reversal in direction of this relationship such that in the younger sample, higher shifting-specific ability was associated with higher participation coefficient in primary sensory cortex. In the older, LTS sample, higher ability was associated with less participation coefficient of the same region. This direction flip could be an indicator of some underlying developmental process or changes related to the finalization of brain development (e.g., white matter integrity, cortical thickness). Future work is necessary to comment on the specific role of somatomotor connectivity in shifting-specific EF.

The graph theoretic properties of several other regions were associated with individual differences in shifting-specific EF in the CS sample. Another node related to motoric function that was associated with shifting-specific EF was observed in the cerebellum (*a priori* region 4), which resides within lobule VI. As demonstrated by Bernard et al. (2012), this region has strong connectivity to motoric regions (dorsal premotor cortex) as well as regions within the frontoparietal network including the dorsolateral prefrontal cortex, the inferior frontal gyrus and the inferior parietal lobule (see Bernard et al. (2012), Figure 3). Greater shifting-specific EF was associated with less global connectivity of this node, perhaps indicating greater specific connectivity to these frontoparietal regions.

In addition, shifting-specific EF was also associated with the connectivity of nodes within the cingulo-opercular network, a characteristic also not observed for common EF. Higher shifting-specific EF was associated with decreased betweenness centrality of nodes in the rostral portion of the dorsal anterior cingulate cortex (exploratory regions 10 and 11). A recent meta-analysis of functional terms significantly associated with this region (as found within Neurosynth database; Yarkoni et al. (2011)) by our group (De La Vega et al., in press) includes shifting (as well as inhibition and conflict). Associations between shifting-specific EF and betweenness centrality were also observed for anterior opercular regions (exploratory regions 12 an 13), but with the direction varying by hemisphere (higher shifting-specific EF associated with increased betweenness centrality in the left hemisphere, but decreased betweenness centrality in the right hemisphere). At least some research suggests that the cingulo-opercular network is associated with task sets (e.g., Petersen and Posner (2012)) although it remains unclear whether its role is to maintain task sets or to implement the selection process associated with motoric aspects of task sets (e.g. see Banich et al. (2000b) for a discussion of the role of lateral prefrontal cortex in maintaining task sets and Milham and Banich (2005) for discussion of the role of cingulate regions in late-stage response selection). Hence, variations in betweenness centrality, which reflects the degree to which a node connects disparate brain regions, may influence the ability to impose the task sets required to shift between tasks.

Finally, a number of lateral prefrontal nodes from our a priori analysis and exploratory whole-brain analysis were associated with shifting-specific EF. The location of these nodes ranged from frontopolar regions to ventrolateral regions to mid-dorsolateral regions. One a priori region of interest (a priori Region 11) for shifting-specific EF came from Smolker et al. (2014) who found decreased volume and gyrification of an orbitofrontal/ventrolateral prefrontal cortex region in individuals with high shifting-specific EF. We found an association for a ventral orbitofrontal node (BA 10/47) within that region such that decreased global connectivity and eigenvector centrality was associated with increased shifting-specific EF. Traditionally, this region has been associated with reward processing and valuation (Sescousse et al., 2010), however, some task-based studies of task-set shifting have found involvement of lateral orbitofrontal regions as well (Hampshire and Owen, 2006). In addition, we found individuals with high shifting-specific EF had a decreased clustering coefficient in a node within the vlPFC portion of this a priori right hemisphere region. This region has been clearly implicated in set shifting in functional neuroimaging studies (Goel and Vartanian, 2005; Hampshire and Owen, 2006; Konishi et al., 1998; Monchi et al., 2001), with a suggested specific role in the dimensional change aspect of shifting rather than stimulus-response mapping or other shifting-related processes (Hampshire and Owen, 2006). Our study suggests that shifting-specific EF is supported by a less encapsulated role of this region; however, we did not find complementary evidence of high integration of this area being associated with high shifting-specific. Future work is required to clarify the potential link between decreased clustering coefficient in vlPFC and dimensional change ability.

We also observed a relationship for regions of left dorsolateral prefrontal cortex. One node falls within mid-dorsolateral prefrontal regions (i.e. BA 46), which is classically considered to be associated with working memory (Petrides, 2000). Higher shifting EF was associated with an increased clustering coefficient, indicating enhanced local processing, and reduced participation, which is associated with connections to a wider diversity of modules. As such, it appears that this region has a more focal organization in individuals with higher shifting-specific EF. We speculate that such an organization may allow for less interference of task-sets and responses as one shift for this region and another more posterior region associated with increased global connectivity. This was an priori region of interest due to a study that found lateral prefrontal cortex was more globally connected in individuals with high fluid intelligence (Cole et al., 2012). We were especially interested in this finding for two reasons. First, there is strong co-linearity between general intelligence and common EF, updating-specific EF, and to a lesser extent, shifting-specific EF (Friedman et al., 2008). Second, the 3-back task used in that study, like all EF tasks, suffers from a task impurity limitation in that both common EF and updating-specific EF explain some of the variability in performance on the task (Miyake & Friedman, 2012). Using our multicomponent approach, however, we were able to disentangle the relationships between connectivity of lateral prefrontal cortex an each of these EF dimensions separately. We found an association with updating specific EF but not with common EF.

We also found associations with a node within a more posterior section of the left dorsolateral prefrontal cortex that is situated at the inferior frontal junction. This region has been implicated in meta-analyses as being involved in switching (Derrfuss et al., 2005). While there are a variety of theories with regards to the function of this region, at least one prominent idea is that it is involved in linking goal-related information to action-related information (De Baene et al., 2012). For this node greater shifting-specific EF was associated with increased global connectivity, which may allow for better integration of these two types of information (i.e., goal-related, action-related).

3.5.3 Updating-specific EF

We found a graph theoretic property of one regions was significantly associated with individual differences in updating-specific EF in both the CS and LTS samples in the same direction. One might have expected that connectivity of the DLPFC would be important for updating-specific EF as this region has also been implicated as important for the manipulation of information in working memory by a number of task-based fMRI studies and meta-analyses of working memory processes (Barbey et al., 2013; Wager and Smith, 2003). In fact, we found higher updating-specific EF ability was associated with decreased participation coefficient in DLPFC (a priori region 17). This same relationship was found in the LTS sample as well. This result could indicate that the cognitive functions of DLPFC depends, in part, on a more circumscribed connectivity pattern rather than broad connectivity to many functional communities in the brain. In fact, both empirical research and computational modeling (Frank et al., 2001; Hazy et al., 2007), suggest that the updating of working memory relies heavily on the specific functional connectivity between the DLPFC and the basal ganglia. If so, higher updating-specific EF may be associated with less broad-based connectivity of the DLPFC. Given this relationship was the only feature found to be significantly associated with individual differences in EF in both samples and in the same direction and magnitude, participation coefficient of DLPFC presents as a possibly special feature of the resting brain. Unlike other features which are present in one or the other sample, the connectivity profile of DLPFC may be less context or demographic specific. Future work should explore the predictive value of this feature.

One feature from the CS study, the betweenness centrality of frontal pole (Region 20) was significantly associated with individual differences in updating-specific EF in the LTS sample as well, however, the direction of the relationship in the LTS sample was opposite of the relationship found in the CS study. For LTS participants, higher updating-specific EF was associated with increased betweenness centrality. Although this direction flip is perplexing, it could perhaps be driven by developmental differences in the two samples. Adding to our confidence in this finding it how close in proximity this frontal polar (BA10) area (X = 31, Y = 56, Z = 14) is to an area found by Collette et al. (2005) to be implicated in updating-specific EF processes in a task-based PET context (X = 34, Y = 51, Z = 9).

The remaining set of results for updating-specific EF were found only in the CS sample. In general, updating-specific EF was associated with less hublike and less central properties in a variety of nodes spanning laterally from frontopolar to dorsolateral to premotor cortex, and medially from sub- to supragenual portions of anterior cingulate cortex. Better updating-specific EF was associated with reduced betweenness centrality, which reflects how much a node connects disparate parts of the graph, in dorsolateral frontal pole (a priori region 15) as well as supragenual anterior cingulate cortex, frontal pole, and premotor cortex (exploratory regions 19, 20, and 23). In addition, higher updating-specific EF was associated with reduced eigenvector centrality of primary sensory cortex (exploratory region 22). Higher updating-specific EF was also associated with lower global connectivity in a left cerebellar lobule VI region (a priori region 6).

Individual differences in updating-specific EF also seem to rely on reduced segregated connectivity in some areas, as we found an association between reduced clustering coefficient in the inferior temporal gyrus, supplementary motor area, and lateral occipital gyrus (exploratory regions 3 ,7, and 21). This decreased segregation was not accompanied by increased centrality or more hublike connectivity in these regions. Take together, higher updating-specific EF seems to rely on the connectivity of a diverse set of regions spanning those responsible for both higher-level and lower-level cognitive functions.

3.5.4 General Discussion

One of the more perplexing aspects of EF is that it seems to rely rather generally on the frontoparietal network across many tasks and individuals, with little or no specificity to the regions involved. Explorations using an individual differences approach, such as in the present study, begin to provide insight into how variations in brain function within the regions of this critical network might be associated with both the nature and the level of executive control. In our prior work, we have demonstrated that individual differences in each of the aspects of EF explored here - common EF, shifting-specific EF, and updating-specific EF - are associated with unique patterns of gray matter volume and white matter characteristics (Smolker et al., 2015) as well as with the strength and spatial composition of resting-state networks as determined by ICA (Reineberg et al., 2015). Here we expand that picture by showing that, in addition to variation in the size or composition of resting-state networks, EF ability may be linked to complex measures of the connectivity profile of a number of brain regions.

As mentioned above, the frontoparietal network appears to modulate processing in other brain regions so as to exert control (Miller and Cohen, 2001). Hence, how connected these frontoparietal regions are to the rest of the brain may modulate how accessible different regions are to control by frontal regions, and such accessibility may in turn influence individual differences in dimensions of EF. Nonetheless, an important aspect of the current results is the finding that it is not just connectivity of nodes within the frontoparietal network, but also nodes outside of it that influences individual differences in EF. For example, connectivity of temporal lobe regions as well as sensori-motor regions also appears to influence dimensions of EF. These findings require a reconceptualization of the neural systems underlying EF and suggest that they may be more broad-based than is typically conceptualized.

Finally, our results provide an interesting perspective on the unity and diversity model of individual differences in EF, providing converging evidence for its validity. For the most part the nodes whose connectedness is related to individual differences in EF were distinct for the three major facets of EF: common EF, switching-specific EF, and updating-specific EF. Such anatomical specificity suggests that indeed these constructs are tapping into distinct networks, which support each of these three dimensions of EF.

3.5.5 Comments on Consistency in Parallel Analyses

Overall, we found only one rs-fMRI graph theory metric that was associated with individual differences in updating-specific in both the CS and LTS samples. This relationship was strong and robust to the many differences between the two samples, suggesting it could perhaps be a neuromarker of EF. Future work should explore the predictive value of this measurement in a variety of other contexts. Although that single feature is an exciting area for future exploration, there is a question of the usefulness of graph theoretic measures for investigations of individual differences in behavior given the lack of consistency between our parallel analyses and, especially, the two relationships that went in opposite directions between the two samples (participation coefficient of postcentral gyrus for shifting-specific and betweenness centrality of frontal pole for updating-specific). The features we've identified as significantly associated with individual differences in EF in the CS sample are not also associated with individual differences in EF in the LTS sample. It is unknown why this is the case, however, these results indicate caution should be taken when interpreting the generalizability of brain-behavior relationships (i.e., results should be read as specific to the sample or experimental context).

One notable difference between the two samples that could have contributed to this lack of consistency in the parallel analyses is the mean age difference between the groups. Because the two samples were collected on either side of the period of time when brain connectivity and structure slows down considerably, the cognitively relevant aspects of rs-fMRI could differ in the two age groups. It would be entirely inappropriate to discount the older LTS samples usefulness in increasing our understanding of the neural basis of EFs (via graph theory analyses) because no new exploratory analyses were performed on these data. An ideal follow up analysis considering the features identified in the CS sample are not associated with individual differences in the LTS sample would be to perform a new data driven analysis of the LTS sample to determine which features are most associated with individual differences. Such an analysis could possibly identify nodes very close in proximity to those discussed in the CS sample results or even an entirely new set of features. Additionally, it is still possible for a new set of exploratory features is associated with a substantial about variance in each of the three EFs in the LTS sample. Future work should explore this possibility. If a new exploratory analysis does not reveal a set of regions whose connectivity explains a substantial amount of variance in EF, perhaps graph theory only has utility before individual reach a common developmental maturity. Additionally, future studies that include a sample of individuals whose age range from late adolescents to young adulthood might be able to more directly examine the predictive power of the specific rs-fMRI features identified above in the analysis of the CS sample.

3.5.6 Limitations

The current study is not without limitations. Limitations of the current study are similar to those of other investigations of individual differences in cognitive abilities as a function of rs-fMRI. Notably, we cannot disentangle whether differences in rs-fMRI are due to sculpted history of neural activity or differences in the quality of cognition or unconstrained thoughts between high and low ability individuals. On the one hand, a dominant theme emerging from prior literature is that fluctuations in rs-MRI reflect the intrinsic functional organization of the brain (Fox & Raichle, 2007), sculpted by a history of coherent neuronal firing and anatomical wiring between distributed brain regions (Wig, Schlaggar, & Petersen, 2011). Lending support to this hypothesis is observed stability across multiple time points within individuals (Guo et al., 2012; Shehzad et al., 2009) and under various stages of consciousness and anesthesia (Boly et al., 2008; Greicius et al., 2008). On the other hand, an individual's state at the time of scanning may influence the patterns we observed. Several recent findings suggest that patterns of functional connectivity may be partially influenced by the participant's mental/task state (Andrews-Hanna et al., 2010; Doucet et al., 2012; Shirer et al., 2012), and can be modified on a rapid time scale (Lewis et al., 2009; Stevens, Buckner, & Schacter, 2010; Tambini, Ketz, & Davachi, 2010).

Our studies to date have been limited to relatively static aspects of brain organization - white matter integrity and connectivity, grey matter volume, thickness and gyrification (Smolker et al,. 2015), and patterns of organization and connectivity during resting state (Reineberg et al,. 2015; the current study). Whether the same regions implicated in these studies as associated with individual differences in EF are also implicated in more dynamic aspects of brain function (such as variations in connectivity during different EF tasks) remains an open question.

Although we believe our findings establish a strong groundwork for further exploration of neuropsychological correlates of EF as assessed during resting state, it will be important for future studies to replicate our findings. For example, while in our exploratory analysis we found that the strongest associations between graph theory metrics for a given brain region and a particular EF dimension accounted for 35-55% of the variance in that EF, there is always the likelihood of such regression models overfitting the data. Nonetheless, the amount of variance accounted for is still likely to be relatively robust given the statistical approaches (e.g., bootstrapping) that were taken. It will also be important to determine the possible implications of the current findings for reduced EF in psychiatric and neurological disorders, that is, whether the relationships we have identified are reduced or altered in such populations. In addition to replication and extension, future studies might want to consider genetic and/or behavioral variation that might account for differences in resting-state functional connectivity between high and low EF individuals.

3.5.7 Conclusion

Here we have provided evidence that the connectivity pattern of the intrinsic fluctuations in the BOLD signal explains a substantial portion of variance in individual differences in dimensions of EF within a college student sample. Of many features identified in the CS sample, three were similar in the LTS sample suggesting, at least for shifting-specific and updating-specific EFs, there is some consistency across ages and and other factors that differentiate the CS sample from the LTS sample in the resting-state brain features most relevant to individual differences in EFs. We have built upon an existing theoretical model of EF by showing separable patterns of brain connectivity influence individual differences in each of three dimensions of EF - common EF, shifting-specific EF, and updating-specific EF. The results are notable for providing a fine-grained picture of both the regions involved and their connectivity, as assessed by different graph theoretic measures. While prior work has established how a given region contributes to online EF in the form of group mean effects in typical task-based fMRI, we have shown that variability in the degree to which specific regions (or nodes) are integrated or segregated, as assessed by their resting-state connectivity profile, underlies individual variability in dimensions of EF. The current study significantly expands our knowledge of neural influences on individual difference in EF and can serve an important hypothesis-generating role for future large-scale studies of inter-individual variability in EF as it related to patterns of brain activation either at rest, or during task, as we are currently exploring.

