Wandering minds, restless brains and mindful thinking: A network-based perspective

by

Joseph Barrington Keller

B.S., Biological Sciences, University of Maryland, Baltimore County (2007)
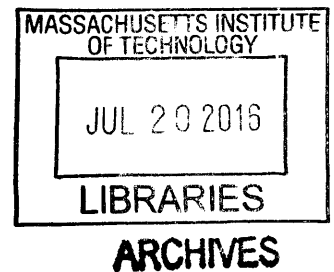M.A., Cognitive and Neural Systems, Boston University (2009)

Submitted to the Department of Brain and Cognitive Sciences
in Partial Fulfillment of the Requirements for the Degree of

DOCTOR OF PHILOSOPHY in COGNITIVE SCIENCE

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

June 2016

Signature redacted

Signature of the Author.
Joseph Barrington Keller
Department of Brain and Cognitive Sciences
May 11th, 2016

Signature redacted

Certified by.
John D.E. Gabrieli
Professor of Health Sciences, Technology and Cognitive Neuroscience
Thesis Supervisor

Signature redacted

Accepted by.
Matthew A. Wilson
Sherman Fairchild Professor of Neuroscience and Picower Scholar
Director of Graduate Education for Brain and Cognitive Sciences

Wandering minds, restless brains and mindful thinking: A network-based perspective

by

Joseph Barrington Keller

Submitted to the Department of Brain and Cognitive Sciences
on May 11th, 2016 in Partial Fulfillment of the Requirements for the
Degree of Doctor of Philosophy in Cognitive Science

People vary significantly across multiple cognitive domains, and that variation may be related to individual differences in the intrinsic functional architecture of the human brain. Such individual differences can be characterized via resting-state measurement of temporal synchrony between brain regions (i.e. functional connectivity). Here, I examine individual differences in working memory and mindfulness in relation to connectivity between the medial prefrontal cortex (MPFC) and dorsolateral prefrontal cortex (DLPFC). The DLPFC is a major component of the executive control network that increased in activation during tasks involving working memory and mental control. Young adults exhibit greater working memory capacity (how much information could be maintained and manipulated in mind) with greater MPFC-DLPFC negative correlation (whereas older adults show reduced working memory capacity and MPFC-DLPFC correlation relative to younger adults). Increased dispositional mindfulness (everyday awareness of the present moment) is associated with greater MPFC-DLPFC positive correlations, at rest. Thus, variation in two advantageous human abilities, working memory capacity and mindfulness, may be related to opposite patterns of inter-network functional connectivity (MPFC-DLPFC). The MPFC is a prominent component of the default-mode network (DMN), which typically decreases in activation during attention-demanding task requiring external focus. Given its relevance to mindfulness tendencies, mind-wandering (MW) episodes engage distributed regions within the DMN. I also investigate mind-wandering frequency using experience sampling with fMRI. MW transiently engages cortical regions associated with executive control and state-level mind wandering is reduced in those with greater trait-level mindfulness, as measured by resting-state functional connectivity.

Thesis Supervisor: John D.E. Gabrieli
Title: Professor, Department of Brain & Cognitive Sciences

TABLE OF CONTENTS   **PAGE**

CHAPTER 1: Resting-state connectivity and correlations with aging, working memory and individual differences

Chapter 2: fMRI assessment of mind-wandering frequency via experience sampling

Chapter 3: Resting-state indicators of variation in trait-level mindfulness

ACKNOWLEDGEMENTS

I would like to take this opportunity to express my immense gratitude and thanks to all those individuals who have helped me reach this stage and greatly shaped my life.

I'm enormously appreciative for all of the support I've received through the years in my research and academic pursuits. I thank John and Susan Gabrieli for providing a supportive research environment in which I could flourish as a scientist and grow as a person. I appreciate being continuously pushed because it sent the message to me that the both of you had confidence in my abilities and potential. For that, I will be forever grateful for the opportunity. Within the lab, I would like to thank mentors past and present for their guidance and counsel on matters both academic and otherwise: Joanna Christodoulou, Elizabeth Norton and Tyler Perrachione. Each of you has acted as an incredible role model and I looking forward to continue learning from you. In addition, the following lab members have been invaluable to development and helped to engage in thought-provoking scientific research: Satra Ghosh, Jenni Minas, Anne Park and Adam Horowitz. My committee members, Emery Brown, Nancy Kanwisher and Brad Dickerson, have been incredible models in life and in science throughout my tenure. I thank each of you for your guidance and mentorship. My scientific journey has been enriching with countless informative experiences along the way. I thank Chantal Stern for the chance join the lab while at Boston University. Your personal support and endorsements have been much appreciated over the years. I'd also like to thank the Meyerhoff and MARC Programs at the University of Maryland, Baltimore County (UMBC) for providing me with solid grounding in academia, research and helped me to set high goals. Thanks to Mike Cataldo at Hopkins/KKI for providing me with my first research internship, on a whim and I greatly value the relationship that has developed over the past decade. Lastly, I'm thankful for my education at Gilman School in Baltimore and such teachers like Dan Christian, that challenge me to push beyond my comfort zone.

Coming from a small family of three, the relationships that I've developed in the Boston area over the years have been extremely important to me. There are too many people to name individually, but just know that I love and appreciate all of you and your friendships have all contributed to the person that I have become today. All of you are my family.

Finally, there aren't sufficient words to convey that thanks I have for my parents, Mignonette and Royce Keller. I will never know the full extent of the sacrifices you made for me. But, I strive each day to make you proud.

This thesis is dedicated to the memory of Altherine G. Sands, who is with me every day of my life.

General Introduction and Background

As neuroscientists, we strive to gain a more comprehensive understanding of the organization, structure and function of the brain through variety of modalities. Brain imaging techniques, utilizing humans and non-human primates, have been integral to establish the foundation for cognitive neuroscience; investigating the biological substrates of cognitive function and behavior. It provides for an opportunity to link the manifestation of mental processes back to an underlying neural basis.

With the implementation of non-invasive imaging methods such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), one is able to measure the functional response properties of the cerebral cortex within a living organism (Kwong et al., 1992; Ogawa et al., 1992). In addition, structural imaging techniques like diffusion tensor imaging (DTI) visualize the myelinated white matter tracts in the brain that are essential to facilitate effective transmission of neurological signals, while disruption may indicate disease, aging or a cognitive deficiency. fMRI measures local changes in magnetic susceptibility caused by dynamic fluctuations in the concentration of deoxyhemoglobin in the vasculature, due to neuronal activation (Logothetis et al., 2001). Conclusions drawn from these methods should always be scrutinized appropriately and carefully interpreted due to the fact that fMRI actually measure the changes in the blood-oxygenation-level-depending (BOLD) signal, which we use as an indirect proxy for neural activity (Logothetis, 2008) and offer limited spatial resolution (Engel et al., 2007). However,

these imaging methods have proven invaluable to the neuroscience field and effective in visualizing the functional organization of the brain across multiple contexts. Many neuroimaging studies have investigation the brain's task-induced physiological response to stimuli, as we attempt to assess of the human brain response to variation in the external environment. Nevertheless, as of late, much attention has been paid to evaluating the intrinsic neural activity that is constantly fluctuating throughout the brain, in the absence of an explicit task, instruction or goal.

The brain's "dark energy"

Initially, this intrinsic activity was thought to be noise within the BOLD signal (Biswal et al., 1995). Indeed, some noise may be created by nuisances that include the following: scanner electronics, subject movement, respiration, and systemic variations in cardiovascular dynamics. These can confound results and significantly effect interpretability. But, those spontaneous fluctuations, or noise, have since provided an extraordinary degree of insight regarding the neural architecture of the human brain (van Dijk et al., 2010). During wakeful rest, in the absence of an explicit task, the functional organization of the brain can be observed through the intrinsic activity of slow, neural fluctuations that exhibit reliable spatial and temporal coherence. Temporally synchronous, low frequency (<0.1Hz) spontaneous activity is found between regions of the brain that are functionally related, but may not be anatomically connected (Honey et al., 2009).
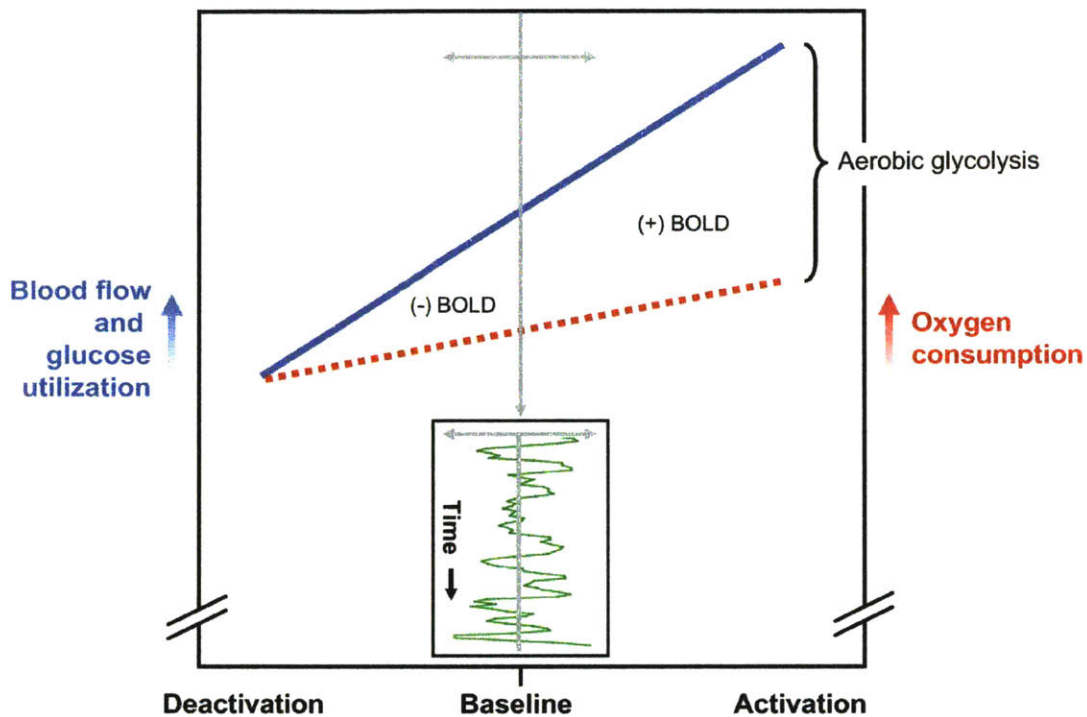
Figure 1. A schematic representation of the relationship of blood flow and glucose utilization (blue) to oxygen consumption (red) and cellular activity (x-axis) at baseline and during increases (activation) and decreases (deactivation) in neuronal activity. The presence of aerobic glycolosis causes activity-dependent variations in oxygen availability in the brain that are detectable by fMRI. Activations as seen by fMRI result from a disproportionate increase in blood flow and glucose utilization, whereas deactivations result from the opposite. At baseline, time-varying fluctuations in neuronal activity are seen as spontaneous fluctuations in the fMRI BOLD signal (insert, green line) (Raichle & Mintun 2006).

Studies that focus on resting-state networks (RSNs) have become increasingly popular due to several important properties that make it a powerful research endeavor for neuroimaging studies. A sufficient amount of neurophysiological evidence for RSNs have been gathered from electrophysiological recordings (He et al., 2008; Scholvinck et al., 2010). Given the low "cost" of task-related neural activity, we can postulate that the majority of the brain's energy may be purely

allocated to intrinsic activity. Many in the field consider a significant fraction of the BOLD signal, below 0.1Hz, to reflect fluctuating neuronal activity (Raichle & Mintun, 2006; **Figure 1**). Task-induced increases neuronal metabolism are typically small (about 2%) compared the energy consumed in the interest of "running" the brain at baseline. Undoubtedly, one may be tempted to assume that this ration of energy utilization reflects the processes necessary for housekeeping like neuronal repair or protein trafficking. However, the vast majority of evidence suggests that those proposed functions consume relatively small fraction of the brain's energy "budget" (Raichle & Mintun, 2006). Future research will be necessary to execute a more in-depth exploration of the distribution of energy throughout the brain. The spontaneous fluctuations are also extremely reliable across studies and there is a tremendous amount of reproducibility across datasets and healthy individuals (Biswal et al., 2010; Damoiseaux et al., 2006). In addition, resting-state neural activity can be observed across various levels of consciousness and studies have consistently demonstrated their presence in other species (Fox & Raichle, 2007; Vincent et al., 2007). Distinct RSNs have been shown to resemble networks that are coactive with cortical regions cited in task-induced activation studies (Smith et al., 2009). However, in some instances, intra-network temporal coherence does not reliably predict structural connectivity between spatially distributed cortical regions. Resting-state functional connections can be perceived without direct, monosynaptic connections between respective brain regions. This phenomenon was demonstrated between the right and left visual cortices (Vincent et al., 2007). When investigating several anatomically distinct brain areas that share temporal

synchrony across functionally related regions, these temporal correlations can reveal "functional connectivity" showing multiple details maps of complex neural networks, which is indicative of shared cognitive function (Beckmann et al., 2005). Within these RSNs, we observe variations in the strength of correlation between nodes under certain conditions, with age and disease (Fair et al., 2008; Zhang & Raichle, 2010). It appears that alterations in the coherence between anatomical structures within a RSN may be an indicator of incipient disease. In addition intrinsic neural activity contributes to the variability in evoked signals (Fox et al., 2006) and associated behavior (Fox & Raichle, 2007). Finally, in combination with the existence of several identifiable RSNs that demonstrate unique spatial and temporal synchrony, there are dynamic interactions between them and other task-related functional networks (Raichle, 2011).

Techniques for characterizing inter-/intra-network relationships

Resting-state networks illustrate low frequency, spontaneous fluctuations in the BOLD signal, which represent the intrinsic organization and activity of the brain. Recent work has also shown that intrinsic connectivity measures are potentially beneficial as biomarkers for monitoring disease progression and treatment effects in clinical trials and individual patients (Chou et al., 2012). Using resting-state functional connectivity MRI (rs-fcMRI), one is able to quantify the degree of functional coupling (temporal) between nodes within a network and between distinct functional networks.

Functional connectivity, indicative of segregated neural processing, is essential to the active process of defining distinct and distributed networks in the brain. Connectivity can be seen at varying levels of scale; individual neurons exhibit connectivity at the cellular level. However, we also detect correlations between neuronal populations and large-scale networks (Rubinov & Sporns, 2010; Sporns et al., 2007). We can infer functional coupling through correlations of neural activity based on measured statistical dependencies between remove neurophysiological events, estimated by measure correlation, coherence or phase-locking. Given that these spontaneous fluctuations are compared at a fine temporal scale, measures of functional connectivity are highly time-dependent (**Figure 2**).
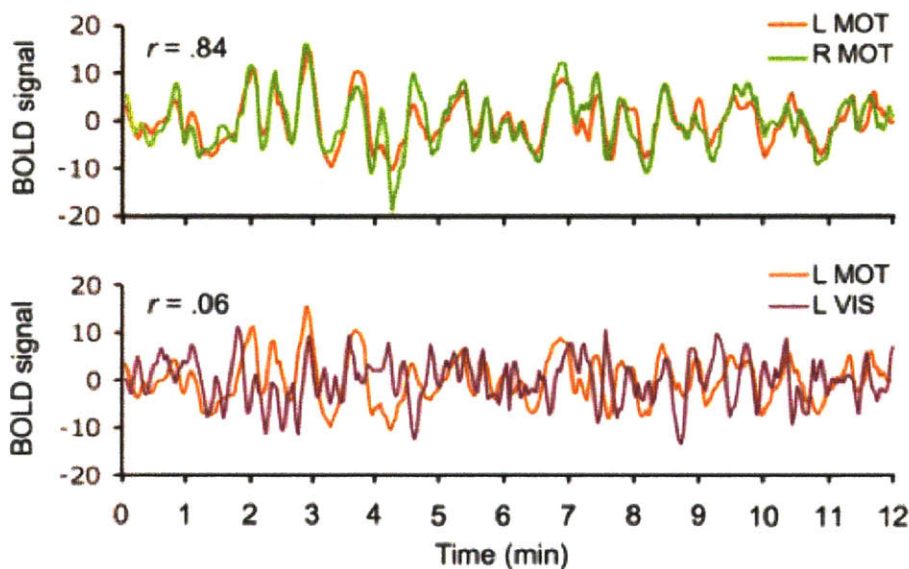

Figure 2. The basis of functional connectivity MRI (fcMRI). Examples from a single subject depict correlated spontaneous fluctuations between right and left motor cortex (top) and absence of correlation between motor and visual regions (bottom) (van Dijk et al., 2010).

The neural activity patterns of these systems can change on multiple time scales. Unfortunately, functional coupling between two regions and the specific direction of correlation or underlying structure cannot be definitively inferred (Friston, 2011). Rs-fcMRI is using to identify networks in gray matter at rest and quantify the relationship between specific network regions and other spatially distributed networks. Functional networks are most commonly generated from correlation maps using either seed-based correlation mapping or independent component analysis (ICA).

Seed-based correlation mapping, the primary method implemented in this thesis, is a widely used approach to resting-state connectivity. A region of interest (ROI) must be chosen as the seed, often based on *a priori* knowledge. The BOLD signal time course is extracted from the seed region and ever other voxel in the brain to create a whole-brain correlation map. The time course illustrates the spontaneous temporal fluctuations of each voxel during the acquisition of the resting functional images. Correlations are computed between the seed-ROI time series and that of every other voxel in the brain. Measures of connectivity, or temporal coupling, within and between networks are commonly quantified using the Person product-moment correlation method. However, there are many other techniques that are currently being implemented in the field.

Rs-fcMRI has significant potential for application for the following reasons: resting, spontaneous, fluctuations provide good signal-to-noise, require minimal patient

compliance, and often can be obtained under anesthesia . Translational work can be
conducted, in part, by focusing on group differences for collecting diagnostic and
prognostic information. It can also be useful as guidance for invasive and non-
invasive treatments (Fox & Greicius, 2010). Many studies have noted changes in
resting functional connectivity in various neurological and psychiatric diseases.
Those network disruptions and alterations may have potential as clinical
biomarkers in the future. Next, we will highlight the need for significant quality
assurance in order to correctly interpret results from functional connectivity
analyses.

Artifacts effects must be carefully mitigated with functional connectivity
Several studies have demonstrated that subject motion can introduce systematic
correlation effects (artifacts) on network measures despite attempts to account for
them (Dijk et al., 2012; Power et al., 2012; Satterthwaite et al., 2012). These studies
demonstrated that varying amounts of head motion translation and rotation may
introduce artificial reductions in long-distance network coupling and increases in
local, short-distance correlations within large-scale distributed networks such as
the default-mode and fronto-parietal control networks. This line of research
emphasizes the importance of effective techniques that mitigate subject motion
effects in task-free functional connectivity, beyond the common corrective steps that
may include spatial registration or regions of motion parameters. This is
particularly important for special populations, like older adults or others, for whom
motion is a considerable concern in the scanner environment. Signal artifacts can

also be created from significant deviations in the global mean intensity, and can be generated from scanner drift of non-neuronal physiological contributions from respiration of cardiac pulsations. In light of these findings, results presented in this thesis have undergone rigorous artifact rejection as an effective method to assure the integrity of our results (Whitfield-Gabrieli & Nieto-Castanon, 2012). These techniques allow for the detection of signal outliers and subject motion and signal intensity beyond designated parameters. The next section will given an in-depth overview of the most prominent resting-state network, one that is more engaged during passive than active cognitive states.

Default brain activity

The default-mode network (DMN) is a collection of brain regions that are primarily characterized by expressing greater neural activity during rest, while tending to concurrently deactivate during external, attention-demanding tasks require mental control (Gusnard & Raichle, 2001). Shulman and colleagues (Shulman et al., 1997) were the first to conduct a meta-analysis of task-inducted deactivations to determine the coactive brain regions during passive mental states. The term "deactivation" is used to describe neural activity relative to a target experimental task. Brain areas showing more activity in the target condition are considered "activated," while regions less active relative to the target condition were label is "deactivated.

Anatomically, the DMN is composed of the medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), and the lateral parietal cortices and shown nearly complete convergence across studies. The hippocampal formation and lateral temporal cortex have also been linked to this network, however both are far less robust compared to the aforementioned cortical regions (Buckner et al., 2008). Rs-fcMRI also reflects its structural connectivity and projections (Buckner et al., 2009; Damoiseaux & Greicius, 2009). The specific role of this network has yet to be determined in concrete terms. However, this thesis will explore its role in certain cognitive states involving self-generated thoughts and many studies have shown its engagement across a multitude contexts as well. They suggest that the DMN is involved in episodic memory (Greicius & Menon, 2004), memory consolidation (Miall & Robertson, 2006), self-related or internal processes (Buckner & Carroll, 2007; Christoff et al., 2011; Gusnard et al., 2001; Wicker et al., 2003), when imaging future of remember past events (Schacter et al., 2007; Spreng & Grady, 2010) and other types of social cognition (Schilbach et al., 2008). It has also been associated with more general processes like stimulus-independency (Mason et al., 2007) or task-unrelated thought (McKiernan et al., 2006). Many studies have shown that DMN to play a significant role in spontaneous cognition (Andrews-Hanna et al., 2010) and mind wandering states (Christoff et al., 2009). It increases activity during passive tasks when spontaneous, self-generated thoughts are expected to be at their highest (Binder et al., 1999; Mazoyer et al., 2001) and attenuates its activated with externally demanding tasks become more difficult (McKiernan et al., 2006). Alterations or disruptions in the DMN, specifically, have been reported in several

neuropsychiatric disorders and in normal aging (see Fox & Griecius, 2010; Broyd et al., 2009; Zhang & Raichle, 2010 for review).

Temporally antagonistic brain networks

It has been suggest that some brain systems are intrinsically organized into functional networks with negative functional connectivity, or anticorrelation, given that their spontaneous fluctuations are temporally out of phase. The DMN, prominently reviewed above, has been shown to be anticorrelated with a "task-positive" brain network that includes the dorsal attention (DA) network and fronto-parietal control network (Fox et al., 2005; FPC; can be broken further into executive control and salience networks), often engaged in external, attention-demanding tasks or those involving intense mental focus (Fox et al., 2005; Fransson, 2005; Griecius et al., 2003; Kelly et al., 2008; Uddin et al., 2009; **Figure 3**).
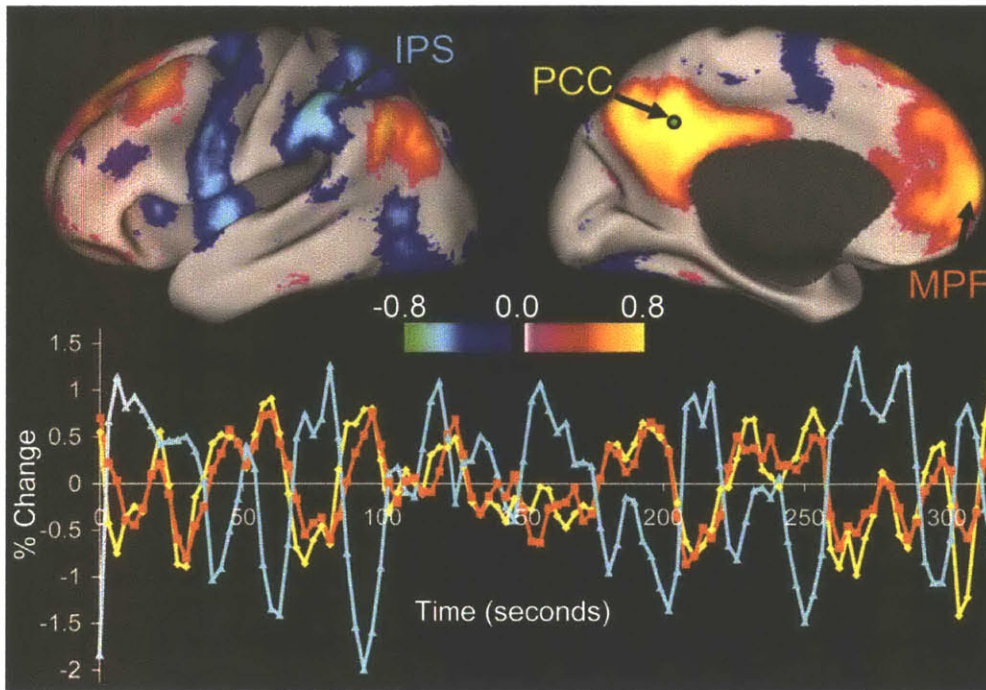
Figure 3. Intrinsic correlations between seed (PCC) and all other voxels in the brain for a single subject during rest. The spatial distribution of the correlation coefficients shows both positive correlations. The time course for a single run is shown for the seed. Regions positively correlated with the seed regions (a component of the DMN) are in orange, while those that are negatively correlated are shown in blue (Fox et al., 2005)

The DA is commonly thought to consist of regions including the intraparietal sulcus, frontal eye fields, visual areas and the middle temporal motion. The FPC, made up of the executive control and salience networks, is made up of the dorsolateral prefrontal cortex (DLPFC), sensorimotor areas (executive control), dorsal anterior cingulate and anterior insula (salience; Fox et al., 2005; Toro et al., 2008). In concert, when active, these exogenous networks suppress activity in the DMN. Literature indicates that the strength of negative coupling, or anticorrelation, between the DMN and task-positive regions is associated with variability in task performance

19

(Hampson et al., 2010; Kelly et al., 2008). Abnormalities in the negative relationship between these networks have been found in patients with ADHD (Uddin et al., 2008), bipolar disorder (Chai et al., 2011), schizophrenia (Whitfield-Gabrieli et al., 2009) and Alzheimer's dementia (Wang et al., 2007).