Chapter 4

Discussion and Future Directions

Summary

4.1 General Discussion

The diversity of human cognitive functions is reflected in the structure and organization of the brain. The question of whether or not individual variation in those abilities is also reflected in the intrinsic structure and organization of the brain is still an open question, especially with regard to the specific aspects of the brain that contributes to variability. Consider, for example, an automotive analogy of individual differences. To a non-expert asked to determine the faster of two cars in a quarter mile race there is a great deal of ambiguity. Some may answer based on size, shape, volume of the engine, or any number of possible features, some of which may be relevant to acceleration/speed, some of which may not. Also consider what would happen if a mechanic was given access to the vehicles or information about the internals of the vehicles such as engine displacement. The mechanic would certainly have a better chance of correctly predicting the race outcome. In the field of cognitive neuroscience, we are faced with a similar question of which of two brains will be less prone to errors after a sudden and unexpected change in the rules of a cognitive task. Early work has investigated some obvious suspects, for example, the age of the brains. Unlike the mechanic, we do not have the ability to dissect a brain prior to observing performance, but some recent developments in neuroimaging have provided a number of methodologies to probe the internals of the human brain in a safe and non-invasive manner. The body of work highlighted in this dissertation is a preliminary look at three families of brain features that have some cognitively-relevant elements. Returning to the automobile analogy, the studies in the previous chapters are much like ruling out the importance of paint color while focusing on the importance of engine displacement when deciding on predictors of automotive race times.

Previous discussion sections consider the implications of specific findings, but we have yet to consider the group of studies together. One recurring theme across many different resting-state analyses is how the unity and diversity model of EF provides constructs rooted in separable neural features. There was minimal overlap in the feature sets that were most associated with each of common EF, shifting-specific EF, and updating specific EF. We identified features in all three analyses that were associated with individual differences in common EF. Individual differences in shifting-specific EF were more restricted to graph theory properties, and to a lesser extent RSN characteristics (RSN expansions as assessed by dual regression of spatial maps and network-to-network time courses). Individual differences in updating specific EF were associated with differences in the graph theoretic properties of individual regions. There were fewer updating/graph theory relationship than for common EF or shifting-specific EF, however, one of the updating-specific features was present in two separate samples, suggesting it may be partially robust. This line of work suggests that common EF and shifting-specific may rely on the connectivity or interaction of large scale brain networks while updating specific relies preferentially on the connectivity of specific regions.

Perhaps the most important finding amongst these studies is the special role of DLFPC participation coefficient as a predictor of updating-specific EF across two samples such that increased updating-specific EF was associated with less diverse DLPFC connectivity. This result suggests a specific functional role for DLPFC that cannot be as easily revealed in the context of task-based fMRI. While task-based fMRI and seed based connectivity measures might identify DLPFC as having a particularly important role during EF tasks or having significant connections in general to a wide network of regions, the measure we've used here quantifies the diversity of DLPFC connections and its possible role as either a diverse connector hub (very diverse connections) or a specialized local hub (minimally diverse set or connection, low participation). We've found that high updating-specific EF is associated with the latter role for DLPFC, a more circumscribed set of connections to a limited number of functional brain communities (i.e., networks, modules). This segregated role is quite dissimilar to the role of another nearby region that is perhaps the only other very well characterized area in a graph theoretic sense with a strong relation to individual differences in higher level cognitive abilities. The work of Cole and colleagues describes the connectivity profile of left lateral prefrontal cortex, only slightly more caudal to the region described above, as having a special connectivity profile that underlies individual differences in fluid intelligence (Cole et al., 2012, 2015). The work of Cole and colleagues has found that more connections across the brain (higher global connectivity) in lateral prefrontal cortex is associated with higher fluid intelligence. Our finding is very interesting taking into account this line of research because we have described a related ability but a drastically different connectivity profile (i.e., less diverse connectivity is associated with better updating-specific EF) in a region only one centimeter away. Future work should attempt to confirm the proposed roles of these regions as well as test the discriminant validity of the relationship between DLPFC and updating-specific EF beyond the other cognitive abilities tested in this work (common EF, shifting-specific EF). One final comment is that this finding (along with the general success of the graph theory analysis) supports our hypothesis that, while the frontoparietal network is broadly implicated in high level cognition, there may be a specificity of function within subregions of that network.

Another important finding is that the intensity of subcomponents of the right frontoparietal RSN from the analysis of spatial maps via dual regression is related to individual difference in common EF. In **Chapter 2** we found higher common EF was associated with increased intensity of crus I/II of the cerebellum, a component of the frontoparietal RSN. In our parallel analysis of the LTS sample, we did not find this exact relationship, however, we did find an relationship such higher common EF was associated with increased intensity of middle frontal gyrus, a core component of the frontoparietal RSN. As mentioned in **Chapter 2 - Discussion**, there is still no consensus interpretation of dual regression results. It may be more appropriate to describe these results simply as variation within the right frontoparietal RSN rather than attribute any special qualities to the specific areas that were more intense in each sample. From this point of view, these findings would be another area of consistency across the two samples. It should also be noted that this result supports one of our primary hypotheses in this line of research - that the frontoparietal network assumes a special role in a variety of high level cognitive tasks and that a history of unique activation of that network in high/low functioning individuals may translate to altered connectivity. Future work should build upon our work by investigating the etiology of variation in the intensity within the frontoparietal network and its behavioral relevance.

Our finding of a positive relationship between common EF and the coupling of task-positive and task-negative RSNs offers a new perspective on an old resting-state feature in that this is the first, to our knowledge, example of positive connectivity between the task-positive and task-negative systems being associated with increased performance within a neurologically-normal population. This finding also offers an interesting take on high common EF ability given the interpretation that increased coupling of networks is due to historical coactivation of those networks. Very few mental actions involve coactivation or positive coupling of frontoparietal and default networks. The only task-based neuroimaging study, to our knowledge, that demonstrates an fMRI contrast in which these RSNs are coupled is the work of (Spreng et al., 2010). In Spreng and colleagues' research, a difficult autobiographical planning task that involves both demanding goal direction along with internal mentation and autobiographical memory is associated with simultaneous increases in BOLD signal within both frontoparietal and defaults networks. Future work must not only replicate our findings, but investigate the mechanism by which this positive connectivity between frontoparietal and default networks is beneficial for some constructs (common EF) but seemingly detrimental in other way (e.g., associated with poor working memory capacity and several clinical disorders).

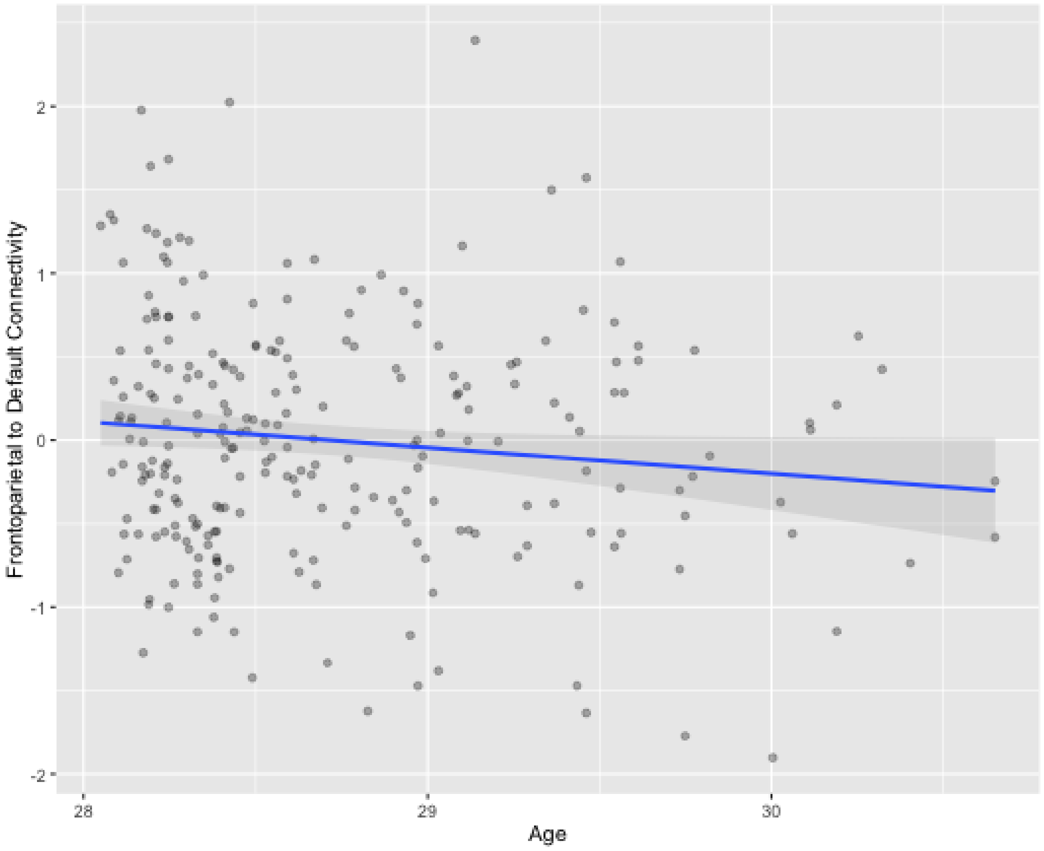
4.2 Comments on Parallel Analyses

Another important aspect of this study was the series of parallel analyses performed on separate data sets. At first glance, the generally weak correspondence between the parallel analysis of two samples might leave one with the opinion that resting-state fMRI is not robustly associated with individual differences in EFs or the analyses were subject to sampling error, chance, or unreliability (although see **Chapter 1** for discussion of high reliability in both behavioral EF tasks and resting-state fMRI analyses). Obviously, the most desired outcome of this series of studies is a set of brain features that, without regard to age or other differences between samples, is associate with a considerable amount of variation in common or specific EFs (i.e., a "neuromarker" of EF ability). And it should be noted that we possibly found this in the participation coefficient of dorsolateral prefrontal cortex. However, and more relevant to the vast majority of features determined to be cognitively-relevant in the CS sample, one could take the perspective that the features that are relevant at one time development point might not be the same in a separate set of conditions. In the automobile analogy, this would be the equivalent of expecting race vehicles to rank the same from year to year without considering any number of possible upgrades or downgrades or expecting the same features to be equally relevant for predicting race times from year to year without considering new technological advances. As previously discussed in the **Chapter 2 - Discussion** and **Chapter 3 - Discussion**, there are a number of possible reasons for the discrepency between results. One of these possibilities is age-related changes in cortical volume (Walhovd et al., 2005; Allen et al., 2005; Jernigan et al., 2001; Walhovd et al., 2011), cortical thickness (Salat et al., 2004; Sowell, 2004; Shaw et al., 2008; Lemaitre et al., 2012), white matter tracts (Asato et al., 2010), functional brain networks (Meunier et al., 2009), and resting-state functional connectivity more generally (Bernard et al., 2013; Hampson et al., 2012; Mowinckel et al., 2012; Yang et al., 2013) that could affect which rs-fMRI features are relevant to cognitive abilities at given points along developmental trajectories.

Regarding differences in age between CS sample and LTS sample, there is no definitive way to demonstrate changes in connectivity between age 21 and 29 contributed to the failures to find similar results across samples given the current study design. That being said, we investigated effects of age on network-to-network connectivity (even within the relatively homogeneous age range of sample B). We found a negative relationship between task positive to task negative RSN connectivity and age (t = -1.983, p = 0.0484, Figure 4.1) even after controlling for movement during the resting state scan (mean translation and mean rotation) which could account for some variation in . We did not observe age differences in connectivity of left to right frontoparietal RSN or frontoparietal RSNs to the dorsal attention RSN. It stands to reason that perhaps connectivity properties of the brain are sensitive to individual differences in EF at certain points in young adulthood but not after neural development has slowed. Several studies have shown age-related changes in connectivity (Bernard et al., 2013; Hampson et al., 2012; Mowinckel et al., 2012; Yang et al., 2013). While not all of these papers report connectivity differences for different age groups in areas that are involved in high level cognitive processes, some do. For example, Yang et al. (2013) found that the role of the precuneus within the default network changes with age such that two precuneus sub-networks that are segregated in youth become less separable with age. Future studies could directly investigate age-related effects on the relationship between rs-fMRI and cognitive abilities. Additionally, re-analysis of data from Reineberg et al. (2015) and Reineberg and Banich (2016) controlling for effects of age (which was quite varied compared to the LTS sample) could be enlightening.

Another possible cause of inconsistency across samples is differences in the behavioral measures. In the analysis of the CS sample, we used a Z-score composite for common EF and residuals for shifting-specific and updating-specific EFs. Only three tasks were used in the creation of the Z-score composite and residuals. In the LTS sample, factor scores were estimated for the three EF constructs in a way that is more in line with historical studies of the unity and diversity of EF, which was by estimating a three factor model where common EF was a general factor and shifting- and updating-specific EF were factors orthogonal to common EF that captured remaining correlation between task set shifting and working memory tasks that wasn't already explained by common EF (see Friedman et al. (2008); Friedman and Miyake (2016)). To our knowledge, these two techniques have not been directly compared. It may be worthwhile directly comparing various means of estimating the EF constructs. If there is a substantial difference between a residual type shifting-specific EF score and a shifting-specific factor score, those difference could partially explain the lack of consistency between the parallel analyses.

Figure 4.1: **Effect of Age on Connectivity in the LTS sample**. Connectivity between frontoparietal and default networks decreased with increases in age (although ages 29-30 were underrepresented in this sample).



A minor difference between the two samples that could possibly lead to less consistency between the analyses is directions during the resting-state scans. Participants from the CS sample were instructed to remain still with their eyes closed while participants in the LTS sample were instructed to remain still and maintain fixation on a cross in the center of a computer screen. A small literature suggests eyes open and fixated is the optimal procedure for acquiring resting-state data due to high reliability (Zou et al., 2015) and decreased variability in visual processing stream activity when participants are instructed to keep their eyes open versus closed during the resting scan (seemingly from top-down imagination/visualization processes although the exact mechanism is unknown; Patriat et al. (2013)). Although it is entirely speculative, the visual processing stream activity induced in the CS sample procedure could in some way be correlated with EF ability. There is also a possibility that the instructions and resulting task states allowed differences in EF ability to emerge in brain activity at "rest" (e.g., high EF individuals try harder to keep their eyes shut).

Even taking these possibilities into account, there is still a chance that a sizable portion of brain/behavior relationship are context-specific. Studies of the resting brain may reveal that certain connectivity measures are related to individual differences in cognitive abilities within a fairly constrained sample or experimental context. But one should not dismiss the possibility that there is more congruency across samples than the analyses in this dissertation may lead one to believe. As discussed later in **Future Directions**, future analysis of the LTS in an unbiased manner could reveal patterns that are only slight deviants from the results in the CS sample.

4.3 Caveats

4.3.1 Questions of Causality and Task-set Inertia

Although our findings clearly demonstrate a relationship between individual differences in EF and resting-state fMRI, our study cannot speak directly to the source of that relationship. On the one hand, a dominant theme emerging from prior literature is that patterns of rs-fcMRI reflect the intrinsic functional organization of the brain (Fox and Raichle, 2007), sculpted by a history of coherent neuronal firing and anatomical wiring between distributed brain regions (Wig et al., 2011). Indeed, patterns of resting-state connectivity are stable across time within individuals (Guo et al., 2012; Shehzad et al., 2009), relate to a variety of genetic factors (Glahn et al., 2010), and persist to some degree under various stages of consciousness and anesthesia (Boly et al., 2008; Greicius et al., 2008). From this perspective, the findings of the present studies may potentially reflect an individual's biological heritage, such as genetic influences on EF that might influence the structural and/or functional connectivity of the brain (see Friedman et al. (2008) for evidence of genetic influences on EF). However, this does not preclude environmental influences also working to sculpt brain activity, such as the amount of training/schooling during childhood with regards to activities or tasks that require EF (Diamond, 2012), SES (Hackman and Farah, 2009), or other such factors. The relationship between behavior-related RSN variability and specific individual traits, whether they have genetic and/or experiential causes, is an important direction for future work.

It is also possible that aspects of an individual's state at the time of scanning may influence the patterns we observed and that those cognitive state may be consistent over time (i.e, what individuals do while being scanned is also reliable). Several recent findings suggest that patterns of functional connectivity may be partially influenced by the participant's mental/task state (Andrews-Hanna et al., 2010; Doucet et al., 2012; Shirer et al., 2012), and can be modified on a rapid time scale (Lewis et al., 2009; Stevens, Buckner, & Schacter, 2010; Tambini, Ketz, & Davachi, 2010). One specific example of alterations in rs-fMRI due to a recently performed task (i.e., task-set inertia) is the work of (Gordon et al., 2012) who showed that connectivity changes that occur during performance of an N-back working memory task, specifically the correlation strength between the default and task-positive RSNs and homogeneity of task-positive RSNs, persist beyond the task and into the resting-state scan that followed. Additionally, they observed individual variation such that participants' speed during the working memory task predicted connectivity strength in resting scan. Future work should be cautious both with regard to placement of the resting-state scan within the scanning session (i.e., preferably before cognitive tasks) due to possible task-set inertia effects.

Future research should also explore the possibility that behavior-related rs-fMRI is caused by differences in the cognitive processes of high versus low EF individuals during resting-state scans (e.g., high EF individuals plan their day, while low EF individuals daydream). Some progress is being made to develop experience-sampling protocols that are sufficient for capturing the wide variety of possible mental processes that could happen during the resting scan. One example is the resting-state questionnaire (ReSQ) which targets a variety of mental processes visual mental imagery, inner speech, auditory mental imagery, somatosensory awareness, inner musical experience, and mental manipulation of numbers (Delamillieure et al., 2010).

4.3.2 Considering Demographic Differences in rs-fMRI and Other Confounds

One potentially problematic aspect of most rs-fMRI studies is lack of adequate control for demographic differences in rs-fMRI. As previously mentioned, a set of studies have shown age-related changes in connectivity (Bernard et al., 2013; Hampson et al., 2012; Mowinckel et al., 2012; Yang et al., 2013). Gender also affects rs-fMRI. For example, Scheinost et al. (2014) found age-related connectivity trajectories are different for males and females. Another non-demographic factor that presents as a possible confound when investigating individual differences in behavior is personality. A few studies have investigated how different facets of personality usually assessed by personality questionnaires such as the NEO five factor inventory - affect rs-fMRI (Adelstein et al., 2011; Sampaio et al., 2013; Wei et al., 2012). Finally, socioeconomic status may act a moderator or mediator of relationships between behavior and rs-fMRI. One recent high-impact paper performed a massive exploratory analysis on a feature-rich public dataset the 500 participants release from the Human Connectome Project (Smith et al., 2015). This analysis revealed a single factor of demographic, personality, life history, and cognitive variables was extremely well predicted by a similar conglomerate measure of rs-fMRI (Pearson's r between behavior and brain = 0.87). While this study is important for demonstrating the utility of rs-fMRI as a predictive measure of behavior, their brain/behavior correlation may be overshadowed by the possibility that the demographic and life history measures account for the most variance in the observed relationship. In conclusion, future studies must acquire and account for demographic and personality differences. Time will tell whether or not individual differences in cognitive abilities are predictable after controlling for these confounding factors.

4.4 Future Directions

One obvious future direction for this line of research is to exploit the family structure of the LTS sample by exploring the genetic etiology of the brain connectivity measures discussed throughout this manuscript. In the LTS sample, data from pairs of monozygotic and dizygotic twins were acquired. By exploiting the twin design, we could see if cognitively-relevant rs-fMRI features are correlated to different degrees in pairs of monozygotic versus dizygotic twins. Because monozygotic twins share 100% of their genetic heritage, within-pair differences could indicate environmental influences on brain connectivity. This future analysis would be among the first to investigate the genetic versus environmental influence on certain feature of the resting brain altogether and, more importantly, could speak to how genetics versus environment influences behaviorally-relevant features of the resting brain.

Another follow up analysis of the LTS sample could be a series of analyses designed as if we were not attempting to replicate earlier work. Since the time of analysis of Reineberg et al. (2015) and Reineberg and Banich (2016), our lab has taken further interest in machine learning techniques to be used specifically in a predictive manner to predict EF from neuromarkers. Given the large sample size of the LTS data set, we could exploit a nested cross-validation analysis scheme in which feature selection and prediction of EFs are cross-validated. Such a scheme could provide more robust estimates of the features that are cognitively relevant in the age and demographic distribution of the LTS sample which is designed to be representative of Colorado. Regarding feature engineering and selection, there are many possible schemes to explore from principal components analysis to L1-based feature selection to fully cross-validated recursive feature elimination.

On a related note, future studies should be more open to the idea that data-driven analysis plans may produce minimally-interpretable but maximally applicable results. One such example is the recent work by Smith et al. (2015) who utilized a canonical correlation analysis to investigate brain behavior relationships (although many modern machine learning techniques that rely heavily on feature reduction and engineering are quite similar). Canonical correlation analysis is a technique that reduces both exogenous (behavior) and endogenous (brain) variable matrices while maximizing overlap in the two matrices. The output is essentially a set of brain measures that are highly correlated with a set or combination of different behavioral measures. Such a scheme has produced a high degree of overlap in the measures (e.g., Pearson's $r > 0.85$) at the cost of not being able to precisely or concisely label how the brains of high versus low ability/functioning individuals differ. To maximize the practical application of neuroimaging research, the field may need to embrace these fuzzy and computationally expensive techniques.

Regarding more specific ideas for tweaking the network-based studies reported in this dissertation, there are several possible follow ups. First, as mentioned in Chapter 2, a dimensionality estimation should be run on the LTS data set prior to ICA in order to determine the best group ICA solution in that sample. This procedure would make the LTS analysis truly parallel to the analysis of the CS sample. Also related to the analysis of networks, we could utilize other popular techniques to investigate the correlation of different brain areas and network as a test of the robustness of our effects. More specifically, we could perform seed-based connectivity analyses such as seed-to-seed connectivity or seed-to-whole-brain connectivity analyses (as can be implemented in the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012)) as a proxy for network-based measures. There are a variety of reasons one might prefer this method, such as being able to precisely specify a particular area of interest or avoiding smoothing-like processes associated with analysis of very large clusters of voxels. Studies that utilize seed-based techniques are popular and numerous (e.g., Chai et al. (2012); Keller et al. (2015); Fox et al. (2005); Whitfield-Gabrieli et al. (2009)), however, they are also subject to controversy surrounding questionable preprocessing steps such as global signal regression (Murphy et al., 2009). Still, a seed-based follow up with a different preprocessing pipeline could speak to the robustness of the observed network-to-network results. Finally, another obvious future direction for the network-to-network analysis is a parallel network-to-network correlation analysis in the CS sample to make all three studies reported in this dissertation have a common structure.

Regarding the graph theory analysis, one clear weakness of the current approach is a reliance on subjective threshold choices. For all measures except global connectivity, an informed decision was made to threshold subject-specific connectivity matrices by retaining only the top 15% strongest edge weights. This is a somewhat consensus procedure across the field and certainly makes any given paper more easily interpretable. However, there has been some discussion of unbiased reporting of results at multiple thresholds or debate regarding the proper choice of threshold if a single threshold were to be selected (Wang et al., 2011a; van Wijk et al., 2010; Santarnecchi et al., 2014). A conservative approach to publishing graph theory based studies in the future would be to perform all analyses at a variety of sparsity threshold. This may be not only methodologically prudent, but could comment on the ability of weak versus strong connections to predict individual differences in EFs and other behaviors. For example, it may be that the relationships we observed in the CS would be present in the LTS sample but at a different threshold. A related future direction is based on the robust finding that decreased participation coefficient is associated with higher updating-specific EF. In this relationship participation coefficient represented the diversity of DLPFC's connections based on a particular *a priori* definition of diversity. A novel analysis could modify that *a priori* definition of diversity by exploring the network structure of graphs in more detail. As it is currently implemented, calculation of participation coefficient relies on counting the number of different resting-state communities a given area is connected to. In the case of our graph theory analysis we utilized an *a priori* community parcellation provided by the creators of the reference atlas used in that study. A hierarchical modularity analysis (via hierarchical clustering or the Louvain algorithm) could provide multiple native parcellations to feed into calculation of participation coefficient. This analysis would show how a given region connects to a diversity of small, specialized clusters (low in the branching tree generated by the hierarchical algorithms) or larger, more general network. This analysis could also be personalized and scaled to an individuals brain connectivity matrix such that participation coefficient scales with how many modules an individual actually has in their brain network. One caveat is that as module/network/community size decreases in size, this participation coefficient measure would more strongly correlated with degree centrality and global connectivity. Modification of participation coefficient could be an important future direction given a lack of agreement in the field about what is considered a gold standard brain parcellation and also the ability to focus on particular *a priori* communities of interest (e.g., investigating only task-positive participation or participation in the communities as defined by the ICA analyses discussed in **Chapter 2**).

4.5 Conclusion

Here we've provided a multifaceted approach to investigating how intrinsic dynamics in the brain may relate to individual differences in specific aspects of behavior, executive functions. These studies are among the first to do so, and also are among the largest investigations of the neural basis of executive functions (i.e., with regard to sample size). Moreover, this work is grounded in a mature, well-vetted, and multifaceted theoretical model of behavior rather than relying on behavioral data from a single cognitive control task. These studies can be broken down into two complementary analyses - investigations of networks versus individual regions. Taking the results of these network and regional connectivity analyses together, we provide a new perspective on the neural bases of EFs that complements the enormous amount of effort spent understanding the mechanisms of cognitive control (e.g., using a computational modeling approach as in Chatham et al. (2011); Herd et al. (2014)) and the areas implicated in online cognitive control (e.g., using a brain mapping approach via fMRI studies of demanding versus non-demanding conditions as in Banich et al. (2001); Chatham et al. (2012)). First, individual differences in common EF were associated with the intensity of the frontoparietal network at rest and connectivity among networks of regions implicated in high level cognition (both "task-positive" and "task-negative" networks). Because common EF captures variance in a wide array of cognitive tasks, these features perhaps underlie the unity of the neural basis of EFs. The diversity aspects from the unity and diversity model of

EF are also associated with variation in separable neural substrates as assessed by resting-state connectivity. Individual differences in shifting-specific EF were associated with a more distributed set of resting-state connectivity measures than task-based neuroimaging studies may lead one to believe, for example, the spatial extent of a network of regions implicated in top-down biasing and the diversity of connections in sensorimotor cortex. Individual differences in updating-specific EF are not supported by variation in resting-state networks in the way common EF and shifting-specific EF are but rather by variation in a limited set of graph theoretic properties of individual regions. Some results for updating-specific EF are novel, such as a less integrated frontal pole being associated with higher updating-specific EF ability, while others are in agreement with findings from the computation modeling literature which suggests updating depends upon connectivity of lateral prefrontal cortex. Our work builds upon those findings by showing that not only do the mechanisms of working memory updating depend upon a certain type of connectivity, but variation in the degree to which individuals can update is associated with how connected dorsolateral prefrontal cortex is to a diverse set of other brain areas. The results of this dissertation are evidence that assessment of brain connectivity during the resting state may be a very lucrative avenue for a more thorough understanding of individual differences in ability.

Bibliography

Adelstein, J. S., Shehzad, Z. E., Mennes, M., Deyoung, C. G., Zuo, X.-N., Kelly, C., Margulies, D. S., Bloomfield, A., Gray, J. R., Castellanos, F. X., and Milham, M. P. (2011). Personality is reflected in the brain's intrinsic functional architecture. PloS one, 6(11):e27633.

Allen, E. A., Erhardt, E. B., Damaraju, E., Gruner, W., Segall, J. M., Silva, R. F., Havlicek, M., Rachakonda, S., Fries, J., Kalyanam, R., Michael, A. M., Caprihan, A., Turner, J. a., Eichele, T., Adelsheim, S., Bryan, A. D., Bustillo, J., Clark, V. P., Feldstein Ewing, S. W., Filbey, F., Ford, C. C., Hutchison, K., Jung, R. E., Kiehl, K. a., Kodituwakku, P., Komesu, Y. M., Mayer, A. R., Pearlson, G. D., Phillips, J. P., Sadek, J. R., Stevens, M., Teuscher, U., Thoma, R. J., and Calhoun, V. D. (2011). A baseline for the multivariate comparison of resting-state networks. Frontiers in systems neuroscience, 5(February):2.

Allen, J. S., Bruss, J., Brown, C. K., and Damasio, H. (2005). Normal neuroanatomical variation due to age: The major lobes and a parcellation of the temporal region. Neurobiology of Aging, 26(9):1245–1260.

Alvarez, J. A. and Emory, E. (2006). Executive function and the frontal lobes: a meta-analytic review. Neuropsychology review, 16(1):17–42.

Andrews-Hanna, J. R. (2011). The brain's default network and its adaptive role in internal mentation. The Neuroscientist, pages 1–20.

Asato, M. R., Terwilliger, R., Woo, J., and Luna, B. (2010). White matter development in adolescence: A DTI study. Cerebral Cortex, 20(9):2122–2131.

Baddeley, A. D. (1992). Working Memory. Science, 255(ii):556–559.

Badre, D. (2008). Cognitive control, hierarchy, and the rostro-caudal organization of the frontal lobes. Trends in Cognitive Sciences, 12(5):193–200.

Banich, M. T. (2009). Executive function: The search for an integrated account. Current Directions in Psychological Science, 18(2):89–94.

Banich, M. T., Milham, M. P., Atchley, R., Cohen, N. J., Webb, A. G., Wszalek, T., Kramer, A. F., Liang, Z.-p., Wright, A., Shenker, J., and Magin, R. (2000a). fMRI studies of Stroop tasks reveal unique roles of anterior and posterior brain systems in attentional selection. Journal of Cognitive Neuroscience, 12(6):988–1000.

Banich, M. T., Milham, M. P., Atchley, R. A., Cohen, N. J., Webb, A. G., Wszalek, T., Kramer, A. F., Liang, Z.-p., Barad, V., Gullett, D., Shah, C., and Brown, C. (2000b). Prefrontal regions play a predominant role in imposing an attentional set ’: evidence from fMRI. Cognitive Brain Research, 10:1–9.

Banich, M. T., Milham, M. P., Jacobson, B. L., Webb, A. G., Wszalek, T., Cohen, N. J., and Kramer, A. F. (2001). Attentional selection and the processing of task-irrelevant information : insights from fMRI examinations of the Stroop task. Progress in Brain Research, 134:1–12.

Barbey, A. K., Koenigs, M., and Grafman, J. (2013). Dorsolateral prefrontal contributions to human working memory. Cortex, 49(5):1195–1205.

Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: COnstructing a unifying theory of ADHD. Psychological Bulletin, 121(1):65–94.

Beckmann, C. F., Mackay, C. E., Filippini, N., and Smith, S. M. (2009). Group comparison of resting-state FMRI data using multi-subject ICA and dual regression. Technical report.

Beckmann, C. F. and Smith, S. M. (2004). Probabilistic Independent Component Analysis for Functional Magnetic Resonance Imaging. IEEE Trans. Med. Imaging, 1(23):137–152.

Bernard, J. a., Peltier, S. J., Wiggins, J. L., Jaeggi, S. M., Buschkuehl, M., Fling, B. W., Kwak, Y., Jonides, J., Monk, C. S., and Seidler, R. D. (2013). Disrupted cortico-cerebellar connectivity in older adults. NeuroImage, 83:103–19.

Boly, M., Phillips, C., Tshibanda, L., Vanhaudenhuyse, A., Schabus, M., Dang-Vu, T. T., Moonen, G., Hustinx, R., Maquet, P., and Laureys, S. (2008). Intrinsic brain activity in altered states of consciousness: How conscious is the default mode of brain function? Annals of the New York Academy of Sciences, 1129:119–129.

Braun, U., Plichta, M. M., Esslinger, C., Sauer, C., Haddad, L., Grimm, O., Mier, D., Mohnke, S., Heinz, A., Erk, S., Walter, H., Seiferth, N., Kirsch, P., and Meyer-Lindenberg, A. (2012). Test-retest reliability of resting-state connectivity network characteristics using fMRI and graph theoretical measures. NeuroImage, 59(2):1404–12.

Braver, T. S. (2012). The variable nature of cognitive control: a dual mechanisms framework. Trends in cognitive sciences, 16(2):106–13.

Braver, T. S., Cohen, J. D., Nystrom, L. E., Jonides, J., Smith, E. E., and Noll, D. C. (1997). A parametric study of prefrontal cortex involvement in human working memory. NeuroImage, 5(1):49–62.

Braver, T. S., Cole, M. W., and Yarkoni, T. (2010). Vive les differences! Individual variation in neural mechanisms of executive control. Current opinion in neurobiology, 20(2):242–250.

Buckner, R. L. (2013). The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging. Neuron, 80(3):807–15.

Buckner, R. L., Krienen, F. M., Castellanos, A., Diaz, J. C., and Yeo, B. T. T. (2011). The organization of the human cerebellum estimated by intrinsic functional connectivity. Journal of neurophysiology, 106(5):2322–45.

Buckner, R. L., Raichle, M. E., Squire, L. R., and Petersen, E. (1995). Functional Anatomical Retrieval Tasks Studies of Explicit and Implicit Memory. 15(January).