Some suggest that these anticorrelations may be artificially produced by global signal regression, a preprocessing technique for removing noise in the fMRI BOLD time series (Desjardins et al., 2001; Macey et al., 2004; Zarahn et al., 1997). However, this complication can be resolved by ensuring the global signal is kept intact and correcting for physiological noise by regressing principal components from noise regions of interest, in which the signal is unlikely to be related to neural activity (Chai et al., 2012). These and other results indicate that there is a neuronal basis for observed task-independent negative response in the brain (Lin et al., 2011). This thesis will describe experiments that utilize these methodological advancements to improve the quality of empirical findings.

The analyses to follow

And, it is from this context that this thesis will focus; examining the networks of the brain that are task-independent and spontaneous that fulfill important role within functional neuroimaging. The first chapter will present a study that utilizes individual differences in intrinsic neural architecture to establish associations with cognitive performance and the progression of aging. Next, an experiment will be presented that focuses on a brain network and its associated cognitive states that is

more active during passive states and exhibits a marked task-induced deactivation. Finally, the third chapter will implement resting-state analyses presented in chapter one toward stimulus-independent cognition presented in chapter two in order to further test that predictive abilities of these methodologies for higher order cognition.

References for General Introduction and Background

Andrews-Hanna JR, Reidler JS, Huang C, Buckner RL (2010) Evidence for the default network's role in spontaneous cognition. Journal of Neurophysiology 104:322-335

Beckmann C, DeLuca M, Devlin J, Smith S (2005) Investigations into resting-state connectivity using independent component analysis. Philosophical Transactions of the Royal Society B: Biological Sciences 360:1001.

Binder J, Frost J, Hammeke T, Bellgowan P, Rao S, Cox R (1999) Conceptual processing during the conscious resting state: A functional MRI study. Journal of Cognitive Neuroscience 11:80–93.

Biswal B, Yetkin FZ, Haughton VM, Hyde JS (1995) Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magnetic Resonance in Medicine. 34:537-541.

Biswal BB, Mennes M, Zuo X-N, Gohel S, Kelly C, Smith SM, Beckmann CF, Adelstein JS, Buckner RL, Colcombe S, Dogonowski A-M, Ernst M, Fair D, Hampson M, Hoptman MJ, Hyde JS, Kiviniemi VJ, Kotter R, Li S-J, Lin C-P, Lowe MJ, Mackay C, Madden D J, Madsen KH, Margulies D S, Mayberg H S, Mcmahon K, Monk CS, Mostofsky SH, Nagel BJ, Pekar JJ, Peltier SJ, Petersen SE, Riedl V, Rombouts SARB, Rypma B, Schlaggar BL, Schmidt S, Seidler RD, Siegle GJ, Sorg C, Teng G-J, Veijola J, Villringer A, Walter M, Wang L, Weng X-C, Whitfield-Gabrieli S, Williamson P, Windischberger C, Zang Y-F, Zhang H-Y, Castellanos FX, Milham MP (2010) Toward discovery science of human brain function. Proceedings of the National Academy of Sciences 107:4734–4739.

Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJS (2009) Default-mode brain dysfunction in mental disorders: A systematic review. Neuroscience and Biobehavioral Reviews 33:279–296.

Buckner RL, Carroll DC (2007) Self-projection and the brain. Trends in Cognitive Sciences. 11:49-57.

Buckner RL, Andrews-Hanna JR, Schacter DL (2008) The Brain's Default Network: Anatomy, Function, and Relevance to Disease. Annals of the New York Academy of Sciences 1124:1–38.

Buckner RL, Sepulcre J, Talukdar T, Krienen FM, Liu H, Hedden T, Andrews-Hanna JR, Sperling RA, Johnson KA (2009) Cortical Hubs Revealed by Intrinsic Functional Connectivity: Mapping, Assessment of Stability, and Relation to Alzheimer's Disease. Journal of Neuroscience 29:1860–1873.

Chai XJ, Castañón AN, Öngür D, Whitfield-Gabrieli S (2012) Anticorrelations in

resting state networks without global signal regression. Neuroimage 59:1420-1428.

Chai X, Whitfield-Gabrieli S, Shinn A, Gabrieli JDE, Nieto-Castanon A, McCarthy JM, Cohen BM, Ongur D (2011) Abnormal Medial Prefrontal Cortex Resting-State Connectivity in Bipolar Disorder and Schizophrenia. Neuropsychopharmacology. 36:2009-20017.

Chou YH, Panych LP, Dickey CC, Petrella JR, Chen NK (2012) Investigation of Long-Term Reproducibility of Intrinsic Connectivity Network Mapping: A Resting-State fMRI Study. American Journal of Neuroradiology.

Christoff K, Gordon A, Smallwood J, Smith R, Schooler J (2009) Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. Proceedings of the National Academy of Sciences 106:8719.

Christoff K, Cosmelli D, Legrand D, Thompson E (2011) Specifying the self for cognitive neuroscience. Trends in Cognitive Sciences. 15:104-112.

Damoiseaux J, Rombouts S, Barkhof F, Scheltens P, Stam C, Smith S, Beckmann C (2006) Consistent resting-state networks across healthy subjects. Proceedings of the National Academy of Sciences 103:13848.

Damoiseaux JS, Greicius MD (2009) Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. Brain Structure and Function 213:525–533.

Desjardins AE, Kichl KA, Liddle PF (2001) Removal of confounding effects of global signal in functional MRI analyses. Neuroimage 13: 751-758.

Van Dijk KRA, Hedden T, Venkataraman A, Evans KC, Lazar SW, Buckner RL (2010) Intrinsic Functional Connectivity As a Tool For Human Connectomics: Theory, Properties, and Optimization. Journal of Neurophysiology 103:297–321.

Dijk KRAV, Sabuncu MR, Buckner RL (2012) The influence of head motion on intrinsic functional connectivity MRI. Neuroimage 59:431-438.

Engel SA, Glover GH, Wandell BA (1997) Retinotopic organization in human visual cortex and spatial precision of functional MRI. Cerebral Cortex. 7:1047–3211.

Fair D, Cohen A, Dosenbach N, Church J, Miezin F, Barch D, Raichle M, Petersen S, Schlaggar B (2008) The maturing architecture of the brain's default network. Proceedings of the National Academy of Sciences 105:4028.

Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005) The human brain is intrinsically organized into dynamic, anticorrelated functional

networks. Proceedings of the National Academy of Sciences 102:9673–9678.

Fox M, Corbetta M, Snyder A, Vincent J, Raichle M (2006) Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. Proceedings of the National Academy of Sciences 103:10046.

Fox MD, Raichle ME (2007) Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nature Reviews Neuroscience 8:700–711.

Fox MD, Greicius M (2010) Clinical applications of resting state functional connectivity. Frontiers in Systems Neuroscience:1–13.

Fransson P (2005) Spontaneous low-frequency BOLD signal fluctuations: An fMRI investigation of the resting-state default mode of brain function hypothesis. Human Brain Mapping 26:15–29.

Friston, KJ (2011) Functional and effective connectivity: A review. Brain Connectivity. 1:13-36.

Greicius MD, Menon V (2004) Default-mode activity during a passive sensory task: Uncoupled from deactivation but impacting activation. Journal of Cognitive Neuroscience. 16:1484-1492.

Greicius M, Krasnow B, Reiss A, Menon V (2003) Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proceedings of the National Academy of Sciences 100:253.

Gusnard D, Raichle M (2001) Searching for a baseline: functional imaging and the resting human brain. Nature Reviews Neuroscience 2:685–694.

Gusnard D, Akbudak E, Shulman G, Raichle M (2001) Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. Proceedings of the National Academy of Sciences 98:4259.

Hampson M, Driesen NR, Roth JK, Gore JC, Constable RT (2010) Functional connectivity between task-positive and task-negative brain areas and its relation to working memory performance. Magnetic Resonance Imaging 28:1051-1057.

Harrison B, Pujol J, López-Solà M, Hernández-Ribas R, Deus J, Ortiz H, Soriano-Mas C, Yücel M, Pantelis C, Cardoner N (2008) Consistency and functional specialization in the default mode brain network. Proceedings of the National Academy of Sciences. 105:9781-9786.

He BJ, Snyder AZ, Zempel JM, Smyth MD, Raichle ME (2008) Electrophysiological correlates of the brain's intrinsic large-scale functional architecture Proceedings of the National Academy of Sciences. 105:16039-16044.

Honey CJ, Sporns O, Cammoun L, Gigandet X, Thiran JP, Meuli R, Hagmann P (2009) Predicting human resting-state connectivity from structural connectivity. Proceedings of the National Academy of Sciences. 106:2035-2040.

Kelly AM, Uddin LQ, Biswal BB, Castellanos FX, Milham MP (2008) Competition between functional brain networks mediates behavioral variability. Neuroimage 39:527-537.

Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, Kennedy DN, Hoppel BE, Cohen MS, Turner R, Cheng H, Brady TJ, Rosen BR (1992) Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proceedings of the National Academy of Sciences. USA 89:5675-5679.

Lin P, Hasson U, Jovicich J, Robinson S (2011) A Neuronal Basis for Task-Negative Responses in the Human Brain. Cerebral Cortex 21:821–830.

Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A (2001) Neurophysiological investigation of the basis of the fMRI signal. Nature. 412:150-157.

Logothetis NK (2008) What we can do and what we cannot do with fMRI. Nature. 453:869-878.

Macey P, Macey K, Kumar R, Harper R (2004) A method for removal of global effects from fMRI time series. Neuroimage 22:360–366.

Mason MF, Norton MI, Van Horn JD, Wegner DM, Grafton ST, Macrae CN (2007) Wandering Minds: The Default Network and Stimulus-Independent Thought. Science 315:393–395.

Mazoyer B, Zago L, Mellet E, Bricogne S, Etard O, Houde O, Crivello F, Joliot M, Petit L, Tzourio-Mazoyer N (2001) Cortical networks for working memory and executive functions sustain the conscious resting state in man. Brain Research Bulletin 54:287–298.

McKiernan KA, D'Angelo BR, Kaufman JN, Binder JR (2006) Interrupting the "stream of consciousness": An fMRI investigation. Neuroimage 29:1185-1191.

Miall RC, Robertson EM (2006) Functional imaging: Is the resting brain resting? Current Biology. 16

Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H, Ugurbil K (1992) Intrinsic signal changes accompanying sensory stimulation: functional brain

mapping with magnetic resonance imaging. Proceedings of the National Academy of Sciences USA. 89:5951-5955.

Power J, Barnes K, Snyder A, Schlaggar B, Petersen SE (2012) Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage 59:2142-2154.

Raichle, MA (2011) The restless brain. Brain Connectivity. 1:3-11.

Raichle ME, Mintun MA (2006) Brian work and brain imaging. Annual Review of Neuroscience. 29:449-476.

Rubinov M, Sporns O (2010) Complex network measures of brain connectivity: uses and interpretations. Neuroimage. 52:1059-1069.

Satterthwaite TD, Wolf DH, Loughead J, Ruparel K, Elliott MA, Hakonarson H, Gur RC, Gur RE (2012) Impact of in-scanner head motion on multiple measures of functional connectivity: Relevance for studies of neurodevelopment in youth. Neuroimage 60:623-632.

Schacter D, Addis D, Buckner RL (2007) Remembering the past to imagine the future: the prospective brain. Nature Reviews Neuroscience. 8:657-661.

Schilbach L, Eickhoff SB, Rotarska-Jagiela A, Fink GR, Vogeley K (2008) Minds at rest? Social cognition as the default mode of cognizing and its putative relationship to the "default system" of the brain. Consciousness and Cognition 17:457–467.

Scholvinck ML, Maier A, Ye FQ, Duyn JH, Leopold DA (2010) Neural basis of global resting-state fMRI activity. 107:10238–10243.

Smith S, Fox P, Miller K, Glahn D, Fox P, Mackay C, Filippini N, Watkins K, Toro R, Laird A, Beckmann CF (2009) Correspondence of the brain's functional architecture during activation and rest. Proceedings of the National Academy of Sciences 106:13040.

Sporns O, Honey CJ, Kötter R (2007) Identification and Classification of Hubs in Brain Networks. PLoS One 2:e1049

Spreng R, Grady C (2010) Patterns of brain activity supporting autobiographical memory, prospection, and theory of mind, and their relationship to the default mode network. Journal of Cognitive Neuroscience 22:1112–1123.

Shulman G, Fiez J, Corbetta M, Buckner R, Miezin F, Raichle M, Petersen S (1997) Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. Journal of Cognitive Neuroscience 9:648–663.

Toro R, Fox PT, Paus T (2008) Functional coactivation map of the human brain. Cerebral Cortex 18:2553-2559.

Uddin LQ, Kelly AM, Biswal BB, Margulies DS, Shehzad Z, Shaw D, Ghaffari M, Rotrosen J, Adler LA, Castellanos FX, Milham, MP (2008) Network homogeneity reveals decreased integrity of default-mode network in ADHD. Journal of Neuroscience Methods. 169:249-254

Uddin LQ, Kelly AM, Biswal BB, Castellanos FX, Milham MP (2009) Functional connectivity of default mode network components: correlation, anticorrelation, and causality. Human Brain Mapping 30:625-637.

Vincent JL, Patel GH, Fox MD, Snyder AZ, Baker JT, Van Essen DC, Zempel JM, Snyder LH, Corbetta M, Raichle ME (2007) Intrinsic functional architecture in the anaesthetized monkey brain. Nature 447:83–86.

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

Wicker B, Ruby P, Royet J, Fonlupt P (2003) A relation between rest and the self in the brain? Brain Research Reviews 43:224–230.

Whitfield-Gabrieli, S. & Nieto-Castanon, A. (2012). *Conn*: A functional connectivity toolbox for correlated and anticorrelated networks. *Brain Connectivity, 2,* 125-141.

Whitfield-Gabrieli S, Thermenos H, Milanovic S, Tsuang M, Faraone S, McCarley R, Shenton M, Green A, Nieto-Castanon A, LaViolette P, Wojcik J, Gabrieli JDE, Seidman LJ (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 106:1279.

Zarahn E, Aguirre GK, D'Esposito M (1997) Empirical analysis of BOLD fMRI statistics. Neuroimage 5:179-197.

CHAPTER I: Resting-state connectivity and correlations with aging, working memory and individual differences

Introduction

Working memory (WM) capacity, defined as the amount of goal-relevant information that can be both maintained and manipulated, declines with age (Craik et al. 1990) and varies considerably among individuals (Engle, 2002). In contrast to measures of simple short-term maintenance of information (e.g. digit span), greater WM capacity is associated with superior performance in a broad range of high-level cognitive domains, including reading comprehension, problem solving, and inhibitory control (Conway et al., 2003). WM capacity is thought to reflect central executive capability (Baddeley, 1992; Engle, 2002), and to depend on dorsolateral prefrontal cortex (DLPFC), parietal cortex, anterior cingulate cortex, and the basal ganglia (D'Esposito et al., 1999; D'Esposito et al., 2007; Frank et al., 2001; Levy and Goldman-Rakic, 2000). Here, we asked whether a relationship exists between variation in WM capacity, due to aging or across younger individuals, and the intrinsic functional architecture of the human brain as measured by resting-state functional connectivity.

Spontaneous fluctuations in functionally related brain regions are correlated with each other in the absence of external stimuli, and the patterns of these correlations have been thought to reveal intrinsic relations of brain regions (Beckmann et al., 2005; Biswal et al., 1995; Greicius et al., 2003). During rest, in young adults, there are strong correlations between components of the default-mode network (DMN), brain regions that are commonly deactivated during external

or attention-demanding tasks involving mental control (Fox et al., 2005, Fransson, 2005, Greicius et al., 2003; Raichle et al., 2001). Anatomically, the DMN includes medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), left and right lateral parietal (LLP and RLP) cortices, and bilateral medial temporal lobe (MTL) regions (Buckner et al., 2008).

Resting-state correlations among the components of the DMN appear to be significantly reduced in age-associated pathologies (Greicius et al., 2004; Hedden et al., 2009) and in typically aging older adults (Andrews-Hanna et al., 2007; Balsters et al., 2013; Damoiseaux et al., 2008; Grady et al., 2010; Mowinckel et al., 2012; Sala-Llonch et al., 1202; Sambataro et al., 2010). This may be due, in part, to the particular vulnerability of long-range DMN functional connections to the effects of normal aging (Allen et al., 2011; Andrews-Hanna et al., 2007; Hafkemeijer et al., 2012; Fillippini et al., 2012; Tomasi & Volkow, 2012) or a consequence of more motion-related artifactual time points in elderly participants (Power et al., 2012; Van Dijk et al., 2012). Although widespread reductions in resting functional connectivity are observed with advancing age, some studies also report localized increases in resting-state functional connectivity. Older adults, relative to younger adults, have shown increased frontal-lobe coherence (Filippini et al., 2012) and increased functional connectivity within fronto-parietal cortical regions (Mowinckel et al., 2012).

Networks in the brain appear to have an intrinsic organization such that different networks may exhibit negative functional connectivity, or are anticorrelated with one another at rest. In young adults, components of the DMN are

negatively correlated with brain networks comprised of regions commonly

activated for external tasks that demand attention and mental control, including the

DLPFC (Fox et al., 2005; Fransson, 2005). Evaluation of negatively correlated

networks has proven controversial due to global signal regression, a method used

commonly to mitigate physiological noise in resting-state functional imaging

studies. Global signal regression is known to mathematically generate

anticorrelations (Murphy et al., 2009; Saad et al., 2012). Given these issues, valid

analysis of negatively correlated networks has developed into a topic of particular

interest in the field (Chang and Glover, 2009; Fox et al., 2009; Hampson et al., 2010;

Saad et al., 2012; Van Dijk et al., 2010; Weissenbacher et al., 2009). With the caveat

that prior studies of the influence of age on anticorrelations have employed global

signal regression, there is evidence that healthy aging is also characterized by

reduced negative correlations at rest between the DMN and cortical regions

commonly recruited during attention-demanding tasks (Wu et al., 2011).

Variation in DMN connectivity has been associated with variation in

executive functions and WM capacity. Among older adults, reduced MPFC-PCC

connectivity correlated with worse performance on executive-function and other

cognitive measures (Andrews-Hanna et al., 2007) and reduced connectivity in a

DMN network dominated by the MPFC correlated with worse performance on a

trail-making test (Damoiseaux et al., 2008). Neither study reported a correlation

between these brain measures and variation among young adults, because that was

either not examined (Andrews-Hanna et al., 2007) or was not significant in 10

participants (Damoiseaux et al., 2008). For young adults, there is a report of a

positive correlation between magnitude of MPFC-DLPFC anticorrelation and WM

capacity, as measured by an *n*-back task (Hampson et al., 2010). The relation

between reduced MPFC-DLPFC resting-state anticorrelation and reduced WM

capacity is consistent with findings from patients with schizophrenia (Whitfield-

Gabrieli et al., 2009).

Although variability in resting-state functional connectivity has been

associated with variation in WM in relation to aging and to individual differences

among young adults, there are two major gaps in the current understanding of that

association. First, studies of aging have implicated positive correlations with the

MPFC as being related to age-associated reduction in WM capacity, whereas the one

study of variation among young adults has, instead, implicated negative correlations

with MPFC. This leaves open the question about whether age-related changes in WM

and individual differences among young adults in WM capacity are associated with

shared or distinct variations in intrinsic functional connectivity (no one study has

discovered such common variation in both younger and older adults). Second, the

above functional connectivity findings were reported before it was well understood

that greater movement in older than younger adults can produce artifactual results

(Power et al., 2012; Van Dijk et al., 2012) or that global signal regression can

mathematically generate anticorrelations (Murphy et al., 2009; Saad et al., 2012).

Therefore, it is unknown whether the prior findings would hold when

methodological improvements were implemented.

Here, we explored whether there exists shared or distinct characteristics of

intrinsic brain function for age-related declines in WM capacity and for individual

differences among young adults in WM capacity. We focused on MPFC positive and

negative functional connectivity because bi-directional correlations of the MPFC

with different regions have been implicated across studies of aging or of individual

differences among young adults in relation to executive functions and WM capacity

(Andrews-Hanna et al., 2007; Damoiseaux et al., 2007; Hampson et al., 2010). We

examined the relation of MPFC-DLPFC anticorrelations and MPFC-PCC positive

correlations to WM capacity (Experiment 1) in 27 younger and 27 older healthy

adults with capacity measured by the Letter-Number Sequencing subtest from the

Wechsler Adult Intelligence Scale (WAIS-III), and in 70 younger adults (Experiment

2) with a composite measure of Operation and Reading Span tests (Turner & Engle,

1989; Unsworth et al., 2005). In both experiments, we implemented methods that

minimize the influence of motion artifacts and physiological noise and allow for

valid interpretations of negative correlations (Behzadi et al., 2007; Chai et al., 2012;

Whitfield-Gabrieli and Nieto Castanon, 2012).

Materials and Methods

Experiment 1

Participants

Participants were 27 older adults (15 women) between 65 and 89 years of

age (M = 75.7 years, SD = 6.7) and 27 younger adults (15 women) between 20 and

33 years of age (M = 24.8, SD = 3.4). Written informed consent for participation in

the study was obtained from all participants and approved by the MIT Institutional

Review Board. All participants were healthy, right-handed individuals (Oldfield,

1971) from the Boston metropolitan area who satisfied the following criteria: native English speakers; no contraindications to MRI; and absence of neurological or psychiatric impairments or associated medications. All participants had normal or corrected-to-normal vision. No participant exhibited evidence of mild cognitive impairment or dementia; participants were excluded if they scored <27 on the Mini-Mental State Examination (Folstein & Folstein, 1975).

Neuropsychological and Demographic Measures

The Letter-Number Sequencing subtest from the Wechsler Adult Intelligence Scale (WAIS-III) was used as the measure of WM capacity. Participants were read a combination of numbers and letters, and then asked to recall first the numbers in ascending order and then the letters in alphabetical order. The score was the maximum number of items reordered and recalled correctly from WM (Wechsler, 2002). Two measures were used to assess comparability of the age groups. The American version of the National Reading Test (AMNART) (Grober & Sliwinksi, 1991) was used to estimate crystallized IQ. Socioeconomic status (SES) was measured with the Hollingshead SES scale, which separately ranks an individual's educational and occupational attainment on scales ranging from 1-7. A weighted score was computed by multiplying the educational score by 4 and the occupational score by 7 and summing the 2 scores (Hollingshead, 1957). Lower scores indicate higher SES. Because the majority of younger participants had not yet completed their educations, we compared the older group to the SES scores for the parents of the younger group.