Cao, H., Plichta, M. M., Schäfer, A., Haddad, L., Grimm, O., Schneider, M., Esslinger, C., Kirsch, P., Meyer-Lindenberg, A., and Tost, H. (2013). Test-retest reliability of fMRI-based graph theoretical properties during working memory, emotion processing, and resting state. NeuroImage, 84C:888–900.

Castellanos, F. X., Di Martino, A., Craddock, R. C., Mehta, A. D., and Milham, M. P. (2013). Clinical applications of the functional connectome. NeuroImage, 80:527–40.

Cattell, R. B. (1943). The measurement of adult intelligence. Psychological Bulletin, 40(3):153–193.

Cattell, R. B. (1963). Theory of fluid and crystallized intelligence: A critical experiment. Journal of educational psychology, 54(1):1–22.

Chai, X. J., Castañán, A. N., Öngür, D., and Whitfield-Gabrieli, S. (2012). Anticorrelations in resting state networks without global signal regression. NeuroImage, 59(2):1420–1428.

Chatham, C. H., Claus, E. D., Kim, A., Curran, T., Banich, M. T., and Munakata, Y. (2012). Cognitive control reflects context monitoring, not motoric stopping, in response inhibition. PloS one, 7(2):e31546.

Chatham, C. H., Herd, S. A., Brant, A. M., Hazy, T. E., Miyake, A., O'Reilly, R. C., and Friedman, N. P. (2011). From an executive network to executive control: a computational model of the n-back task. Journal of cognitive neuroscience, 23(11):3598–619.

Choe, A. S., Jones, C. K., Joel, S. E., Muschelli, J., Belegu, V., Caffo, B. S., Lindquist, M. A., van Zijl, P. C. M., and Pekar, J. J. (2015). Reproducibility and Temporal Structure in Weekly Resting-State fMRI over a Period of 3.5 Years. Plos One, 10(10):e0140134.

Christoff, K., Keramatian, K., Gordon, A. M., Smith, R., and Mädler, B. (2009). Prefrontal organization of cognitive control according to levels of abstraction. Brain research, 1286:94–105.

Cole, M. W., Bassett, D. S., Power, J. D., Braver, T. S., and Petersen, S. E. (2014). Intrinsic and task-evoked network architectures of the human brain. Neuron, 83(1):238–51.

Cole, M. W., Ito, T., and Braver, T. S. (2015). Lateral prefrontal cortex contributes to fluid intelligence via multi-network connectivity. Brain connectivity, pages 1–15.

Cole, M. W., Yarkoni, T., Repovs, G., Anticevic, A., and Braver, T. S. (2012). Global connectivity of prefrontal cortex predicts cognitive control and intelligence. The Journal of neuroscience : the official journal of the Society for Neuroscience, 32(26):8988–99.

Collette, F., Van der Linden, M., Laureys, S., Delfiore, G., Degueldre, C., Luxen, A., and Salmon, E. (2005). Exploring the unity and diversity of the neural substrates of executive functioning. Human brain mapping, 25(4):409–23.

De Baene, W., Albers, A. M., and Brass, M. (2012). The what and how components of cognitive control. NeuroImage, 63(1):203–211.

Delamillieure, P., Doucet, G., Mazoyer, B., Turbelin, M.-R., Delcroix, N., Mellet, E., Zago, L., Crivello, F., Petit, L., Tzourio-Mazoyer, N., and Joliot, M. (2010). The resting state questionnaire: An introspective questionnaire for evaluation of inner experience during the conscious resting state. Brain research bulletin, 81(6):565–573.

Derrfuss, J., Brass, M., Neumann, J., and von Cramon, D. Y. (2005). Involvement of the inferior frontal junction in cognitive control: meta-analyses of switching and Stroop studies. Human brain mapping, 25(1):22–34.

Diamond, A. (2012). Activities and Programs That Improve Children's Executive Functions. Current Directions in Psychological Science, 21(5):335–341.

Donders, F. C. (1969). On the speed of mental processes. Acta psychologica, pages 412–431.

Dosenbach, N. U. F., Fair, D. A., Cohen, A. L., Schlaggar, B. L., and Petersen, S. E. (2008). A dual-networks architecture of top-down control. Trends in cognitive sciences, 12(3):99–105.

Esterman, M., Chiu, Y.-C., Tamber-Rosenau, B. J., and Yantis, S. (2009). Decoding cognitive control in human parietal cortex. Proceedings of the National Academy of Sciences of the United States of America, 106(42):17974–9.

Fedorenko, E., Duncan, J., and Kanwisher, N. (2013). Broad domain generality in focal regions of frontal and parietal cortex. Proceedings of the National Academy of Sciences of the United States of America, 110(41):16616–21.

Fox, M. D. and Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nature reviews. Neuroscience, 8(9):700–11.

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., and Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proceedings of the National Academy of Sciences of the United States of America, 102(27):9673–8.

Fox, M. D., Zhang, D., Snyder, A. Z., and Raichle, M. E. (2009). The global signal and observed anticorrelated resting state brain networks. Journal of neurophysiology, 101(6):3270–83.

Frank, M. J., Loughry, B., and O'Reilly, R. C. (2001). Interactions between frontal cortex and basal ganglia in working memory: a computational model. Cognitive, affective & behavioral neuroscience, 1(2):137–60.

Friedman, N. P., Altamirano, L. J., Miyake, A., Young, S. E., Corley, R. P., and Hewitt, J. K. (2012). Etiology of stability and change in executive functions from late adolescence to adulthood. In Behavioral Genetics.

Friedman, N. P. and Miyake, A. (2016). Unity and Diversity of Executive Functions: Individual Differences as a Window on Cognitive Structure. Cortex, pages 1–19.

Friedman, N. P., Miyake, A., Young, S. E., Defries, J. C., Corley, R. P., and Hewitt, J. K. (2008). Individual differences in executive functions are almost entirely genetic in origin. Journal of experimental psychology. General, 137(2):201–25.

Glahn, D. C., Winkler, A. M., Kochunov, P., Almasy, L., Duggirala, R., Carless, M. a., Curran, J. C., Olvera, R. L., Laird, a. R., Smith, S. M., Beckmann, C. F., Fox, P. T., and Blangero, J. (2010). Genetic control over the resting brain. Proceedings of the National Academy of Sciences of the United States of America, 107(3):1223–8.

Goel, V. and Vartanian, O. (2005). Dissociating the roles of right ventral lateral and dorsal lateral prefrontal cortex in generation and maintenance of hypotheses in set-shift problems. Cerebral Cortex, 15(8):1170–1177.

Gordon, E. M., Breeden, A. L., Bean, S. E., and Vaidya, C. J. (2012). Working memory-related changes in functional connectivity persist beyond task disengagement. Human Brain Mapping.

Gray, J. R. and Thompson, P. M. (2004). Neurobiology of intelligence: science and ethics. Nature Reviews Neuroscience, 5(6):471–482.

Greicius, M. (2008). Resting-state functional connectivity in neuropsychiatric disorders. Current opinion in neurology, 21(4):424–30.

Greicius, M. D., Kiviniemi, V., Tervonen, O., Vainionpää, V., Reiss, A. L., and Menon, V. (2008). Persistent default-mode network connectivity during light sedation. Human brain mapping, 29(7):839–847.

Guimerà, R. and Amaral, L. a. N. (2005). Functional cartography of complex metabolic networks. Nature, 433(February):895–900.

Guo, C. C., Kurth, F., Zhou, J., Mayer, E. a., Eickhoff, S. B., Kramer, J. H., and Seeley, W. W. (2012). One-year test-retest reliability of intrinsic connectivity network fMRI in older adults. NeuroImage.

Hackman, D. A. and Farah, M. J. (2009). Socioeconomic status and the developing brain. Trends in cognitive sciences, 13(2):65–73.

Hagberg, A. A., Schult, D. A., and Swart, P. J. (2008). Exploring network structure, dynamics, and function using NetworkX. Proceedings of the 7th Python in Science Conference (SciPy 2008), (SciPy):11–15.

Hampshire, A. and Owen, A. M. (2006). Fractionating attentional control using event-related fMRI. Cerebral Cortex, 16(12):1679–1689.

Hampson, M., Driesen, N. R., Skudlarski, P., Gore, J. C., and Constable, R. T. (2006). Brain Connectivity Related to Working Memory Performance. The Journal of Neuroscience, 26(51):13338–13343.

Hampson, M., Tokoglu, F., Shen, X., Scheinost, D., Papademetris, X., and Constable, R. T. (2012). Intrinsic brain connectivity related to age in young and middle aged adults. PloS one, 7(9):e44067.

Hazy, T. E., Frank, M. J., and O'reilly, R. C. (2007). Towards an executive without a homunculus: computational models of the prefrontal cortex/basal ganglia system. Philosophical transactions of the Royal Society of London. Series B, Biological sciences, 362(1485):1601–13.

Herd, S. A., Banich, M. T., and O'Reilly, R. C. (2006). Neural Mechanisms of Cognitive Control : An Integrative Model of Stroop Task Performance and fMRI Data. Journal of Cognitive Neuroscience, 18(1):22–32.

Herd, S. a., OReilly, R. C., Hazy, T. E., Chatham, C. H., Brant, A. M., and Friedman, N. P. (2014). A neural network model of individual differences in task switching abilities. Neuropsychologia, 62:1–15.

Hoptman, M. J., Zuo, X.-N., Butler, P. D., Javitt, D. C., D'Angelo, D., Mauro, C. J., and Milham, M. P. (2010). Amplitude of low-frequency oscillations in schizophrenia: A resting state fMRI study. Schizophrenia Research, 117(1):13–20.

Ivry, R. B. and Keele, S. W. (1989). Timing functions of the cerebellum. Journal of cognitive neuroscience, 1(2):136–52.

Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., and Smith, S. M. (2012). FSL. NeuroImage, 62(2):782–90.

Jernigan, T. L., Archibald, S. L., Fennema-Notestine, C., Gamst, A. C., Stout, J. C., Bonner, J., and Hesselink, J. R. (2001). Effects of age on tissues and regions of the cerebrum and cerebellum. Neurobiology of Aging, 22(4):581–594.

Jurado, M. B. and Rosselli, M. (2007). The elusive nature of executive functions: A review of our current understanding. Neuropsychology Review, 17(3):213–233.

Keller, J. B., Hedden, T., Thompson, T. W., Anteraper, S. a., Gabrieli, J. D., and Whitfield-Gabrieli, S. (2015). Resting-state anticorrelations between medial and lateral prefrontal cortex: Association with working memory, aging, and individual differences. Cortex, 64:271–280.

Kelly, A. M. C., Uddin, L. Q., Biswal, B. B., Castellanos, F. X., and Milham, M. P. (2008). Competition between functional brain networks mediates behavioral variability. NeuroImage, 39(1):527–37.

Kelly, R. M. and Strick, P. L. (2003). Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. The Journal of neuroscience : the official journal of the Society for Neuroscience, 23(23):8432–44.

Koechlin, E., Ody, C., and Kouneiher, F. (2003). The architecture of cognitive control in the human prefrontal cortex. Science (New York, N.Y.), 302(5648):1181–5.

Konishi, S., Nakajima, K., Uchida, I., Kameyama, M., Nakahara, K., Sekihara, K., and Miyashita, Y. (1998). Transient activation of inferior prefrontal cortex during cognitive set shifting. Nature neuroscience, 1(1):80–84.

Küblböck, M., Woletz, M., Höflich, A., Sladky, R., Kranz, G. S., Hoffmann, A., Lanzenberger, R., and Windischberger, C. (2014). Stability of low-frequency fluctuation amplitudes in prolonged resting-state fMRI. NeuroImage, 103:249–57.

Lemaitre, H., Goldman, A. L., Sambataro, F., Verchinski, B. A., Meyer-Lindenberg, A., Weinberger, D. R., and Mattay, V. S. (2012). Normal age-related brain morphometric changes: Nonuniformity across cortical thickness, surface area and gray matter volume? Neurobiology of Aging, 33(3):617.e1–617.e9.

Liston, C., Watts, R., Tottenham, N., Davidson, M. C., Niogi, S., Ulug, A. M., and Casey, B. J. (2006). Frontostriatal microstructure modulates efficient recruitment of cognitive control. Cerebral Cortex, 16(4):553–560.

Liu, C., Chen, Z., Wang, T., Tang, D., and Hitchman, G. (2015). Predicting Stroop Effect from Spontaneous Neuronal Activity : A Study of Regional Homogeneity. PloS one, pages 1–14.

Liu, Z., Xu, C., Xu, Y., Wang, Y., Zhao, B., Lv, Y., Cao, X., Zhang, K., and Du, C. (2010). Decreased regional homogeneity in insula and cerebellum: A resting-state fMRI study in patients with major depression and subjects at high risk for major depression. Psychiatry Research: Neuroimaging, 182(3):211–215.

Margulies, D. S., Böttger, J., Long, X., Lv, Y., Kelly, C., Schäfer, A., Goldhahn, D., Abbushi, A., Milham, M. P., Lohmann, G., and Villringer, A. (2010). Resting developments: a review of fMRI post-processing methodologies for spontaneous brain activity. Magma (New York, N.Y.), 23(5-6):289–307.

Matsui, T., Murakami, T., and Ohki, K. (2016). Transient neuronal coactivations embedded in globally propagating waves underlie resting-state functional connectivity. Proceedings of the National Academy of Sciences, 113(23):201521299.

Mayr, U. and Kliegl, R. (2000). Task-set switching and long-term memory retrieval. Journal of Experimental Psychology: Learning, Memory, and Cognition, 26(5):1124–1140.

McNab, F. and Klingberg, T. (2008). Prefrontal cortex and basal ganglia control access to working memory. Nature neuroscience, 11(1):103–7.

Mennes, M., Kelly, C., Zuo, X.-N., Di Martino, A., Biswal, B. B., Castellanos, F. X., and Milham, M. P. (2010). Inter-individual differences in resting-state functional connectivity predict task-induced BOLD activity. NeuroImage, 50(4):1690–701.

Mennes, M., Zuo, X.-N., Kelly, C., Di Martino, A., Zang, Y.-F., Biswal, B., Castellanos, F. X., and Milham, M. P. (2011). Linking inter-individual differences in neural activation and behavior to intrinsic brain dynamics. NeuroImage, 54(4):2950–9.

Meunier, D., Achard, S., Morcom, A., and Bullmore, E. (2009). Age-related changes in modular organization of human brain functional networks. NeuroImage, 44(3):715–723.

Milham, M. P. and Banich, M. T. (2005). Anterior Cingulate Cortex : An fMRI Analysis of Conflict Specificity and Functional Differentiation. Human Brain Mapping, 335:328 –335.

Miller, E. K. and Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. Annual review of neuroscience, 24:167–202.

Miyake, A. and Friedman, N. P. (2012). The Nature and Organization of Individual Differences in Executive Functions: Four General Conclusions. Current directions in psychological science, 21(1):8–14.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., and Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex ”Frontal Lobe” tasks: a latent variable analysis. Cognitive psychology, 41(1):49–100.

Monchi, O., Petrides, M., Petre, V., Worsley, K., and Dagher, A. (2001). Wisconsin Card Sorting revisited: distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. The Journal of neuroscience : the official journal of the Society for Neuroscience, 21(19):7733–7741.

Monsell, S. (2003). Task switching. Trends in cognitive sciences, 7(3):134–140.

Mowinckel, A. M., Espeseth, T., and Westlye, L. T. (2012). Network-specific effects of age and in-scanner subject motion: A resting-state fMRI study of 238 healthy adults. NeuroImage, 63(3):1364–1373.

Murphy, K., Birn, R. M., Handwerker, D. A., Jones, T. B., and Bandettini, P. A. (2009). The impact of global signal regression on resting state correlations: Are anti-correlated networks introduced? NeuroImage, 44(3):893–905.

Newman, M. E. J. (2010). Networks: An Introduction. Oxford University Press.

Niendam, T. A., Laird, A. R., Ray, K. L., Dean, Y. M., and Carter, C. S. (2012). Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. Cognitive, Affective, & Behavioral Neuroscience, 12(2):241–268.

Nieuwenstein, M. R., Aleman, a., and de Haan, E. H. (2001). Relationship between symptom dimensions and neurocognitive functioning in schizophrenia: a meta-analysis of WCST and CPT studies. Wisconsin Card Sorting Test. Continuous Performance Test. Journal of psychiatric research, 35(2):119–25.

Onnela, J. P., Saramäki, J., Kertész, J., and Kaski, K. (2005). Intensity and coherence of motifs in weighted complex networks. Physical Review E - Statistical, Nonlinear, and Soft Matter Physics, 71(6):1–4.

O'Reilly, R. C. and Frank, M. J. (2006). Making working memory work: A computational model of learning in the prefrontal cortex and basal ganglia. Neural computation, 18(2):283–328.

Orr, J. M. and Banich, M. T. (2014). The neural mechanisms underlying internally and externally guided task selection. NeuroImage, 84:191–205.

Orr, J. M., Smolker, H. R., and Banich, M. T. (2015). Organization of the Human Frontal Pole Revealed by Large-Scale DTI-Based Connectivity: Implications for Control of Behavior. Plos One, 10(5):e0124797.

Patriat, R., Molloy, E. K., Meier, T. B., Kirk, G. R., Nair, V. a., Meyerand, M. E., Prabhakaran, V., and Birn, R. M. (2013). The effect of resting condition on resting-state fMRI reliability and consistency: A comparison between resting with eyes open, closed, and fixated. NeuroImage, 78C:463–473.

Pedregosa, F. and Varoquaux, G. (2011). Scikit-learn: Machine Learning in Python. Journal of Machine . . . , 12:2825–2830.

Petersen, S. E. and Posner, M. I. (2012). The attention system of the human brain: 20 years after. Annual Review of Clinical Psychology, 35:73–89.

Power, J. D., Cohen, A. L., Nelson, S. M., Wig, G. S., Barnes, K. A., Church, J. A., Vogel, A. C., Laumann, T. O., Miezin, F. M., Schlaggar, B. L., and Petersen, S. E. (2011). Functional network organization of the human brain. Neuron, 72(4):665–78.

Raichle, M. E., Macleod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., and Shulman, G. L. (2001). A default mode of brain function. Proceedings of the National Academy of Sciences of the United States of America, 98(2):676–682.

Ramnani, N. (2006). The primate cortico-cerebellar system: anatomy and function. Nature reviews. Neuroscience, 7(7):511–22.

Ramnani, N. and Owen, A. M. (2004). Anterior prefrontal cortex: insights into function from anatomy and neuroimaging. Nature reviews. Neuroscience, 5(3):184–94.

Raven, J. (1998). Raven's Progressive Matrices and Vocabulary Scales.

Reineberg, A. E., Andrews-Hanna, J. R., Depue, B. E., Friedman, N. P., and Banich, M. T. (2015). Resting-state Networks Predict Individual Differences in Common and Specific Aspects of Executive Function. NeuroImage, 104:69–78.

Reineberg, A. E. and Banich, M. T. (2016). Functional connectivity at rest is sensitive to individual differences in executive function: A network analysis. Human Brain Mapping, 00.

Repovs, G., Csernansky, J. G., and Barch, D. M. (2011). Brain network connectivity in individuals with schizophrenia and their siblings. Biological Psychiatry, 69(10):967–973.

Rhea, S.-A., Gross, A. a., Haberstick, B. C., and Corley, R. P. (2006). Colorado twin registry. Twin research and human genetics : the official journal of the International Society for Twin Studies, 9(6):941–949.

Rhea, S.-A., Gross, A. A., Haberstick, B. C., and Corley, R. P. (2013). Colorado Twin Registry - An Update. Twin research and human genetics : the official journal of the International Society for Twin Studies, 16(1):1–14.

Roberts, R. J., Hager, L. D., and Heron, C. (1994). Prefrontal Cognitive Processes: Working Memory and Inhibition in the Antisaccade Task. Journal of Experimental Psychology: General, 123(4):374–393.

Rubinov, M. and Sporns, O. (2010). Complex network measures of brain connectivity: uses and interpretations. NeuroImage, 52(3):1059–69.

Rytty, R., Nikkinen, J., Paavola, L., Abou Elseoud, A., Moilanen, V., Visuri, A., Tervonen, O., Renton, A. E., Traynor, B. J., Kiviniemi, V., and Remes, A. M. (2013). GroupICA dual regression analysis of resting state networks in a behavioral variant of frontotemporal dementia. Frontiers in human neuroscience, 7(August):461.

Sakai, K. (2008). Task set and prefrontal cortex. Annual review of neuroscience, 31:219–45.

Sala-Llonch, R., Peña-Gómez, C., Arenaza-Urquijo, E. M., Vidal-Piñeiro, D., Bargalló, N., Junqué, C., and Bartrés-Faz, D. (2011). Brain connectivity during resting state and subsequent working memory task predicts behavioural performance. Cortex, pages 1–10.

Salat, D. H., Buckner, R. L., Snyder, A. Z., Greve, D. N., Desikan, R. S. R., Busa, E., Morris, J. C., Dale, A. M., and Fischl, B. (2004). Thinning of the cerebral cortex in aging. Cerebral Cortex, 14(7):721–730.

Salmi, J., Pallesen, K. J., Neuvonen, T., Brattico, E., Korvenoja, A., Salonen, O., and Carlson, S. (2010). Cognitive and motor loops of the human cerebro-cerebellar system. Journal of cognitive neuroscience, 22(11):2663–76.

Sampaio, A., Soares, J. M., Coutinho, J., Sousa, N., and Gonçalves, O. F. (2013). The Big Five default brain: functional evidence. Brain structure & function.

Santarnecchi, E., Galli, G., Polizzotto, N. R., Rossi, A., and Rossi, S. (2014). Efficiency of weak brain connections support general cognitive functioning. Human brain mapping, 35(9):4566–82.

Schaeffer, D. J., Amlung, M. T., Li, Q., Krafft, C. E., Austin, B. P., Dyckman, K. a., and McDowell, J. E. (2013). Neural correlates of behavioral variation in healthy adults' antisaccade performance. Psychophysiology, 50(4):325–33.

Scheinost, D., Finn, E. S., Tokoglu, F., Shen, X., Papademetris, X., Hampson, M., and Constable, R. T. (2014). Sex differences in normal age trajectories of functional brain networks. Human brain mapping, 00(October).

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., Reiss, A. L., and Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. The Journal of neuroscience : the official journal of the Society for Neuroscience, 27(9):2349–56.

Sescousse, G., Redouté, J., and Dreher, J.-C. (2010). The architecture of reward value coding in the human orbitofrontal cortex. The Journal of neuroscience, 30(39):13095–104.

Shaw, P., Kabani, N. J., Lerch, J. P., Eckstrand, K., Lenroot, R., Gogtay, N., Greenstein, D., Clasen, L., Evans, A., Rapoport, J. L., Giedd, J. N., and Wise, S. P. (2008). Neurodevelopmental trajectories of the human cerebral cortex. The Journal of neuroscience : the official journal of the Society for Neuroscience, 28(14):3586–3594.

Shehzad, Z. E., Kelly, A. M. C., Reiss, P. T., Gee, D. G., Gotimer, K., Uddin, L. Q., Lee, S. H., Margulies, D. S., Roy, A. K., Biswal, B. B., Petkova, E., Castellanos, F. X., and Milham, M. P. (2009). The resting brain: unconstrained yet reliable. Cerebral cortex (New York, N.Y. : 1991), 19(10):2209–29.

Shulman, G. L., Fiez, J. a., Corbetta, M., Buckner, R. L., Miezin, F. M., Raichle, M. E., and Petersen, S. E. (1997). Common Blood Flow Changes across Visual Tasks: II. Decreases in Cerebral Cortex. Journal of Cognitive Neuroscience, 9(5):648–663.

Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., Filippini, N., Watkins, K. E., Toro, R., Laird, A. R., and Beckmann, C. F. (2009). Correspondence of the brain' s functional architecture during activation and rest. Proceedings of the National Academy of Sciences of the United States of America, 106(31):13040–13045.

Smith, S. M., Hyvärinen, A., Varoquaux, G., Miller, K. L., and Beckmann, C. F. (2014). Group-PCA for very large fMRI datasets. NeuroImage, 101:738–49.

Smith, S. M., Nichols, T. E., Vidaurre, D., Winkler, A. M., Behrens, T. E. J., Glasser, M. F., Ugurbil, K., Barch, D. M., Essen, D. C. V., and Miller, K. L. (2015). A positive-negative mode of population covariation links brain connectivity, demographics and behavior. Nature Neuroscience, (September):1–7.

Smolker, H. R., Depue, B. E., Reineberg, A. E., Orr, J. M., and Banich, M. T. (2014). Individual differences in regional prefrontal gray matter morphometry and fractional anisotropy are associated with different constructs of executive function. Brain structure & function.

Snyder, H. R., Miyake, A., and Hankin, B. L. (2015). Advancing understanding of executive function impairments and psychopathology: Bridging the gap between clinical and cognitive approaches. Frontiers in Psychology, 6(MAR).

Song, M., Zhou, Y., Li, J., Liu, Y., Tian, L., Yu, C., and Jiang, T. (2008). Brain spontaneous functional connectivity and intelligence. NeuroImage, 41(3):1168–1176.

Sowell, E. R. (2004). Longitudinal Mapping of Cortical Thickness and Brain Growth in Normal Children. Journal of Neuroscience, 24(38):8223–8231.

Sporns, O., Chialvo, D. R., Kaiser, M., and Hilgetag, C. C. (2004). Organization, development and function of complex brain networks. Trends in cognitive sciences, 8(9):418–25.

Spreng, R. N., Stevens, W. D., Chamberlain, J. P., Gilmore, A. W., and Schacter, D. L. (2010). Default network activity, coupled with the frontoparietal control network, supports goal-directed cognition. NeuroImage, 53(1):303–17.

Stoodley, C. J. and Schmahmann, J. D. (2009). Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. NeuroImage, 44(2):489–501.

Stuss, D. T. and Alexander, M. P. (2000). Executive functions and the frontal lobes: a conceptual view. Psychological research, 63(3-4):289–298.

Takeuchi, H., Taki, Y., Nouchi, R., Hashizume, H., Sekiguchi, A., Kotozaki, Y., Nakagawa, S., Miyauchi, C. M., Sassa, Y., and Kawashima, R. (2012). Effects of working memory training on functional connectivity and cerebral blood flow during rest. Cortex; a journal devoted to the study of the nervous system and behavior, pages 1–20.

Thompson, G. J., Magnuson, M. E., Merritt, M. D., Schwarb, H., Pan, W.-J., McKinley, A., Tripp, L. D., Schumacher, E. H., and Keilholz, S. D. (2012). Short-time windows of correlation between large-scale functional brain networks predict vigilance intraindividually and interindividually. Human brain mapping, 00(May).

Tian, L., Kong, Y., Ren, J., Varoquaux, G., Zang, Y., and Smith, S. M. (2013). Spatial vs. Temporal Features in ICA of Resting-State fMRI - A Quantitative and Qualitative Investigation in the Context of Response Inhibition. PLoS ONE, 8(6).

Tian, L., Ren, J., and Zang, Y. (2011). Regional homogeneity of resting state fMRI signals predicts Stop signal task performance. NeuroImage.

Uddin, L. Q., Supekar, K., Amin, H., Rykhlevskaia, E., Nguyen, D. a., Greicius, M. D., and Menon, V. (2010). Dissociable connectivity within human angular gyrus and intraparietal sulcus: evidence from functional and structural connectivity. Cerebral cortex (New York, N.Y. : 1991), 20(11):2636–46.

Utevsky, A. V., Smith, D. V., and Huettel, S. a. (2014). Precuneus is a functional core of the default-mode network. The Journal of neuroscience : the official journal of the Society for Neuroscience, 34(3):932–40.

Vaidya, C. J. and Gordon, E. M. (2013). Phenotypic variability in resting-state functional connectivity: current status. Brain connectivity, 3(2):99–120.

Van Den Heuvel, M. P., Mandl, R. C. W., Kahn, R. S., and Hulshoff Pol, H. E. (2009). Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. Human Brain Mapping, 30(10):3127–3141.

van den Heuvel, M. P. and Sporns, O. (2013). Network hubs in the human brain. Trends in cognitive sciences, 17(12):683–96.

Van Dijk, K. R. A., Sabuncu, M. R., and Buckner, R. L. (2012). The influence of head motion on intrinsic functional connectivity MRI. NeuroImage, 59(1):431–8.

van Wijk, B. C. M., Stam, C. J., and Daffertshofer, A. (2010). Comparing brain networks of different size and connectivity density using graph theory. PLoS ONE, 5(10).

Vincent, J. L., Kahn, I., Snyder, A. Z., Raichle, M. E., and Buckner, R. L. (2008). Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. Journal of neurophysiology, 100(6):3328–42.

Vossel, S., Geng, J. J., and Fink, G. R. (2014). Dorsal and Ventral Attention Systems Distinct Neural Circuits but Collaborative Roles. The Neuroscientist, 20:150–159.

Wager, T. D., Jonides, J., and Reading, S. (2004). Neuroimaging studies of shifting attention: a meta-analysis. NeuroImage, 22(4):1679–93.

Wager, T. D. and Smith, E. E. (2003). Neuroimaging studies of working memory: a meta-analysis. Cognitive, affective & behavioral neuroscience, 3(4):255–74.

Wager, T. D., Sylvester, C.-Y. C., Lacey, S. C., Nee, D. E., Franklin, M., and Jonides, J. (2005). Common and unique components of response inhibition revealed by fMRI. NeuroImage, 27(2):323–340.

Walhovd, K. B., Fjell, A. M., Reinvang, I., Lundervold, A., Dale, A. M., Eilertsen, D. E., Quinn, B. T., Salat, D., Makris, N., and Fischl, B. (2005). Effects of age on volumes of cortex, white matter and subcortical structures. Neurobiology of Aging, 26(9):1261–1270.

Walhovd, K. B., Westlye, L. T., Amlien, I. K., Espeseth, T., Reinvang, I., Agartz, I., Salat, D. H., Greve, D. N., Fischl, B., Dale, A. M., and Fjell, A. M. (2011). Consistent neuroanatomical age-related volume differences across multiple samples. Neurobiology of Aging, 32(5):916–932.

Wang, J.-H., Zuo, X.-N., Gohel, S., Milham, M. P., Biswal, B. B., and He, Y. (2011a). Graph theoretical analysis of functional brain networks: test-retest evaluation on short- and long-term resting-state functional MRI data. PloS one, 6(7):e21976.

Wang, K., Liang, M., Wang, L., Tian, L., Zhang, X., Li, K., and Jiang, T. (2007). Altered functional connectivity in early Alzheimer's disease: A resting-state fMRI study. Human Brain Mapping, 28(10):967–978.

Wang, L., Song, M., Jiang, T., Zhang, Y., and Yu, C. (2011b). Regional homogeneity of the resting-state brain activity correlates with individual intelligence. Neuroscience Letters, 488(3):275–278.

Warren, D. E., Power, J. D., Bruss, J., Denburg, N. L., Waldron, E. J., Sun, H., Petersen, S. E., and Tranel, D. (2014). Network measures predict neuropsychological outcome after brain injury. Proceedings of the National Academy of Sciences, 111(39).

Wechsler, D. (2003). WISC-IV: Administration and scoring manual. Psychological Corporation.

Wei, L., Duan, X., Zheng, C., Wang, S., Gao, Q., Zhang, Z., Lu, G., and Chen, H. (2012). Specific frequency bands of amplitude low-frequency oscillation encodes personality. Human brain mapping, 000(July).

Whitfield-Gabrieli, S. and Nieto-Castanon, A. (2012). Conn: A Functional Connectivity Toolbox for Correlated and Anticorrelated Brain Networks. Brain Connectivity, 2(3):125–141.

Whitfield-Gabrieli, S., Thermenos, H. W., Milanovic, S., Tsuang, M. T., Faraone, S. V., McCarley, R. W., Shenton, M. E., Green, A. I., Nieto-Castanon, A., LaViolette, P., Wojcik, J., Gabrieli, J. D. E., and Seidman, L. J. (2009). Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. Proceedings of the National Academy of Sciences of the United States of America, 106(4):1279–84.

Wig, G. S., Schlaggar, B. L., and Petersen, S. E. (2011). Concepts and principles in the analysis of brain networks. Annals of the New York Academy of Sciences, 1224:126–46.

Wilcox, R. R. and Keselman, H. J. (2003). Modern robust data analysis methods: measures of central tendency. Psychological methods, 8(3):254–74.

Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., and Nichols, T. E. (2014). Permutation inference for the general linear model. NeuroImage, 92:381–397.

Yang, Z., Chang, C., Xu, T., Jiang, L., Handwerker, D. a., Castellanos, F. X., Milham, M. P., Bandettini, P. a., and Zuo, X.-N. (2013). Connectivity trajectory across lifespan differentiates the precuneus from the default network. NeuroImage, 89:45–56.

Yarkoni, T. and Braver, T. S. (2010). Cognitive neuroscience approaches to individual differences in working memory and executive control: Conceptual and methodological issues. Handbook of individual differences in cognition: Attention, memory, and executive control., pages 87–107.