MRI Data Acquisition

Functional magnetic resonance imaging (fMRI) data were acquired using a

3-Tesla Siemens Tim Trio scanner (Siemens, Erlangen, Germany) paired with a

12-channel phased-array whole-head coil. Head motion was restrained with

foam pillows and extendable padded head clamps—3D T1-weighted magnetization

prepared rapid acquisition gradient echo (MP-RAGE) anatomical images were

collected with the following parameters: time repetition (TR) = 2530ms, time echo

(TE) = 3.39ms, flip angle (FA) = 7°, 1.33 x 1.0 x 1.33 mm resolution, 2x

acceleration. Functional T2*-weighted images were acquired using a

gradient-echo echo-planar pulse sequence sensitive to bold oxygenation

level-dependent (BOLD) contrast (Kwong et al., 1992; Ogawa et al., 1992)

with the following parameters: TR = 2000ms, TE = 30ms, FA = 90°, 3.0mm

isotropic resolution. Thirty-six transverse slices covered the whole brain

and were acquired in an interleaved fashion. Functional data were acquired

while the participant was instructed to rest with eyes open for a period

of 5 minutes consisting of 150 volumes. To allow for T1-equilibration effects, 4

dummy volumes were discarded prior to acquisition. Online prospective acquisition

correction (PACE) was applied to the EPI sequence.

Resting State Preprocessing

Resting-state fMRI data were first preprocessed in SPM5 (Wellcome

Department of Imaging Neuroscience, London, UK;

(*http://www.fil.ion.ucl.ac.uk/spm/spm5.html*). Images were realigned (motion

corrected), spatially normalized to the Montreal Neurological Institute (MNI)

stereotactic space, and smoothed with a six mm kernel. Quality assurance was

performed on the functional time series in order to detect outliers in the motion and

global signal intensity using the in-house software *art*

(*http://www.nitrc.org/projects/artifact_detect*). From each participant, an image

was identified as an outlier if composite movement from a preceding image

exceeded 0.5mm, or if the global mean intensity was greater than 3 standard

deviations from the mean image intensity for the run in which it was collected. This

composite motion measure was defined by the *art* tool. By default, *art* converts the 6

rotation/translation head motion parameters into another set of 6 parameters

characterizing the trajectories of 6 points located on the center of each of the faces

of a bounding box around the brain. It then computes the maximum scan-to-scan

movement of any of these points as the single 'composite' scan-to-scan movement

measure, which is thresholded to determine outliers. Identified outliers were

included as nuisance parameters, as one regressor per outlier, within the first level

general linear models.

Functional Connectivity Analysis

　　　　Functional connectivity analysis was performed with a seed-driven approach

using the in-house, custom software Conn *(http://www.nitrc.org/projects/conn*;

Whitfield-Gabrieli & Nieto-Castanon, 2012). The MPFC seed was defined *a priori*

from the literature (Fox et al., 2005; Whitfield-Gabrieli et al., 2009) as 10mm

spheres around the coordinates for the MPFC (-1, 47, -4) in MNI space. Physiological

and other spurious sources of noise were estimated using the aCompcor method

(Behzadi et al., 2007; Chai et al. 2012; Whitfield-Gabrieli et al., 2012), and removed

together with movement-related and artifactual covariates. The residual BOLD time-

series was band-pass filtered (0.009Hz to 0.08Hz). Each participant's structural

image was segmented into white matter (WM), gray matter (GM), and cerebral

spinal fluid (CSF) using SPM8. WM and CSF masks were eroded by one voxel to

avoid partial volume effects with adjacent gray matter. The first 3 principal

components of the signals from the eroded WM and CSF noise ROIs were removed

with regression.

First-level correlation maps were produced by extracting the residual BOLD

time course from the MPFC seed and computing Pearson's correlation coefficients

between that time course and the time courses of all other voxels in the brain.

Correlation coefficients were Fisher transformed into 'Z' scores, which increases

normality and allows for improved second-level General Linear Model analyses. All

reported clusters were significant at an FDR cluster-corrected threshold of $p < .05$.

<u>Within Group Analyses:</u> MPFC seed-to-voxel group analyses were separately

performed using one-sample t-tests for within the young cohort (n = 27), and the

older cohort (n = 27).

<u>Between Group Analyses (Older vs. Younger):</u> MPFC seed-to-voxel between group

connectivity analyses were performed using two sample t-tests.

<u>MPFC functional connectivity correlation with WM</u>: We investigated the relationship

of (a) the magnitude of resting-state correlations from the MPFC that were either

positively correlated with the PCC or negatively correlated with the bilateral DLPFC

regions and (b) the measure of WM performance assessed outside of the scanner

(Letter-Number Sequencing task). We performed a one-sample t-test for the entire

group (n = 54) and functionally defined (a) the left and right DLPFC clusters (within

BA 46/9) that were significantly anticorrelated with the MPFC, and (b) the PCC

cluster (BA30/31) that was significantly positively correlated with the MPFC seed.

We then extracted the mean Z-values from the bilateral DLPFC and PCC clusters for

each participant of both cohorts and correlated those values with their WM

capacities (as defined by the letter-number sequencing task) within both groups.

Thus, the ROIs were unbiased because they were derived from all participants and

independently from any behavioral measures.

Matched Groups on Motion Artifacts

To ensure that between group results were not driven by age-related

differences in motion artifacts, we performed additional between-group analyses of

subgroups of older and younger adults who did not differ significantly on movement

and other artifacts. Within each cohort, 5 participants were removed (n = 44) to

create groups equated for artifacts. Two-sample t-tests were performed to directly

compare the connectivity maps between older and younger adults in the movement

and artifact-matched groups.

Experiment 2

Participants

Participants were 70 younger adults (39 women) between the ages of 18 and 29 years of age (*M* = 21.6 years, *SD* = 2.6). Written informed consent was approved by the MIT Institutional Review Board. Participants were required to be adults between the ages of 18 and 45, right-handed, in good health, and not taking any drugs. They were recruited through web advertisements, physical flyers, and e-mail to the Northeastern and Tufts college mailing lists.

Neuropsychological and Demographic Measures

The automated Operation Span and Reading Span tasks were used as measures of complex WM capacity (Unsworth et al., 2005). For the Operation Span task, participants were presented with alternating letters and math equations, and asked to remember the letters while assessing whether each equation was valid. Set sizes ranged from 3-letters to 7-letters, with each set size presented for 3 trials over the course of the task, in a random order. At the end of each trial, participants reported the letters in the order they were presented. The dependent measure was the sum of all perfectly remembered letter sets. For the Reading Span task, participants were presented with alternating letters and sentences, and asked to remember the letters while assessing whether each sentence was sensical. Set sizes and scoring were identical to the automated Operation Span. Finally, Operation

Span and Reading Span scores were summed to create a single measure estimating a participant's complex WM capacity (composite score).

MRI Data Acquisition

Data were acquired on a 3T Tim Trio Siemens scanner using a 32-channel head coil. T1-weighted whole brain anatomical images (MPRAGE sequence, 256x256 voxels, 1x1.3-mm in-plane resolution, 1.3-mm slice thickness) were acquired. All participants underwent a resting functional MRI scan of 6 min with the instructions "keep your eyes closed and think of nothing in particular". Resting scan images were obtained in 62 2-mm thick transverse slices, covering the entire brain (interleaved EPI sequence, T2*-weighted images; repetition time = 6 s, echo time = 30 ms, flip angle = 90, 67 slices with 2x2x2 mm voxels). PACE was applied to the EPI sequence.

Data Analysis

Resting-state fMRI data for Experiment 2 were first preprocessed in SPM8 (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm), using standard spatial preprocessing steps. Images were slice-time corrected, realigned and resliced, normalized in MNI space and smoothed with a 4-mm kernel.

Functional Connectivity Analysis

The first four scans were excluded from analysis, as there were no dummy scans during initial acquisition. The preprocessing, artifact detection and rejection, aCompCor denoising to address physiological aliasing and subsequent seed driven functional connectivity analyses were identical to those in Experiment 1. Importantly, the left and right DLPFC clusters were defined from the entire group's anticorrelation with the MPFC (independent of WM) and the mean DLPFC Z-values from the clusters were then correlated with the complex WM scores.

Results

Neuropsychological Measures for Experiment 1

There was no significant difference between younger (M = 119.74, SD = 5.8) and older (M = 120.37, SD = 7.6) groups for AMNART scores ($t(52)$ = 0.36, p = 0.73) or for the Hollingshead SES scale (younger: M = 28.37, SD = 10.0; older: M = 31.96, SD = 11.6; ($t(52)$ = 1.22, p = 0.22). The younger group (M = 15.15, SD = 3.4) performed significantly better than the older group (M = 10.70, SD = 2.5) on the Letter-Number Sequencing Test ($t(52)$ = 5.44, p < 0.001)). Analyses of behavioral measures were performed with two-tailed t tests.

Artifact detection

Relative to younger adults (M = 1.1% of 150 time points, SD = 1.6%), older adults (M = 2.4% of 150 time points, SD = 3.0%) had significantly more artifacts (the union of motion and intensity outliers) ($t(52)$ = 2.05, p < 0.05). MPFC correlations and anticorrelations increased post artifact detection and rejection, most noticeably

in the older adults (**Figure 4.C**). Post artifact rejection, there was a wide-spread

increase in positive MPFC functional correlations in the older adults, but MPFC

anticorrelations only increased in posterior brain regions (**Figure 4.C**).

In order to make certain that group differences between younger and older

adults were not were not driven by age-related differences in motion artifacts, we

performed between group analyses on the groups who were matched on motion

artifacts (after eliminating five participants from each cohort (n = 44)). For these

matched groups, there was no significant difference in motion and other artifacts

$(t(42) = 0.00, p = 1.00)$.

Table. 1.

MPFC Anticorrelations Young > Old, FDR cluster corrected (p < 0.05)

Clusters (x,y,z) (MNI)	Clusters	BA	k
(38, 34, 28)	*right DLPFC*	9	166
(30, 6, 8)	right Insular Cortex	13	131
(48, 38, 4)	*right DLPFC*	46	130
(-40, 40, 30)	*left DLPFC*	9	113
(-18, 2, 60)	left Premotor Cortex	6	185
(18, 22, 6)	right Anterior Cingulate	33	100
(20, 52, -6)	right Anterior PFC	10	98
(32, 38, 0)	right Inferior PFG	47	102
(30, 6, 8)	right Insular Cortex	13	229
(38, 34, 28)	*right DLPFC*	9	161
(48, 38, 4)	*right DLPFC*	46	179

BA=Brodmann Area, k=spatial extent(voxel), FDR=false discovery rate

2.3.3 *Group Differences in Intrinsic Functional Organization*

Using a seed-to-voxel analysis, the positive correlation between the MPFC seed and the PCC was significantly reduced in older relative to younger adults, ($p < 0.05$, cluster-level, FDR corrected). With the MPFC seed, there was a significant reduction in bilateral DLPFC anticorrelations in older relative to younger adults (**Figure 4.A, top row; Table 1**). There was a significant reduction in the magnitude of bilateral DLPFC anticorrelations with the MPFC seed in the artifact-matched groups (**Figure 4.A, second row**).
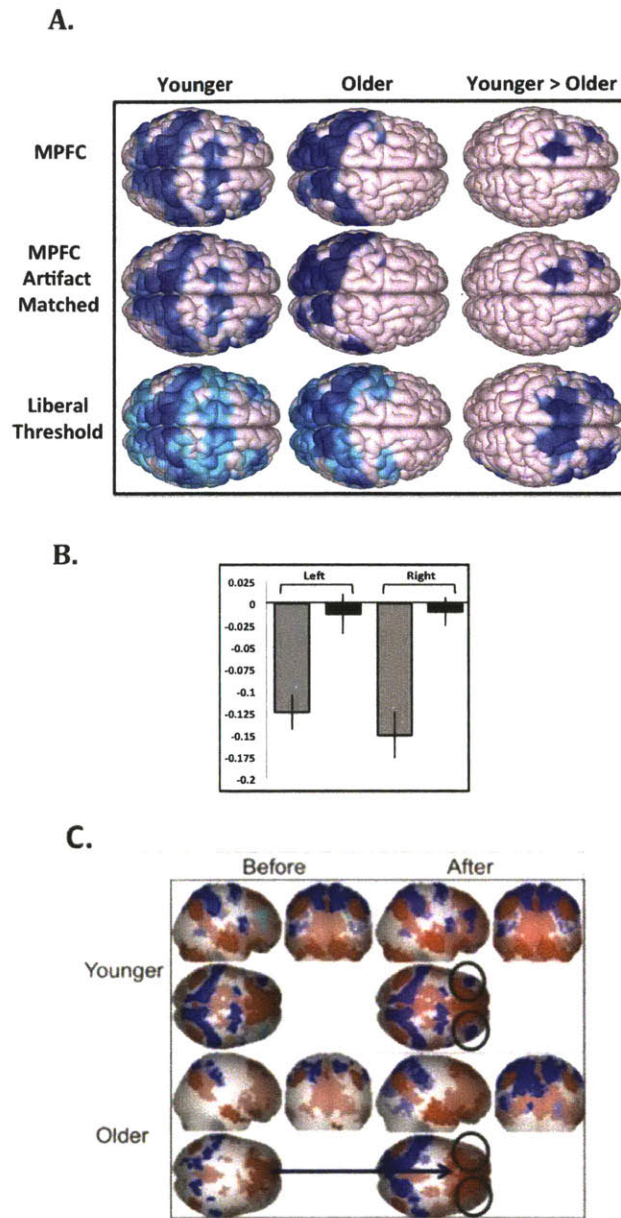
Figure 4. (A) Resting-state anticorrelations for the medial prefrontal cortex (MPFC) seed are reduced in older adults; (top row) for younger adults (left column), older adults (middle column), and younger > older adults (right column). Top row depicts results from all participants. Second row depicts results from groups matched for motion artifacts. Results thresholded at p < 0.05, FDR cluster corrected in top two rows. The third row shows the same analyses at a more liberal threshold (p = .05, unc), and reveals that age-related differences occur only in frontal regions even at this threshold. (B) Resting-state anticorrelation for younger (gray) and older (black) adults between MPFC and bilateral DLPFCs; only younger adults exhibited significant anticorrelations in left and right DLPFC. (C) Positive and negative resting whole-brain correlation changes due to artifact rejection.

The magnitude of the bilateral DLPFC anticorrelations defined by the entire (n = 54) group with respect to the MFPC seed was not significantly different from zero in older participants (right: $t(52) = 0.61$, p = 0.53, left: $t(52) = 0.52$, p = 0.61) (**Figure 4.B**). In fact, there were no observed MPFC-DLPFC anticorrelations in the elderly cohort, even when evaluated at a liberal threshold of p = 0.05 uncorrected (**Figure 4.A, third row**).

Correlations with WM performance

There was not a significant correlation between greater MPFC-PCC correlation and superior performance on the Letter-Number Sequencing task within either the older (r = 0.01, p = 0.95) or the younger group (r = 0.18, p = 0.38). Greater anticorrelation between the MPFC and the right DLPFC was significantly associated with better performance within the younger group (r = -0.43, p < 0.05), but not within the older group (r = -0.11, p = 0.51) (**Figure 5**). The lack of association within the older group may be attributable to a restricted range of variance in the greatly reduced anticorrelation between MPFC and right DLPFC. Correlations in the younger adults remained significant after removing a young adult with an apparent outlier value in the MPFC/DLPFC anticorrelations. The left DLPFC was not significantly correlated with WM performance within either group.
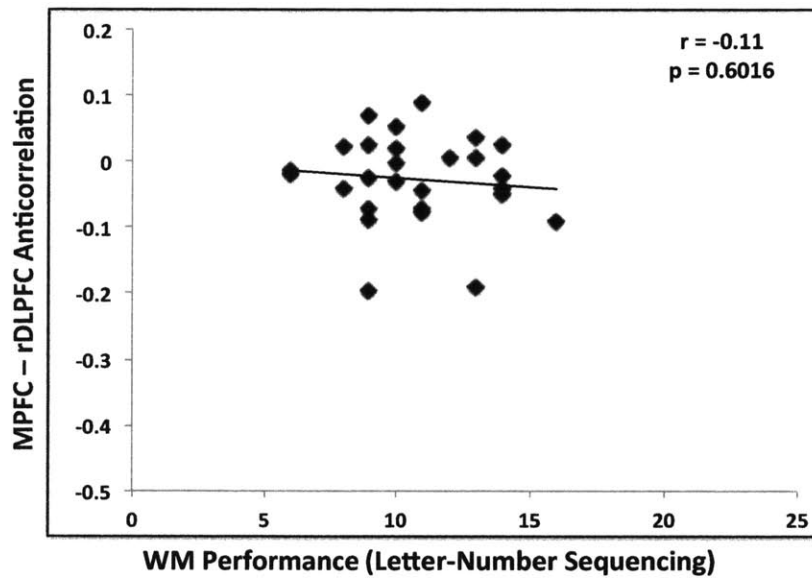
A.
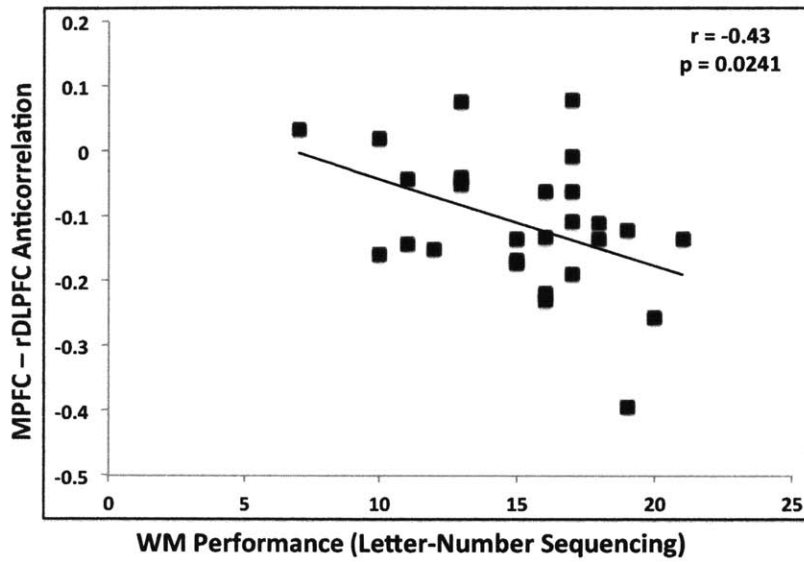
B.

Figure 5. Correlation between the magnitudes of MPFC-right DLPFC anticorrelation and WM performance (Letter-Number Sequencing) for younger (A) and older (B) adults for Experiment 1.

Results for Experiment 2

We replicated and extended our findings in Experiment 1 (that greater resting-state MPFC-DLPFC anticorrelation was associated with greater WM capacity among young adults) with a new independent group with a larger sample size (n=70). The primary analysis was performed with the composite score from two complex WM measures (i.e. Operation Span and Reading Span). Greater MPFC-left DLPFC anticorrelations were significantly correlated with composite WM scores ($r = -0.24$, $p = 0.04$) **(Figure 6)**.
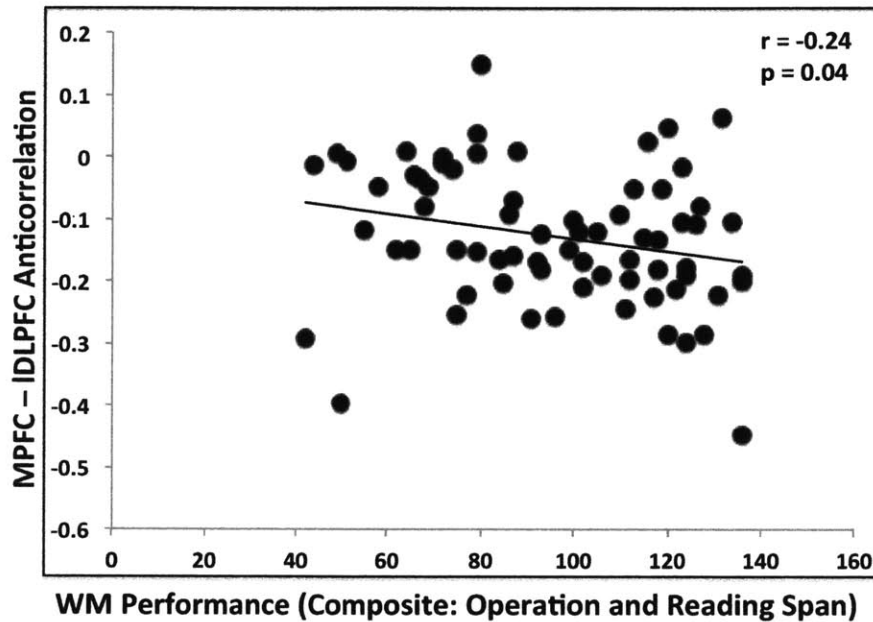
Figure 6. Correlation between the magnitudes of MPFC–left DLPFC anticorrelation and WM performance (composite of Operation and Reading Span) for in younger adults for Experiment 2.

Discussion

We found convergent evidence from aging and from individual differences among young adults of a relation between greater WM capacity and greater magnitude of MPFC-DLPFC anticorrelation. Older adults exhibited both reduced WM and reduced MPFC-DLPFC anticorrelation relative to younger adults. Furthermore, greater WM capacity was associated with greater MPFC-DLPFC anticorrelation in two independent cohorts of young adults (total n = 97) with two different WM measures.

Age-Related Differences in WM Capacity and MPFC-DLPFC Anticorrelation

The behavioral findings were consistent with those generally observed in healthy aging (Hedden & Gabrieli, 2004, 2005). Younger and older participants scored similarly on the AMNART, a measure of vocabulary knowledge, consistent with evidence that crystallized knowledge or intelligence remains relatively intact during healthy aging (Park et al., 2002; Schaie, 1996). In contrast, older participants scored significantly less well on the measure of WM capacity, consistent with evidence that WM or fluid intelligence abilities decline in healthy aging (Park et al., 2002; Schaie, 1996). The validity of comparing these two groups of younger and older participants was supported by similar AMNART scores and similar SES status (with the use of parental SES for the younger adults who have often not completed education or reached final career and economic status).

There was also a significant age-related reduction in MPFC-DLPFC resting-state anticorrelation. This finding is consistent with a prior study that employed a potentially problematic method of global signal regression to examine anticorrelations (Wu et al., 2011). In addition, older adults, relative to younger adults, exhibited significant reductions in MPFC-PCC positive correlations. Reduced positive MPFC-PCC correlations are consistent with prior reports of reduced functional connectivity in normal aging (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008). Aging appeared to have a more severe impact on the MPFC-DLPFC anticorrelation because that anticorrelation was statistically absent, whereas the

reduced MPFC-PCC positive correlation remained significantly above zero in the older adults.

Unlike prior studies reporting associations between MPFC-PCC positive correlations and measures of WM or other executive functions (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008), we did not observe such a correlation within either younger or older adults in Experiment 1. This difference across studies may be due to variations in analytic approaches, sample characteristics, choice of neuropsychological tests, or other factors. For example, some studies do not measure resting-state correlations as in the present study, but perform correlations on the residuals of an event-related activation design (e.g., Andrews-Hanna et al., 2007). Another study found a significant correlation between DMN anticorrelations during a 3-back task and WM performance on the 3-back task (Sala-Llonch et al, 2012). This relationship was not found in any of the less demanding n-back levels, but the anticorrelation during the interleaved fixation periods also correlated with WM performance during the 3-back condition (there was no report of the DMN anticorrelations during the pure rest condition and WM performance on the 3-back task). However, there is evidence that an active n-back task influences the rest periods within the task design, and therefore may be different from calculating the anticorrelations from pure rest (Pyka et al. 2009). In the present study, all resting-state measures were taken from pure resting-state scans, and are therefore not confounded with task performance.