Yarkoni, T., Poldrack, R. A., Nichols, T. E., Van Essen, D. C., and Wager, T. D. (2011). Large-scale automated synthesis of human functional neuroimaging data. Nature Methods, 8(8):665–670.

Yeo, B. T. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., Roffman, J. L., Smoller, J. W., Zöllei, L., Polimeni, J. R., Fischl, B., Liu, H., and Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. Journal of neurophysiology, 106(3):1125–65.

Yntema, D. B. (1963). Keeping track of several things at oncce. Human Factors : The Journal of the Human Factors and Ergonomics Society, 5(7):7–17.

Zhang, D. and Raichle, M. E. (2010). Disease and the brain's dark energy. Nature reviews. Neurology, 6(1):15–28.

Zhang, S. and Li, C.-s. R. (2012). Functional networks for cognitive control in a stop signal task: independent component analysis. Human brain mapping, 33(1):89–104.

Zou, Q., Miao, X., Liu, D., Wang, D. J., Zhuo, Y., and Gao, J.-H. (2015). Reliability comparison of spontaneous brain activities between BOLD and CBF contrasts in eyes-open and eyes-closed resting states. NeuroImage, 121:91–105.

Zuo, X.-N., Di Martino, A., Kelly, C., Shehzad, Z. E., Gee, D. G., Klein, D. F., Castellanos, F. X., Biswal, B. B., and Milham, M. P. (2010). The oscillating brain: Complex and reliable. NeuroImage, 49(2):1432–1445.

Appendix A

Supplemental Information from Review of Resting-state and Individual Differences Literature

Summary

Although cut from the main text for the sake of brevity, this section provides a detailed summary and analysis at studies (prior to December 2015) that investigated individual differences in cognitive abilities as a function of resting-state fMRI.

A.1 Review of rs-fMRI and Individual Differences

A.1.1 Planning and Attention

One of the earliest studies to investigate rs-fMRI-behavior relationships was the work of Seeley et al. (2007) who sought to validate the presence of two newly discovered resting-state networks a salience network and an executive control network - by showing dissociable relationships between these networks and behaviors relevant to the purported role of each network. The salience network was isolated by looking at the connectivity between right orbitofrontal insula and the rest of the brain. The orbitofrontal insula seed region was taken from a GLM-based analysis of the N-back working memory task (2 back condition) that participants performed earlier in the scanning session. This network identified as connected to the orbitofrontal seed (i.e., the salience network) contained frontal insula, dorsal anterior cingulate/paracingulate cortex, temporal pole, dorsolateral prefrontal cortex (DLPFC), supplementary motor area (SMA), operculum, amygdala, thalamus, hypothalamus, and periaqueductal gray regions and was purported to be involved in interoceptive and autonomic processing. They defined the executive control network as a set of regions connected to another seed, DLPFC, again extracted from a GLM-based analysis of the N-back task performed earlier in the scanning session. The executive control network contained bilateral DLPFC, ventrolateral PFC, dorsomedial PFC, lateral parietal, and left frontal insular regions and was purported to be a network critical for the performance of executive tasks such as the N-back working memory task. An independent components analysis of the resting scans was performed to verify both networks presence and independence in a data-driven manner. Seeley and colleagues examined whether or not individual differences in the relative contribution of each region within these networks is related to the behaviors and abilities associated with each network. Specifically, they hypothesized that the connectivity of regions within the salience network would be associated with individual differences in interoceptive and autonomic processing, as measured by and index of anxiety, and that the connectivity of regions within the executive control network would be associated with variation in performance of a planning task the trail-making task (Trails B Trails A time to completion, shorter = superior performance). For purposes of this review, we focus on validation of the executive control network. They found connectivity of two executive control network regions - the left and right intraparietal sulcus and superior parietal lobe (X = -38, Y = -78, Z = 36 and X = 36, Y = -80, Z = 26, respectively) predicted faster trail-making performance. Specifically, they found that individuals with higher loading of these particular regions within the executive control network had faster trail-making performance.

Another early study (Kelly et al., 2008) investigated how the interaction of two well-characterized resting-state networks the dorsal attention network and default network - is associated with performance on an attention task the Eriksen flanker task. Interest in these particular networks emerged from a small literature demonstrating an inherent competition between the networks while performing externally directed attention/cognitive control tasks as well as at rest (Gusnard & Raichle, 2001). When individuals perform such tasks well, activity in the dorsal attention system increases (for this reason it is sometimes referred to as a task positive network) while activity in the default network decreases (for this reason it is sometimes referred to as a task negative network). When individuals are at rest, the negative correlation of these two networks is maintained. Given the importance of the negative correlation of these networks during the performance of tasks, they hypothesized that the degree to which individuals can consistently preserve the negative correlation between the dorsal attention network and default network at rest is an important individual difference and one that may be related to the level of functioning of that individual. They found that indeed individuals who exhibited a strong negative correlation between these two networks performed with less variability on a task that requires attention in the face of distracting information. One possible caveat of this analysis is that the negative correlation between the attention and default networks could be due to task set inertia from the Flanker task, which was performed in the scanner in close proximity to the resting scan (i.e., Flanker task likely proceeded resting scan, but methods are unclear).

A series of studies followed up on the work of Kelly and colleagues by examining the degree to which rs-fMRI can be used to predict BOLD activity during performance of the Eriksen flanker task (Mennes et al., 2010, 2011). First, Mennes and colleagues computed several resting-state connectivity measures for 6 a priori regions of interest - intraparietal sulcus (-25, -57, 46), the middle temporal region (-45, -69, -2), the right frontal eye field region of the precentral sulcus (25, -13, 50), left lateral parietal cortex (-45, -67, 36), medial prefrontal cortex (-1, 47, -4), and posterior cingulate/precuneus (-5, -49, 40) - and the default network and executive control network as a whole. The six regions of interest were chosen as those most representative of core regions within the default and executive control networks based on a prior study (Fox et al., 2005). For each seed region, they computed a whole-brain resting-state connectivity map. For the three seed regions that fell within the executive control network - the intraparietal sulcus, middle temporal, and precentral sulcus - greater resting-state connectivity, as measured by the number of significant positively correlated voxels at rest, predicted higher BOLD signal during performance of the flanker task (incongruent + congruent trials ¿ baseline). For the three seed regions from the default network greater negative functional connectivity between the seeds and the rest of the brain was associated with higher BOLD signal during performance of the Flanker task. The same pattern held when the whole executive control or default network was used as a seed rather than individual seed regions within the networks. One caveat of this study is that no relationships between performance and rs-fMRI were found. Rs-fMRI only predicted task-induced activation during the Flanker task.

The same group also investigated how the amplitude of low frequency fluctuations during rest is associated with BOLD signal during performance of the Flanker task (Mennes et al., 2011). The fractional amplitude of low frequency fluctuation (fALFF) is a measure of the proportion of the total resting-state signal for a given individual that lies within an a priori defined range at the low end of the frequency spectrum (usually 0.01 0.1 Hz). This measure is of interest because fALFF 1. was one of the first resting-state measures that was reliably observed within an individual across multiple time points (Zuo et al., 2010), 2. is an important indicator of increased symptomatology in a number of clinical disorders (e.g., in major depressive disorder (Liu et al., 2010), schizophrenia (Hoptman et al., 2010), and Alzheimers disease (Wang et al., 2007)), and 3. is one of the few resting-state measures that describe an inherent property of an individual region without considering its relationship to other brain regions (i.e., does not rely on parcellations of the cortex/subcortex and is computationally inexpensive). They found that fALFF in a number of regions was associated with increased BOLD signal during performance of the Flanker task (incongruent + congruent trials ¿ baseline). These regions included dorsal and ventral anterior cingulate cortex, bilateral frontal eye fields, bilateral middle frontal gyrus, bilateral insula (operculum), left precentral sulcus, and right precuneus. Most of these regions would be classified as members of the frontoparietal network. Additionally, fALFF in left lateral occipital cortex was associated with increased signal in the incongruent versus congruent contrast potentially indicating a ramping up of processing in sensory areas in the face of increased demand from the incongruent trials. Finally, higher fALFF in anterior cingulate and precuneus was associated with faster and less variable behavior on incongruent and congruent trials in the Flanker task. This final finding is difficult to interpret, however, both regions have been linked to monitoring type processes and could play an important role in regulating the allocation of attention to either relevant aspects of the Flanker task set (for the anterior cingulate) or towards external versus internal processes in general (for the precuneus).

One final study investigated how rs-fMRI is related to vigilance, specifically the ability to monitor for infrequent stimuli (Thompson et al., 2012). Thompson and colleagues were interested in how competition between the default and task positive networks was related to vigilance performance. One theory of the function of the default network theory suggests that its role is in self-referential and related processes (Andrews-Hanna, 2011). This function stands in contrast to the role of the task positive networks such as the frontoparietal and attention networks. As stated previously, task positive networks are those that typically increase in BOLD signal while participants are engaged in a demanding cognitive task. Often time, task positive and default networks are negatively correlated while individuals perform a demanding cognitive task. They found increased negative correlation of these two networks at rest was associated with faster performance on the vigilance task.

In summary, individual differences in planning and attentional processing measures seem to manifest primarily in the integrity of the executive control network (as assessed by connectivity of executive control regions with each other and the rest of the brain) and higher amplitude BOLD signal in frontoparietal network regions. Additionally, increases in the negative correlation of default and task positive networks was associated with less variable and faster performance on attention tasks.

A.1.2 Executive Functions: Inhibitory Control and Common EF

Inhibitory control is the domain of executive function that entails the processes involved in overcoming a prepotent tendency. A classic laboratory task for studying inhibitory control is the Stroop task in which a participant is instructed to state the color of a printed word while ignoring its identity. Increased inhibitory control is required for stimuli in which the identity of the word conflicts with the printed color of the word (i.e., the word red is printed in blue ink). Individual differences in inhibitory control can be investigated by calculating, for each individual, the difference in reaction time for congruent (e.g., the word red printed in red ink) versus incongruent stimuli (the word red printed in blue ink). Regarding the neural bases of inhibitory control, the lateral prefrontal cortex plays an important role (Wager et al., 2005). One common factor across many studies of inhibitory control is the role of right middle and inferior frontal gyri in moderating the output of other regions.

Above we highlighted research that suggests inhibitory control falls under the broader category of common EF, which may be an index of goal maintenance ability (Miyake and Friedman, 2012). In this section of the review we first discuss studies that investigated the neural basis (as assessed by rs-fMRI) of inhibitory control using a single task such as the Stroop task or Stop Signal task. Then we discuss a study that used multiple executive function tasks to model individual differences in rs-fMRI as a function of a common EF composite measure.

One group was interested in how the homogeneity of rs-fMRI signal in cognitive control regions was related to performance on the stop signal task (Tian et al., 2011). Regional homogeneity (ReHo) is a measure of how similar the BOLD response is within all the voxels of an a priori region of interest. This measure is of interest because ReHo 1. is stable over short and long periods of time (Küblböck et al., 2014; Zuo et al., 2010), 2. is computationally inexpensive to calculate, and 3. like fALFF, ReHo is one of the few resting-state measures that describe an inherent property of an individual region without considering its relationship to other brain regions. The stop signal task is a popular measure of inhibitory control that involves monitoring for an infrequent signal to abort the execution of an on-going motoric response. Tian and colleagues were interested in ReHo of several a priori regions of interest taken from task-based fMRI studies of the stop signal task. They found a relationship such that individuals with increased ReHo in bilateral inferior frontal cortex and three default network regions bilateral medial prefrontal cortex, bilateral precuneus, and left inferior parietal lobule had longer stop signal reaction times (longer times = lower performance). They also found a relationship such that individuals with increased ReHo in posterior insula and bilateral middle occipital cortex had shorter stop signal reaction times. They suggest that higher ReHo within the default network may be contributing to processes that detract from task performance, such as stimulus independent thought and lapses in attention. A related possibility is that a more homogenous default network is easier to downregulate when required. The ReHo result for bilateral inferior frontal cortex is in the opposite direction than one might predict for higher performing individuals. Future analyses will hopefully shed light on the role of ReHo in influencing the efficacy of inhibitory processing.

The same group was also interested in how individual differences in resting-state networks are related to inhibitory control processes as assessed by stop signal reaction time (Tian et al., 2013). In this study, independent components analysis was used to extract commonly observed resting-state networks across individuals. To estimate each individual participants version of each of the group level ICA components, they performed a dual regression procedure, which is a method that uses unthresholded group-level maps of each independent component to generate both subject-specific component time courses and subject-specific spatial maps as output for that component (Beckmann et al., 2009). Dual regression can be broken down into two steps: First, for each subject, the group-average set of spatial maps is regressed (as spatial regressors in a multiple regression) on the subjects 4D spatio-temporal dataset (i.e., brain volumes across time). This process results in a set of subject-specific time series, one per group-level component. Next, those time series are regressed (as temporal regressors again in a multiple regression) into the participants 4D dataset, resulting in a set of subject-specific components, one per group-level component. Subject-specific components are whole brain images that represent a particular individuals version of the group-level ICA component. Some subjects express a given RSN that is very similar to the group level RSN while others have variations of the group level RSN (e.g., have an expanded RSN or higher connectivity of a particular regions within a given RSN than average). In addition to analyzing the spatial output of the last step of dual regression, they also analyzed the standard deviation of the time course output from the first stage of dual regression and interpreted this as a measure of resting state network amplitude. Tian and colleagues found a relationship between the amplitude of several resting state networks and stop signal reaction time. These networks included: visual networks, motor network, two dorsal attention subsystems (both contained intraparietal sulcus and frontal eye fields, one with increased visual cortex contribution), and the default network. All relationships were negative such that higher amplitude within the resting-state networks was associated with shorter stop signal reaction times. Many of the amplitude analysis results corresponded to differences in the spatial composition of the same networks. They found additional spatial variation in the visual and motor network corresponded to decreased stop signal reaction time. Unfortunately, Tian and colleagues do not specify which areas within these network were altered in individuals with higher ability. They take a holistic approach and simply describe their results in terms of network alteration.

Another group investigated ReHo of cognitive control regions as it relates to performance on a different inhibitory control task, the Stroop task (Liu et al., 2015). They found increased ReHo of the left inferior frontal gyrus, left insula, ventral anterior cingulate cortex, and medial frontal gyrus was associated with greater interference from incongruent trials on the Stroop task when controlling for age, gender, and movement during the resting-state scan. They also found a negative correlation between the Stroop effect and ReHo of left precentral gyrus, such that increased homogeneity of the region was associated with less Stroop-related interferences. Interestingly, all the positive ReHo-Stroop relationships were with classic cognitive control regions such as anterior cingulate cortex. This result is a partial replication of Tian et al. (2011) who also found increased ReHo in inferior frontal cortex was associated with lower performance on an inhibitory control task.

Research from our group has attempted to circumvent the task impurity problem that is a caveat of the work described in the paragraphs above (Reineberg et al., 2015). The task impurity problem is the issue of a single task measuring both the psychological construct of interest in addition to other performance-affecting factors. Assessing the psychological construct of interest with multiple measures can minimize this problem. We sought to measure inhibitory control ability in this manner by creating a multi-measure composite called common EF that is analogous to the common EF latent variable measure from the unity and diversity model of executive function. In an analysis similar to that of Tian et al. (2013), we first sought to investigate how variation in resting-state networks was associated with participants average performance on a number of executive function tasks. To decompose the functional brain data into various independent spatiotemporal components, a group-level independent components analysis was performed on 91 participants resting-state data. This procedure yielded 29 spatiotemporal components. While one common approach for identifying classical resting-state networks from a pool of ICA components is to have an expert subjectively label ICA components as signal (e.g., right frontoparietal network, default network, etc.) or noise (edge effects, movement, etc.), we opted to use a more objective means of selecting RSNs for further analysis. We statistically compared the spatial map of each ICA component to a set of 7 well-defined RSNs from analysis of resting-state data from approximately 1000 participants (Yeo et al., 2011). This procedure identified and helped label 15 RSNs, and identified 14 ICA components that did not significantly correlate with a reference network. ICA components that did not significantly correlate with a reference network were eliminated from further analysis. Additional inspection confirmed that the eliminated components were likely artifactual (e.g., edge effects) or were predominantly high frequency signal according to a power frequency distribution curve and hence likely physiological noise such as heartbeat-induced movement. The dual regression follow-up procedure showed higher common EF was associated with two differences in resting-state networks. Higher common EF was associated with increased connectivity of frontal pole with the dorsal attentional network and increased connectivity of Crus I and II of the cerebellum with the right frontoparietal network.

Our group followed up this work by asking a complementary question of the same 91 participants resting-state data (Reineberg & Banich, 2016). We were interested in whether or not the connectivity profile of specific regions (as opposed to whole networks as in the first study) is associated with differences in common EF. We used a graph theoretic approach to characterize the connectivity profiles of various cortical areas of interest. Graph theory is used to mathematically characterize the functional architecture of the brain as a set of interconnected regions. In a graph theoretic approach, typically, the connections (edges) between regions (nodes) are Pearsons r-values for each possible pairwise relationship. Summarizing a single nodes pattern of edges to the rest of the brain (or to the subset of regions to which it is most highly connected) can provide an abundance of information about the propagation of information through a complex system like the brain, and specifically, what a given regions role might be in the context of a larger system. Graph theoretic measures can be broadly classified into several groups: measures of system integration and system segregation. Measures of integration, such as betweenness centrality, participation coefficient, eigenvector centrality, and degree centrality, assess a regions ability to link disparate parts of the brain. Measures of segregation, such as clustering coefficient, assess a regions ability to engage in specialized processing via dense interconnections to regions involved in the same type of processing without connectivity to more distant brain regions whose input might cause interference.

In this particular study, our selection of graph theoretic measures was based on the desire to sample a variety of connectivity characteristics. First, we chose a basic quantification of the connectedness of a region, unthresholded degree centrality, or global connectivity. Global connectivity has previously been linked to individual differences in intelligence and cognitive control (Song et al. (2008); Cole et al. (2012); see intelligence section below). Second, we chose a measure that weighs a given regions important connections more heavily than connections to less important regions, eigenvector centrality. Third, we chose a measure that reflects how important a region is for connecting disparate parts of the brain, betweenness centrality. This measure provides an index of how frequently a given region is part of the shortest path between all other pairs of regions in the brain and is one way of measuring the degree to which a region can be considered a connector hub (van den Heuvel and Sporns, 2013), which provides the fastest or most efficient route through which information from disparate regions of the brain can flow. Fourth, we chose a measure that reflects how diverse a given regions connections are, participation coefficient. This measure quantifies how many significant connections a region has with a priori defined functional communities. For example, one region may be connected to only members of its own community (e.g., regions within the visual network), while another region may have significant connections to a variety of communities (e.g., frontoparietal network, dorsal attention network, cingulo-opercular network). Lesions to regions with a high participation coefficient produce more severe and broad cognitive deficits than lesions to areas with a lower participation coefficient (Warren et al., 2014), suggesting that such regions play a more central role across a variety of processes. Participation coefficient was of interest to this follow-up study given the finding in the prior network-centric study (Reineberg et al., 2015) that dorsal and ventral attention networks of individuals with high EF are expanded to include regions not observed in the networks of individuals with lower EF such as the frontal pole and angular gyrus. Finally, we chose a measure thought to reflect the degree to which a given region is involved in specialized processing, clustering coefficient. Clustering coefficient is a measure of local segregation. Regions with a high clustering coefficient have a large percentage of neighbors who are neighbors of each other.

We found higher common EF was associated with the graph theoretic properties of several region-of-interest derived from previous studies that investigated the relationship between executive function and rs-fMRI (Reineberg et al., 2015; Cole et al., 2012) or anatomical variability in frontal lobe (Smolker et al., 2014). Specifically, higher common EF was associated with lower global connectivity of frontal pole; lower clustering and lower eigenvector centrality of angular gyrus; lower clustering and lower eigenvector centrality of vmPFC; and lower betweenness centrality of DLPFC. Higher common EF was marginally associated with higher global connectivity and lower participation of LPFC. In summary, higher common EF was consistently associated with less hub-like frontal regions. One notable exception was dorsolateral prefrontal which exhibited higher global connectivity in individuals with high common EF.

An exploratory follow up analysis of graph theoretic properties of the brain that were most important for common EF show higher common EF was associated with a) increased global connectivity, increased betweenness centrality, and lower clustering coefficient of a region in left cuneal cortex/precuneus, b) increased betweenness centrality of right inferior frontal gyrus and left SMA, c) decreased eigenvector centrality of right precuneus and right middle frontal gyrus, d) increased eigenvector centrality of left temporooccipital cortex, and e) decreased clustering of two left frontal pole and left temporal pole. In contrast to the analysis of a priori regions above, many of the most powerful graph theoretic predictors of common EF were increases in the centrality of regions. Additionally, many of these regions were outside the frontoparietal network.

In summary, individual differences in inhibitory control and common EF seem to manifest in the greater ReHo of frontoparietal and default network regions, higher amplitude of BOLD signal and spatial variation in default, attention, visual, and motor networks (for inhibitory control), expanded dorsal attention network (expanded role of frontal pole), increased role of the cerebellum in the frontoparietal network, as well as less central frontal regions.

A.1.3 Executive Functions: Task-set Shifting

Task set shifting is the domain of executive function that entails the processes involved in flexibly shifting between different goals. In the laboratory, mental flexibility is tested with a variety of tasks that require an individual to perform some action (e.g., sorting a deck of cards) in the face of rapidly changing sub-goals (e.g., sometimes categorizing based on card color and sometimes categorizing based on odd/even number). Monsell (2003) provides a thorough review of task set shifting tasks. Regarding the neural bases of task set shifting, meta-analyses have shown the involvement of posterior regions of dorsolateral prefrontal cortex (e.g., inferior frontal junction) as well as parietal regions (e.g., intraparietal sulcus; Derrfuss et al. (2005); Wager et al. (2004).

In our groups analysis of how resting-state networks spatially vary with individual differences in shifting-specific EF, we found higher shifting-specific abilities were associated with increased connectivity of angular gyrus with a ventral attention RSN (Reineberg et al., 2015). The angular gyrus is a region that contributes to a diverse set of functions such as visuospatial attention, episodic memory, and math skill. It is located in parietal cortex near the superior border of the temporal lobes and is anatomically connected to a variety of regions implicated in higher order cognitive process, such as ventrolateral prefrontal cortex, among others (Uddin et al., 2010). The ventral attention network is involved in lower order attention processing and somatomotor functions. The angular gyrus may assume a different role in individuals with higher shifting ability that is, it couples to a lower order attention network rather than a higher order network such as the frontoparietal network.

In our follow-up analysis of the connectivity of individual regions (Reineberg & Banich, 2016), we found higher shifting-specific EF was associated with lower clustering and higher global connectivity of vmPFC; lower eigenvector centrality of vlPFC; higher clustering, lower betweenness centrality, and lower participation of DLPFC; and higher betweenness centrality of angular gyrus.

These results are similar to the common EF results in that ability is associated with decreases in centrality in frontal regions. Interestingly, we found increases in centrality in angular gyrus associated with higher shifting, which could suggest higher ability individuals transfer shifting-related processing to a region that is typically considered lower on the control hierarchy than frontal regions.

An exploratory follow up analysis of graph theoretic properties of the brain that were most important for shifting-specific EF show higher shifting-specific EF was associated with a) increased global connectivity in left precentral gyrus as well as right pre- and postcentral gyrus, b) higher participation coefficient of left and right precentral gyrus, c) increased betweenness centrality of left lateral occipital cortex, d) decreased betweenness centrality of two anterior cingulate cortex regions, and e) decreased clustering coefficient of posterior cingulate cortex. One notable aspect of these results is that a large portion of the features that best explain variance in shifting-specific EF are increased centrality measures in somatomotor areas, specifically bilateral sensory and motor strips. These areas are not typically thought of as task set shifting regions, however, all shifting tasks do require monitoring and processing the relevant sensory task dimensions as well as making a motoric response.

A.1.4 Executive Function: Working Memory

Working memory is a psychological construct that corresponds to the processes involved in the temporary maintenance and manipulation of information (Baddeley, 1992). One popular model of working memory suggest that working memory ability relies on the several component processes a central executive, a visuospatial sketchpad, the phonological loop, and episodic buffer (Baddeley, 2000). These components are responsible for the capture and maintenance of visual and auditory information (visuospatial sketchpad and phonological loop, respectively), binding of multimodal representation into an episode (episodic buffer), and a higher-order subsystem that control the interaction of the other components (central executive). This historical model suggests working memory ability is composed of multiple component processes, a notion that is in line with the unity and diversity framework. One interpretation of both frameworks may be that the maintenance and manipulation aspects of working memory are separable, with the maintenance aspects categorized as common EF (in terms of the unity and diversity framework) and the manipulation aspects associated with updating-specific EF (again, in terms of the unity and diversity framework). One caveat of this section is that, for studies that assessed working memory ability with only a single measure, this measure may reflect varying levels of maintenance and updating-specific EF related processing, as in the case of complex working memory span tasks and the keep track task. Different groups have assessed the relationship between rs-fMRI and performance on each of these working memory tasks or latent variable level working memory measures.

One early investigation of individual differences in working memory sought to characterize the integrity of the default network as a potential predictor of BOLD signal during performance of an N-back working memory task (3-back condition ¿ baseline; Hampson et al. (2006)). These researchers were interested in how the connectivity between two key regions within the default network medial frontal gyrus/ventral anterior cingulate cortex and posterior cingulate cortex is related to behavior. They found a positive relationship between connectivity of the two seed regions at rest and during the 3-back condition and also between resting connectivity and performance during the three back condition (percent correct, misses, and false hits) such that increased connectivity between the two default network regions was associated with higher performance. This result was a little surprising given the cognitive functions that are more commonly associated with the default network (such as self-referential processing) would compete with demanding cognitive tasks like the N-back task. Perhaps the integrity of the default network as assessed by resting correlations within the network itself is indicative of the degree to which that network can be regulated while individuals are performing a demanding task. One caveat of this particular study was the small sample size (n = 9) and the lack of a test of specificity. While Hampson and colleagues report the positive association between the connectivity of two default network regions and working memory performance, they do not report if connectivity between task-positive/executive control regions or a pair of control regions is also positively associated with working memory ability.

Sala-Llonch et al. (2011) also investigated the role of the default network in working memory ability. In this study, the degree of negative correlation between the default network and the frontoparietal network (termed a working memory network, although it is the same network that is largely implicated in a variety of cognitive control tasks) was assessed for each individual. They found that the stronger the negative correlation between these two networks, the higher performance was during a 3-back working memory condition (which was performed in the scanner just after the resting scan). The authors suggested the negative correlation of the networks was due to some preparatory processing for the upcoming N-back working memory task with higher ability individuals being able to segregate the two networks prior to the demanding task. This explanation is certainly possible but not in line with the theme of this review, which suggests the negative correlation may be a trait-like marker of increased ability. The authors reported one additional finding; after extracting the default network for each participant, they investigated whether any region within the network was associated with behavioral performance. They found that higher functional connectivity of a precuneus region within the default network at rest was associated with higher performance during the subsequent 3-back working memory task. The authors dont provide a firm explanation of this result. Given the precuneus status as a crucial hub within the default network (Utevsky et al., 2014), it could be assuming an organizing role in establishing the negative correlation between the default and executive control network. One caveat of this study is that a training session involving performance of the 3-back working memory condition until 80% accuracy was performed just prior to the resting scan leading to the possibility that the network anti-correlation was induced by training and carried over into the resting scan.

Takeuchi et al. (2012) were interested in building upon the literature describing the interaction of the default and executive control networks during performance of working memory tasks and at rest. They tested whether a working memory training intervention modified relationship between default and executive control networks and the regions within them at rest. It should be noted that connectivity in this study was assessed with both a standard resting-state fMRI scan and a resting-state arterial spin labeling scan. Arterial spin labeling is a more direct measure of cerebral blood flow than fMRI. They hypothesized working memory training would either alter within-network dynamics (e.g., regions within the default and/or executive control networks would be more correlated with other regions within the default or executive control network, respectively) or between-network dynamics (e.g., regions within the default network would be more negatively correlated with executive control network regions). These types of changes in dynamics would be in line with the small prior literature highlighted above demonstrating differences among individuals of varying working memory ability. Indeed, they found increased connectivity between medial prefrontal cortex and precuneus in the intervention group as assessed by rs-fMRI. Medial prefrontal cortex was chosen because it is a hub of the default network and, as Hampson and colleagues (2006) reported, its resting-state connectivity is linked to individual differences in working memory performance. Precuneus is also a hub within the default network. This result of increased coherence of two critical default network regions is in line with the work of Hampson and colleagues (2006). Additionally, this result is important in that it lends support to the hypothesis that rs-fMRI may be sculpted over time by a history of particular action/s. In this case, rs-fMRI was altered in a way that reflects the type of processing that each participant did during the training sessions. Additionally, they found working memory training was associated with a decrease in functional connectivity between medial prefrontal cortex and right lateral prefrontal cortex and also increased cerebral blood flow in right lateral prefrontal cortex as assessed by arterial spin labeling. Medial prefrontal cortex, again is a hub of the default network, and right lateral prefrontal cortex is an important region within the executive control system. This latter result also supports the hypothesis that rs-fMRI reflects a history of the brains prior states. In this case, successful performance of a variety of demanding cognitive tasks invokes anticorrelation of the default and executive control system. Over the course of the month long (25 session) training regimen, perhaps this brain dynamic became engrained. Two caveats of this study are the lack of an active control condition and lack of a long-term follow up scanning session (to test the stability of the training-induced rs-fMRI changes).

In summary, aspects of rs-fMRI related to working memory are increased within default network connectivity and decreased default-to-task positive network connectivity associated with both higher working memory ability and training in working memory. Additionally, increased updating-specific EF ability was associated with less central frontal regions (with the exception of a lateral prefrontal cortex region and superior frontal gyrus) and more central somatomotor regions.

A.1.5 Intelligence

Fluid intelligence is another high-level cognitive ability that is the focus of several resting-state studies. Fluid intelligence (Gf) is a term attributed to Cattell (1943, 1963) who attempted to describe problem-solving and reasoning abilities that are independent of the ability to effectively remember and use prior knowledge (i.e., crystallized intelligence, Gc). Common measures of Gf include Ravens progressive matrices and the performance IQ aspects of the Wechsler Adult Intelligence Scales (Raven, 1998; Wechsler, 2003). Because general intelligence explains variance in such a wide array of high-level cognitive tasks, it has become the behavior of interest for a number of preliminary rs-fMRI studies.

Song et al. (2008) were interested in how connectivity between DLPFC and the rest of the brain is associated with individual differences in intelligence as assessed by the full scale Wechsler Adult Intelligence Scale. Lateral prefrontal cortex is an area of interest in intelligence research due to previous associations between anatomical differences (e.g., grey matter volume controlling for intracranial volume) in this area and individual differences in intelligence(e.g., Gray and Thompson (2004)). In a seed-based connectivity analysis restricted to frontal and parietal regions, Song and colleagues found increased functional connectivity between DLPFC and inferior frontal gyrus, medial frontal gyrus, superior frontal gyrus, and the inferior parietal lobules is associated with higher intelligence. After expanding the analysis to the whole brain and making the statistical threshold more conservative, they found increased functional connectivity between DLPFC and the brainstem, hippocampus, caudate, cuneus, and lingual gyrus is associated with higher intelligence (in addition to the relationships from the a priori analysis).

Another study was interested in whether or not global graph theoretic characterizations of the brain are associated with individual differences in intelligence as assessed by the WAIS (Van Den Heuvel et al., 2009). Global graph theory measures are summary measures of the resting-state scanning session that describe how each individuals brain acts as an interconnected (by edges, or the correlation in BOLD activity between the areas) set of regions (i.e., nodes from an a priori parcellation of the brain into regions of interest). Some of these global measures attempt to describe how globally efficient the individuals brain is or how much of a small world the brain is. Global efficiency in the context of this study is a measure of how interconnected the nodes in a brain graph are that is, the average number of edges you must traverse to get between any two nodes in the graph is low in highly efficient systems. Small world graphs are ones with a balance between highly segregated subnetworks (sometimes referred to as communities of modules e.g, the frontoparietal network) but also a sufficient number of connections between the subnetworks. They found a positive relationship between the global efficiency of the resting brain and intelligence while controlling for age individuals with high intelligence had few edges to traverse when making paths between pairs of brain regions. As a test of specificity of this relationship, they verified that intelligence was not related to the total number of edges. In a series of follow up tests, they investigated how the average path length between various regions of interest and every other region in the brain is related to individual differences in intelligence. They found significant negative relationships between intelligence and this path length measure for medial prefrontal gyrus, precuneus/posterior cingulate gyrus, bilateral inferior parietal cortex, left superior temporal, and left inferior frontal gyrus longer path lengths between these regions and every other region in the graph were associated with lower intelligence. This study showed a very simple global graph theoretic measure had predictive utility in the study of intelligence. Additionally, it is also one of several studies to show a possible special role of lateral prefrontal regions as connector hubs for individuals with high intelligence.