The age-associated alteration in functional connectivity may be associated with age-related alteration in structural connectivity of white matter pathways as

measured by diffusion tensor imaging (DTI). Older adults exhibit reduced integrity

relative to younger people, especially in anterior regions near the DLPFC (e.g., Head

et al., 2004; Pfefferbaum et al., 2005; Salat et al., 2005). Altered integrity of anterior

white-matter pathways has been associated with age-related reductions in cognitive

control and executive functions (Charlton et al., 2006; Deary et al., 2006; Grieve et

al., 2007; O'Sullivan et al., 2001, Penke et al., 2010). Indeed, such region-specific

alterations of white matter in typical aging have been related to individual

differences in cognitive control among older adults, whereas cortical thickness and

age-related alterations of temporal and parietal lobe white matter were unrelated

(Ziegler et al., 2010).

Because many neural and psychological changes occur in concert with aging,

it is difficult to make strong causal assertions between specific neural and specific

psychological changes (Salthouse, 2010). Nevertheless, it is noteworthy that the

MPFC is particularly vulnerable to aging functionally as the MPFC-DLPFC

anticorrelation was statistically eliminated (also Wu et al., 2011).

Individual Differences in WM Capacity and MPFC-DLPFC

Greater MPFC-DLPFC anticorrelation at rest was associated with greater WM

capacity across two independent samples totaling 97 young adults and using two

different measures of WM capacity. In Experiment 1, greater WM capacity among

young adults, as measured by a Letter-Number Sequencing task, was associated

with greater right-lateralized MPFC-DLPFC anticorrelation. In Experiment 2, greater

WM capacity among young adults, as measured by a composite score from the Operation-Span and Reading-Span tasks, was associated with greater left-lateralized MPFC-DLPFC anticorrelation. Importantly, all of these correlations were observed in an analysis in which MPFC-DLPFC anticorrelations were defined consistently and independently from the WM capacity measures. The observation that greater MPFC-DLPFC anticorrelation was associated with greater WM capacity regardless of the specific measure of WM capacity indicates that this brain-behavior relation is generalizable.

Among young adults, the laterality of the MPFC-DLPFC anticorrelation shifted across different measures of WM capacity, and it is unclear what factor explains this difference. All three WM capacity measures involved simultaneous maintenance and manipulation of information in WM, with variation in the amount of that information. An advantage of such complex tasks is that they tax WM capacity, but a disadvantage is all the tasks involve many kinds of mental operations. In Experiment 2, the primary WM measure was a composite of the Operation-Span and Reading-Span tasks. Such a composite has the virtue that it provides a task-independent latent measure of the underlying construct of WM capacity that is not overly sensitive to the measurement properties of a single task. It is also possible that different WM measures are related to different neural circuits. Overall, however, the two experiments converged in showing that greater magnitudes of MPFC-DLPFC resting-state anticorrelations were associated with greater WM capacity among young adults.

Methodological Considerations

Compared to previous resting-state fMRI studies examining aging and individual differences, the present study had a number of potential methodological advantages. First, we used the aCompCor method of noise reduction (Behzadi et al., 2007) as implemented in Conn (Whitfield-Gabrieli and Nieto Castanon, 2012). This method avoids explicit global signal regression, a widely used preprocessing technique known to mathematically generate anticorrelations (Murphy et al., 2009; Saad et al., 2012; Van Dijk et al, 2010; Wong et al., 2012) which as a result renders anticorrelations uninterpretable (e.g., Chang & Glover, 2009) and may compromise the interpretability of positive correlations (Saad et al., 2012). The approach used in the present study is more likely to yield interpretable negative correlations and provides higher sensitivity and specificity for positive correlations (Chai et al., 2012). The differences in anticorrelations observed across age groups and individual differences within age groups observed in the present study are therefore less likely attributable to artifacts from data processing methods and may reflect biological processes. Second, we employed a method of artifact rejection above and beyond motion regression in order to reduce motion-related artifacts common in aging. As expected, the older adults had significantly more artifactual time points removed from analysis (although the percentage of time points removed was small for both groups). After artifact rejection, there was an apparent increase of posterior anticorrelations in the older adults, whereas frontal anticorrelations remained eliminated even at a liberal threshold of $p = 0.05$ uncorrected. These findings suggest that aging disproportionately degrades MPFC-DLPFC anticorrelations.

Greater movement in older relative to younger adults raised the possibility that differential connectivity findings could reflect differential movement. This appears unlikely, however, because age-related differences were also found when comparing younger and older groups after they were matched for movement and artifact outliers. Thus, the age-related differences are more likely to reflect actual differences in intrinsic brain organization.

Finally, the major findings regarding individual differences in intrinsic functional brain organization in relation to WM capacity were based on brain imaging correlations independent of behavioral measures. Specifically, the DLPFC regions were defined without reference to the WM behavior. Thus, the relations between the MPFC-DLPFC anticorrelations and WM performance were not contingent upon a whole-brain search for correlations with performance.

Limitations

One limitation to this study is that the older adult population may have substantially more cortical atrophy and more CSF, which may have differentially affected the normalization procedure. Another limitation is that although the use of different WM measures in Experiments 1 and 2 promote the generalizability of the findings, the different measures precluded a direct replication. Finally, anticorrelations are consistently found in young adults between specific neuroanatomical systems (e.g., the default mode network and the frontal-parietal network) and the magnitude of these anticorrelations relate to individual

differences in behavior (e.g., WM performance), but the neural mechanisms underlying these anticorrelations remain unknown.

Conclusion

In older adults, there was reduced WM capacity and the apparent elimination of MPFC-DLPFC anticorrelation. In younger adults, there were associations between greater magnitudes of WM capacity and greater MPFC-DLPFC anticorrelations. These results suggest that intrinsic anticorrelations between the MPFC, a node in the DMN, and DLPFC, a cortical region involved in cognitive control, may serve as a shared indicator of WM capacity both in aging and in individual differences among young adults. Also, just as WM capacity declines in older adulthood, WM capacity grows markedly in development from childhood to young adulthood, and so do MPFC-DLPFC anticorrelations (Chai et al., 2014).

Differences in intrinsic functional organization in the resting state may reflect the ongoing history of interactions among brain regions during active cognitive performance in everyday life. Ultimately, it will be valuable to relate directly such resting-state and active-performance network dynamics. Resting-state studies are limited in interpretation by the absence of ongoing behavioral measures. Conversely, active performance studies are limited by the interpretation of brain activations occurring at different levels of performance in younger and older adults or among younger adults. Thus, one study reported that age-related reductions in activation during a WM task can be understood essentially in terms of variation in WM capacity (Schneider-Garces et al., 2009). Conversely, another study reported

that age-related differences activation cannot be explained solely by variation in WM capacity (Bennett et al., 2013). Future studies that integrate resting-state and active-performance measures in younger and older adults with varying WM capacities in both age groups may clarify the extent to which individual differences among younger adults and age-related declines in older adults reflect shared and unique brain differences.

References for Chapter 1:

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., Calhoun, V.D. (2011). A baseline for the multivariate comparison of resting-state networks. *Frontiers in Systems Neuroscience*, 5, 2.

Andrews-Hanna, J.R. (2012). The brain's default network and its adaptive role in internal mentation. *The Neuroscientist, 18*, 251-270.

Andrews-Hanna, J.R., Snyder, A., Vincent, J., Lustig, C., Head, D., Raichle, M., Buckner, R. (2007). Disruption of large-scale brain systems in advanced aging. *Neuron, 56*, 924-935.

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage 38*, 95-113.

Ashburner, J., & Friston, K.J. (2005). Unified segmentation. *NeuroImage, 36*, 839-851.

Baddeley, A. (1992). Working memory. *Science, 255*, 556-559.

Balsters, J.H., O'Connell, R.G., Galli, A., Nolan, H., Greco, E., Kilcullen, S.M., Bokde, A.L.W., Lai, R., Upton, N., Robertson, I.H. (2013). Changes in resting connectivity with age: a simultaneous electroencephalogram and functional magnetic resonance imaging investigation. *Neurobiology of Aging, 34*, 2194-2207.

Beckmann, C., DeLuca, M., Devlin, J., Smith, S. (2005). Investigations into resting-state connectivity using independent component analysis. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 360, 1001-1013.

Behzadi, Y., Restom, K., Liau, J., Liu, T.T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *NeuroImage, 37*, 90-101.

Bennett, I.J., Rivera, H.G., Rypma, B. (2013). Isolating age-group differences in working memory load-related neural activity: Assessing the contribution of working memory capacity using a partial-trial fMRI method. *NeuroImage, 72*, 20-32.

Biswal, B., Yetkin, F., Haughton, V., Hyde, J. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine, 34*, 537–541.

Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L. (2008). The brain's default network: Anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences, 1124,* 1-38.

Buckner, R.L. & Carroll, D.C. (2007). Self projection and the brain. *Trends in Cognitive Science, 11,* 50-57.

Chai, X.J., Castañón, A.N., Ongür, D., Whitfield-Gabrieli, S. (2012). Anticorrelations in resting state networks without global signal regression. *NeuroImage, 59,* 1420-1428.

Chai, X.J., Ofen, N., Gabrieli, J.D., Whitfield-Gabrieli, S. (2014). Selective development of anticorrelated networks in the intrinsic functional organization of the human brain. *Journal of Cognitive Neuroscience, 26,* 501-513.

Chang, C. & Glover, G.H. (2009). Effects of model-based physiological noise correction on default mode network anti-correlations and correlations. *NeuroImage, 47,* 1448–1459.

Charlton, R.A., Barrick, T.R., McIntyre, D.J., Shen, Y., O'Sullivan, M., Howe, F.A., Clark, C.A., Morris, R.G., Markus, H.S. (2006). White matter damage on diffusion tensor imaging correlates with age-related cognitive decline. *Neurology, 66,* 217–222.

Craik, F.I.M., Morris, R.G., Gick, M. (1990). Adult age differences in working memory. In: *Neuropsychological impairments of short-term memory* (Vallar, G., Shallice, T., ed), 247-267. Cambridge: Cambridge University Press.

Christoff, K., Cosmelli, D., Legrand, D., Thompson, E. (2011). Specifying the self for cognitive neuroscience. *Trends in Cognitive Science, 15,* 104-112.

Conway, A.R.A., Kane, M.J., Engle, R.W. (2003). Working memory capacity and its relation to general intelligence. *Trends in Cognitive Science, 7,* 547-552.

Damoiseaux, J.S., Beckmann, C.F., Arigita, E.J., Barkhof, F., Scheltens, P., Stam, C.J., Smith, S.M., Rombouts, S.A. (2008). Reduced resting-state brain activity in the "default network" in normal aging. *Cerebral Cortex, 18,* 1856-1864.

Deary, I.J., Bastin, M.E., Pattie, A., Clayden, J.D., Whalley, L.J., Starr, J.M., Wardlaw, J.M. (2006). White matter integrity and cognition in childhood and old age. *Neurology, 66,* 505–512.

D'Esposito, M., Postle, B.R., Ballard, D., Lease, J. (1999). Maintenance versus manipulation of information held in working memory: an event-related fMRI study. *Brain Cognition, 41,* 66-86.

D'Esposito ,M. (2007). From cognitive to neural models of working memory. *Philosophical Transactions of the Royal Society B, 362,* 761-772.

Engle, R.W. (2002). Working memory capacity as executive attention. *Current Directions in Psychological Science, 11*, 19-23.

Fillippini, N., Nickerson, L.D., Beckmann, C.F., Ebmeier, K.P., Frisoni, G.B., Matthews, P.M., Smith, S.M., Mackay, C.E. (2012). Age-related adaptations of brain functions during a memory task are also present at rest. *NeuroImage, 59*, 3821-3828.

Fjell, A.M., McEvoy, L., Holland, D., Dale, A.M., Walhovd, K.B. (2013). Brain changes in older adults at very low risk for Alzheimer's Disease. *Journal of Neuroscience, 33*, 8237-8242.

Folstein, M.F. & Folstein, S.E. (1975). Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research 12*, 189-198

Fox, M., Snyder, A., Vincent, J., Corbetta, M., Van Essen, D., Raichle, M. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Procceedings of the National Academy of Sciences, 102*, 9673-9678.

Frank, M.J., Loughry, B., O'Reilly, R.C. (2001). Interactions between the frontal cortex and basal ganglia in working memory: a computational model. *Cognitive, Affective, & Behavioral Neuroscience, 1*, 137-160.

Fransson, P. (2005). Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. *Human Brain Mapping, 26*, 15-29.

Gao, W. & Lin, W. (2012). Frontal parietal control network regulates the anti-correlated default and dorsal attention networks. *Human Brain Mapping, 33*, 192-202.

Grady, C.L., Protzner, A.B., Kovacevic, N., Strother, S.C., Afshin-Pour, B., Wojtowicz, M., Anderson, J.A.E., Churchill, N., McIntosh, R.A. (2010). A multivariate analysis of age-related differences in default mode and task-positive networks across multiple cognitive domains. *Cerebral Cortex, 20*, 1432-1447.

Greicius, M.D., Krasnow, B., Reiss, A.L., Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proceedings of the National Academy of Science, 100*, 253-258.

Greicius, M.D., Srivastava, G., Reiss, A.L., Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proceedings National Academy of Science, 101*, 4637-4642.

Grieve, S.M., Williams, L.M., Paul, R.H., Clark, C.R., Gordon, E. (2007). Cognitive aging, executive function, and fractional anisotropy: A diffusion tensor MR imaging study.

American Journal of Neuroradiology, 28, 226-235.

Grober, E. & Sliwinski, M. (1991). Development and validation of a model for estimating premorbid verbal intelligence in the elderly. *Journal of Clinical and Experimental Neuropsychology, 13,* 933-949.

Gusnard, D. & Raichle, M. (2001). Searching for a baseline: functional imaging and the resting human brain. *Nature Reviews Neuroscience, 2,* 685–694.

Gusnard, D.A., Akbudak, E., Shulman, G.L., Raichle, M.E. (2001). Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proceedings of the National Academy of Science, 98,* 4295-4264.

Hafkemeijer, A., van der Grond, J., Rombouts, S.A.R.B. (2012). Imaging the default mode network in aging and dementia. *Biochimica et Biophysica Acta, 1822,* 431-441.

Hampson, M., Driesen, N.R., Roth, J.K., Gore, J.C., Constable, R.T. (2010). Functional connectivity between task-positive and task-negative brain areas and its relation to working memory performance. *Magnetic Resonance Imaging, 28,* 1051-1057.

Hampson, M., Driesen, N.R., Skudlarski, P., Gore, J.C., Constable, R.T. (2006). Brain connectivity related to working memory performance. *Journal of Neuroscience, 26,* 13338–13343.

Harrison, B.J., Pujol, J., López-Solà, M., Hernández-Ribas, R., Deus, J., Ortiz, H., Soriano-Mas, C., Yücel, M., Pantelis, C., Cardoner, N. (2008) Consistency and functional specialization in the default mode brain network. *Proceedings of the National Academy of Science, 105,* 9781-9786.

Head, D., Buckner, R.L., Shimony, J.S., William, L.E., Akbudak, E., Conturo, T.E., McAvoy, M., Morris, J.C., Snyder, A.Z. (2004). Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in dementia of the Alzheimer type: Evidence from diffusion tensor imaging. *Cerebral Cortex, 14,* 410–423.

Hedden, T. & Gabrieli, J.D.E. (2004). Insights into the ageing mind: a view from cognitive neuroscience. *Nature Reviews Neuroscience, 5,* 87–96.

Hedden, T. & Gabrieli, J.D.E. (2005). Healthy and pathological processes in adult development: new evidence from neuroimaging of the aging brain. *Current Opinion in Neurology, 18,* 740-747.

Hedden, T., Van Dijk, K.R., Becker, J.A., Mehta, A., Sperling, R.A., Johnson, K.A., Buckner, R.L. (2009). Disruption of functional connectivity in clinically normal older adults harboring amyloid burden. *Journal of Neuroscience, 29,* 12686-12694.

Hollingshead, A.B. (1957). Two factor index of social position. *Mimeo.* New Haven (CT): Yale University.

Kwong, K.K., Belliveau, J.W., Chesler, D.A., Goldberg, I.E., Weisskoff, R.M., Poncelet, B.P., Kennedy, D.N., Hoppel, B.E., Cohen, M.S., Turner, R. (1992). Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proceedings of the National Academy of Science, 89,* 5675-5679.

Levy, R. & Goldman-Rakic, P.S. (2000). Segregation of working memory functions within the dorsolateral prefrontal cortex. *Experimental Brain. Research, 133,* 23-32.

Mander, B.A., Rao, V., Lu, B., Saletin, J.M., Lindquist, J.R., Ancoli-Israel, S., Jagust, W., Walker, M.P. (2013). Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. *Natural Neuroscience, 16,* 357-364.

Mckiernan, K., Kaufman, J., Kucera-Thompson, J., Binder, J. (2003). A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. *Journal of Cognitive Neuroscience, 15,* 394–408.

Mowinckel, A.M., Espeseth, T., 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,* 1364-1373.

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

Ogawa, S., Tank, D.W., Menon, R., Ellermann, J.M., Kim, S.G., Merkle, H., Ugurbil, K. (1992). Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proceedings of the National Academy of Science, 89,* 5951-5955.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9,* 97-113.

O'Sullivan, M., Jones, D., Summers, P., Morris, R., Williams, S., Markus, H. (2001) Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. *Neurology, 57,* 632.

Park, D. C., Lautenschlager, G., Hedden, T., Davidson, N.S., Smith, A.D., Smith, P.K. (2002). Models of visuospatial and verbal memory across the adult life span. *Psychology of Aging, 17,* 299–320.

Penke, L., Maniega, S.M., Murray, C., Gow, A.J., Hernández, M.C.V., Clayden, J.D., Starr, J.M., Wardlaw, J.M., Bastin, M.E., Deary, I.J. (2010). A general factor of brain white matter integrity predicts information processing speed in healthy older people.

Journal of Neuroscience, 30, 7569-7574.

Pfefferbaum, A., Adalsteinsson, E., Sullivan, E.V. (2005). Frontal circuitry degradation marks healthy adult aging: Evidence from diffusion tensor imaging. *NeuroImage, 26,* 891–899.

Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage, 59,* 2142-2154.

Pyka, M., Beckmann, C.F., Schöning, S., Hauke, S., Heider, D., Kugel, H., Arolt, V., Konrad, C. (2009). Impact of working memory load on fMRI resting state pattern in subsequent resting phases. *PLoS One. 4(9):* e7198.
doi:10.1371/journal.pone.0007198

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L. (2001). A default mode of brain function. *Proceedings of the National Academy of Science, 98,* 676-82.

Saad, Z.S., Gotts, S.J., Murphy, K., Chen, G., Jo, H.J., Martin, A., Cox, R.W. (2012). Trouble at rest: How correlation patterns and group differences become distorted after global signal regression. *Brain Connectivity, 2,* 25-32.

Sambataro, F., Murty, V.P., Callicott, J.H., Tan, H-Y, Das, S., Weinberger, D.R., Mattay, V.S. (2010). Age-related alterations in default mode network: impact on working memory performance. *Neurobiology of Aging, 31,* 839-852.

Sala-Llonch, R., Peña-Gómez, C., Arenaza-Urquijo, E.M., Vidal-Piñeiro, D., Bargalló, N., Junqué, C., Bartrés-Faz, D. (2012). Brain connectivity during resting state and subsequent working memory task predicts behavioural performance. *Cortex, 48,* 1187-1196.

Salat, D., Tuch, D., Greve, D., van der Kouwe, A., Hevelone, N., Zaleta, A., Rosen, B., Fischl, B., Corkin, S., Rosas, H. (2005). Age-related alterations in white matter microstructure measured by diffusion tensor imaging. *Neurobiology of Aging, 26,* 1215–1227.

Salthouse, T. (2011). Neuroanatomical substrates of age-related cognitive decline. *Psychological Bulletin, 137,* 753-784.

Schaie, K.W. (1996). Intellectual Development in Adulthood: The Seattle Longitudinal Study (Cambridge Univ. Press, Cambridge).

Schneider-Garces, N.J., Gordon, B.A., Brumback-Peltz, C.R., Shin, E., Lee, E., Sutton, B.P., Maclin, E.L., Gratton, G., Fabiani, M. (2012). Span, CRUNCH, and Beyond:

Working memory capacity and the aging brain. *Journal of Cognitive Neuroscience. 22*, 655-669.

Shulman, G.L., Fiez, J.A., Corbetta, M., Buckner, R.L., Miezin, F.M., Raichle, M.E., Petersen, S.E. (1997). Common blood flow changes across visual tasks: II. decreases in cerebral cortex. *Journal of Cognitive Neuroscience, 9*, 648-663.

Sowell, E.R., Peterson, B.S., Thompson, P.M., Welcome, S.E., Henkenius, A.L., Toga, A.W. (2003). Mapping cortical change across the human life span. *Nature Neuroscience, 6*, 309-315.

Spreng, R.N., Stevens, W.D., Chamberlain, J.P., Gilmore, A.W., Schacter, D.L. (2010) Default network activity, coupled with the frontoparietal control network, supports goal-directed cognition. *NeuroImage, 53*, 303-317.

Tomasi, D. & Volkow, N.D. (2012). Aging and functional brain networks. *Molecular Psychiatry, 17*, 549-558.

Turner, M.L. & Engle, R.W. (1989). Is working memory capacity task dependent? *Journal of Memory and Language, 28*, 127-154.

Unsworth, N., Heitz, R.P., Schrock, J.C., Engle, R.W. (2005). An automated version of the operation span task. *Behavior Research Methods, 37*, 498-505.

Van Dijk, K.R., Hedden, T., Venkataraman, A., Evans, K.C., Lazar, S.W., Buckner, R.L. (2010). Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. *Journal of Neurophysiology, 103*, 297-321.

Van Dijk, K.R., Sabuncu, M.R., Buckner, R.L. (2012). The influence of head motion on intrinsic functional connectivity MRI. *NeuroImage, 59*, 431-438.

Vincent, J.L., Kahn, I., Snyder, A.Z., Raichle, M.E., Buckner, R.L. (2008). Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. *Journal of Neurophysiology, 100*, 3328-3342.

Wechsler, D. (1999). Wechsler abbreviated scale of intelligence. Psychological Corporation.

Wechsler, D. (2002). WAIS-III/WMS-III technical manual: updated. San Antonio (TX): Psychological Corporation.

Weissenbacher, A., Kasess, C., Gerstl, F., Lanzenberger, R., Moser, E., Windischberger, C. (2009). Correlations and anticorrelations in resting-state functional connectivity MRI: a quantitative comparison of preprocessing strategies. *NeuroImage, 47*, 1408–1416.

West, R.L. (1996). An application of prefrontal cortex function theory to cognitive aging. *Psychological Bulletin, 120,* 272-92.

West, R. & Schwarb, H. (2006). The influence of aging and frontal function on the neural correlations of regulative and evaluative aspects of cognitive control. *Neuropsychology, 20,* 468-481.

Wicker, B., Ruby, P., Royet, J., Fonlupt, P. (2003). A relation between rest and self in the brain? *Brain Research Reviews, 43,* 224-230.

Whitfield-Gabrieli, S. & Nieto-Castanon, A. (2012). *Conn*: A functional connectivity toolbox for correlated and anticorrelated networks. *Brain Connectivity, 2,* 125-141.

Whitfield-Gabrieli, S., Thermenos, H., Milanovic, S., Tsuang, M., Faraone, S., McCarley, R., Shenton, M., Green, A., Nieto-Castanon, A., LaViolette, P., Wojcik, J., Gabrieli, J.D.E., 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, 106,* 1279-1284.

Wong, C.W., Olafsson, V., Tal, O., Liu, T.T. (2012) Anti-correlated networks, global signal regression, and the effects of caffeine in resting-state functional MRI. *NeuroImage, 63,* 356-364.

Wu, J-T., Wu, H-Z., Yan, C-G., Chen, W-X., Zhang, H-Y., He, Y., Yang, H-S. (2011). Aging-related changes in the default mode network and its anti-correlated networks: A resting-state fMRI study. *Neuroscience Letters, 504,* 62-67.

Ziegler, D.A., Piguet, O., Salat, D.H., Prince, K., Connally, E., Corkin, S. (2010). Cognition in healthy aging is related to regional white matter integrity, but not cortical thickness. *Neurobiology of Aging, 31,* 1912–1926.

fMRI assessment of mind-wandering frequency via experience sampling

Introduction

In the previous chapter, substantial connections were established regarding functional brain networks and their respective cognitive abilities, in the absence of a direct external stimulus or task. One of these networks in particular, the default-mode network (DMN), exhibits task-induced deactivation in the presence of an attention-demanding task. However, many studies have revealed that this network is associated with a myriad of additional cognitive states that all tap into a similar underlying thread: thoughts that are generated at one's on volition (self-generated), independent of explicit task instructions or stimuli. For example, many of these tasks necessitate that participants recruit neural resources to engage in the following cognitive activities: to retrieve episodic, autobiographical, or semantic information, to think about or plan aspects of his or her personal future, to imagine novel scenes, to infer the mental states of others, to reason about moral dilemmas, to comprehend narratives, to self-reflect, to reference information to one's self and appraise or reappraise emotional information (Andrews-Hanna et al., 2014). In addition, neural activity in the DMN has been related to mind wandering (MW), which will be extensively examined going forward (Christoff et al., 2009; Stawarczyk et al., 2011). This next chapter will outline the cognitive neuroscience of MW, the empirical investigation of human MW frequency and sustained attention using fMRI and the relationship between MW and functional networks, like the aforementioned DMN.

The cognitive neuroscience of mind wandering

Within the literature concerning human functional brain imaging, considerable attention has been paid to the intrinsic neural activity that is constantly fluctuating throughout the brain with a certain degree of cohesiveness, in the absence of an explicit task or goal. These fluctuations have since provided an extraordinary degree of insight into the functional organization of brain, and studies suggest that this continuous neural activity may also be linked to spontaneous conscious thought (Andrews-Hanna, 2012). This type of cognition, loosely connected to or independent from our current environmental input, has become a significant point of interest in the fields of both psychology and neuroscience (Raichle et al., 2001;Smallwood & Schooler, 2006). Providing substantive credibility, these fluctuations are consistent across studies, various levels of consciousness, ages and in other species (Biswal et al., 2010). However, additional research is necessary in order to increase our understanding of the thoughts that are typically associated with these networks.

Many have termed these cognitive phenomena as *"self-generated mental activity"* which has, historically, been used as an overarching category to describe a complex and heterogeneous class of cognition. Within this class, certain terms may accentuate their independence from ongoing events such as task-unrelated thought (TUT), and stimulus-independent thought (SIT) and mind-wandering (MW), while

others may capture the locus of our attention: internally directed, spontaneous, or autobiographical thought (Andrews-Hanna et al., 2014). These terms refer to a specific cognitive state during which an associated conscious experience is relatively more dependent on individual's internal personal concerns, preoccupations and hopes (self-generated), rather than explicit perceptual input (perceptually-generated) in the external environment. These frequent thoughts can also be characterized according to multiple interacting dimensions: personal significance, temporal orientation, valence, social orientation, level of specificity/detail and representational format (inner speech vs. visual imagery).

The number of studies exploring these research topics, regarding undirected thought in cognitive neuroscience, (i.e., mind-wandering) have increased (Callard et al., 2013) in the past decade. For our purposes, we define MW as the unconscious and spontaneous interruption of, or deviation from, a cognitively engaging task requiring deliberate attention or focus to internal mental representations of personal thoughts, often at the cost of task-relevant perceptual stimuli (Gruberger et al., 2011; Fox et al., 2013; Mrazek et al., 2014 Andrews-Hanna et al., 2014; Smallwood & Schooler, 2015). TUT, or unconstrained mental activity, is relevant to the field given research that shows we spend a sizeable portion of our waking thought in these psychological states (Killingsworth & Gilbert, 2010).

Since MW is one of the most ubiquitous and common of all mental activities, many can appreciate the normal, daily occurrence when one's thoughts may stray

momentarily (or longer) from a task at hand. Recent scientific efforts have attempted to uncover the neural correlates of MW in combination with its associated behavioral characteristics. Historically, there has been an extensive body of literature regarding the behavioral aspects of mind wandering in the laboratory setting. These studies have, creatively, developed experimental designs in order to establish an environment that is conducive to mind wandering, while also a designing methods by which instances of task-unrelated thoughts can be recorded and measured.

Studies have also shown that, for young adults, the majority of thoughts that occur during MW episodes are future-oriented, or prospective in nature (Klinger, 1971, 1999; Mason et al., 2007; Singer, 1966; Smallwood et al., 2009). This particular cognitive state may reflect people's ongoing and unresolved concerns, and perhaps the anticipation and planning of personally relevant future goals (autobiographical planning) (Klinger, 1971; Smallwood et al., 2009). Often, mind wandering is framed in a negative light, at the expense of performance on a task at hand. However, moments of MW may also be helpful in allowing for dishabituation or relieving tedium (Schooler et al., 2014). In addition, several investigations of task-unrelated thinking (mind-wandering) have proposed that these episodes can provide some cognitive benefit, with two important daily activities in particular: future thinking/planning and creative thinking/creative incubation. In the face of semantic satiation, mind wandering is also able to reduce mind-numbing of repetitive stimuli as facilitated by perceptual decoupling

(Mooneyham & Schooler, 2016). It is also conceivable that TUTs may come at some cost to task performance. Most people would go to great lengths to avoid being left alone to contend with their own thoughts; many prefer to be cognitive engaged rather than remain idle, even if that activity could have negative or physically harmful implications (Wilson et al., 2014). Studies investigating the disruptive effects of MW (the majority) have been explored most thoroughly in educational settings, where the frequency of MW is negatively correlated with reading comprehension performance (Schooler et al., 2004). In addition, MW can result in changes in mood (Killingsworth & Gilbert, 2010) and deficits associated with executive processing such as sustained attention, working memory and tests of aptitude or general intelligence (Mooneyham & Schooler, 2013). Using brain imaging techniques like fMRI, we can attempt to visualize the cortical regions that contribute to the experience of mind-wandering episodes.

Functional neuroimaging with mind-wandering thoughts

Neuroimaging studies utilize fMRI in order to visualize the mental activity of spontaneous self-generated, task-unrelated thoughts. However, to date, very few experiments have directly examined periods of MW against non-MW (Christoff et al., 2009; Stawarczyk et al., 2011; Hasenkamp et al., 2013; Allen et al., 2013; Fox et al., 2013; Kucyi & Davis, 2014; Tusche et al., 2014; Xu et al., 2014; Fox et al., 2015; Stawarczyk & D'Argembeau, 2015), although several studies have addressed it indirectly (e.g. Mason et al., 2007; Andrews-Hanna et al., 2010) (they tend to assume an *a priori* link between default-mode network (DMN) activity and MW). These

studies suggest that self-generated cognition is linked to functional activation in the medial prefrontal cortex (MPFC) and posterior cingulate cortex (PCC), which are significant midline components of the DMN (Buckner et al., 2008). In concert with DMN recruitment, MW is also associated with neural activity in executive regions of the dorsal anterior cingulate cortex (dACC) and dorsolateral prefrontal cortex (DLPFC), which may help to explain why MW can undermine task performance under cognitively demanding conditions (Christoff et al., 2009; Fox et el., 2015). A significant distinction has also been made regarding meta-awareness, or the knowledge of locus of one's thoughts at any given time. Those that tend to be aware of their thoughts, during mind-wandering states, will exhibit reduced activity in the cortical regions associated with task-unrelated thoughts (Brewer et al., 2011)

However, there remain two significant gaps in the extant literature regarding neuroimaging investigations of MW frequency in humans: 1) There has yet to be a replication of study with an experimental design optimized to measure the quantitative aspects of mind wandering with online experience-sampling, using fMRI and 2) MW studies have yet to combine self-reported instances of MW frequency with an extensive characterization of the subjects with variables that may measure cognitive function, trait tendencies of personality and daily thoughts and mindfulness (Christoff et al., 2009). Previous studies have not sufficiently evaluated their subject populations on dimensions of attention-deficit hyperactivity disorder or expertise with mindfulness meditation. Both of these issues have the potential to present significant confounds in this type of research, if they are not accounted for sufficiently. This research is designed to address some of these unmet needs.

Here, we explore the neural correlates of mind-wandering frequency and meta-awareness in young adults with experience sampling by extending previous experimental designs in the field. Prior studies have ether assessed experience while measuring neural activity online (Allen et al., 2013; Christoff et al., 2009; Kucyi & Davis, 2014; Smallwood & Andrews-Hanna, 2013; Stawarczyk & D'Argembeau, 2015), or have relied on retrospective measures of thoughts that emerge during the collection of resting-state images (Andrews-Hanna et al., 2010; Gorgolewski et al., 2014). Studies have yet to reliably and consistently demonstrate the cortical substrates of these cognitive states and results would have significant implications (Christoff et al., 2009). A cohort of 29 young adults subjects completed an exhaustive cognitive assessment that included measurements of memory, executive function and processing speed. These cognitive metrics were collected alongside additional personal information from each participant regarding tendencies for task-unrelated thought, mindfulness and personality. Each participant completed a task of sustained attention in the scanner that contains intermittent thought probes in order to gauge the loci and awareness of thoughts, in an online manner. Based on a previous study (Christoff et al., 2009), we hypothesized that mind-wandering episodes will be associated with activation of default mode network regions. In addition, executive control regions may also be coactivated to indicate control over, and manipulation of, self-generated content.

Materials and Methods

Participants

Participants were 30 younger adults (23 women) between 18 and 32 years of age

(M = 23.4, SD = 3.8). Written informed consent for participation in the study was

obtained from all participants and approved by the MIT Institutional Review Board.

All participants were healthy, right-handed individuals from the Boston

metropolitan are who satisfied the following criteria: native English speakers; no

contraindications to MRI; and absence of neurological or psychiatric impairments or

associated medications that could affect the central nervous system or brain. All

participants had normal or corrected-to-normal vision. One subject was excluded

due to fatigue, which left her unable to sufficiently complete the task (n = 29).

Participants were also asked to provide information regarding their experience

with, or expertise in, the practice of mindfulness meditation. Individuals were also

screened for attention-deficit-hyperactivity-disorder (ADHD) given its relevance for

the subject matter in this research study

Neuropsychological and demographic measures

The Wechsler Test of Adult Reading (WTAR) (Holdnack, 2001) was administered to

estimate crystallized IQ. The examiner began by presenting the first of a list of

words, while prompting the subject to pronounce each word out load until all 50

words have been spoken. The procedure was discontinued if the subject provided

12 consecutive incorrect pronunciations. Lists of acceptable pronunciations and

tape recordings were provided by the publisher to account for words with multiple

pronunciation variants. Each correct pronunciation was given a score of 1, with 50

as the maximum raw score. The raw score was standardized by age and compared

to the scores predicted for a particular demographic classification. Trait-level

mindfulness of each subject was collected prior to the scanning session, using two

separate measures. The Kentucky Inventory of Mindfulness Skills (KMS; Baer et al.,

2004) is a self-report inventory of mindfulness in which individuals are asked to

rate the degree to which each statement applies to them on a 5 – point Likert-style

scale ranging from 1 (never or very rarely true) to 5 (almost always or always true).

The KMS is designed to assess 4 mindfulness skills: observing, describing, accepting

and acting. Items reflect either direct descriptions of the mindfulness skills, or they

describe the absence of that skill and are reverse scored. High scores indicated more

mindfulness. The Mindful Attention Awareness Scale (MAAS; Brown & Ryan, 2003)

is a 5 – item, single dimension measure of trait mindfulness. The MAAS measures

the frequency of open and receptive attention to, and awareness of, ongoing events

and experiences. Response options range from 1 (almost never) to 6 (almost

always). Example items include the following: "I could be experiencing some

emotion and not be conscious of it until some time later," or "I find it difficult to stay

focused on what's happening in the present," and "I rush through activities without

being really attentive to them." The MAAS focuses on the presence or the absence of

awareness of what is occurring in the present moment. Item scores were reverse-

coded and the mean was computed, making higher scores indicated a greater level

of dispositional or trait mindfulness. The validity of our measure of interest for trait-

level mindfulness, the MAAS, was established through a significant correlation ($r = 0.59$, $p < 0.001$) with the KMS for these participants.

Characterization of experience with mindfulness practice

In order to account for previous experience with mindfulness meditation practice that may contribute to changes in neural architecture, subjects were classified into two groups based on their responses to the following questions: "Have you ever practiced mindfulness or meditation? If so, how often have you practiced mindfulness or meditation in the past year? Please tell us about your experience." They were categorized as either 'advanced practitioners' or 'meditation-naïve'. This classification was based on cutoffs established in previous studies concerning expertise in mindfulness meditation practice (Garrison et al., 2013).

Screening for ADHD

In order to obtain information about ADHD diagnosis from the healthy controls participating in this study, a researcher from Massachusetts General Hospital (MGH) contacted the subjects by phone. After providing verbal consent the researcher completed the AHDH module of the KSADS-E, a structured psychiatric interview designed to elicit and record past episodes of child and adolescent psychiatric disorder. The results were reviewed with a clinician associated with the study and the subject was used as a member of included subjects only if they do not meet criteria for diagnosis of ADHD. If the subject met criteria for DSM-V ADHD diagnosis after completion of the KSADS-E module, they may be considered an ADHD subject

for a subsequent experiment. However, no other assessments or procedures would be conducted with those subjects.

Study data were collected and managed using REDCap electronic data capture tools hosted at Massachusetts Institute of Technology (Harris et al., 2009). REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies by providing the following capabilities: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

fMRI task procedure: Experience sampling

To assess the frequency of MW instances and extent of meta-awareness for individuals in a scanner environment, participants completed a version of the sustained attention to response task (SART) (Robertson et al., 1997) paradigm. However, this particular version was adapted from Christoff et al., 2009 and allowed for online experience sampling in the form of thought probes, during fMRI session. The SART has been widely accepted and considered to be effective in imaging conditions for the following reasons: 1) successful execution of the task seems to require executive control over habitual responding; 2) it has featured prominently in research investigating mind wandering, and; 3) it demonstrates that task-

unrelated thoughts (MW) reliably predict errors at the level of occasions and individuals. Specifically, errors in the SART have been shown to result from attentional disengagement, with lapses being independent of motor response decoupling (Seli, 2016). In addition, the methodology implemented in this study (the combination of the thought-probe method with the SART) has successfully been used in previous brain imaging studies, which illustrates a strong relationship between off-task, conscious experiences and decreased task performance (Christoff et al., 2009; Stawarczyk et al., 2011; Sakai et al., 2013). Although experience sampling in the scanner environment provides a connection between current neural activity and subjective reports, this method may disrupt the normal time course of brain activity signals (Smallwood & Schooler, 2015).

The sustained attention to response task (SART)

In the scanner environment, numbers were presented serially on a screen that was back-projected at the end of the scanner bore, and each will be centered and followed by a mask. The task, (**FIGURE 7**) a version of a go/no-go paradigm, required subjects to respond frequently to 'non-targets' via button press and withhold response to infrequent 'target' stimuli. The frequency of 'go' stimuli effectively generates a habitual response in each subject that must eventually be suppressed on the 'target' no-go trial presentations.

fMRI – Sustained Attention to Response Task
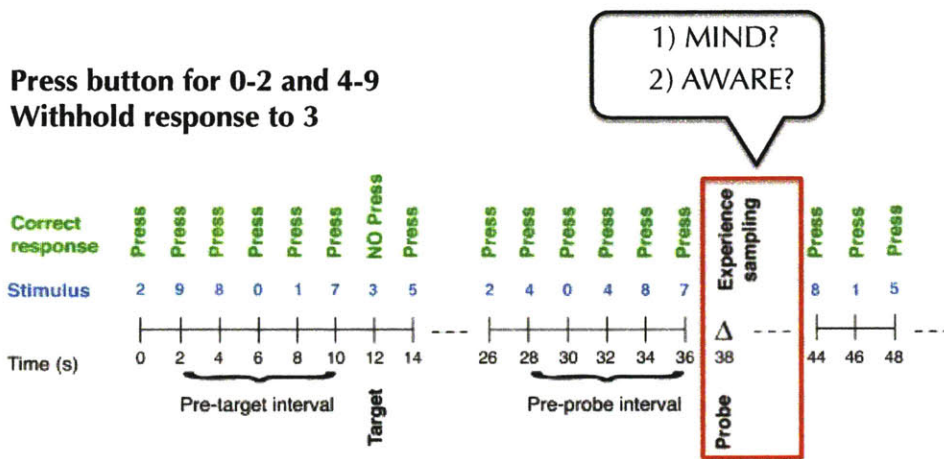
adapted from Christoff et al., 2009, PNAS

FIGURE 7. An experience sampling approach was used to collect self –reports about subjects' focus of attention while they performed a concurrent task (the SART). Also, task accuracy at targets was used as a behavioral index of mind wandering. Analyses focused on the interval of time immediately prior to experience sampling probes to dissociate the effects of mind wandering from the effects of answering the probe.

Each of 4 sessions (≈15 min in duration) consisted of 340 trials (stimulus

presentations) and includes 16 thought probes, 16 targets and 308 nontargets. Each

digit (target and non-target) was presented for 300ms, with an interstimulus

interval of 1700ms (fixation/response period), using python-based presentation

software (Peirce, 2007; 2009). At the same frequency as the target, thought probes

were presented to each subject pseudorandomly. Both the targets and thought

probes were presented at moments that interrupted the task, unpredictable to the

subjects. Each trial presented non-target stimuli as random numbers between 0 and

9, which required a single button response. The target stimuli were the number 3's,

which require subjects to inhibit responding as an exercise of vigilance. The order of

each event of interest (target and thought probes) was pseudocounterbalanced so

that there was a variable distance (5-15 trials) between events, uniformly

distributed within each session (4 total). The structure of this paradigm was similar

to previous studies (see Christoff et al., 2009). The thought probes were presented

to assess the participant's cognitive state immediately prior to the interruption.

Two questions were posed to each participant at the moment of the thought probes,

and displayed on the screen for of 4 seconds, to allow sufficient time for a response.

The first question asked subjects to respond with the type of thoughts they

experienced right before the probe presentation. Possible answers reflected one of

two mental states: task engagement and focus or thoughts that could not be

categorized as such. The second question assessed the ability to notice, or be aware

of, the locus one's thoughts. Possible answer reflected either the awareness or lack thereof, regarding the first question that was asked. Given the novelty of the questions during this experiment, explicit instructions were given to each participant in order to minimize against the natural bias of reporting task-unrelated thoughts. Experimenters stressed the normalcy of off-tasks thoughts during this situation by conveying the following statements to the subject: "During the task, you may find yourself periodically thinking about something other than the task that's in front of you. We are interested in the types of thoughts people have during tasks like this, and it would be completely normal to think about things that are unrelated to the task during these periods. We ask that you try your best to honestly report the content of your thoughts by choosing the response that most accurately reflects them, at the times they are requested. In addition, once you become familiar with these methods, please try to respond consistently if certain types of thoughts arise frequently during the scanning session." In order to familiarize participants with this thought-sampling method, they performed a practice version of the SART with though-probes outside the scanner immediately prior to the imaging session (5 minutes of practice). During this time, all other questions regarding the experiment were answered.

MRI data acquisition

Functional magnetic resonance imaging (fMRI) data were acquired using a 3-Tesla Siemens Tim Trio scanner (Siemens, Erlangen, Germany) paired with a 32-channel

phased-array whole-head coil. Head motion was restrained with foam pillows and

additional padding, when appropriate. 3-dimensional T1-weighted magnetization

prepared rapid acquisition gradient echo (MP-RAGE) anatomical images were

collected with the following parameters: time repetition (TR) = 2530 msec, time

echo (TE) = 4.43 msec flip angle (FA) = 7°, 1.0 x 1.0 x 1.0 mm resolution, 2x

acceleration. Functional T2*-weighted images were acquired using a gradient-echo

echo-planar pulse sequence sensitive to bold oxygenation level-dependent (BOLD)

contrast (Kwong et al., 1992; Ogawa et al., 1992) with the following parameters: TR

= 2500 msec, TE = 30 msec, FA = 90°, 3.0 mm isotropic resolution. Forty transverse

slices covered the whole brain and were acquired in an interleaved fashion. Resting-

state functional data were acquired while the participant was instructed to rest with

eyes open for a period of 6 minutes, 25 seconds, consisting of 150 volumes. During

task periods, functional images were collected with the following with the same

parameters as those during the resting-state scans. However, task-related data

contained forty interleaved, transverse slices that covered the whole brain. Runs

lasted for a period of 14 minutes, 55 seconds during which 354 volumes were

collected. Online prospective acquisition correction was applied to the EPI

sequence.

Data processing

Imaging data were converted to the OpenfMRI format (openfmri.org) and processed

using Nipype, a flexible Python-based framework for interfacing across imaging

software platforms. The software packages used in this analysis pipeline included

FMRIB Software Library (FSL 5.0.8), FreeSurfer (5.3.0; Fischl, 2012), Advanced

Normalization Tools (ANTS; Avants et al., 2009), and Nipype's implementation of

Artifact Detection Tools (ART).

FreeSurfer was used for cortical parcellation and subcortical segmentation of each

subject's T1 – weighted anatomical image; surfaces were visually inspected for

quality and manually edited. Functional images were realigned using FSL's

MCFLIRT, with the reference volume labeled as the first in the run. Functional data

were spatially smoothed with a 6mm FWHM Gaussian kernel, with a high-pass filter

of 1/120Hz. ART was used as quality assurance in order to identify outlier volumes

based on composite motion (greater than 2mm of volume-to-volume) and global

signal intensity. This composite measure was defined specifically for the toolbox. By

default, it converts the 6 rotation/translation head motion parameters into another

set of 6 parameters characterizing the trajectories of 6 points located on the center

of each of the faces of a bounding box around the brain. It then computes the

maximum volume-to-volume movement of any of these points as the single

'composite' movement measure, which is thresholded at 2mm to determine outliers.

Outliers were included as nuisance parameters, as one regressor per outlier, within

the first level general linear models. Participants were excluded from the group

analysis if greater than 20% of their functional runs were flagged by ART as motion

outliers. The average of the median of each realigned functional run was calculated,

and this image was coregistered to the structural scan using FreeSurfer's *bbregister*.

ANTS was used to register the structural image of each subject to MNI space (Oasis-

30 Atropos template in MNI152, 2mm version).

First-level analyses were performed using a general linear model approach.

Regressors in the design matrix included eleven task conditions, as demonstrated in

previous experimental designs (Christoff et al., 2009). These conditions were

convolved with a double gamma hemodynamic response function. Realignment

parameters and motion outliers detected by ART were included in the model as

nuisance regressors. Several contrasts of interest were examined: OFF task > ON

task (mind wandering > focused engagement), Incorrect responses > Correct

responses (attentional lapses > response inhibition). A fixed effect analysis was

performed to combine contrast images across runs, and a composite transform

(*bbregister* and ANTS transformations) was used to normalize the resulting contrast

images to MNI space in a single interpolation step. The normalized contrast and

variance images were entered into a random – effects group – level analysis using

FSL's *flameo.* Whole – brain z –statistic images were corrected for multiple

comparisons using a threshold of $Z > 2.3$ and a cluster significance threshold of $p <$

0.05 (Gaussian Random Field Theory).

Results

Characterization of experience with mindfulness meditation practice

None of the subjects qualified as advanced practitioners of mindfulness meditation

within this cohort of young adults. Self-reported meditation practice hours were

compared to hours required by the most widely used mindfulness training program

for non-practitioners, mindfulness-based stress-reduction (MBSR), which is associated with significant structural and functional brain alterations (Hölzel et al., 2011; Kabat-Zinn, 1990; Kilpatrick et al., 2011). These steps were taken to ensure that participants were meditation-naïve and had not surpassed the minimal threshold of meditation practice sufficient to introduce confounds of practice-mediated brain effects. MBSR requires 31 hours of direct instruction over 8 weeks and additional practice at home, at a minimum of 4 hours per week. Almost all subjects (n = 29) did not exceed 1 hour per week for that duration of time. One subject, in particular, indicated consistent practice close to 3 times per week, but failed to provide sufficient description of practice duration in order to compare practice to standard MBSR protocol.

Task performance

During the intervals before off-task probes, subjects made errors that were not significantly different than before on-task probes ($t(56) = 1.47$, p = 0.15). There was a significant difference in reaction time in the moments prior to thought probes, subjects were faster in their responses to stimuli before on-task reports than off-task ($t(56) = 4.3$, p < 0.001). Subjects reported being off-task for 47% of thought probes (SE=2,2%) and on-task on 53% of the probes ($t(56) = 1.06$, p = 0.29). And, participants were more likely to be aware of the locus of their thoughts at any given moment, when they are probed ($t(56) = 3.7$, p < 0.005). Of the off-task intervals, subjects reported being unaware of the locus of their attention about half of the time, relative to reports of being aware ($t(56) = 0.19$, p = 0.85)
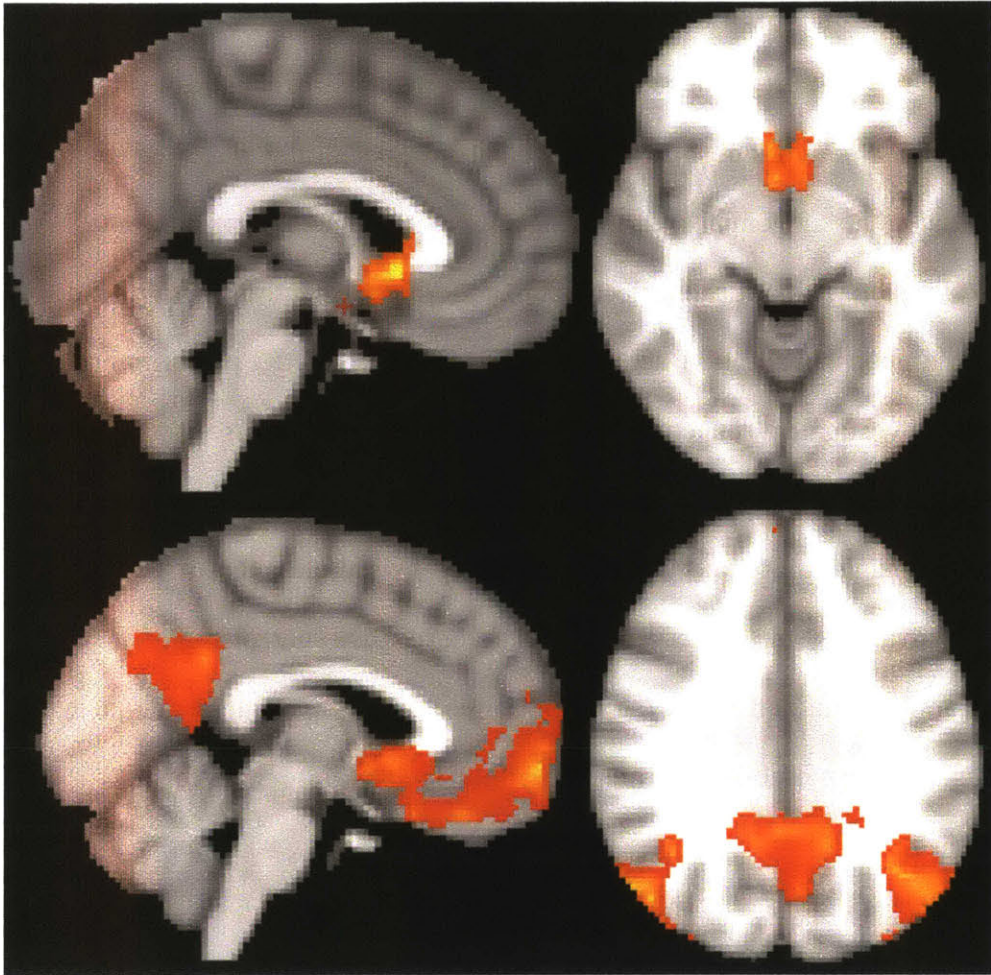
Figure 8. Activations preceding mind-wandering episodes as measured by thought probes (top) and task performance accuracy. Top images illustrate activation preceding reports of mind wandering (intervals prior to off-task vs. on-task probes). Regions for activation reports of OFF > ON occur in subgenual anterior cingulate cortex. Bottom images shot activations preceding SART errors (intervals prior to incorrect vs. correct targets). Regions of activation include the following: ventral/medial/anterior prefrontal cortex, orbitofrontal cortex, posterior cingulate cortex, bilateral inferior lateral parietal lobules(**Table 2**). n = 29, Z = 2.3, p = 0.05

83

Functional imaging during task

When episodes of mind wandering were compared with those of being on task (intervals before off-task probes vs. intervals before on-task probes), activation of the default mode network observed (**Figure 8, top**). Specifically, recruited regions were located in the subgenual anterior cingulate cortex (BA 25), a prominent subcortical region with critical projections to and from the ventral striatum and nucleus accumbens. In addition, activations associated with SART performance errors were investigated, reflecting theory that goo/no-go errors are associated with lapses in attention due to mind wandering (intervals before SART commission errors compared with intervals before correct target withholds) (**Figure 8, bottom**). Activations were observed in DMN and executive control regions : left pre/postcentral gyrus, left midde/superior temporal gyrus, parahippocampal gyrus, precuneus, angular gyri, bilateral inferior parietal lobules.. All regions of activation are noted in **Table 2.**

Table. 2.

Task activations for OFF > ON reports

Clusters (x,y,z) (MNI)	Clusters	BA	k
(0, 14, -2)	Subgenual Cingulate Cortex	25	554

BA=Brodmann Area, k=spatial extent(voxel), FDR=false discovery rate

Task activations for Incorrect > Correct trials

Clusters (x,y,z) (MNI)	Clusters	BA	k
(70, 29, 53)	left Pre/Postcentral Gyrus	6	920
(-64, -20, -16)	left Middle/Superior TG	21/22	1411
(2, 60, -8)	MPFC	25/10/11	3336
(50, -70, 34)	r/l Inferior Parietal Lobule	31/39	4897

BA=Brodmann Area, k=spatial extent(voxel), FDR=false discovery rate

Discussion

This study set out to assess the neural recruitment associated with mind wandering

and in humans, as measured by self-report. In addition, it provides the first potential

replication of empirical evidence of mind-wandering frequency, independent of

thought content (Christoff et al., 2009).

Indeed, results indicate that midline regions of the DMN are involved with mind

wandering and related cognitive states. There are, however, several points of

contrast to highlight between previous studies and we will address each of them

individually. There is only one previous experiment that is constructed similarly, by

focusing on the frequency of human mind wandering the meta-cognition while allowing for sufficient opportunities to observe individual variability in attention over long periods. As such, most comparisons will be made to this study, in particular (Christoff et al., 2009).

Behaviorally, there were differences in reaction time during the SART that were not observed previously in mind-wandering assessments in the fMRI environment. Participants were slower to respond to stimuli immediately prior to off-task reports, which indicate mind wandering. A vast behavioral literature cites faster reaction times prior to errors that are often attributed to pre-error "speeding" (McVay et al., 2013). In these cases, individuals fall into a continual motor response which may leave them prone to make mistakes if vigilance is not appropriately high. However, previous fMRI studies of MW have not found the behavioral differences that we discovered in this study (Christoff et al., 2009; Stawarcyzk et al., 2011). It's possible that, given the rigor of scanner versus laboratory environment, faster response are associated with better task engagement (more on-task responses) compared to the possible decoupling of thought, which may contribute to slower responses times as a result of inattention. In addition, differences were found in the frequency of reports reflecting meta-awareness. Christoff et al., 2009 found that subjects were as likely to aware of the focus of their thoughts as they are unaware, as measured by self-report. Our results indicated the subjects, on average, spent significantly more time with some degree of meta-awareness. There area a couple of points that could explain this difference. This study presents about a 70% increase in the number of

subjects compared to the previous investigation. It's possible that the fewer number of subjects was not sufficient to elicit group differences in this response that would have been seen eventually, with greater power. Individual interpretations of the instructions could also explain behavioral differences in reports of meta-cognition. Instructions, detailed in the method section above, could have been different than those in other studies. Given the reliance on subjective response for these thought probes, the interpretation of the subjects and their ability to accurately report may explain some variability in empirical studies that implement experience sampling. Lastly, results indicated that there was not a significant difference in the occurrence of errors prior to thought probes, that would predict response. The previous study observed, during the intervals before off-task reports, subjects made significantly more errors on the SART than during the intervals before on-task reports. This result appears in line with findings that suggest performance errors are associated with off-task, or mind wandering thoughts. It's not entirely clear why our results do not support this line of thinking, even in the context of the scanner environment, which could elicit different behavior that differs from that of a laboratory setting. One reason could be an insufficient number of errors in the intervals of interest prior to the thought probes. There may not have been enough errors during those time periods, compared to errors made outside of those intervals, to establish the validity of an association between errors and subsequent thought probe reports. Further studies are necessary to resolve some of these behavioral issues.

Out brain imaging findings demonstrated that self-reported mind-wandering episodes are associated with activation in the subgenual anterior cingulate cortex (ventral MPFC; BA25). In addition, performance errors activated the distributed network of the DMN including left lateralized activations of task positive regions (precentral gyrus) and extending in the medial temporal cortex.

Mind-wandering episodes were characterized by generating a contrast of off-task reports greater than on task. Our results show significant, but focal activation along the midline near the ventral MPFC and subgenual cingulate cortex. The ventral MPFC activation is in line with previous findings, but lacks the spatial extent of results that demonstrate activation in the PCC/precuneus, inferior lateral parietal lobule and later prefrontal cortex (Christoff et al., 2009). There are a couple of reasons that may explain the differences in results between these two similarly constructed experiments. First differences in the subject number could facilitate the differences in contrasts of interests. It's possible that effects that were seen at a fewer number of subjects reflect the coherent responses of those subjects that may not have survived when the cohort was doubled. Second, given the subjective nature of self-reports and the administration of instruction, there could be significant variability between subjects (**Figure 9**). Participants could be biased to avoid reporting responses that do not show them in a positive light. Also, it assumes that individuals possess the ability to appraise and evaluate their own thoughts in ways that are most likely unique to them. Differences in interpretation of instruction could drive variability within a group and explain differences between these studies,

particularly with a smaller sample size. In a similar vein, these data showed distinct

results from our hypothesized activations for OFF > ON, so we further scrutinized

each subject to find what individual differences in subject performance may be

driving these images. In our search, we discovered several subjects that projected

the activations we expected but were in the negative direction (**Figure 10**). It's

unclear what's driving these "flipped" subjects. But, it's clear that these regions are

occurring in the predicted spatial locations based on our hypotheses. Further

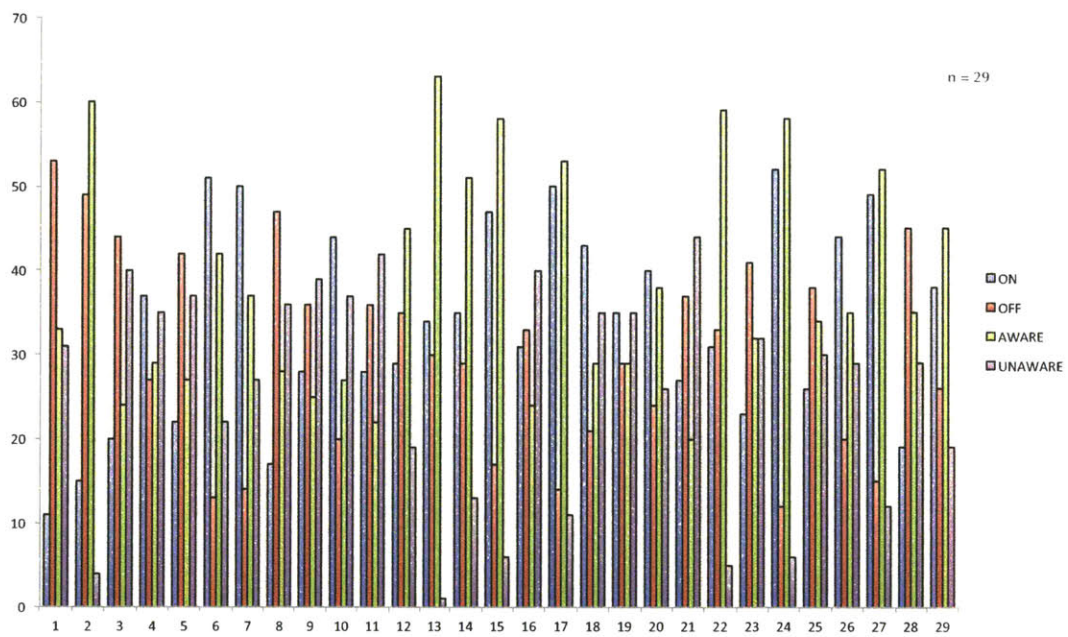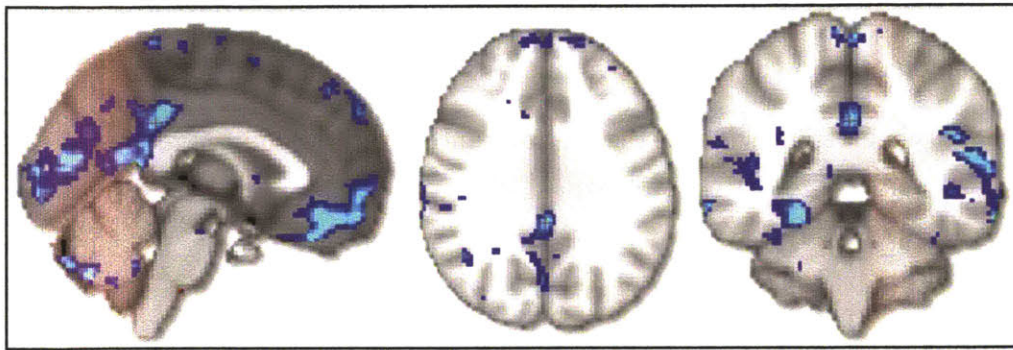research will be necessary in order to resolve these issues.

Figure 9. This figure illustrates the enormous variability between subjects regarding their response to thought probes.

OFF > ON Reports

unthresholded, z stat image
n = 7

Figure 10. Group-level images for activations greater during off-task than off-task reports (n = 7). The specific subjects, at the first-level contrast, demonstrated activation patterns that appear to be "flipped" or the exact opposite direction of expected activations. It is unclear as to what is driving the differences for these subjects compared to others in the cohort.

Our second contrast of interest, the regions of activation prior to errors, shows recruitment throughout components of the default mode network (medial temporal cortex, MPFC, PCC, bilateral IPLs) in addition to the left precentral gyrus. Indeed, a previous study has shown the similar regions are activated preceding errors that are recruited in mind wandering (Christoff et al., 2009). This provides further support for the idea that SART performance errors can be attributed to attentional lapses due to mind wandering (Seli et al., 2016). However, Christoff et al., 2009 only cited small and concentrated regions of the MPFC as associated with brain activation preceding performance errors. In context, this result may seem a bit odd. One should consider that two measures of mind wandering in these studies: subjective measures by self report and objective measures by performance errors. This statement suggests that, by definition, activation preceding SART errors should

be able to provide an accurate depiction on mind wandering, as there is no possible subjective bias involved. It is uncertain as to why previous studies have not been able to demonstrate such robust activations as shown here, and this provides sufficient brain imaging evidence that performance errors are indicative of mind-wandering states.

Limitations

There are several limitations associated with this study that should be considered in order to evaluate the significance of observed findings. A replication of a previous study of mind-wandering frequency was demonstrated, however stark differences in methods make it difficult to interpret findings relative to the initial experiment. Variation in methodology is not exclusive to the comparison within this thesis. Few studies employ similar data acquisition methods and behavioral assessments, and reporting of these aspects can be lacking at times. Going forward, the field would benefit greatly from more transparent documentation of steps taken and more frequent replication in order solidify findings that have become accepted in the field. In addition, we recognized that forcing subjects to choice between focused attention in mind wandering is nuanced. However, our investigation was not currently interested in the qualitative aspects of the mind-wandering experience.

Conclusion

This study investigated the frequency of human mind wandering using experience sampling with fMRI. Findings indicate that both subjective and objective measures

of mind wandering to engage neural recruitment in component regions of the DMN that may include the executive control network. Results should be evaluated in the context of massive improvements in technical methods and analytic approaches over a previous study years ago (Christoff et al., 2009). In addition to replicating some of the cited empirical results, these findings extend the narrative on mind-wandering research by bringing to light weaknesses in current studies and implementing steps to ensure the validity of brain activations. Future studies should continue to improve methodology while concurrently investigating special populations for which this type of research could be incredibly helpful, such as the elderly or those with ADHD.

References for Chapter 2

Allen, M., Smallwood, J., Christensen, J., Gramm, D., Rasmussen, B., Jensen, C.G., Roepstorff, A., Lutz, A. (2013). The balanced mind: The variability of task-unrelated thoughts predicts error monitoring. *Frontiers in Human Neuroscience*, Article 743.

Andrews-Hanna, J.R., Reidler, J.S., Huang, C., Buckner, R.L. (2010). Evidence for the default networks role in spontaneous cognition. *Journal of Neurophysiology, 104*, 322-335.

Andrews-Hanna, J. R., Smallwood, J. and Spreng, R. N. (2014), The default network and self-generated thought: component processes, dynamic control, and clinical relevance. Annals of the New York Academy of Sciences, 1316: 29–52.

Baer, R. A., Smith, G. T., & Allen, K. B. (2004). Assessment of mindfulness by self-report the Kentucky inventory of mindfulness skills. *Assessment, 11*(3), 191-206.

Biswal, B.B., Mennes, M., Zuo, X-N., Gohel, S., Kelly, C., Smith, S.M., Beckmann, C.F., Adelstein, J.S., Buckner, R.L., Colcombe, S., Dogonowski, A-M., Ernst, M., Fair, D., Hampson, M., Hoptman, M.J., Hyde, J.S., Kiviniemi, V.J., Kotter, R., Li, S-.J, Lin, C-P., Lowe, M.J., Mackay, C., Madden, D.J., Madsen, K.H., Margulies, D.S., Mayberg, H.S., Mcmahon, K., Monk, C.S., Mostofsky, S.H., Nagel, B.J., Pekar, J.J., Peltier, S.J., Petersen, S.E., Riedl, V., Rombouts, S.A.R.B., Rypma, B., Schlaggar, B.L., Schmidt, S., Seidler, R.D., Siegle, G.J., Sorg, C., Teng, G-J., Veijola, J., Villringer, A., Walter, M., Wang, L., Weng, X-C., Whitfield-Gabrieli, S., Williamson, P., Windischberger, C., Zang, Y-F., Zhang, H-Y., Castellanos, F.X., Milham, M.P. (2010). Toward discovery science of human brain function. *Proceedings of the National Academy of Sciences 107*:4734–4739.

Brown, K. W., & Ryan, R. M. (2003). The benefits of being present: mindfulness and its role in psychological well-being. *Journal of personality and social psychology, 84*(4), 822.

Callard, F., Smallwood, J., Golchert, J., Margulies, D.S. (2013). The era of the wandering mind? Twenty-first century research on self-generated mental activity. *Frontiers in Psychology*. Article 891.

Christoff, K., Gordon, A.M., Smallwood, J., Smith, R., Schooler, J.W. (2009). Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. *Proceedings of the National Academy of Sciences, 106*, 8719-8724.

Davanger, S. (2014). Nondirective meditation activates default mode network and areas associated with memory retrieval and emotional processing. *Frontiers in Human Neuroscience, 8*(86)

Fox, K.C.R., Nijeboer, S., Solomonova, E., Domhoff, G.W., Christoff, K. (2013). Dreaming as mind wandering: evidence from functional neuroimaging and first-person content reports. *Frontiers in Human Neuroscience,* Article 412. Killinsworth, M.A., Gilbert, D.T. (2010). A wandering mind is an unhappy mind. *Science, 330,* 932.

Gruberger, M., Ben-Simon, E., Levkovitz, T., Zangen, A., Hendler, T. (2011). Towards a neuroscience of mind-wandering. *Frontiers in Human Neuroscience,* Article 56.

Fox, K.C.R., Nijeboer, S., Solomonova, E., Domhoff, G.W., Christoff, K. (2013). Dreaming as mind wandering: evidence from functional neuroimaging and first-person content reports. *Frontiers in Human Neuroscience,* Article 412.

Fox, K. C., Spreng, R. N., Ellamil, M., Andrews-Hanna, J. R., & Christoff, K. (2015). The wandering brain: Meta-analysis of functional neuroimaging studies of mind-wandering and related spontaneous thought processes. *Neuroimage, 111,* 611-621.

Garrison, K. A., Santoyo, J. F., Davis, J. H., Thornhill, T. A., Kerr, C. E., & Brewer, J. A. (2013). Effortless awareness: using real time neurofeedback to investigate correlates of posterior cingulate cortex activity in meditators' self-report. *Front. Hum. Neurosci, 7*(440), 10-3389.

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of biomedical informatics, 42*(2), 377-381.

Hasenkamp, W., Wilson-Mendenhall, C.D., Duncan, E., Barsalou, L.W. (2012). Mind wandering and attention during focused meditation: A fine-grained temporal analysis of fluctuating cognitive states. *NeuroImage, 59,* 750-760.

Hölzel, B. K., Carmody, J., Vangel, M., Congleton, C., Yerramsetti, S. M., Gard, T., & Lazar, S. W. (2011). Mindfulness practice leads to increases in regional brain gray matter density. *Psychiatry Research: Neuroimaging, 191*(1), 36-43.

Kabat-Zinn, J. (1990). Full catastrophe living: A practical guide to mindfulness, meditation, and healing. *Nova York: Delacorte.*

Kane, M.J., Brown, L.E., Little, J.C., Silvia, P.J., Myin-Germeys, I., & Kwapil, T.R. (2007). For whom the mind wanders, and when: An experience-sampling study of working memory and executive control in daily life. *Psychological Science,* 18, 614-621.

Kane, M.J., McVay, J.C. (2012). What mind wandering reveals about executive-control abilities and failures. *Current Directions in Psychological Science, 21*, 348-354.

Kilpatrick, L. A., Suyenobu, B. Y., Smith, S. R., Bueller, J. A., Goodman, T., Creswell, J. D., Tillisch, K., Mayer, E.A. & Naliboff, B. D. (2011). Impact of mindfulness-based stress reduction training on intrinsic brain connectivity. *Neuroimage, 56*(1), 290-298.

Klinger, E. (1971). *Structure and functions of fantasy.* New York, NY: Wiley-Interscience.

Klinger, E. (1999). Thought flow: Properties and mechanisms underlying shifts in content. In J. A. Singer & P. Salovey (Eds.), At play in the fields of consciousness: Essays in honor of Jerome L. Singer (pp. 29 –50).

Levin (Ed.), *Thinking and seeing: Visual metacognition in adults and children* (pp. 203-226). Cambridge, MA: MIT Press.

Levinson, D. B., Smallwood, J., & Davidson, R. J. (2012). The persistence of thought evidence for a role of working memory in the maintenance of task-unrelated thinking. *Psychological Science, 23*(4), 375-380.

Mason, M.F., Norton, M.I., Van Horn, J.D., Wegner, D.M., Grafton, S.T., Macrae, C.N. (2007). Wandering minds: The default network and stimulus-independent thought. *Science, 315*, 393-395.

McVay, J.C., Unsworth, N., McMillan, B.D., Kane, M.J. (2013). Working memory capacity does not always support future-oriented mind-wandering. *Canadian Journal of Experimental Psychology, 67*, 41-50.

Mooneyham, B.W., Schooler, J.W. (2013). The costs and benefits of mind-wandering: A review. *Canadian Journal of Experimental Psychology, 67*, 11-18.

Mooneyham, B. W., & Schooler, J. W. (2016). Mind wandering minimizes mind numbing: Reducing semantic-satiation effects through absorptive lapses of attention. *Psychonomic Bulletin & Review*, 1–7. Springer.

Morrison, A. B., & Jha, A. P. (2015). Mindfulness, Attention, and Working Memory. In *Handbook of Mindfulness and Self-Regulation* (pp. 33-45). Springer New York.

Mrazek, M.D., Mooneyham, B.W., Schooler, J.W. (2014). Insights from quiet minds: The converging fields of mindfulness and mind-wandering. In S. Schmidt and H. Walach (eds.), *Meditation – Neuroscientific Approaches and Philosophical Implications*, Studies in Neuroscience, Consciousness and Spirituality 2. (pp. 227-241). Switzerland: Springer International Publishing.

Poldrack, R. A. (2007). Region of interest analysis for fMRI. *Social cognitive and affective neuroscience, 2*(1), 67-70.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L. (2001). A default mode of brain function. *Proceedings of the National Academy of Science, 98*, 676-82.

Robison, M. K., & Unsworth, N. (2015). Working Memory Capacity Offers Resistance to Mind-Wandering and External Distraction in a Context-Specific Manner. *Applied Cognitive Psychology, 29*(5), 680-690.

Rummel, J., & Boywitt, C. D. (2014). Controlling the stream of thought: Working memory capacity predicts adjustment of mind-wandering to situational demands. *Psychonomic bulletin & review, 21*(5), 1309-1315.

Seli, P. (2016). The Attention-Lapse and Motor Decoupling accounts of SART performance are not mutually exclusive. *Consciousness and cognition, 41*, 189-198.

Schooler, J. W., Mrazek, M. D., Franklin, M. S., Baird, B., Mooneyham, B. W., Zedelius, C., & Broadway, J. M. (2014). The middle way: Finding the balance between mindfulness and mind-wandering. *The Psychology of Learning and Motivation, 60*, 1-33.

Smallwood, J. & Schooler, J.W. (2006). The restless mind. *Psychological Bulletin, 132*, 946-958.

Schacter, D.L., Addis, R., Buckner, R.L. (2008). Episodic simulation of future events: Concepts, data and applications. *Annals of the New York Academy of Sciences, 1124*, 39-60.

Singer, J. L. (1966). Daydreaming: An introduction to the experimental study of inner experience . New York, NY: Random House.

Smallwood, J. & Schooler, J.W., (2015). The Science of Mind Wandering: Empirically Navigating the Stream of Consciousness. *Annual Review of Psychology, 66:* 487 -518.

Smallwood, J., Nind, L., O'Connor, R.C. (2009). When is your head at? An exploration of the factors associated with the temporal focus of the wandering mind. *Conscious and Cognition, 18*, 118-125.

Schooler, J. W., Mrazek, M. D., Franklin, M. S., Baird, B., Mooneyham, B. W., Zedelius, C., & Broadway, J. M. (2014). The middle way: Finding the balance between mindfulness and mind-wandering. *The Psychology of Learning and Motivation, 60*, 1-33.

Smeekens, B., & Kane, M. (2016). Working Memory Capacity, Mind Wandering, and Creative Cognition: An Individual-Differences Investigation Into the Benefits of Controlled Versus Spontaneous Thought.

Stawarczyk, D., Majerus, S., Catale, C., D'Argembeau, A. (2014). Relationships between mind-wandering and attentional control abilities in young adults and adolescents. *Acta Psychologica, 148,* 25-36.

Stawarczyk, D., Majerus, S., Maquet, P., D'Argembeau, A. (2011). Neural correlates of ongoing conscious experience: Both task-unrelatedness and stimulus-independence are related to default network activity. *PLoS ONE,* e16997.

Stawarczyk, D., & D'Argembeau, A. (2015). Neural correlates of personal goal processing during episodic future thinking and mind-wandering: An ALE meta-analysis. *Human brain mapping, 36*(8), 2928-2947.

Wilson, T.D., Reinhard, D.A., Westgate, E.C., Gilbert, D.T., Ellerbeck, N., Hahn, C., Brown, C.L., Shaked, A. (2014). Just think: The challenges of the disengaged mind. *Science, 345,* 75-77.

Resting-state indicators of variation in trait-level mindfulness

Introduction

This thesis initially demonstrated that the intrinsic architecture of the brain can be used to identify individual differences in cognitive abilities (Keller et al., 2015). Resting-state connectivity revealed individual differences in working memory capacity and changes due to aging. Chapter 2 referenced those aforementioned functional networks and regions of interest, which were investigated (DMN and its component regions) in order to determine their contribution to other cognitive states, independent of the external environment. The components of the default-mode network are recruited during mind-wandering episodes, while performing a sustained attention task in the scanner (Christoff et al., 2009; Keller et al., *in prep*). Finally, this third chapter integrates methods utilized in Chapter 1 (seed-driven, resting-state connectivity) with cortical regions networks of interest presented previously (Chapter 2; DMN) to investigate how the intrinsic architecture of the brain can reveal individual differences in the tendency to engage in certain cognitive states in daily life. Given the relevance to mind-wandering research, this chapter explores the capacity for intrinsic functional connectivity to identify individual differences in dispositional mindfulness, within a normal population.

Mindfulness meditation

Parallel to the growing popularity of mind-wandering research (Callard et al., 2013), mindfulness meditation has become increasingly prevalent within mainstream culture and in empirical studies spanning the fields of philosophy, psychology, medicine and cognitive neuroscience. However, interest in this subject matter is not new. Mindfulness meditation practice is thought to build a compelling set of capabilities with broad and positive effects across a range of human behaviors: improved vigilance, working memory capacity, emotional regulation, executive function, and metacognition; reduced mind wandering; and recovery from psychological disorders such as depression, anxiety, or posttraumatic stress disorder (Baird et al., 2014; Hofmann et al., 2010; MacLean et al., 2010; Mrazek et al., 2012; Mrazek et al., 2013; Polusny et al., 2015; Tang et al., 2007; Teper et al., 2013). These benefits, derived from significant meditation practice, have also been explored to establish the functional and structure brain alterations that accompany improvements in health, cognitive ability and affect.

Within this field, there is a diversity of opinion as to the exact definition of mindfulness. This may create conflicts as practices and studies may not be comparable in the methods implemented. It still remains, today, as an issue of contention among scientist and practitioners, particularly as it increases in prevalence within the field of cognitive neuroscience (Awasthi, 2013; Bishop et al., 2004; Grossman & Van Dam, 2011; Kabat-Zinn, 1994). For our purposes, we use one

of the most widely circulated as "paying attention on purpose, in the present moment, and non-judgmentally, to the unfolding of experience moment to moment" (Kabat-Zinn, 1994). Outside of the laboratory, this might be exhibited through the control of one's locus of attentional thought, the inhibition of elaborative or perseverative thinking and the reorientation after disengagement due to attentional lapses (Mooneyham et al., 2016). Although much of the aforementioned literature cites the positive attributes of mindfulness meditation interventions, we will focus on the inherent tendency for an individual to exhibit mindful behaviors, without intervention, practice or training.

Cognitive neuroscience of mindfulness

Cognitive neuroscientists are just one of many groups intrigued by mindfulness meditation practice and implications for brain health and cognitive function. Recently, the field has endeavored to understand the neural underpinnings of this cognitive state and establish the brain bases for mindfulness within the context of mind wandering (lack of mindfulness) and the cognitive machinery of attention. Mind wandering engages a distributed cortical network (Christoff et al., 2009; Keller et al., in prep) and the inter and intra-network interactions have been investigated using a variety of neuroimaging methods (Christoff et al., 2009; Stawarczyk et al., 2011; Hasenkamp et al., 2013; Allen et al., 2013; Fox et al., 2013; Kucyi & Davis, 2014; Tusche et al., 2014; Xu et al., 2014; Fox et al., 2015; Stawarczyk & D'Argembeau, 2015). In this vein, particular attention is given to the default-mode

network (DMN) in addition cognitive control regions involved with executive function. Many brain imaging studies investigate how these brain networks and their component nodes are changes as a result of mindfulness meditation training or a cross-sectional analysis comparing naïve participants to expert practitioners (see Fox et al., 2016 for review). Often, the communication between cortical regions can be quantified by using functional connectivity, which assesses temporal synchrony of brain fluctuations, either spontaneously generated or task-induced. However, before investigating the influence of connectivity on the manifestation of mindful behaviors, it is necessary to review the contribution of each respective cortical region to the experience of mindfulness.

The experience of mindfulness is often associated with the ability to control the direction of one's attention, to regulate emotions effectively and increase self-awareness and knowledge of one's thoughts at any given time. Mindful meditation, a form of mental training, can improve these abilities even as it is practiced in many different ways, which can often make it challenging to compare findings within the field. Studies have shown that mindfulness is associated with the interaction between default-mode, salience and executive networks, in addition to the individual regions of which they are comprised (Fox et al., 2016; Mooneyham et al., 2016). Within these networks, there are notable regions that are frequently referenced within the context of mindful thinking.

The default mode network, deactivated during the external focus of attention, is also

involved with the spontaneous internal generation of stimulus independent thought.

Therefore, mindfulness practice has great relevance to the DMN because it often

requires an individual to sample and appraise the content of thoughts frequently.

This periodic sampling of the content of thoughts may be linked to individual

differences in mind-wandering frequency during daily life (Smallwood, 2013). As

previously mentioned, the DMN is comprised of a core midline network that

includes the medial prefrontal cortex (MPFC) and posterior cingulate cortex (PCC).

This functional network (core) is well-connected in function and structure to many

other regions distributed throughout the brain and is known as an important zone

of integration. Studies have frequently cited it's involvement with self-related

processes that include the following types of thought: self-referential,

autobiographical, judgmental, moral, emotionally evaluative and socially valent. In

particular, the PCC has been linked to autonomic arousal, meta-awareness and

mental monitoring for behaviorally relevant information. (Brewer et al., 2011).

Integrated with the core network within the DMN, is the medial temporal subsystem

with includes the hippocampal and parahippocampal complex, ventromedial

prefrontal and retrospenial cortices. This subsystem has been noted to be heavily

involved with mentalizing about the past or future and retrieving episodic memory.

The final subsystem of the DMN, the dorsal medial subsystem, is comprised of the

dorsomedial prefrontal cortex, the inferior frontal gyrus, lateral temporal cortex and

the lateral superior and ventral frontal cortices. These cortical regions have been

associated with social cognition, theory of mind and semantic or conceptual

processing (Andrews-Hanna et al., 2010; Andrews-Hanna et al., 2014; Mooneyham et al., 2016). In a collaborative manner, these subsystems can combine the support a broad collection of cognitive states and processes.

Frequently considered to be antagonistic to the DMN, the executive network falls within a greater task-positive collection of regions, typically recruited during goal-oriented external focus or mental control. These brain regions are grouped underneath the fronto-parietal control network (FPC: Spreng, 2012), in combination with the salience network, which will be subsequently addressed. The executive network includes the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortices (Spreng et al., 2012). Given the role of the executive control network in contrast to the DMN, it is thought to be involved with the maintenance and manipulation of memory in mind, the ability to make decisions or informed judgments, updating behavioral rules to meet task demands, inhibiting irrelevant information, planning for the future by manipulating the content of memory from the past and active control of the locus of attention. In the bigger picture, these cognitive abilities can be thought to hold significant relevant for the experience of mindful thought with may require the sustained attention and control of inward-facing focus or thoughts. It is proposed that these cognitive mechanisms are similar to those necessary to maintain the focus or mental control of external elements. However, there are conditions under which the executive control network becomes functionally coupled with the DMN, principally those involved goal-directed cognition that is focused internally (autobiographical planning) (Spreng et al., 2010). The coactivation of these normally antagonistic networks provides the

introduction to certain cognitive states for which the connectivity flexibly changes. Indeed, some brain regions within both of these networks (DMN and executive) are recruited under mind-wandering conditions, particularly with a lack of meta-awareness (Christoff et al., 2009).

Often recruited in coordination with executive network regions, the salience network is made up of the dorsal anterior cingulate (dACC) and bilateral insulae (Ham et al., 2013; Menon & Uddin, 2010; Yeo et al., 2011;). These regions may be most relevant to the experience of mindfulness, given their role in interoception and reallocating/redirecting attentional resources. It is also worthwhile to note the considerable connections these salience nodes have to other subcortical regions like the amygdala, hypothalamus and sustantia nigra (Seeley et al., 2007). Given functional connectivity to these regions, it is reasonable to assume that this network has significant involvement with affective and autonomic processing, in addition to receiving multimodal sensory information. (Craig, 2009). The salience network is also well positioned, in function and structure, to facilitate the integration of sensory and cognitive information. Specifically, it allows for the dynamic and flexible coupling of the executive control and default-mode network as the insula plays a significant role. It appears to activate and deactivate these respective networks, and its activations peaks also tend to precede those of the executive control and default mode networks (Sridharan et al., 2008). Much of the field converges on the idea that the salience network serves an integral role in modulating the allocation of attentional resources towards external or internal loci. Most importantly, it possesses the ability to inhibit DMN activity and guide executive control network

processing toward relevant targets (Mooneyham et al., 2016), In sum, we consider this network vital to the maintenance of cognitive states that comprise the experience of mindfulness.

Mindfulness training and resting-state functional connectivity

fMRI studies often use functional connectivity analyses to quantify the degree of temporal correlation between components of a network. This approach can characterize functional changes that may occur following meditation training. Typical studies will examine pre/post training effects or compare naïve controls to experienced practitioners, as defined by the hypotheses of each individual study (Fox et al., 2016; Mooneyham et al., 2016; Tang et al., 2015). For the training studies, resting-state analyses are often implemented post-training to assess the impact of mindfulness practice on intrinsic networks, relative to controls. Experiments have shown that correlated intra-network connectivity of the DMN, salience and executive networks, respectively, is associated with mindfulness. (Berkovich-Ohana et al., 2014; Hasenkamp & Barsalou, 2012; Kilpatrick et al., 2011; Prakash et al., 2013; Taylor et al., 2013). Other studies, however, have explored the association with inter-network resting-state connectivity and mindfulness, particularly with executive control (Creswell et al., 2016; Doll et al., 2015; Hasenkamp & Barsalou, 2012; King et al., 2016). These findings demonstrate the effects of mindfulness training on intrinsic brain connectivity. Between networks, mindfulness is also correlated with connectivity of the DMN and salience networks. Specifically, the

more mindful individuals showed a decreased correlation between the anterior and posterior components of the DMN and a stronger anticorrelation between the insula (salience network) and posterior DMN (PCC; Doll et al., 2015). Results also demonstrate that mindfulness meditation training (compared to relaxation training without a mindfulness component) increased resting-state functional connectivity between the DMN (PCC) and left DLPFC (executive). This may suggest that mindfulness meditation training may couple one's resting-state DMN with regions implicated in executive control (DLPFC; Creswell et al., 2016). In addition, training regimens have been helpful in mitigating the negative effects of post-traumatic stress disorder (PTSD). A pilot study of a novel mindfulness-based intervention for PTSD reports preliminary evidence of changes in resting-state functional connectivity in DMN (PCC) and DLPFC (bilateral) and dorsal anterior cingulate (dACC; salience) following a mindfulness-based exposure therapy. Increasing DMN-DLPFC connectivity at rest was related to PTSD symptom improvement and consistent with other cross-sectional and longitudinal studies in meditators and psychiatric patients (King et al., 2016). It's also important to note that, along with the PCC seed (DMN), the ventral MPFC was also used as a seed but no significant clusters were discovered in any contrast. Finally, in a study by Haskencamp and Barsalou (2012), an anterior MPFC/ACC seed was established resting-state functional connectivity between high and low meditation practitioners was compared. High practice participants exhibited increased connectivity to many regions, including the left inferior frontal gyrus and right DLPFC (executive). These findings demonstrated that inter-network connectivity between the DMN (or its

component regions) and other task positive regions (salience and executive networks) is associated with mindfulness meditation training. Furthermore, because altered connectivity of brain regions in experienced meditators was observed in a non-meditative state (resting), this may represent a transference of cognitive abilities "off the cushion" into daily life (Hasenkamp & Barasalou, 2012)

Trait-level mindfulness effects

Mindfulness can be viewed as an important trait that reflects one's greater tendency to pay attention to and be aware of surroundings and experience the present moment without judgment. Although mindfulness can be trained or cultivated through various forms of meditation, it has been conceptualized as a trait-like or dispositional characteristic, in which levels can vary naturally in the general population. (Brown & Ryan, 2003). This presents the question of whether resting-state connectivity patterns can reveal dispositional mindfulness tendencies in a normal population, without significant meditation training? One previous study investigated this issue by using measures of trait-level mindfulness and resting-connectivity with a population of meditation-naïve subjects. Specifically, they employed regional homogeneity (ReHo) to measure the local synchronization of spontaneous activity during rest. This approach is a voxel-based measure of brain activity, which evaluates the similarity or synchronization between the time series of a given voxel and its nearest neighbors (Zang et al., 2004). This measure is based

on the hypothesis that intrinsic brain activity is manifested by clusters of voxels rather than single voxels. Kendall's coefficient is used as an index to evaluated the similarity of the time series within a cluster of a given voxel and its nearest neighbors. ReHo requires no *a priori* definition of ROIs and can provide information about local/regional activity of regions throughout the brain. The degree of ReHo was then compared to each participant's mindfulness, as measured by the MAAS. They hypothesized that individual differences in dispositional mindfulness would be correlated with resting connectivity in brain regions associated with executive attention emotion processing, body awareness and self-related processing (Kong et al., 2015). These ReHo results concluded that dispositional mindfulness was associated with resting-state connectivity signals in left orbitofrontal cortex, left parahippocampal gyrus, right insula, and negatively associated with ReHo in right inferior frontal gyrus.

Given these previous findings, we conducted a seed-based, resting-state functional connectivity analysis in order to identify neural correlates of individual differences in trait-level mindfulness. The same subjects from Chapter 2 are used in this analysis, providing the unique opportunity to evaluate results in the context of in-scanner task performance data.

Materials and Methods

Participants

Participants were 30 younger adults (23 women) between 18 and 32 years of age

(M = 23.4, SD = 3.8). Written informed consent for participation in the study was

obtained from all participants and approved by the MIT Institutional Review Board.

All participants were healthy, right-handed individuals from the Boston

metropolitan are who satisfied the following criteria: native English speakers; no

contraindications to MRI; and absence of neurological or psychiatric impairments or

associated medications that could affect the central nervous system or brain. All

participants had normal or corrected-to-normal vision. Participants were also asked

to provide information regarding their experience with, or expertise in, the practice

of mindfulness meditation. Individuals were also screened for attention-deficit-

hyperactivity-disorder (ADHD) given its relevance for the subject matter in this

research study.

Neuropsychological and demographic measures

The Wechsler Test of Adult Reading (WTAR) (Holdnack, 2001) was administered to

estimate crystallized IQ. The examiner began by presenting the first of a list of

words, while prompting the subject to pronounce each word out load until all 50

words have been spoken. The procedure was discontinued if the subject provided

12 consecutive incorrect pronunciations. Lists of acceptable pronunciations and

tape recordings were provided by the publisher to account for words with multiple

pronunciation variants. Each correct pronunciation was given a score of 1, with 50

as the maximum raw score. The raw score was standardized by age and compared

to the scores predicted for a particular demographic classification. Trait-level

mindfulness of each subject was collected prior to the scanning session, using two separate measures. The Kentucky Inventory of Mindfulness Skills (KIMS; Baer et al., 2004) is a self-report inventory of mindfulness in which individuals are asked to rate the degree to which each statement applies to them on a 5 – point Likert-style scale ranging from 1 (never or very rarely true) to 5 (almost always or always true). The KMS is designed to assess 4 mindfulness skills: observing, describing, accepting and acting. Items reflect either direct descriptions of the mindfulness skills, or they describe the absence of that skill and are reverse scored. High scores indicated more mindfulness. The Mindful Attention Awareness Scale (MAAS; Brown & Ryan, 2003) is a 5 – item, single dimension measure of trait mindfulness. The MAAS measures the frequency of open and receptive attention to, and awareness of, ongoing events and experiences. Response options range from 1 (almost never) to 6 (almost always). Example items include the following: "I could be experiencing some emotion and not be conscious of it until some time later," or "I find it difficult to stay focused on what's happening in the present," and "I rush through activities without being really attentive to them." The MAAS focuses on the presence or the absence of awareness of what is occurring in the present moment. Item scores were reverse-coded and the mean was computed, making higher scores indicated a greater level of dispositional or trait mindfulness. The validity of our measure of interest for trait-level mindfulness, the MAAS, was established through a significant correlation (r = 0.59, p < 0.001) with the KIMS for these participants.

Characterization of experience with mindfulness practice

In order to account for previous experience with mindfulness meditation practice that may contribute to changes in neural architecture, subjects were classified into two groups based on their responses to the following questions: "Have you ever practiced mindfulness or meditation? If so, how often have you practiced mindfulness or meditation in the past year? Please tell us about your experience." They were categorized as either 'advanced practitioners' or 'meditation-naïve'. This classification was based on cutoffs established in previous studies concerning expertise in mindfulness meditation practice (Garrison et al., 2013).

Screening for ADHD

In order to obtain information about ADHD diagnosis from the healthy controls participating in this study, a researcher from Massachusetts General Hospital (MGH) contacted the subjects by phone. After providing verbal consent the researcher completed the AHDH module of the KSADS-E, a structured psychiatric interview designed to elicit and record past episodes of child and adolescent psychiatric disorder. The results were reviewed with a clinician associated with the study and the subject was used as a member of included subjects only if they do not meet criteria for diagnosis of ADHD. If the subject met criteria for DSM-V ADHD diagnosis after completion of the KSADS-E module, they may be considered an ADHD subject for a subsequent experiment. However, no other assessments or procedures would be conducted with those subjects.

Study data were collected and managed using REDCap electronic data capture tools

hosted at Massachusetts Institute of Technology (Harris et al., 2009). REDCap

(Research Electronic Data Capture) is a secure, web-based application designed to

support data capture for research studies by providing the following capabilities: 1)

an intuitive interface for validated data entry; 2) audit trails for tracking data

manipulation and export procedures; 3) automated export procedures for seamless

data downloads to common statistical packages; and 4) procedures for importing

data from external sources.

MRI data acquisition

Functional magnetic resonance imaging (fMRI) data were acquired using a 3-Tesla

Siemens Tim Trio scanner (Siemens, Erlangen, Germany) paired with a 32-channel

phased-array whole-head coil. Head motion was restrained with foam pillows and

additional padding, when appropriate. 3-dimensional T1-weighted magnetization

prepared rapid acquisition gradient echo (MP-RAGE) anatomical images were

collected with the following parameters: time repetition (TR) = 2530 msec, time

echo (TE) = 4.43 msec flip angle (FA) = 7°, 1.0 x 1.0 x 1.0 mm resolution, 2x

acceleration. Functional T2*-weighted images were acquired using a gradient-echo

echo-planar pulse sequence sensitive to bold oxygenation level-dependent (BOLD)

contrast (Kwong et al., 1992; Ogawa et al., 1992) with the following parameters: TR

= 2500 msec, TE = 30 msec, FA = 90°, 3.0 mm isotropic resolution. Forty transverse

slices covered the whole brain and were acquired in an interleaved fashion.

Functional data were acquired while the participant was instructed to rest with eyes open for a period of 6 minutes, 25 seconds, consisting of 150 volumes. Online prospective acquisition correction was applied to the EPI sequence.

Resting-state data processing

Resting-state fMRI data were first preprocessed in SPM12 (Wellcome Department of Imaging Neuroscience, London, UK). Images were realigned (motion corrected), spatially normalized to the Montreal Neurological Institute (MNI) stereotactic space, and smoothed with a six mm kernel. Quality assurance we performed on the functional time series in order to detect outliers in the motion and global signal intensity using the *art* toolbox. From each subject, an image was identified as an outlier if composite movement from a preceding imaged exceeded 1mm, or if the global mean intensity was greater than 3 standard deviations from the mean image intensity for the run in which it was collected. This composite motion measure was defined by the *art* tool. By default, *art* converts the 6 rotation/translation head motion parameters into another set of 6 parameters characterizing the trajectories of 6 points located on the center of each of the faces of a bounding box around the brain. It then computes the maximum scan-to-scan movement of any of these points as the single 'composite' scan-to-scan movement measure, which is thresholded to determine outliers. Outliers, as identified by this process, were included as nuisance parameters within the first level general linear models, as one regressor per outlier.

Resting-state functional connectivity analysis

Functional connectivity analysis was performed with a seed-driven approach using Conn (Whitfield-Gabrieli & Nieto-Castanon, 2012). The MPFC seed was defined *a priori* from the literature (Fox et al., 2005; Keller et al., 2015; Whitfield-Gabrieli et al., 2009) as 10mm spheres around the coordinates for the medial prefrontal cortex (-1, 47, -4) in MNI space. Physiological and other spurious sources of noise were estimated using the aCompcor method (Behzadi et al., 2007; Chai et al., 2012; Keller et al., 2015; Whitfield-Gabrieli et al., 2009), and removed together with movement-related and artifactual covariates. The residual BOLD time-series was band-pass filtered (0.008 Hz - 0.09 Hz). Each subject's structural image was segmented into white matter, gray matter and cerebral spinal fluid using SPM12. White matter and cerebral spinal fluid masks were eroded by one voxel to avoid partial volume effects with adjacent gray matter. The first 3 principal components of the signals from the eroded white matter and cerebral spinal fluid noise ROIs were removed with regression.

First-level correlation maps were produced by extracting the residual BOLD time course from the MPFC seed and computing Pearson's correlation coefficients between that time course and the time courses of all other voxels in the brain. Correlation coefficients were Fisher transformed into 'Z' scores, which increases normality and allows for improved second-level General Linear Model analyses. All reported clusters were significant at an FDR cluster-corrected threshold of $p < 0.05$.

MPFC functional connectivity with mindfulness

We investigate the relationship of the magnitude of resting-state correlations from the MPFC and a measure of trait-level mindfulness assessed outside of the scanner (MAAS). A whole-brain search was conducted with the mindfulness score (MAAS) of each subject as covariates of interest. A cluster corrected threshold of $p < 0.05$ FDR cluster-corrected was set.

Results

Correlations with dispositional mindfulness

Subjects reported an average mindfulness score on the MAAS of 3.82 out of 5 (*SD* = 0.61). Greater connectivity from the MPFC to a cluster of regions spanning the superior and middle frontal gyri (-22, 42, 8; 412 voxels) was significantly associated with higher mindfulness (MAAS) (r = 0.77)(**Figure 11**). In addition, a second measure of mindfulness (KIMS) was also significantly correlated with greater left-lateralized functional connectivity to similar regions. (**Figure 12**). In addition, MPFC resting-state connectivity patterns associated with increase mindfulness also correlated with reduced mind wandering during and fMRI assessment of off-task thoughts using experience sampling (**Figure 13**).
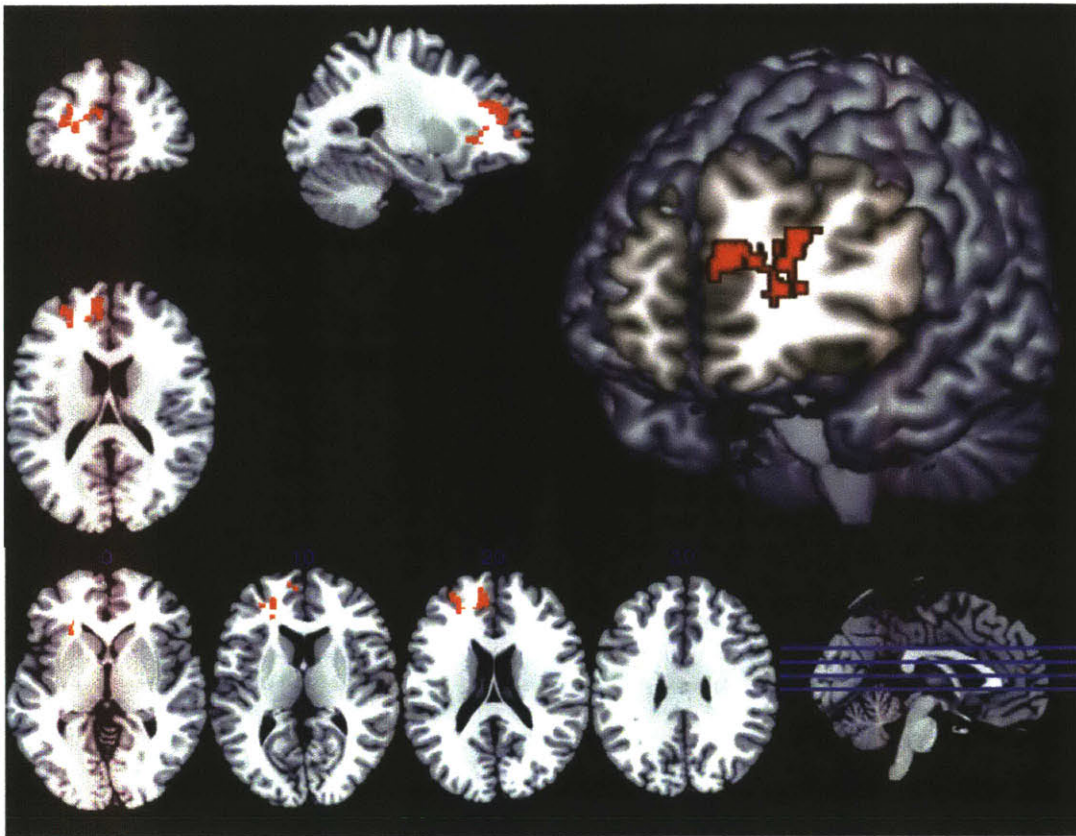
Figure 11. Seed-to-voxel resting-state analysis revealed that increasing connectivity between MPFC and left frontal gyrus is correlated with greater dispositional mindfulness(412 voxels, peak coordinate= -22, 42, 8.)
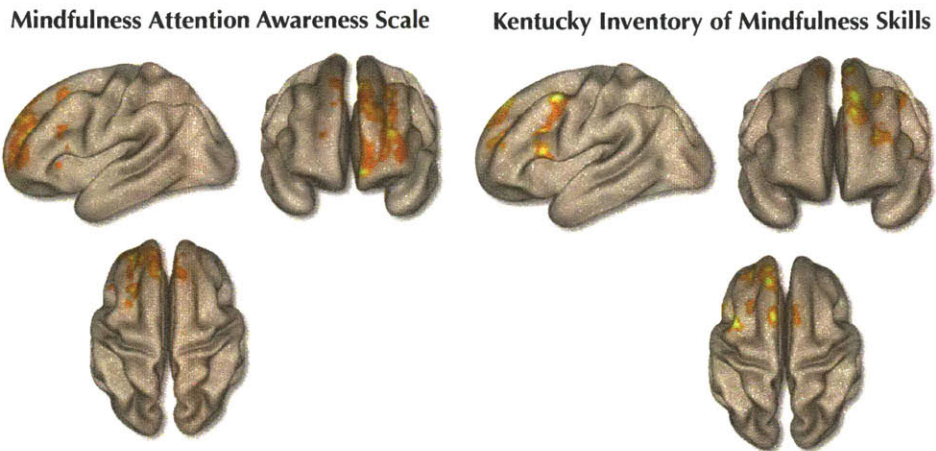
Mindfulness Attention Awareness Scale   **Kentucky Inventory of Mindfulness Skills**

Figure 12. Figure illustrates the left-lateralization of mindfulness, as measured by seed-to-voxel connectivity from the MPFC at rest. Images are shown under more liberal threshold than primary analysis (p = 0.05 whole-brain, uncorrected), in order to demonstrate the spatial extent and consistency of effects across different measures. All cluster shown are p < 0.05 FDR cluster-corrected.
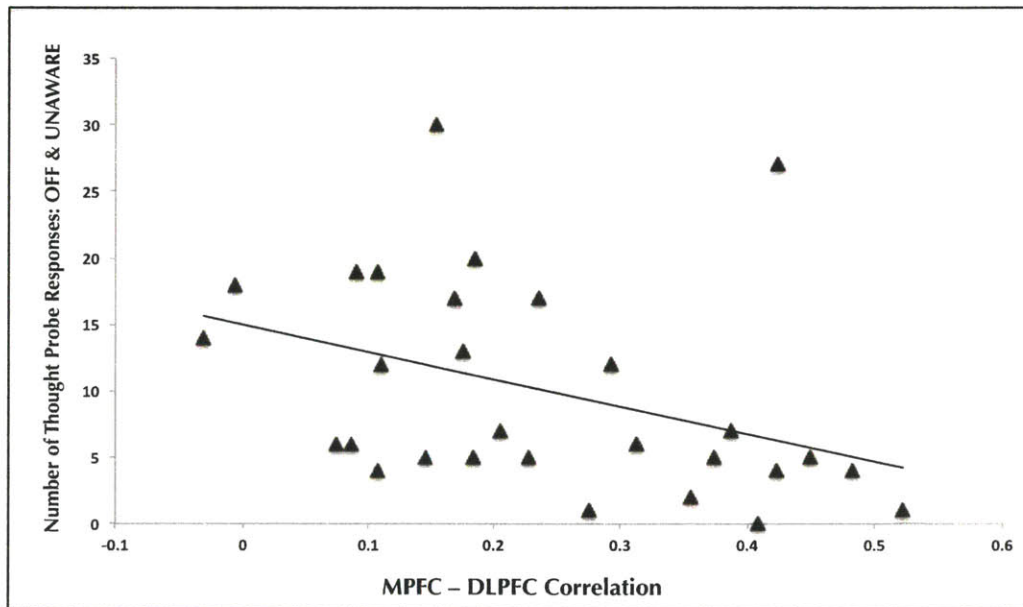

Figure 13. Greater MPFC-left DLPFC connectivity at rest was associated with less mind wandering (without meta-awareness) during the SART, as measured by the number of off-task and unaware subjective reports during thought probes (r = -0.39, p = 0.03).

Discussion

We found evidence from individual differences among young adults of a relation between greater trait-level mindfulness (with 2 different measures) and MPFC connectivity to left-lateralized frontal regions, at rest. These regions span frontal DMN and executive regions, and effects do not appear exclusively in one network or the other. Instead, it suggests, a combination of intrinsic connectivity effects may explain individual differences for those with higher self-reported mindfulness in his or her daily life.

This study suggests, like others comparing meditators to controls, that trait-level mindfulness is associated with differences in the intrinsic architecture of the brain, with a particular focus on the DMN and executive network regions. In particular, there are two interesting aspects to this finding as it relates to individual dispositional mindfulness and associated behavior.

First, it indicates that, for those with greater train-level mindfulness, they demonstrated functional connectivity patterns they trend toward those of experienced meditators and practitioners. This proposes that higher degrees of trait mindfulness exhibit intrinsic connectivity patterns that resemble (trending toward) those of practitioners that are consistent across resting-state and meditation conditions, but to a less significant degree. The consistency of connectivity across both meditation and resting periods suggests that meditation practice may transform the resting-state experience into one that resembles a meditative state.

(Brewer et al., 2011). We can postulate that those individuals in our study, with greater trait-level mindfulness, possess a moderate form of the intrinsic connectivity that meditators observe as a function of experience dependent plasticity of default mode and executive networks. However, results also indicate that individual differences in intrinsic connectivity due to mindfulness cannot be attributed to effects in one network or another. It may be a combination of resting-state effects that have been cited in the literature, that manifest in an intermediate left-lateralized, frontal cortical region that expresses both of these mechanisms. One study has shown that individual differences in trait-level mindfulness can be explained by increases in resting-state homogeneity at rest (Kong et al., 2015). Results could reflect the increased local connectivity of the voxels surrounding the MPFC seed, which may have contributed to increased connectivity to brain regions that are functionally connected to the DMN in frontal cortex. In addition, studies have shown that individual differences in dispositional connectivity are associated with greater inter-network connectivity between salience/executive and default-mode networks at rest, post-training Creswell et al., 2016; Doll et al., 2015; Hasenkamp & Barsalou, 2012; King et al., 2016). Our results illustrated connectivity patterns that also support these findings, but in a naïve population that has not been trained. Therefore, correlations between the DMN and other task positive networks perhaps reflect the stronger ability for these individuals to manipulate internal information and control their self-generated thoughts.

Second, it generates questions about the daily practices and tendencies necessary,

in parallel with associated behavior, to induce functional changes in the brain. We

know that frequent mindfulness meditation practice can induce network

connectivity changes, but it is possible that certain individuals naturally develop

intrinsic connectivity that resembles the "mindful brain" more than the average

person. It is also possible that an accumulation of unintended mindful behaviors,

over time, has an effect on intrinsic architecture of the brain.

The consistent left-lateralization of increased mindfulness may be associated with

the dorsal medial subsystem of the DMN (Mooneyham et al., 2016). Typically

involved with mentalizing and conceptual processing, it includes the dorsomedial

prefrontal cortex and the tempoparietal junction. The regions are widely appreciate

for their for their role in mentalizing, the metacognitive process of inferring or

reflecting upon the mental state of other people and/or one's self. It is also known to

contribute to social and/or self-reflective aspects of autobiographical memory or

future thought. (Andrews-Hanna et al., 2014). Results suggest that the cognitive

processes that support dispositional mindfulness without training may be explained

by underlying connectivity differences within this subsystem of the DMN and it's

spontaneous interactions with regions in the salience/executive network regions.

Future studies are necessary to investigate these issues.

It should be noted that the region of interest, identified via resting-state connectivity

with MAAS, is quite heterogeneous. The cluster, defined via whole-brain search as

positive correlated with mindfulness measures as a covariate, spans regions that may include both the superior frontal gyrus (region not distinct from DMN) and executive network(DLPFC). This result could indicate that, in addition to increased intra-network connectivity of the DMN (regional homogeneity; Kong et al., 2015), greater mindfulness is accompanied by stronger positive connectivity with executive regions to which they are not normally positively correlated. Increased connectivity within DMN could be associated with a greater extent of self-related processes and the executive control regions are necessary to manipulate and organize these thoughts internally.

Limitations

There are several challenges associated with conducting research on the neural basis of mindfulness. One issue is the diversity of mindfulness scales that have been shown to be associated with different types of functional connectivity (Doll et al., 2015). Also, a variety of different methodological designs are used to investigate patterns of functional connectivity including the following: correlational studies, longitudinal training studies, and cross-sectional studies comparing expert meditators, or practitioners with moderate meditation experience (Mooneyham et al., 2016). The methods in the acquisition of resting-state functional also vary considerably. In our study, we instructed subjects to rest and remain with their eyes open. However, some studies allow participants to close their eyes (Kong et al., 2015) which makes it difficult to compare between environmental conditions. We also acknowledge that cortical region identified in the whole-brain search for

correlations with mindfulness was not identified independent of the covariates. Methods employed in Chapter 1, in which a region of interest was defined independent of cognitive measures, may be a more robust demonstration of this analysis.

Conclusion

In young adult controls, individual differences trait-level mindfulness were related to resting-state connectivity. Greater mindfulness was correlated with increased connectivity to left lateralized DLPFC and superior frontal gyrus regions, from a seed in the MPFC. These results suggest that intrinsic functional connectivity between MPFC, a node of the DMN, and DLPFC, a component of the executive network, may serve as an indicated of individual differences in dispositional mindfulness within a normal populations of healthy young adult controls. It also indicates that this unique and intermediate connectivity pattern could reflect the parallel mechanisms of increased intra-network connectivity to the local region of the MPFC and increased inter-network connectivity between DMN and executive regions.

For a typical population, greater trait-level mindfulness is accompanied by increased intra-network resting-state connectivity using metrics of regional homogeneity (Kong et al., 2015) and increased inter-network connectivity to executive cortical regions. Ultimately, it will be valuable to relate directly such resting-state and active-performance network dynamics. Resting-state studies are

limited in interpretation by the absence of online behavioral measures. Future

studies that integrate resting-state and active-performance measures of

mindfulness for naïve participants and clarify the extent to which individual

differences in intrinsic brain connectivity can explain variations in mindfulness and

predict behavior during empirical studies of mindfulness training.

REFERENCES FOR CHAPTER 3

Awasthi, B. (2013). Issues and perspectives in meditation research: in search for a definition. *Frontiers in psychology, 3*(316), 1-9.

Baird, B., Mrazek, M. D., Phillips, D. T., & Schooler, J. W. (2014). Domain-specific enhancement of metacognitive ability following meditation training. *Journal of Experimental Psychology: General, 143*(5), 1972.

Berkovich-Ohana, A., Glicksohn, J., & Goldstein, A. (2014). Studying the default mode and its mindfulness-induced changes using EEG functional connectivity. *Social cognitive and affective neuroscience, 9*(10), 1616-1624

Bishop, S. R., Lau, M., Shapiro, S., Carlson, L., Anderson, N. D., Carmody, J., ... & Devins, G. (2004). Mindfulness: A proposed operational definition. *Clinical Psychology: Science and Practice, 11*(3), 230-241.

Brewer, J. A., Worhunsky, P. D., Gray, J. R., Tang, Y. Y., Weber, J., & Kober, H. (2011). Meditation experience is associated with differences in default mode network activity and connectivity. *Proceedings of the National Academy of Sciences, 108*(50), 20254-20259.

Callard, F., Smallwood, J., Golchert, J., Margulies, D.S. (2013). The era of the wandering mind? Twenty-first century research on self-generated mental activity. *Frontiers in Psychology.* Article 891.

Craig, A. D. (2009). How do you feel—now? the anterior insula and human awareness. *Nature Reviews Neuroscience, 10*(1).

Creswell, J. D., Taren, A. A., Lindsay, E. K., Greco, C. M., Gianaros, P. J., Fairgrieve, A., ... & Ferris, J. L. (2016). Alterations in Resting-State Functional Connectivity Link Mindfulness Meditation With Reduced Interleukin-6: A Randomized Controlled Trial. *Biological Psychiatry.*

Doll, A., Hölzel, B. K., Boucard, C. C., Wohlschläger, A. M., & Sorg, C. (2015). Mindfulness is associated with intrinsic functional connectivity between default mode and salience networks. *Frontiers in human neuroscience, 9.*

Fayed, N., Cifre, I., Garcia-Campayo, J., & Viguera, L. (2015). Mindfulness and Neuroimaging. In *Psychiatry and Neuroscience Update* (pp. 389-401). Springer International Publishing.

Fox, K. C., Dixon, M. L., Nijeboer, S., Girn, M., Floman, J. L., Lifshitz, M., ... & Christoff, K. (2016). Functional neuroanatomy of meditation: A review and meta-analysis of 78 functional neuroimaging investigations. *Neuroscience & Biobehavioral Reviews.* 65. 208-228.

Grossman, P., & Van Dam, N. T. (2011). Mindfulness, by any other name...: trials and tribulations of sati in western psychology and science. *Contemporary Buddhism*, *12*(01), 219-239.

Ham, T., Leff, A., de Boissezon, X., Joffe, A., & Sharp, D. J. (2013). Cognitive control and the salience network: an investigation of error processing and effective connectivity. *The Journal of Neuroscience*, *33*(16), 7091-7098.

Hasenkamp, W., & Barsalou, L. W. (2012). Effects of meditation experience on functional connectivity of distributed brain networks. *Frontiers in Human Neuroscience*, *6*.

Hofmann, S. G., Sawyer, A. T., Witt, A. A., & Oh, D. (2010). The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. *Journal of Consulting and Clinical Psychology*, *78*(2), 169.

Kabat-Zinn, J. (2009). *Wherever you go, there you are: Mindfulness meditation in everyday life*. Hachette Books.

Keller, J. B., Hedden, T., Thompson, T. W., Anteraper, S. A., Gabrieli, J. D., & 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.

Kilpatrick, L. A., Suyenobu, B. Y., Smith, S. R., Bueller, J. A., Goodman, T., Creswell, J. D., ... & Naliboff, B. D. (2011). Impact of mindfulness-based stress reduction training on intrinsic brain connectivity. *Neuroimage*, *56*(1), 290-298.

King, A. P., Block, S. R., Sripada, R. K., Rauch, S., Giardino, N., Favorite, T., ... & Liberzon, I. (2016). Altered default mode network (DMN) resting state functional connectivity following a mindfulness-based exposure therapy for posttraumatic stress disorder (PTSD) in combat veterans of Afghanistan and Iraq. *Depression and Anxiety*, *33*(4), 289-299.

Kong, F., Wang, X., Song, Y., & Liu, J. (2015). Brain regions involved in dispositional mindfulness during resting state and their relation with well-being. *Social Neuroscience*, 1-13.

MacLean, K. A., Ferrer, E., Aichele, S. R., Bridwell, D. A., Zanesco, A. P., Jacobs, T. L., ... & Wallace, B. A. (2010). Intensive meditation training improves perceptual discrimination and sustained attention. *Psychological science*, *21*(6), 829-839.

Manuello, J., Vercelli, U., Nani, A., Costa, T., & Cauda, F. (2016). Mindfulness meditation and consciousness: An integrative neuroscientific perspective. *Consciousness and Cognition, 40,* 67-78.

Mrazek, M. D., Smallwood, J., & Schooler, J. W. (2012). Mindfulness and mind-wandering: finding convergence through opposing constructs. *Emotion, 12*(3), 442.

Mrazek, M. D., Franklin, M. S., Phillips, D. T., Baird, B., & Schooler, J. W. (2013). Mindfulness training improves working memory capacity and GRE performance while reducing mind wandering. *Psychological Science,* 0956797612459659.

Polusny, M. A., Erbes, C. R., Thuras, P., Moran, A., Lamberty, G. J., Collins, R. C., ... & Lim, K. O. (2015). Mindfulness-based stress reduction for posttraumatic stress disorder among veterans: a randomized clinical trial. *JAMA, 314*(5), 456-465.

Prakash, R. S., De Leon, A. A., Klatt, M., Malarkey, W., & Patterson, B. (2013). Mindfulness disposition and default-mode network connectivity in older adults. *Social cognitive and affective neuroscience, 8*(1), 112-117.

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., ... & Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of Neuroscience, 27*(9), 2349-2356.

Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences, 105*(34), 12569-12574.

Tang, Y. Y., Ma, Y., Wang, J., Fan, Y., Feng, S., Lu, Q., ... & Posner, M. I. (2007). Short-term meditation training improves attention and self-regulation. *Proceedings of the National Academy of Sciences, 104*(43), 17152-17156.

Tang, Y. Y., Hölzel, B. K., & Posner, M. I. (2015). The neuroscience of mindfulness meditation. *Nature Reviews Neuroscience, 16*(4), 213-225.

Taylor, V. A., Daneault, V., Grant, J., Scavone, G., Breton, E., Roffe-Vidal, S., ... & Beauregard, M. (2013). Impact of meditation training on the default mode network during a restful state. *Social cognitive and affective neuroscience, 8*(1), 4-14.

Teper, R., Segal, Z. V., & Inzlicht, M. (2013). Inside the Mindful Mind How Mindfulness Enhances Emotion Regulation Through Improvements in Executive Control. *Current Directions in Psychological Science, 22*(6), 449-454.

Zang, Y., Jiang, T., Lu, Y., He, Y., & Tian, L. (2004). Regional homogeneity approach to fMRI data analysis. *Neuroimage, 22*(1), 394-400.