Wang et al. (2011b) followed up on this work and investigated how regional homogeneity in the resting brain relates to intelligence as assessed by the Chinese version of the WAIS. They found intelligence was positively correlated with the ReHo (regional homogeneity) of bilateral inferior parietal lobules, middle frontal, parahippocampal and inferior temporal gyri, right thalamus, superior frontal and fusiform gyri, and left superior parietal lobule while controlling for age and gender.

Repovs et al. (2011) investigated how resting-state network-to-network connectivity predicted intelligence. One caveat is that their group of participant included schizophrenic patients and healthy controls. They were particularly interested in the connectivity between fronto-parietal, cerebellar, and cingulo-opercular networks as extracted using templates from a prior study (Fox et al., 2009). They found greater functional connectivity between the frontal-parietal and cerebellar networks was associated with higher performance on all four facets of cognitive behavior they measured including intelligence as assessed by the Wechsler Adult Intelligence Scale and Wechsler Abbreviated Scales of Intelligence. Results observed in this study were across the entire group of schizophrenia-affected and -unaffected individuals.

Finally, Cole and colleagues were interested in how the global connectivity of lateral prefrontal cortex (LPFC) contributes to individual variation in intelligence (Cole et al., 2012). Their hypothesis was based on prior work suggesting lateral prefrontal cortex is a particularly suitable region to perform the complex dynamic switching that may be required for complex reasoning and problem solving. If this particular regions needs to flexibly connect to a variety of other cortical areas to support reasoning and problem solving, it may have a diverse set of connections at rest. They found higher global connectivity of lateral prefrontal cortex (specifically, a region in left middle frontal gyrus) was associated with higher fluid intelligence. A follow up analysis of the same data investigated the specificity of the previously reported intelligenceglobal connectivity relationships by breaking the global connectivity measure down into its within-network and outside-network components. Specifically, they calculated separate measures for LPFCs connectivity to its own network (i.e., the frontoparietal network) and all regions outside its own network (Cole et al., 2015). They found the relationship between global connectivity of LPFC and intelligence may be driven primarily be LPFCs connections outside its own network. That is, after controlling for global connectivity they found a positive relationship between LPFC outside network connectivity and intelligence. This result suggests that LPFCs ability to connect disparate parts of the brain may underlie its role in intelligence related processing.

In summary, connectivity of dorsolateral prefrontal cortex is an important neural substrate that is altered in individuals of varying intelligence.

Appendix B

Comparison of Resting-state Networks from Multiple Studies

Summary

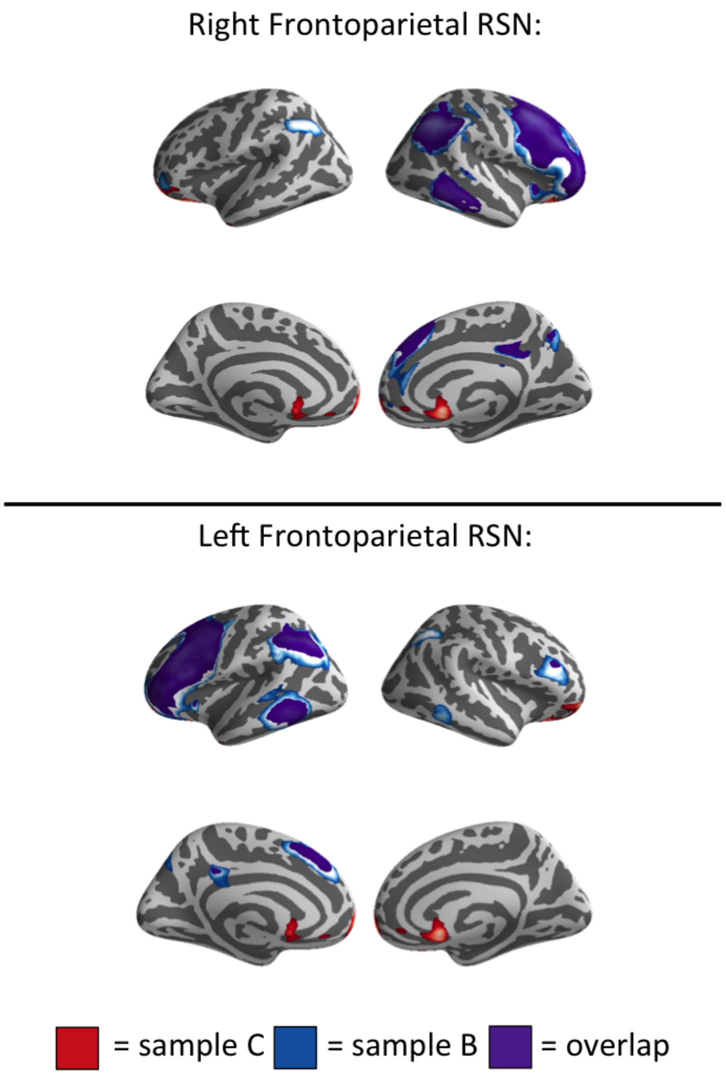
Here we compare group-level resting-state networks (RSNs) from sample B, a study of 251 28-30 year old individauls, to ICA components from sample C, a study of 230 15-18 year old individuals.

B.1 Comparison of ICA components

In the process of deciding how to best replicate the analyses of sample A in sample B (Chapter 2), we realized the use of a priori RSNs from sample A might not best capture the networks structure of sample B. This was partially true because we did observe some differences between the matched ICA components in each sample, although the networks were very highly correlated overall. One possibility is that the large sample size in sample B allowed us to detect slightly different and possibly better RSNs. By comparing the networks from sample B to a third (and also large) sample, we are afforded an opportunity to see if RSNs in these two samples are almost perfectly correlated. They were not. Had this been the case, we may have opted to replicate the analyses described in Reineberg et al. (2015) by solely performing a native group ICA and dual regression on sample B. There does not seem to be a set of RSNs perfectly preserved across the samples discussed in this dissertation, so we decided to report results from several pipeline variations in the main text of this document. In this appendix, we report the supplemental results of the comparison of samples B and C which assisted in our decision to pursue multiple processing pipelines.

Figures B.1, B.2, B.3, and B.4 show comparisons of select networks from the group ICA results of sample B and a large study of 230 adolescents. Due to a bad update in the Pysurfer plotting software, an artifactual orbitofrontal activation (red) was plotted on each of the comparisons. This orbitofrontal cluster is to be ignored. For the sake of visual comparison, the output of FSL's Melodic program was thresholded at the same value for each set of results (z > 3.5) although for numerical comparison, unthresholded whole brain group-level components were correlated. Overall, group-level ICA components were similar in each sample (average of pairwise correlations = 0.71) but less similar than samples A and B were to one another. There were some notable differences. First, both left and right frontoparietal networks had considerable overlap in the main frontal and parietal areas of the canonical frontoparietal RSN (Pearson's $r_{\text{left frontoparietal}} = 0.89$, Pearson's $r_{\text{right frontoparietal}} = 0.88$, Figure B.1). Overall, these are the only networks that seem to have higher spatial similarity across samples B and C than across samples A and B. The dorsal attention network was larger in sample B (Pearson's $r = 0.48$, Figure B.2a). The dorsal attention network in sample C seems to be composed of both dorsal and ventral attention areas. There were large differences in ventral attention network as well, with sample C having a much more focal superior temporal cluster and less inferior frontal activation (Pearson's $r = 0.66$, Figure B.2b). In samples B and C, the hubs of he default network - medial prefrontal cortex and posterior cingulate cortex - parceled into multiple ICA components (Figure B.3a). The middle temporal lobe subsystem of the default network was very dissimilar in samples B and C with sample C completely lacking the classis middle temporal areas and only overlapping substantially in medial superior frontal gyrus (Pearson's $r = 0.60$, Figure B.3b). The sensory-somatomotor networks in samples B and C were quite similar with both tightly tracking the superior aspects of sensory and motor strips (Pearson's $r = 0.71$, Figure B.4a). Finally, the cingulo-opercular network was larger in sample B (Pearson's $r = 0.70$, Figure B.4b).

Figure B.1: **Comparison of Frontoparietal Networks in Samples B and C**. Due to a bad update in the Pysurfer plotting software, an artifactual orbitofrontal activation (red) was plotted on each of the comparisons. This orbitofrontal cluster is to be ignored.



Right Frontoparietal RSN:

Left Frontoparietal RSN:

Figure B.2: **Comparison of Attention Networks in Samples B and C**. Due to a bad update in the Pysurfer plotting software, an artifactual orbitofrontal activation (red) was plotted on each of the comparisons. This orbitofrontal cluster is to be ignored.

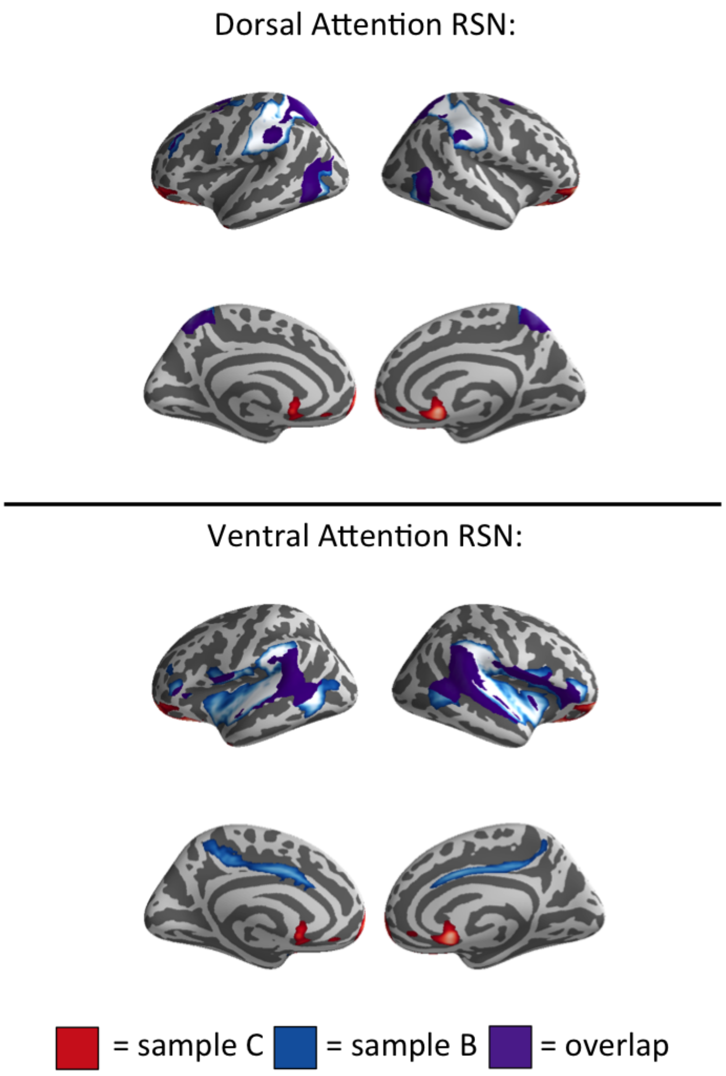


Figure B.3: **Comparison of Default Networks in Samples B and C**. Due to a bad update in the Pysurfer plotting software, an artifactual orbitofrontal activation (red) was plotted on each of the comparisons. This orbitofrontal cluster is to be ignored.

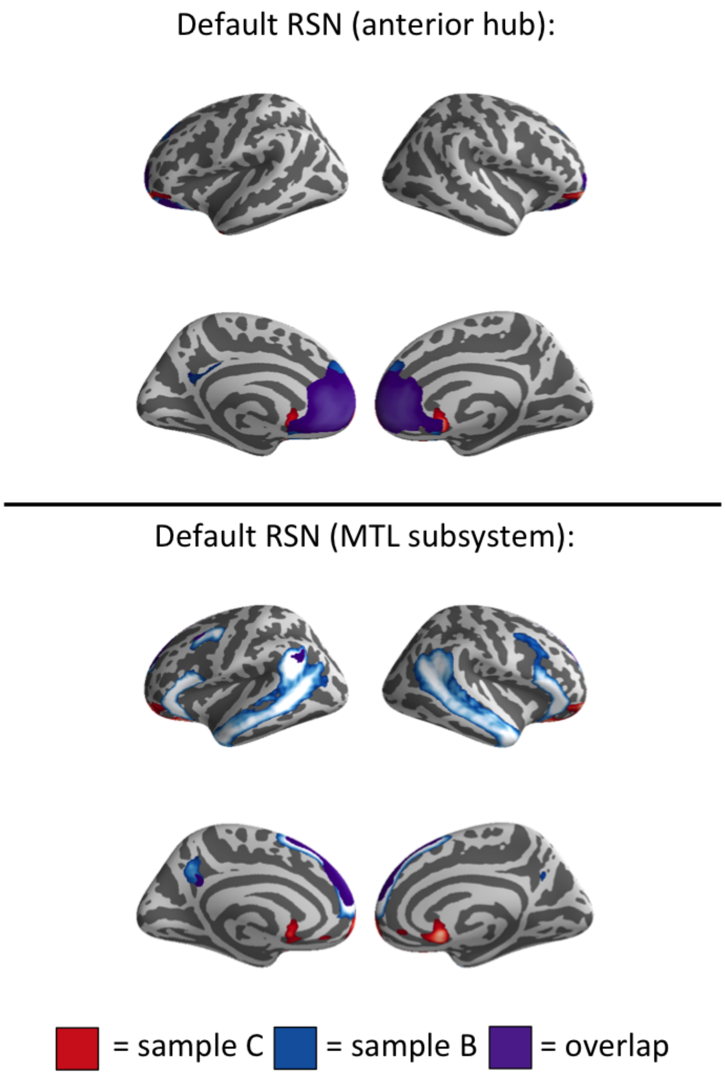
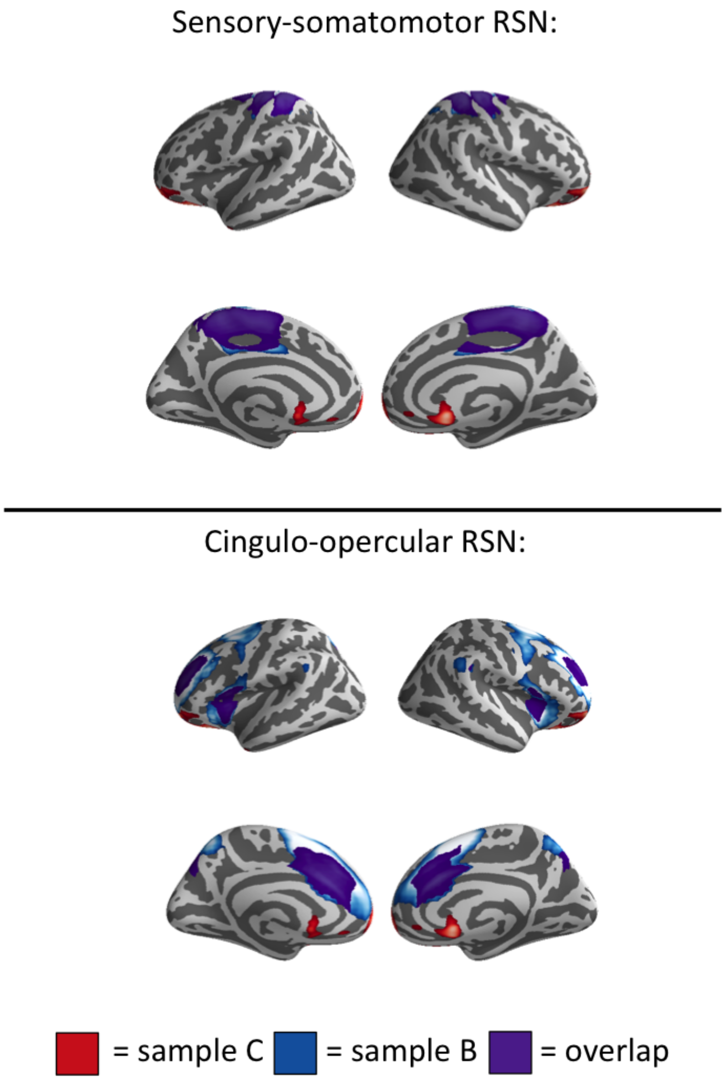


Figure B.4: **Comparison of Sensory-somatomotor and Cingulo-opercular Networks in Samples B and C**. Due to a bad update in the Pysurfer plotting software, an artifactual orbitofrontal activation (red) was plotted on each of the comparisons. This orbitofrontal cluster is to be ignored.


Sensory-somatomotor RSN:

Cingulo-opercular RSN: