UNIVERSITY OF CALIFORNIA, SAN DIEGO

SAN DIEGO STATE UNIVERSITY

Neural Correlates of Successful Cognitive Aging

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

Allison Renee Kaup

Committee in charge:

University of California, San Diego

Professor Lisa T. Eyler, Chair
Professor Susan F. Tapert, Co-Chair
Professor Sean P.A. Drummond
Professor William S. Kremen

San Diego State University

Professor Paul E. Gilbert
Professor Claire Murphy

2012

The Dissertation of Allison Renee Kaup is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

_____

_____

_____

_____

_____
Co-Chair

_____
Chair

University of California, San Diego

San Diego State University

2012

DEDICATION

This dissertation is dedicated to all who supported me throughout my doctoral studies, including, but not limited to, the following individuals:

Lisa T. Eyler, Ph.D., my phenomenal graduate research advisor

Natalie L. Denburg, Ph.D., who introduced me to the field of neuropsychology

My family and friends, and in particular, my parents, Stephen and Denise Kaup, for their continued support and encouragement throughout the years

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

I would like to thank and acknowledge Lisa T. Eyler, Ph.D., for her support as my graduate research adviser and the co-chair of my committee. Her guidance has been invaluable, and I could not have found a better mentor. I would also like to thank and acknowledge Sean P.A. Drummond, Ph.D., who generously agreed to collaborate on this project and share data that he and his laboratory collected so that I could analyze those data for inclusion in my dissertation. Further, I would like to thank and acknowledge Wesley K. Thompson, Ph.D., for providing statistical consultation. He was instrumental in guiding me in the use of multivariate statistical techniques to analyze these data.

This study was funded by the NIMH T-32 Fellowship in Geriatric Mental Health (T32 MH019934) awarded to Dilip V. Jeste, M.D., R01 MH083968 awarded to Lisa T. Eyler, Ph.D., and R01 AG024506 awarded to Sean P.A. Drummond, Ph.D.

Material from this dissertation will be prepared to be submitted for publication. The dissertation author, Allison Kaup, will be the primary author of publications that result from this material. Lisa T. Eyler, Sean P.A. Drummond, and Wesley K. Thompson will be co-authors.

VITA

EDUCATION

2012	Doctor of Philosophy in Clinical Psychology, San Diego State University / University of California, San Diego
2009	Master of Science in Clinical Psychology, San Diego State University
2006	Bachelor of Science in Psychology, University of Iowa

RESEARCH APPOINTMENTS

2006-2012	Graduate Research Assistant in the Department of Psychiatry and Pre-Doctoral Fellow in Geriatric Mental Health, University of California, San Diego
2004-2006	Research Assistant in the Department of Neurology, University of Iowa Hospitals and Clinics

PUBLICATIONS

Bangen, K.J., Kaup, A.R., Mirzakhanian, H., Wierenga, C.E., Jeste, D.V., & Eyler, L.T. (*in press*). Compensatory brain activity during encoding among older adults with better recognition memory for face-name pairs: An integrative functional, structural, and perfusion imaging study. *Journal of the International Neuropsychological Society.*

Kaup, A.R., Dunn, L.B., Saks, E.R., Jeste, D.V., & Palmer, B.W. (2011). Decisional capacity and consent for schizophrenia research. *IRB: Ethics & Human Research, 33*(4), 1-9.

Kaup, A.R., Mirzakhanian, H., Jeste, D.V., & Eyler, L.T. (2011). A review of the brain structure correlates of successful cognitive aging. *Journal of Neuropsychiatry and Clinical Neurosciences, 23*(1), 6-15.

Eyler, L.T., Prom-Wormley, E., Panizzon, M.S., Kaup, A.R., Fennema-Notestine, C., Neale, M.C., et al. (2011). Genetic and environmental contributions to regional cortical surface area in humans: A magnetic resonance imaging twin study. *Cerebral Cortex, 21*(10), 2313-2321.

Eyler, L.T., Sherzai, A., Kaup, A.R., & Jeste, D.V. (2011). A review of functional brain imaging correlates of successful cognitive aging. *Biological Psychiatry, 70*(2), 115-122.

Eyler, L.T., Kaup, A.R., Mirzakhanian, H., & Jeste, D.V. (2009). Schizophrenia patients lack normal positive correlation between age and brain response during verbal learning, *American Journal of Geriatric Psychiatry, 17*(1), 43-55.

Denburg, N.L., Weller, J.A., Yamada, T.H., Shivapour, D.M., Kaup, A.R., LaLoggia, A. et al. (2009). Poor decision making among older adults is related to elevated levels of neuroticism. *Annals of Behavioral Medicine, 37*(2), 164-172.

ABSTRACT OF THE DISSERTATION

Neural Correlates of Successful Cognitive Aging

by

Allison Renee Kaup

Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2012
San Diego State University, 2012

Professor Lisa T. Eyler, Chair
Professor Susan F. Tapert, Co-Chair

Even in the absence of pathology such as Alzheimer's disease, aging is associated with cognitive decline. Nevertheless, some older individuals appear to maintain their cognitive abilities, raising the question of what neural factors might promote "successful" cognitive aging (SCA). From the current literature, it is unclear whether there are unique neural factors that give rise to individual differences in SCA, or whether the same neural factors relate to cognition across adulthood. Little is known about the relative importance of different aspects of neural integrity

(i.e. brain structure, task-related functional response, and functional connectivity) to promoting SCA or how different neural factors interact in their contribution to SCA.

We aimed to characterize the neural signature of SCA, defined by working memory performance. Sixty-four healthy adults, ages 23 to 78, underwent structural and functional magnetic resonance imaging during a working memory task. We focused on measuring the cortical thickness and surface area of the dorsolateral prefrontal cortex (DLPFC) and task-related activation within the DLPFC including laterality effects. We also focused on the "default-mode network" by measuring task-related deactivation in the medial prefrontal cortex (MPFC), functional connectivity between the MPFC and posterior cingulate (PC), and MPFC structure. We aimed to determine how these neural measures related to working memory and whether or not these brain-cognition relationships differed by age. We also explored the relative contribution of and inter-relationships between these neural measures in predicting SCA.

Larger DLPFC surface area, greater left and right DLPFC activation, more bilateral DLPFC activation, and greater MPFC deactivation were each associated with better working memory performance. These brain-cognition relationships did not differ with age, thus SCA did not result from a unique neural signature but occurred when older adults maintained the same brain-cognition relationships present throughout adulthood. Results of multivariate analyses showed how different aspects of the neural system (i.e., brain structure and function) work together to achieve good cognitive function in aging. Right DLPFC activation and MPFC deactivation were the strongest contributors to SCA, suggesting that brain-based interventions should focus on preventing or reversing age-related alterations in those aspects of the neural system.

INTRODUCTION

The Aging of the Population

Across the globe, the older adult population is rapidly increasing in number, a trend which is expected to continue for several years to come. Gains in longevity and the aging of the "baby boomer" generation are contributing to the increasing number of older adults, and decreasing birth rates are causing older adults to represent a larger proportion of the total population (Kinsella & He, 2009). While 10% of the world's population was age 60 or older in 2000, this proportion is projected to climb to 17% by 2030 and 32% by 2100 (Lutz, Sanderson, & Scherbov, 2008).

Given the rising numbers of older adults, the well-being of older individuals is a major public health issue. This includes the physical health, as well as the quality of life, of older individuals. Accordingly, important research is being conducted aimed at understanding, treating, and preventing age-related illnesses, including dementias such as Alzheimer's disease. Prevalence estimates suggest that approximately 14% of individuals age 71 or older in the United States have dementia (Plassman et al., 2007). While far from insignificant, these estimates do indicate that the majority of older adults do not suffer from dementia. Thus, factors influencing the well-being of healthy older adults also warrant study, in hopes of maintaining and/or improving quality of life among the elderly.

Cognitive Decline in Aging and Evidence for "Successful" Cognitive Aging

Even among individuals free of dementia and other neurocognitive disorders, aging is associated with declines in several cognitive domains. Specifically, performance differences between healthy older and younger adults have been observed in the following domains: executive functions (e.g., working memory), episodic memory, processing speed, visuospatial

function, complex attention (e.g., divided attention), and word-finding (Drag & Bieliauskas, 2010). In contrast, crystallized knowledge, such as vocabulary, has been shown to remain stable or even improve in older age (Park et al., 2002; Salthouse, 2004). Although several domains appear to be affected in aging, some have argued that age-related declines are more prominent in some domains compared to others. For example, the "frontal lobe hypothesis" posits that age-related declines are first seen in cognitive abilities supported by the frontal lobes, such as executive function (West, 1996). Others have argued that slowed processing speed accounts for the declines seen in other cognitive domains (Salthouse, 1996).

Despite group differences in cognition (i.e., comparing younger to older adults), individual differences in cognitive functioning are apparent among healthy older adults, suggesting that cognitive decline is not an inevitable consequence of aging. Ylikoski et al. (1999) conducted a cluster analysis using older individuals' performances on several cognitive measures and identified subgroups of individuals representing those with average performance, those with above-average performance, and those considered "at risk" for cognitive impairment. When older adults are followed longitudinally, different trajectories of cognitive aging emerge, reflecting decline, stability, and even improvement within individuals (Wilson et al., 2002). Together, these findings indicate that it is possible to maintain cognitive functioning in aging, a phenomenon first referred to as "successful" aging by Rowe and Kahn (1987). Although there are many factors that lead to good quality of life, maintenance of good cognitive performance is cited by older adults as a crucial component of success in aging (Reichstadt, Depp, Palinkas, Folsom, & Jeste, 2007) and is one of the most frequent criteria found in the myriad of researcher-based definitions of successful aging (Depp & Jeste, 2006).

What factors promote this "successful" cognitive aging (SCA), and how might we intervene to improve cognition (and hence, quality of life) among older adults? Much research effort has been devoted to identifying correlates of SCA. Although progress has been made in

identifying neural changes with aging and understanding how these changes relate to SCA (reviewed below), there are also several areas that still need to be examined in order to completely appreciate the neural signature (or signatures) of maintaining good cognitive performance into old age.

Age-Related Differences in Brain Structure

On a neuronal level, non-pathological aging is associated with decreased dendritic aborization and reductions in dendritic spines and synaptic connections (Dickstein et al., 2007; Uylings & de Brabander, 2002). While present in normal aging (Uylings & de Brabander, 2002), neuronal loss is much less prominent than that seen in age-related pathologies such as Alzheimer's disease (Dickstein et al., 2007).

Volumetric studies show that brain regions are not uniformly affected by aging. In a cross-sectional study of 148 healthy adults, Raz et al. (1997) found that negative associations between age and volume were greatest for the prefrontal cortex. Negative age associations were also found for prefrontal white matter, superior parietal cortex and white matter, inferior temporal cortex, hippocampal formation, and fusiform gyrus. Similarly, via a multivariate analysis of voxel-based morphometry data, Bergfield et al. (2010) found the strongest evidence for age-associated volume differences in frontal regions such that older age was associated with reduced volume, although negative associations between age and volume were also seen in temporal and parietal regions and the caudate. In a longitudinal study of healthy adults aged 55 to 90, significant volume loss was found after just one year in regions including the prefrontal cortex, temporal lobe (e.g., hippocampus), and parietal lobe (e.g., precuneus) (Fjell, Walhovd, et al., 2009).

To date, most studies of structural differences in aging have focused on volume as the measure of interest. However, a recent study of genetic influences on brain size (Panizzon et al.,

2009) suggests that the two measures of which cortical volume is composed – thickness and surface area – are determined by different genetic factors. This finding raises the possibility that cortical thickness and surface area might be differentially affected in aging. Fjell et al. (2009) examined cortical thickness across the adult lifespan in six samples of healthy individuals and found that older age was associated with thinner cortex in frontal and temporal regions, and, to a lesser extent, in parietal and occipital regions. In contrast, regions including the inferior temporal lobes and anterior cingulate did not show age effects. Dickerson et al. (2009) examined both cortical thickness and surface area in medial temporal regions in normal aging and Alzheimer's disease and found that normal age -related volumetric differences were primarily driven by older adults having decreased surface area compared to younger adults. Volumetric differences between younger adults and older adults with Alzheimer's disease were primarily driven by differences in cortical thickness. To our knowledge, only one study has examined age effects on surface area on a whole-brain level (Ostby et al., 2009). Although this study only included young individuals (ages 8 to 30), a negative relationship was found between age and total surface area and surface area in all lobes.

Studies of white matter integrity using diffusion-tensor imaging have also revealed age-associated differences (Sullivan & Pfefferbaum, 2006). Like volumetric and cortical thickness studies, the greatest age-effects are observed in frontal regions; such that healthy older adults have lower fractional anisotropy and greater diffusivity than younger adults, findings which are thought to indicate an age-related breakdown in white matter integrity such as through demyelination and/or reductions in the number of white matter fibers.

How are these structural differences seen in normal aging related to cognitive performance? In other words, can SCA be predicted by size and integrity of brain structure? Relationships between brain volume and cognitive performance among older adults have been widely studied (Kaup, Mirzakhanian, Jeste, & Eyler, 2011). In general, larger global and regional

brain volume measures are associated with better cognitive performance among older adults, with the most support existing for positive relationships between frontal volume and executive functioning and hippocampal formation volume and global cognition and memory. White matter integrity has also been found to be related to cognition in aging (Madden, Bennett, & Song, 2009), with the most evidence available supporting a positive relationship with processing speed and executive functioning. There are several gaps in the existing literature, however, that prevent a full understanding of how brain structural integrity might help to preserve good cognitive function in old age. First, it is unclear whether positive structure-cognition relationships originate in older adulthood or whether these relationships merely persist across the adult lifespan. There is a lack of longitudinal studies examining this issue, and few cross-sectional studies have directly tested whether structure-cognition relationships differ in direction or magnitude between older and younger adults. Thus, it is unknown whether special mechanisms may come into play during aging that increase the coupling between brain size and cognitive performance or if better structural integrity is a life-long advantage. Second, in contrast to the plethora of volumetric studies and a growing number of studies of white matter integrity, few studies have examined relationships between age-related differences in cortical thickness and cognition, and no studies to our knowledge have examined relationships between surface area and cognition in aging. In a study of cortical thickness, Fjell et al. (2006) found that high-performing older adults (on a composite measure of fluid cognitive functioning) had thicker cortex than average-performing older adults in several regions including right posterior cingulate and left subcallosal gyrus. Interestingly, cortical thickness in these two regions was greater in high-performing older adults compared to high-performing younger adults, as well. Although these findings are based on cross-sectional data, they raise the possibility that neural compensation in the form of thickening of cortex may have helped to improve performance among those older adults. As surface area is a great source of individual variability in neural structure size (Im et al., 2008; Pakkenberg &

Gundersen, 1997), the lack of studies examining how individual differences in surface area relate to cognition in aging represents an important gap in our knowledge.

Age-Related Differences in Brain Function during Cognitive Challenge

In addition to structural brain changes, the responsiveness of the brain during cognitive tasks has also been shown to differ between younger and older adults. In particular, frontal "over-activation" has been observed in aging, such that older adults show increased bilateral activation during cognitive challenge tasks compared to younger adults. Cabeza (2002) describes this pattern as the *hemispheric asymmetry reduction in older adults* (HAROLD) model, and reviews studies showing this pattern for a variety of cognitive challenge tasks, including executive functioning, working memory, memory, and facial perception tasks. Another activation pattern seen in aging is the *posterior-anterior shift in aging* (PASA), in which older adults show less occipital activation and greater frontal activation compared to younger adults (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008), a pattern first observed by Grady et al. (1994) and subsequently replicated using a variety of cognitive challenge tasks (Davis et al., 2008).

How these age-related differences in brain activation relate to SCA is less clear. As reviewed in Reuter-Lorenz and Cappell (2008), findings of age-related over-activation, such as those consistent with the HAROLD model, have been interpreted in several ways. First, if the degree of over-activation is positively related to cognitive performance, over-activation is generally interpreted as being compensatory and beneficial for cognition. Similarly, if older adults show over-activation but do not differ in their level of cognitive performance from young adults, the over-activation is again interpreted as compensatory. When over-activation in older adults has been found to be related to poorer cognitive performance, such findings have been interpreted as representing dedifferentiation (i.e., activation that is more generalized and/or less efficient) or as reflecting different cognitive strategies.

Eyler et al. (2011) reviewed studies relating brain function to cognition in aging. Of the 80 studies reviewed, findings from 29 of the studies reflected HAROLD and/or PASA patterns. Thus, while there is support in the literature for these age-related functional pattern differences, there are also a number of studies that do not find these patterns. Among the reviewed studies showing HAROLD and/or PASA patterns, findings were mixed regarding whether or not these patterns were compensatory (i.e., associated with better performance). A recent meta-analysis (Spreng, Wojtowicz, & Grady, 2010) aggregated findings across 80 functional magnetic resonance imaging (fMRI)/positron emission tomography (PET) studies of young and older adults during performance of various cognitive tasks. Most activation differences between young and older adults were found in frontal regions, such that older adults had greater frontal activation. When older adults performed as well as young adults, they showed greater activation in the left dorsolateral prefrontal cortex (DLPFC). When older adults performed worse than young adults, they showed greater activation in the right DLPFC and right rostrolateral PFC. These findings led the authors to conclude that over-activation of the left PFC is beneficial for cognition, while recruitment of right PFC regions is not. Furthermore, the PASA pattern was also supported, such that when older adults performed worse than young adults, they had less posterior activation, suggesting that this pattern is not compensatory.

Several questions remain regarding the relationship between brain activation and cognition in aging. For example, if there are age-related differences in brain response that are compensatory in nature, what neural factors are driving the need for this compensation? Alternatively, if age-related differences in brain response reflect dedifferentiation and/or neural inefficiency, what components of neural integrity are breaking down and causing this inefficiency? These issues have not been adequately addressed as few studies have examined the association between age-related differences in brain activation and other measures of neural integrity, such as brain structure. This issue is discussed further below.

Age-Related Functional Differences in the "Default-Mode Network"

In healthy young adults, particular brain regions, including medial prefrontal cortex (MPFC), posterior cingulate (PC), and inferior parietal lobule, have been found to be consistently more active during rest than during task performance. In other words, these areas deactivate during task performance. Because of this, these regions have been referred to as the "default mode network" (DMN) (Buckner, Andrews-Hanna, & Schacter, 2008). Functional connectivity studies, which involve the analysis of blood-oxygen-level-dependent (BOLD) fluctuations that occur in the absence of the demands of a specific task (Fox & Raichle, 2007), have also confirmed the existence of the DMN (Greicius, Krasnow, Reiss, & Menon, 2003). In addition, functional connectivity studies have revealed that the DMN shows negative functional correlations (i.e., anti-correlations) with the "task-positive network", a group of regions such as the DLPFC that are more active during task performance than during rest (Fox et al., 2005).

The DMN has been interpreted as reflecting several possible processes such as thinking about oneself or one's environment, recalling the past, planning for the future, considering the viewpoints of others (i.e., theory of mind) (Buckner et al., 2008; Buckner & Vincent, 2007), as well as representing "intrinsic" brain activity (Fox & Raichle, 2007). Indeed, in comparison to the brain's total energy expenditure, relatively little additional energy is spent responding to tasks, further arguing for the existence and importance of intrinsic neural activity (Raichle & Mintun, 2006; Raichle & Snyder, 2007). Abnormal DMN activity and/or DMN resting state functional connectivity have been found in several neuropsychiatric disorders, including autism, schizophrenia, depression, and Alzheimer's disease (Buckner et al., 2008; Buckner & Vincent, 2007; Fox & Raichle, 2007; Greicius, 2008).

Studies have found age-related differences in DMN deactivation, such that older adults show less DMN deactivation compared to younger adults (Grady, Springer, Hongwanishkul,

McIntosh, & Winocur, 2006; Lustig et al., 2003; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007; Sambataro et al., 2010). Functional connectivity analyses have provided supporting evidence that the DMN during rest (Damoiseaux et al., 2008; Esposito et al., 2008; Koch et al., 2010) and during task performance (Andrews-Hanna et al., 2007; Sambataro et al., 2010) is reduced among healthy older adults compared to young adults. However, Beason-Held et al. (2009) conducted an 8-year longitudinal PET study of regional cerebral blood flow among older adults (mean age at baseline = 68.4, *SD* = 6.8) and found that the DMN generally remained stable over time and concluded that, after a certain age, the DMN does not appear to change.

Some relationships between DMN function and cognitive performance in aging have emerged. Sambataro et al. (2010) found that greater DMN deactivation and greater functional connectivity between DMN regions during a working memory task were associated with better working memory performance among younger and older adults. In Andrews-Hanna et al. (2007), less DMN functional connectivity during task performance among older adults was associated with worse cognitive performance (executive functioning, processing speed, and memory). Damoiseaux et al. (2008) found that, among older adults but not younger adults, resting state activity in anterior DMN was positively associated with a measure of executive function (Trails B) but unassociated with another measure of executive function (WISC Maze), processing speed, or memory. In contrast to these studies finding relationships between DMN and cognition, Lustig et al. (2003) did not find significant associations between deactivation within DMN regions and cognitive performance among healthy younger or older adults.

Findings of less deactivation of the DMN during task performance among older adults in comparison to younger adults (Grady et al., 2006; Lustig et al., 2003; Persson et al., 2007; Sambataro et al., 2010) and greater DMN activation during task performance among older adults in comparison to younger adults (Grady et al., 2006) have been interpreted to suggest that older adults might have difficulty disengaging from the DMN when faced with cognitive challenge.

Further investigation is needed to explore DMN function in aging, how it relates to cognitive performance, and how the nature of the relationship might change with age.

Relationship between Different Measures of Neural Integrity in Aging

As reviewed above, relationships between cognition, on the one hand, and measures of brain structure, brain activation during task performance, DMN deactivation and functional connectivity, on the other hand, have been found within the context of aging. While each of these neural measures is interesting in its own right, the brain is a complex system and its overall integrity likely depends on a combination of structural size, task-related activation and deactivation, and functional connectivity between regions. How do these different measures of neural integrity work together to yield good cognitive performance, particularly when parts of the system might be comprised or altered due to aging?

When considering the findings reviewed above as a whole, some unexpected, and perhaps counterintuitive, associations emerge. Namely, prominent age-related shrinkage is seen in the frontal lobe, yet older adults show increased and more bilateral activation in frontal regions compared to younger adults. This increased frontal brain activation during task performance among older adults also occurs within the context of older age being associated with less DMN deactivation and functional connectivity. As few studies have combined imaging modalities (e.g., structural, functional, and functional connectivity) within the same samples in studies of aging, it is not yet possible to draw conclusions regarding the inter-relationships of these measures in aging, and even less is known about how these inter-relationships impact cognition.

Several theories have been posited in attempts to conceptualize how structural integrity and brain activation might interact to contribute to cognition in aging. For example, Greenwood (2007) has hypothesized that age-related decreases in brain structure size lead to strategy changes among older adults, which in turn leads to increased brain activation. Stern et al. (2009)

discusses the ideas of brain reserve, cognitive reserve, and neural compensation. Brain/cognitive reserve refer to factors that, if present, make individuals less susceptible to the deleterious effects of age-related declines in neural integrity. These might include having larger brain structures to begin with or having completed higher levels of education. Neural compensation is a term that refers to when either 1) older adults engage at least some brain regions different from those engaged by younger adults to perform the same task, or 2) young and older adults engage the same brain regions but these regions interact differently in the old. Per Stern's definition, neural compensation only means that older adults' brains are working differently, not that these changes are necessarily beneficial to cognitive performance.

A particularly comprehensive theory, posited by Park and Reuter-Lorenz (2009) is the "scaffolding theory of aging and cognition." They propose that, in order to handle cognitive tasks in the face of age-related declines in the structural integrity of the brain, older adults might rely on "scaffolds" to boost cognitive performance, in the form of recruiting additional brain regions to do a task. The authors apply the same theory to younger adults as well, positing that younger adults might recruit additional brain areas when faced with a particularly challenging cognitive task. For older adults, the "challenge" that calls for scaffolding includes both the cognitive task itself, as well as coping with a degraded brain structural system. Park and Reuter-Lorenz further propose that the aging brain's ability to scaffold is limited, because of reductions in neural integrity, and consequently, neural plasticity. Thus, at some point, scaffolding processes are no longer enough to maintain good cognition, potentially explaining why some older adults do show cognitive decline while others maintain cognition. This theory also proposes a role for intervention work, as the authors hypothesize that the brain's ability to scaffold may be facilitated by cognitive training exercises or physical activity.

Some empirical findings regarding relationships between grey matter volume and function in response to a challenge task in aging have been reported; however, they do not

correspond with the ideas proposed in the theories above. Kannurpatti et al. (2010) found that older adults had less total gray matter volume and showed less activation during a Digit-Symbol Verification Task than younger adults. Gray matter volume was correlated with activation, such that age-related reduction in gray matter volume contributed to, but did not totally explain, age-related differences in activation. The same pattern of results was seen in Brodtmann et al. (2009), such that age was negatively associated with total gray matter volume and with activation in striate and ventral extrastiate cortices during a visuoperception task among adults across a wide age range, and volume was positively correlated with activation. Similarly, Thomsen et al. (2004) found that older adults had less gray matter density (measured via voxel-based morphometry) in the left middle frontal gyrus and less activation in the same region during a dichotic listening task compared to young adults. In contrast to these findings, Johnson et al. (2000) found that degree of atrophy was unrelated to activation during a semantic decision task among healthy individuals (including both young and older adults), although significant relationships were found among patients with Alzheimer's disease such that greater atrophy in the left inferior frontal gyrus was associated with *greater* activation in that area. Further work is needed in this area regarding SCA, especially as none of the above studies commented on how the relationships between brain structure and function related to cognition. Unlike the above reviewed theories that posit that declines in structural integrity would promote increased brain activation, these studies suggest that volumetric decreases were associated with decreased activation. However, none of these studies examined structure-function relationships in the prefrontal cortex, the region where most age-related brain activation increases have been found and the region about which Park and Reuter-Lorenz (2009) and Greenwood (2007) make the strongest hypotheses.

How might DMN function interact with other measures of neural integrity to contribute to SCA? This issue has not been fully addressed. One relevant study found a positive association

between white matter integrity and functional connectivity within the DMN during task performance among older adults (Andrews-Hanna et al., 2007). Whereas brain volume has been used as a covariate in analyses of the DMN in aging (Beason-Held et al., 2009; Damoiseaux et al., 2008), to our knowledge, direct relationships between DMN deactivation and/or functional connectivity and structural measures such as volume, cortical thickness, or surface area have not been examined. Furthermore, there is a need to understand how DMN function might relate to brain activation in task-positive regions in aging. While Sambataro et al. (2010) found that, compared to younger adults, older adults showed reduced functional correlations between DMN regions during task performance, they also found that older adults showed reduced anti-correlations between the DMN and the task-positive network. It may be that these networks and the opposing relationship between them are broken down in aging. How the two facets of brain response (i.e., response in task-positive regions and DMN regions), as well as how DMN function and brain structure, might interact in predicting cognitive success in aging warrants further examination.

Many questions remain regarding how various aspects of neural integrity inter-relate and interact in their contribution to SCA. It may be that there are several ways in which neural integrity promotes SCA. For example, one possibility is that some older adults may show minimal age-related changes in brain structure and youthful brain functioning patterns, and consequently maintain good cognitive performance. Alternatively, brain function may alter among older adults in order to successfully compensate for structural changes, resulting in maintenance of cognitive performance levels. Furthermore, increases in brain response during task performance may help to compensate for DMN reductions in older adults, facilitating good cognition. All of these possibilities require exploration, in order to fully understand how neural integrity contributes to SCA.

Another unanswered question is whether some aspects of neural integrity are more important than others in regard to their effects on SCA. For instance, compensatory brain activation could be sufficient to negate the negative effects of other aspects of neural integrity on cognition. If particular components of neural integrity are identified as being more important for SCA, intervention efforts could then be focused on the improving the integrity of those components. For example, in regards to possible interventions targeting brain function, it may be beneficial to attempt to increase task-related activation among older adults (assuming that it would be compensatory), or, to make older adults' task-related activation more similar to that of younger adults.

Summary and Rationale for the Present Study

Due to the aging of the population, the well-being of older adults has become a prominent public health concern. One factor influencing the quality of life among older adults is cognitive functioning. Although aging is associated with declines in several cognitive domains, SCA is possible as evidenced by the heterogeneity in cognitive performance seen among older adults. Several measures of neural integrity, including brain structure, brain activation in response to cognitive challenge, and DMN function, have been found to relate to SCA. Specifically, positive relationships between brain volume and cognition are relatively well-established among older adults, while relationships with cortical thickness and surface area have not been widely studied. It has also not been established whether the structure-cognition relationships that have been observed are specific to aging, or whether these relationships merely persist from younger adulthood. Studies of age-related differences in brain activation during task performance have generally found that older adults show greater bilateral activation in frontal regions and less activation in posterior regions. Furthermore, most evidence suggests that such age-related differences in activation are associated with better cognitive performance among older adults.

The limited evidence available suggests that coordinated activity of the DMN is positively associated with cognition among older adults. Although such individual neural correlates of SCA have been found, to our knowledge, there have been no studies examining the inter-relationships between multiple types of neural measures (i.e., brain structure, brain activation in response to task performance, DMN function) and their interactive contribution to cognition in aging. The overall integrity of the neural system likely depends on each of these different brain measures. Thus, truly understanding how neural factors influence SCA requires simultaneous examination of these components.

In the present study, we plan to address gaps in the current literature on the neural correlates of SCA. Specifically, we will provide evidence regarding whether there are brain-cognition relationships unique to the aging process, by investigating whether brain-cognition relationships differ by age in a sample including younger, middle-aged, and older adults. We will also help to establish the relationships between measures of cortical thickness and surface area and SCA, as these measures have been understudied in comparison to volume. Finally, this study will represent a first examination of how multiple measures of neural integrity (i.e. brain structure, task-related activation, and DMN function) relate to SCA. The latter analysis is particularly important given that the ultimate goal of SCA research is to develop interventions that could improve cognitive functioning among older adults. Understanding the relative contribution of different types of neural integrity would provide needed information regarding where [i.e. on which aspect(s) of neural integrity] to focus such interventions and in what way to attempt to change neural integrity (i.e., by making the brain structurally and/or functionally more similar to the brains of young adults or by promoting neural compensation).

Aims and Hypotheses

Aim 1: To characterize the neural signature of SCA by determining whether and how brain-cognition relationships differ by age.

Hypothesis 1A: Cortical thickness and surface area of the DLPFC will be positively associated with working memory performance across all ages, but these relationships will be significantly stronger among older adults.

Hypothesis 1B: Greater bilateral DLPFC activation in response to the working memory challenge task will be associated with better working memory performance among older adults, but more lateralized DLPFC activation will be associated with better performance among younger and middle-aged adults.

Hypothesis 1C: Greater MPFC deactivation will be positively associated with working memory performance among older adults, but these factors will be unassociated in younger and middle aged adults.

Hypothesis 1D: Functional connectivity between regions of the DMN [i.e., medial prefrontal cortex (MPFC) and posterior cingulate (PC)] will be positively associated with working memory performance among older adults, but these factors will be unassociated in younger and middle aged adults.

Aim 2: To characterize the neural signature of SCA by exploring the relative contribution and inter-relationships of different measures of neural integrity to predicting cognitive performance. Specifically, we will use a variable selection technique [the least absolute shrinkage and selection operator (LASSO)] method to explore the strength and relative contributions of multiple neural measures (DLFPC cortical thickness and surface area, task-related DLPFC activation, MPFC cortical thickness and surface area, task-related MPFC deactivation, and functional connectivity between the MPFC and PC) in predicting working memory performance in aging. We will also

use partial least squares regression to examine what linear combinations of these variables best relate to SCA.

METHODS

Participants

Data for this study were drawn from one of three previous studies, in which healthy adults completed structural magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI) during an N-back working memory task. Thus, the current participant pool reflects a combination of study samples.

Recruitment methods for the original studies included flyers and advertisements posted in the community. Some of the older adult participants were recruited as a result of their previous participation in studies of healthy aging and their agreement to be contacted by other research projects. For each study, participants were initially screened for eligibility over the telephone, and later completed questionnaires that assessed for exclusion criteria during their study visit. Exclusion criteria common across the studies included the following: 1) contraindications for undergoing the MRI scan, 2) left-handedness, 3) history of loss of consciousness > 15 minutes, or a 4) history of an Axis I disorder. One of the three studies also excluded for evidence of mild cognitive impairment (i.e., defined in as a Dementia Rating Scale total score < 130 and/or a memory subscale score < 22).

103 healthy adults in total had completed the original studies at the time of the present analyses. Individuals who did not have complete structural MRI, fMRI, and/or N-back performance data were not included in the present analyses. Specifically, 23 individuals were excluded due to poor quality anatomical data and/or measurements in Freesurfer, 5 individuals were excluded due to poor quality fMRI data (e.g., due to excessive motion or poor signal-to-noise ratio), 5 individuals were excluded due to loss of fMRI data, and 6 individuals were excluded due to missing N-back performance data. Thus, 64 healthy adults, ages 23 to 78, were included in the present analyses. Table 1 lists demographic characteristics of the entire sample,

as well as characteristics separately for the young (ages 23 to 39), middle-aged (ages 40 to 59), and older adults (ages 60 to 78).

Procedures

Demographic variables and health status were obtained via interview and/or questionnaires. Neuroimaging data collection was completed at the UCSD Keck Center for Functional Magnetic Resonance Imaging. All but 6 of the participants also completed neuropsychological assessments, but the same batteries were not given across studies. To estimate premorbid verbal intellectual functioning, participants in two studies were administered the American National Adult Reading Test (ANART) (Grober, Sliwinski, & Korey, 1991), and participants in one study were administered the North American Adult Reading Test (NAART) (Blair & Spreen, 1989). Estimated verbal IQ data for the entire sample, and separately for the young, middle-aged, and older adults, are presented in Table 1.

Cognitive Measure: N-Back Working Memory Accuracy

During fMRI data collection, participants were administered an N-back working memory task. In the N-back task, single letters appear on the screen for 500 msec, followed by an asterisk for 1000 msec. The task is composed of the following conditions: In *0-back,* participants are asked to press a button whenever they see the letter "X". In *1-back,* participants are asked press a button whenever the current letter matches the previous letter that they saw. In *2-back,* participants are asked to press a button whenever the current letter matches the letter they saw two letters before. In *3-back,* participants are asked to press a button whenever the current letter matches the letter they saw three letters before. The N-back task is a block-design fMRI paradigm. Each block contains 11 letters, including three targets. Two of the original studies used a version of the N-back task that includes 4 blocks of all of the above conditions, while one

of the original studies used a version that includes 6 blocks of *0-back*, 5 blocks of *1-back*, and 5 blocks of *2-back* but no blocks of *3-back*. Accuracy and reaction time for each condition are recorded. For the present study, we used participant's mean accuracy across the *1-* and *2-back* conditions as the outcome measure (henceforth referred to as N-back accuracy), as not all participants had *3-back* data and the *0-back* condition is more a measure of attention than working memory.

Rationale for Selection of Working Memory Measure: The domain of working memory was chosen as a measure of SCA for the following reasons: 1) age-related group differences are well-documented, such that older adults perform more poorly than younger adults (Drag & Bieliauskas, 2010), 2) heterogeneity in working memory performance has been observed among older adults (Wilson et al., 2002) implying that there are some individuals who are still "successful" in regards to working memory performance in aging, 3) working memory has shown to correlate with other cognitive domains, such as fluid intelligence (Kane & Engle, 2002; Kane et al., 2004), that show declines in aging (Bugg, Zook, DeLosh, Davalos, & Davis, 2006; Horn & Cattell, 1967), and 4) working memory performance has been shown to relate to everyday functioning, such as medication adherence (Insel, Morrow, Brewer, & Figueredo, 2006), among older adults.

Our measure of working memory, N-back accuracy averaged across the *1-* and *2-back* conditions, is from an experimental fMRI paradigm task. From a practical standpoint, this measure was chosen as our primary outcome because all participants were administered this measure in the original studies. To validate the use of this measure as an index of working memory ability, we examined its relationship to a standardized, more commonly used measure of working memory, Digit Span Backwards from the *Wechsler Adult Intelligence Scale – Third Edition* (Wechsler, 1997). Specifically, in a sample of 52 healthy adults including some

participants in the present study, we found that N-back accuracy is significantly positively correlated with Digit Span Backwards ($r = .36$, $p < .01$), suggesting that these indices measure a similar construct.

As older adults evidence decline, as well as variability, in several cognitive domains, other measures (e.g., processing speed, episodic memory) might have been just as appropriate to examine as indices of SCA. Examining a more global measure of cognitive function as an SCA outcome measure may be ideal, so as to define SCA in a broader fashion. However, the present study is limited from doing this by lack of overlapping cognitive measures administered to the participants in the original studies.

Neuroimaging Procedures and Measures:

All images were collected on one of two 3 Tesla General Electric magnetic resonance scanners with an 8-channel head coil at the UCSD Keck Center for Functional Magnetic Resonance Imaging (54 individuals were scanned on one scanner, 10 on the other). A localizer scan was obtained prior to the following scans in order to ensure that participants were aligned well inside the scanner. As described below, specific scan parameters differed between studies, and one study used two variations of scan parameters. To account for differences in the scanner and scanning parameters, a categorical variable reflecting the study that each individual participated in was included in the statistical models.

Study 1 (n = 9):

Scanner: 1

Structural MRI collection: A high-resolution T1-weighted anatomical image was acquired using a magnetization prepared rapid acquisition gradient echo (MPRAGE)

sequence with the following parameters: 166 slices, Slice thickness = 1.2mm, TR = 7.02, TI = 900, Flip angle = 8 deg, Echo = 3.0 ms.

N-back fMRI collection: BOLD signal was measured using gradient echo echoplanar imaging. Images were acquired with the following parameters: 32 slices, 195 reps, slice thickness = 4mm, TR = 2500ms, TE = 32, Flip angle = 90 deg, Echo = 30ms. Field maps were collected and applied to correct for image distortion. (Field map corrections were not available for two individuals because of technical problems).

Study 2 (n = 29):

Scanner: 2

Structural MRI collection: A high-resolution T1-weighted anatomical image was acquired using an FSPGR sequence with the following parameters: 172 slices, slice thickness = 1.2mm, TR = 8.1, TI = 600, Flip Angle = 8 deg, Echo = 3.2 ms.

N-back fMRI collection: BOLD signal was measured using gradient echo echoplanar imaging. Images were acquired with the following parameters: 32 slices, 195 reps, slice thickness = 4mm, TR = 2500ms, TE = 32, Flip angle = 90 deg, Echo = 30ms. Field maps were applied to correct for image distortion.

Study 3A (n = 25):

Scanner: 2

Structural MRI collection: A high-resolution T1-weighted anatomical image was acquired using an FSPGR sequence with the following parameters: 124 slices, Slice thickness = 1.3mm, TR = 9.4 to 9.9ms, TI = 300ms, Flip Angle = 15 deg, Echo = 4.0 to 4.1 ms.

N-back fMRI collection: BOLD signal was measured using gradient echo echoplanar imaging. Images were acquired with the following parameters: 32 slices, 195 reps, Slice thickness = 4mm, TR = 2500ms, TE = 30, Flip angle = 90 deg, Echo = 30ms. Field maps were not collected.

Study 3B (n = 11):

Scanner: 2 (except for 1 subject collected on scanner 1).

Structural MRI collection: A high-resolution T1-weighted anatomical image was acquired using an FSPGR sequence with the following parameters: 124 slices, Slice thickness = 1.3mm, TR = 7.9ms, TI = 300ms, Flip Angle = 15 deg, Echo = 3.1ms.

N-back fMRI collection: BOLD signal was measured using gradient echo echoplanar imaging. Images were acquired with the following parameters: 32 slices, 195 reps, Slice thickness = 4mm, TR = 2500ms, TE = 30, Flip angle = 90 deg, Echo = 30ms. Field maps were not collected.

Neuroimaging Data Analysis

Structural Analysis

FreeSurfer, a publicly available software package, was used to generate cortical thickness and surface area measurements from the structural MRI scans. FreeSurfer conducts an automated, fully 3D whole-brain segmentation procedure that uses a probabilistic atlas and applies a Bayesian classification rule to assign a neuroanatomical label to each voxel (Fischl et al., 2002; Fischl et al., 2004). Cortical surface reconstruction was accomplished in a multi-step process using FreeSurfer tools (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999). The cortical surface model was manually reviewed and edited for technical accuracy and the surface was then parcellated into 66 cortical regions-of-interest (ROIs) (33 per hemisphere) based on a

probabilistic atlas (Desikan et al., 2006). For each ROI, cortical thickness was calculated as the distance between the pial surface and the gray/white boundary (Fischl & Dale, 2000) and surface area was calculated as the sum of the areas of each tessellation within the ROI. All calculations are done in individuals' native space.

Freesurfer methods have shown good validity, in that segmentation and volumetric calculations derived from Freesurfer are comparable to measurements made using manual methods (Fischl et al., 2002). Although studies focused on comparing Freesurfer measurement and manual measurement of hippocampal volume in particular have shown that Freesurfer tends to give larger hippocampal volumes, the Freesurfer measures and manual-based measures were still strongly correlated (Cherbuin, Anstey, Reglade-Meslin, & Sachdev, 2009; Tae, Kim, Lee, Nam, & Kim, 2008). Despite the volumetric differences between the measurement methods, Cherbuin (2009) found that, when relating volume to other variables (e.g., age, cognitive performance), similar relationships were observed regardless of whether the Freesurfer-based or manual-based measurements were used. In further support of Freesurfer's validity, when comparing patient and control groups, Freesurfer and manual methods have been shown to yield similar volumetric differences (Lehmann et al., 2010).

Cortical thickness and surface area of the DLPFC were the focus of our analyses. We chose to focus on DLPFC cortical thickness and surface area because age-related shrinkage is prominent in prefrontal regions (Bergfield et al., 2010; Raz et al., 1997), and the DLFPC has been implicated in contributing to working memory performance (Kane & Engle, 2002). As FreeSurfer does not generate an ROI specific to the DLPFC, left and right hemisphere DLPFC ROIs were created following methods used in Boes et al. (2011). The DLPFC ROIs were created on the Freesurfer "fsaverage" brain and then applied to each participant's native image space using the Freesurfer program "mri_label2label." The DLPFC ROIs are depicted in Figure 1.

We also measured global surface area (i.e., a sum of the surface area of all Freesurfer-generated ROIs) and global mean cortical thickness (i.e., mean cortical thickness of each hemisphere's ROIs weighted by the surface area of each hemisphere) in order to determine whether any observed brain-cognition relationships were specific to the DLPFC, rather than merely being reflective of correlations between cognition and global brain measures.

Although we did not have specific hypotheses regarding the potential relationship between MPFC structure and working memory performance in aging, we measured MPFC surface area and cortical thickness to complement our analyses, described below, of MPFC function. Freesurfer was used to create an MPFC ROI following methods described in Holt et al. (2011). As with the DLPFC ROIs, the MPFC ROI was initially created on the fsaverage brain and then applied to each participant's native image space. The boundaries of the MPFC ROI are shown in Figure 1.

fMRI during Working Memory Challenge (N-Back)

AFNI software (Cox, 1996) was used to correct for motion within each functional run, and extreme motion outliers were excluded. A 6mm FWHM spatial filter was applied. For examination of regional activation, a general linear model that included a baseline and linear trend plus regressors for each trial type (*0-*, *1-*, *2-*, or *3-back*)/(*0-*, *1-*, and *2-back*) and parameters to account for any residual motion were calculated. A map of the fit coefficient for the predictor of interest (i.e., the contrast between the *2-back* and *1-back* conditions or "*2- minus 1-back*") was created for each participant. The contrast of *2- minus 1-back* was chosen to examine brain response specific to the most challenging condition (i.e. *2-back*) that all of the participants completed.

We focused our analyses on DLPFC activation, because age-related differences in brain response during working memory tasks, as well as correlations with performance, have been

observed in the DLPFC. Reuter-Lorenz et al. (2000) found that older adults show more bilateral activation in frontal regions than younger adults during a verbal working memory task, such that young adults activated the left DLPFC and older adults showed significant activation in the right DLFPC and weak activation in the left DLPFC. Others have shown that activation in the DLPFC (combined across hemispheres) is equivalent or even lower among older adults compared to young adults (Rosano et al., 2005). Mixed findings have emerged when examining the relationship between DLFPC activation and performance on working memory tasks. Reuter-Lorenz et al. (2000) found that older adults showing more bilateral DLFPC activation performed faster on a verbal working memory task. Rypma et al. (2008) found that DLFPC activation (combined across hemispheres) was positively associated with accuracy among older adults, but not related to accuracy in younger adults. Rypma et al. (2005) found that DLPFC activation (combined across hemispheres) was negatively associated with reaction time among older adults (i.e., greater activity correlates with faster reaction time), while the opposite relationship was found among younger adults. A similar pattern with reaction time was found in Rypma et al. (2008); however the relationship in the old group was not significant.

We applied individuals' FreeSurfer-generated DLPFC ROIs to their N-back functional MRI data so that both the structural and functional analyses would be conducted in individuals' native image space. To accomplish this, SUMA software (Saad, Reynolds, Argall, Japee, & Cox, 2004), which enables the integration of surface-based analyses and AFNI analyses, was used to align the FreeSurfer surfaces to the functional run for each individual. The FreeSurfer ROIs were converted to SUMA format for each individual using the AFNI program @FSlabel2dset. Then, AFNI programs SurfPatch and 3dSurfMask were used to generate left and right DLPFC ROI masks viewable in AFNI.

Because studies of brain activation in aging have emphasized differences in laterality of frontal activation between younger and older adults, we examined the laterality of DLPFC

activation. We first counted the number of positively-activated voxels above a specified threshold ($p < .05$) within the left and right DLPFC ROI masks and then divided these counts by the total number of voxels contained within each mask, thus giving the percentage of activated voxels within the left and right DLPFC ROI masks. Using these percentages, a laterality index was calculated based on the following formula:

$$\text{Laterality Index} = \frac{\text{Left hemisphere} - \text{Right Hemisphere}}{\text{Left hemisphere} + \text{Right Hemisphere}} \quad \text{(Seghier, 2008)}$$

Thus, a laterality index of 0 reflects bilateral activation. Various cut-off values, ranging from |0.1| to |0.3| have been used to identify laterality, where a positive laterality index value over the cut-off indicates left lateralization while a negative value indicates right lateralization (Seghier, 2008). In addition the DLPFC lateralization, we also examined DLPFC activation separately within each hemisphere. To be consistent with the laterality index measurement, hemispheric DLPFC activation was also calculated by counting the number of positively-activated voxels above a specified threshold ($p < .05$) within the left DLPFC ROI and right DLPFC ROI masks and dividing by the total number of voxels contained within each ROI mask.

In addition to DLPFC activation, we examined N-Back task-related deactivation in the MPFC. As mentioned above, studies have shown that older age is associated with less deactivation of DMN regions such as the MPFC (Grady et al., 2006; Lustig et al., 2003; Persson et al., 2007; Sambataro et al., 2010), and there is evidence suggesting a relationship between these age-related differences and cognitive performance (Sambataro et al., 2010). To measure MPFC deactivation, we calculated a count of the number of voxels negatively activated (i.e., deactivated) above a specified threshold ($p < .05$) within the MPFC ROI and divided by the total number of voxels contained within the ROI, giving the percentage of deactivated voxels within the MPFC ROI.

Functional Connectivity during Working Memory Challenge (N-Back)

In order to examine functional connectivity between regions during the N-back task, residual motion, whole brain signal (averaged across the whole brain), white matter signal (averaged across white matter ROIs), and ventricular signal (averaged across all ventricular ROIs) were removed by regression, following Fox et al. (2011). Participants were engaged in task-related activity at all times, i.e., there were no "resting" blocks in which no response was required. It has been demonstrated that low-frequency correlated fluctuations in BOLD signal within the default mode can be observed under many conditions, including rest with eyes closed and rest while viewing visual stimuli (Greicius et al., 2003), as well as during performance of cognitive tasks (Hampson, Driesen, Skudlarski, Gore, & Constable, 2006). Indeed, the initial "discovery" of the default mode network came as a result of observing consistent spatial patterns in the regions that were deactivated during a variety of challenge tasks (Raichle & Snyder, 2007). Thus, we examined the task-negative or default mode network, across the entire time course of the working memory task.

We focused our analysis on the functional connectivity between regions of the DMN, given evidence of age-related reductions in DMN connectivity during rest (Damoiseaux et al., 2008; Esposito et al., 2008; Koch et al., 2010) and task performance (Andrews-Hanna et al., 2007; Sambataro et al., 2010) and associations with cognition (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Sambataro et al., 2010). Similar to Andrews-Hanna et al. (2007), we focused our analyses on the functional correlations between the MPFC and PC. Specifically, we created a subject-specific "seed region" reference function in the PC, by averaging BOLD response across all voxels in a spherical ROI surrounding specified Talairach coordinates (-5 -49 +40) as in Fox et al. (2011). We then calculated the mean correlation between time courses in the seed region and voxels within the MPFC ROI.

Statistical Analysis

The distributions of the independent and dependent variables were examined for potential outliers and normality. One-way Analysis of Variance (ANOVA) and Chi-Square tests were conducted to examine sample characteristics and identify potential confounding variables, in order to determine whether there were any confounding variables to include as covariates in the following statistical models.

Aim 1:

Hypothesis 1A: Cortical thickness and surface area of the DLPFC will be positively associated with working memory performance in all age groups, but these relationships will be significantly stronger among older adults. These effects will be found above and beyond relationships between global brain measures (i.e., global mean cortical thickness and global surface area) and working memory performance.

We tested four regression models, each with N-back accuracy as the outcome measure. Model 1 predictor variables: 1) age (as a continuous variable), 2) right DLPFC cortical thickness, and 3) age X right DLPFC thickness. Model 2 predictor variables: 1) age (as a continuous variable), 2) left DLPFC cortical thickness, and 3) age X left DLPFC thickness. Model 3 predictor variables: 1) age (as a continuous variable), 2) right DLPFC surface area, and 3) age x right DLPFC surface area. Model 4 predictor variables: 1) age (as a continuous variable), 2) left DLPFC surface area, and 3) age x left DLPFC surface area. All predictor variables were mean-centered.

We tested Hypothesis 1A by determining if 1) there is a significant effect of DLPFC cortical thickness/surface area, and 2) there is a significant interaction of DLPFC cortical thickness/surface area with age. The second condition would mean that the relationship between DLPFC cortical thickness/surface area and working memory differs by age.

To explore whether observed significant effects were specific to the DLPFC, models with the above predictors were conducted with the DLPFC cortical thickness and/or surface area variables adjusted for global mean cortical thickness and/or global surface area, respectively.

Hypothesis 1B: Greater bilateral DLPFC activation in response to the working memory challenge task will be associated with better working memory performance among older adults, but more lateralized DLPFC activation will be associated with better performance among younger and middle-aged adults.

We focused our analyses on the DLPFC laterality index. In a regression model with N-back accuracy as the outcome measure, we tested the following predictor variables: 1) age (as a continuous variable), 2) DLPFC laterality index, and 3) age x DLPFC laterality index. We tested Hypothesis 1B by determining if 1) there is a significant effect of DLPFC laterality index, and 2) there is a significant interaction between DLFPC laterality index with age. A significant interaction would mean that the relationship between the laterality of DLPFC activation with working memory differs by age.

We also examined DLPFC activation separately for each hemisphere. In regression models with N-back accuracy as the outcome measure, we tested the following predictor variables: 1) age (as a continuous variable), 2) right/left DLPFC activation, and 3) age x right/left DLPFC activation.

Hypothesis 1C: Greater MPFC deactivation will be positively associated with working memory performance among older adults, but these factors will be unassociated in younger and middle aged adults.

In a regression model with N-back accuracy as the outcome measure, we tested the following predictor variables: 1) age (as a continuous variable), 2) MPFC deactivation, and 3) age

x MPFC deactivation. We tested Hypothesis 1C by determining if 1) there is a significant effect of MPFC deactivation, and 2) there is a significant interaction of MPFC deactivation with age. A significant interaction would mean that the relationship MPFC deactivation with working memory differs by age.

Hypothesis 1D: Functional connectivity between regions of the default-mode network (i.e., MPFC and PC) will be positively associated with working memory performance among older adults, but these factors will be unassociated in younger and middle aged adults.

In a regression model with N-back accuracy as the outcome measure, we tested the following predictor variables: 1) age (as a continuous variable), 2) functional connectivity between the MPFC and PC seed region, and 3) age x functional connectivity between these regions. We tested Hypothesis 1D by determining if 1) there is a significant effect of functional connectivity between the MPFC and PC seed region, and 2) there is a significant interaction of functional connectivity between these regions with age. A significant interaction would mean that the relationship between functional connectivity between MPFC and PC and working memory differs by age.

<u>Aim 2:</u>

Exploratory Analysis A: We used a variable selection technique (the least absolute shrinkage and selection operator (LASSO)) method to explore the strength and relative contributions of the examined neural measures (cortical thickness and surface area of the DLPFC, task-related activation in the DLFPC, task-related deactivation in the MPFC, and functional connectivity between the MPFC and PC) in predicting SCA.

The following variables were standardized into Z-scores (calculated by subtracting the mean for each variable from each participant's value and dividing by the variable's standard

deviation) and entered into the LASSO analysis to test their relationship to N-back accuracy: 1) age (as a continuous variable), 2) global surface area, 3) global mean cortical thickness, 4) right DLPFC surface area, 5) left DLPFC surface area, 6) right DLPFC cortical thickness, 7) left DLPFC cortical thickness, 8) right DLPFC activation, 9) left DLPFC activation, 10) DLPFC laterality index, 11) MPFC surface area, 12) MPFC cortical thickness, 13) MPFC deactivation, and 14) mean functional connectivity between the MPFC and PCC seed. All age X brain measure interaction terms were also included in the model.

The LASSO method is designed to select predictor variables to yield a sparse model (i.e. a model achieving good model fit with the fewest number of predictor variables). The LASSO works by shrinking regression coefficients of the predictor variables such that some are reduced to zero and eliminated from the model (Bunea et al., 2011; Tibshirani, 1996). The LASSO method is capable of handling a large number of predictor variables, even when the number of variables exceeds the sample size (Bunea et al., 2011). Results from this analysis show which measures of neural integrity are most predictive of working memory performance, and which measures do not contribute to working memory performance when included within the same model as other measures of neural integrity.

Exploratory Analysis B: We also used partial least squares regression to examine what linear combinations of the above variables best relate to our measure of SCA.

The same predictor variables in Exploratory Analysis A were entered into a partial least squares (PLS) regression analysis with N-back accuracy as the outcome measure. Specifically, in PLS, latent variables are created based on the predictor variables in a way that maximizes the covariance between those latent variables and the outcome measure. Like LASSO, PLS regression is capable of handling a large number of predictor variables, even within the context of a relatively small sample size (Abdi, 2010). Results from this analysis reflect the linear

combination of variables that best predicts working memory performance. In other words, this analysis shows how the predictor variables relate to one another in their ability to predict working memory performance.

RESULTS

Identification of Outliers and Examination of Variable Distributions

SPSS boxplots were used to identify potential outliers in the N-back performance variable and among the neural variables. For each variable, outliers were defined as cases falling greater than or equal to 1.5 times the interquartile range below the first quartile and cases falling greater than or equal to 1.5 times the interquartile range above the third quartile. No outliers were identified for global surface area, global mean cortical thickness, right DLPFC surface area, right or left DLPFC mean thickness, or right or left DLPFC activation. One outlier was identified for N-back performance, one outlier for left DLPFC surface area, 5 outliers for the DLPFC laterality index, two outliers for MPFC surface area, one outlier for MPFC mean thickness, one outlier for MPFC deactivation, and 3 outliers for MPFC-PC seed functional connectivity. These outliers were excluded from analyses including these variables.

Histograms were used to examine the distributions of the N-back performance and neural variables. The N-back performance distribution was negatively skewed. Common transformations, including log, inverse, and square-root transformations, were applied but did not result in improved normality. Thus, we chose to use the N-back performance variable in its original metric in the following analyses to facilitate interpretability. The neural variables tended to follow a normal distribution, with the exception of MPFC deactivation and right DLPFC activation, which were positively skewed. Left DLPFC activation was also slightly positively skewed. These variables were also kept in their original metric, rather than applying transformations, in order to facilitate interpretability.

Identification of Potential Confounding Variables

As listed in Table 1, by treating age as a categorical variable, chi-square tests showed that the younger, middle-aged, and older adult groups are well-matched in regards to gender (X^2_2 =

3.0, p = .22) and proportion of ethnic minorities (X^2_8 = 8.8, p = .36), and a one-way ANOVA showed that the age groups are well-matched in regards to estimated premorbid verbal intelligence ($F_{2,55}$ = 2.29, p = .11). Based on a one-away ANOVA, the age groups are discrepant in regards to education ($F_{2,61}$ = 3.8, p = .027), such that the older adults have significantly more education than middle aged adults (*Tukey HSD* = 2.00, p = .021). The older and younger adults did not differ in their mean level of education (*Tukey HSD* = 1.14, p = .22), nor did the younger and middle aged adults (*Tukey HSD* = .86, p = .42).

Years of education was not significantly correlated with N-back accuracy in any age group (Young: r = .05, p = .81; Middle: r = .065, p = .79; Older: r = -.006, p = .98) or across all age groups (r = -.04, p = .76). There was also no significant correlation between estimated premorbid verbal IQ and N-back accuracy in any age group (Young: r = .17, p = .42; Middle: r = .12, p = .64; Older: r = .088, p = .75) or across all age groups (r = .10, p = .44). Thus, we did not include years of education or estimated IQ as covariates in models predicting N-back accuracy.

To ascertain whether participant characteristics, N-back accuracy, or the neural measures differed depending on the specific study under which individuals' data were collected, we conducted a one-way ANOVA examining the effect of study on those variables. The following variables did not differ by study: Age (treated as a continuous variable), education, estimated premorbid verbal IQ, N-back accuracy, global surface area, global mean cortical thickness, right or left DLPFC surface area, right or left DLPFC cortical thickness, DLPFC laterality index, left or right DLPFC activation, MPFC surface area, MPFC deactivation, and functional connectivity between the PC seed and MPFC (all p > .05). MPFC cortical thickness did differ by study (p = .028), thus a study variable is used as a covariate in the regression analyses involving MPFC cortical thickness.

Relationship of Age to Working Memory Performance

Age (treated as a continuous variable) is significantly negatively correlated with N-back accuracy (r = -.25, p = .045), as shown in Graph 1. Mean N-back accuracy was .83 (*SD* = .18) among the younger adults, .83 (*SD* = .14) among the middle-aged adults, and .75 (*SD* = .16) among the older adults.

Relationship of Age to Brain Variables

Bivariate correlations showed that age (treated as a continuous variable) is negatively correlated with global mean thickness (r = -.61, p < .0005), left DLPFC thickness (r = -.37, p =.003), and right (r = -.36, p = .004) and left (r = -.32, p = .01) DLPFC activation. Age is positively correlated with the DLPFC laterality index (r = .33, p = .011); younger adults' mean laterality index is .01 (*SD*=.18), middle-aged adults' mean laterality index is .09 (*SD*=.17), and older adults' mean laterality index is .18 (*SD*=.20). Scatterplots of these relationships are shown in Graphs 2 and 3. Although all of the correlations were negative, age was not significantly related to global surface area (r = -.24, p = .053), right DLPFC surface area (r = -.24, p = .06), left DLPFC surface area (r = -.17, p = .20), right DLPFC thickness (r = -.21, p = .09), or MPFC-PC seed functional connectivity (r = -.22, p = .09). Age was also not related to deactivation within the MPFC ROI (r = -.08, p = .55), MPFC surface area (r =-.06, p = .63), or MPFC cortical thickness (r = -.033, p = .80). A regression model with MPFC cortical thickness as the dependent variable and study and age as predictors was also non-significant (p > .05).

In order to explore possible non-linear effects of age on the above brain variables, regression models were conducted including the linear and quadratic terms of age (mean-centered) as predictor variables, with the above brain variables as the dependent variables. All quadratic age effects were non-significant (p > .05). A regression model with MPFC cortical thickness as the dependent variable and study, age, and age-squared as predictors was also non-significant (p > .05).

Relationships between SCA and DLPFC Structure:

Bivariate correlations showed that N-back accuracy is positively correlated with left DLPFC surface area (r = .30, p = .02), but not significantly correlated with global surface area (r = .25, p = .051), right DLPFC surface area (r = .21, p = .11), global mean thickness (r = .054, p = .68), right DLPFC thickness (r = -.046, p = .72), or left DLPFC thickness (r = .065, p = .61).

A regression model with N-back accuracy as the outcome measure and predictors of 1) age (as a continuous variable), 2) left DLPFC surface area, and 3) age X left DLPFC surface area was significant ($F_{3,58}$ = 2.89, p = .043, R^2 = .13, Cohen's f^2 = .15), with left DLPFC surface area being the only significant predictor (standardized β = .29, t = 2.21, p = .031). To examine whether this relationship was potentially driven by a relationship with global surface area, a regression model for N-back accuracy with the predictors of 1) age, 2) left DLPFC surface area adjusted for global surface area, and 3) age X adjusted left DLPFC surface area was also conducted. The model was significant ($F_{3,58}$ = 2.86, p = .044, R^2 = .13, Cohen's f^2 = .15), with adjusted left DLPFC surface area being the only significant predictor (standardized β = .27, t = 2.20, p = .032). Thus, left DLPFC surface area is positively associated with N-back accuracy, with or without adjusting for global surface area, and this relationship did not differ with age. Graph 4 depicts this relationship between N-back accuracy and left DLPFC surface area, adjusted for global surface area. A regression model with N-back accuracy as the outcome measure and predictors of 1) age, 2) right DLPFC surface area, and 3) age X right DLPFC surface area was not significant ($F_{3,59}$ = 1.88, p = .14, R^2 = .09).

A regression model with N-back accuracy as the outcome measure and predictors of 1) age (as a continuous variable), 2) right DLPFC cortical thickness, and 4) age X right DLPFC thickness was not significant ($F_{3,59}$ = 2.17, p = .10, R^2 = .10). A regression model with N-back accuracy as the outcome measure and predictors of 1) age (as a continuous variable), 2) left

DLPFC cortical thickness, and 3) age X left DLPFC thickness was also not significant ($F_{3,59}$ = 1.40, p = .25, R^2 = .07).

Relationship between SCA and DLPFC Activation during Working Memory Challenge

Figure 2 shows the whole-brain fMRI analysis for the N-back *2- minus 1-back* contrast, specifically, one-sample T-test results calculated separately for each age group in Talairach space. We first focus on brain response in the DLPFC following our hypotheses.

Bivariate correlations showed that N-back accuracy is negatively correlated with the DLPFC laterality index (r = -.34, p = .008), measured based on the DLPFC ROI. A regression model with N-back accuracy as the outcome variable and predictors of 1) age (as a continuous variable), 2) DLPFC laterality index, and 3) age X DLPFC laterality index was significant ($F_{3,54}$=3.43, p = .023, R^2 = .16, Cohen's f^2 = .19), with the only significant predictor being DLPFC laterality index (standardized β = -.29, t = -2.21, p = .032). Graph 5 depicts the relationship between N-back accuracy and the DLPFC laterality index, and suggests that bilateral DLPFC activation is associated with the best performance while individuals with more left-lateralized activation performed the worst.

Bivariate correlations showed that N-back accuracy is positively correlated with activation within the right (r = .33, p = .009) and left (r = .29, p = .020) DLPFC ROIs. A regression model with N-back accuracy as the outcome variable and predictors of 1) age (as a continuous variable), 2) right DLPFC activation, and 3) age X right DLPFC activation was significant ($F_{3,59}$ = 2.97, p = .039, R^2 = .13, Cohen's f^2 = .15), with right DLPFC activation (standardized β = .28, t = 2.1, p =.039) being the only significant predictor. A regression model with N-back accuracy as the outcome variable and predictors of 1) age (as a continuous variable), 2) left DLPFC activation, and 3) age X left DLPFC activation was not significant ($F_{3,59}$ = 2.66, p = .057, R^2 = .12).

Given that we did not find age-related increases in DLPFC activation as we expected following the HAROLD or PASA models, we chose to examine whether regions outside of the DLPFC showed increased activation in aging in support of these models. A whole-brain fMRI regression analysis was conducted using AFNI program 3dRegAna. Study, age (as a continuous variable), N-back accuracy, and age x N-back accuracy were included as predictor variables. The AFNI program AlphaSim was used to determine the cluster size (65 voxels) needed to achieve statistical significance when setting the whole-brain threshold to $p = .05$. As shown in Figure 3, there were significant clusters of age and performance main effects. However, there were no significant clusters of age X N-back accuracy interaction. Correlations between the mean fit coefficient within each significant cluster, calculated using the AFNI program 3dROIstats, and age and N-back accuracy are shown in Table 2.

Contrary to our expectations, the whole-brain analysis did not show increased frontal or greater bilateral activation in aging. Negative associations with age were found for a cluster containing bilateral frontal regions, bilateral cingulate, and bilateral caudate and for a cluster containing bilateral inferior and superior parietal lobules. In these regions, older age was associated with reductions in the activation seen among the young, and these age-related reductions in activation were associated with poorer performance. Positive age associations were found for clusters containing nodes of the DMN, the medial frontal gyrus and posterior cingulate, such that older age was associated with reduced deactivation. A positive age association was also found for a cluster containing right temporal and occipital regions, such that younger adults showed slight deactivation while older adults showed slight activation. None of these age-related differences in deactivation appeared to affect performance, as performance correlations with these clusters were non-significant.

Positive associations with performance were found for clusters that included bilateral middle frontal gyrus, right inferior frontal gyrus, bilateral precuneus, bilateral inferior parietal

lobule, and bilateral superior parietal lobule. Greater activation in these regions was associated with better performance, and older age was associated with significantly reduced activation in all of these regions, except for one of the two clusters containing right middle frontal gyrus.

Relationship between SCA and MPFC Structure

Bivariate correlations showed that N-back accuracy is positively correlated with MPFC surface area (r = .28, p = .032), while N-back accuracy is not related to MPFC thickness (r = .074, p = 57). A regression model with N-back accuracy as the outcome measure and predictors of 1) age (as a continuous variable), 2) MPFC surface area, and 3) age X MPFC surface area was significant ($F_{3,57}$ = 2.82, p = .047, R^2 = .13) but there were no significant individual predictors (all p > .05). A regression model with N-back accuracy as the outcome measure and predictors of 1) study, 2) age, 3)MPFC thickness, and 4) age X MPFC thickness was not significant ($F_{4,57}$ = 1.32, p = .27, R^2 = .09).

Relationship between SCA and Deactivation within the MPFC ROI

Bivariate correlations showed that N-back accuracy is positively correlated with deactivation with the MPFC ROI (r = .29, p = .020). A regression model with N-back accuracy as the outcome variable and predictors of 1) age (as a continuous variable), 2) deactivation within the MPFC ROI, and 3) age X MPFC deactivation was significant ($F_{3,58}$ = 3.21, p = .030, R^2 = .14, Cohen's f^2 = .16), with MPFC deactivation being the only significant predictor (standardized β = .28, t = 2.29, p =.025). Thus, as shown in Graph 6, greater deactivation within the MPFC ROI is associated with better N-back accuracy. This relationship did not differ with age.

Relationship between SCA and DMN Functional Connectivity

Figure 4 shows whole-brain functional connectivity maps using the PC seed point, specifically one-sample T-test results calculated separately for each age group. As can be seen, even though participants were engaged in the N-back task, a DMN connectivity pattern was revealed. Following our hypotheses, we focus on functional connectivity between the PC seed and MPFC ROI.

Bivariate correlations showed that N-back accuracy (r = .077, p = .56) is not significantly correlated with the degree of synchrony between the MPFC ROI and PC seed. A regression model with N-back accuracy as the outcome variable and predictors of 1) age (as a continuous variable), 2) MPFC-PC seed functional connectivity, and 3) age X MPFC-PC seed functional connectivity was not significant ($F_{3,56}$ = 1.22, p = .31, R^2 =.06).

Strength and Relative Contribution of the Neural Measures in Predicting SCA

Using the R package "lars" (Efron, Hastie, Johnstone, & Tibshirani, 2004), a LASSO analysis was conducted with N-back accuracy (z-score) as the outcome variable. The following Z-score transformed variables were entered as predictors: 1) age (as a continuous variable), 2) global surface area, 3) global mean cortical thickness, 4) right DLPFC surface area, 5) left DLPFC surface area, 6) right DLPFC cortical thickness, 7) left DLPFC cortical thickness, 8) right DLPFC activation, 9) left DLPFC activation, 10) DLPFC laterality index, 11) MPFC surface area, 12) MPFC cortical thickness, 13) MPFC deactivation, and 14) mean functional connectivity between the MPFC and PCC seed. All age X brain interaction terms were also included as predictors. As the previously identified outliers were excluded, data from 52 participants were included in this LASSO analysis.

The LASSO model resulted in an R^2 value of 0.55. A two-step model minimized the C_p statistic, meaning that two steps (i.e., a model containing the intercept=0 and two predictor variables) provided the best balance between including variables in the model versus over-fitting

the data. The resulting model includes right DLPFC activation as the strongest predictor of N-back accuracy (β = .08), followed by MPFC deactivation (β =.05). None of the age x brain measure predictors were strongly associated with N-back working memory performance.

Linear Combinations of the Neural Measures in Predicting SCA

Using the R package "pls" (Mevik & Wehrens, 2007), a partial least squares regression (PLS) analysis was conducted with N-back accuracy (z-score) as the outcome variable and all of the same predictor variables as were included in the LASSO analysis. As in the LASSO analysis, data from 52 participants were included. The PLSR was run using "leave-one-out" cross validation, which gives the root mean squared error of prediction (RMSEP) for each number of components.

A one component result minimized the RMSEP value (RMSEP = 0.98). This component explained 14% of the variance among the predictor variables and 29% of the variance in the outcome variable (N-back accuracy). Table 3 lists the loading values, showing how each variable relates to the component. The variables of age, DLPFC laterality index, and right and left DLPFC activation had among the strongest loading values, followed closely by global surface area, left DLPFC surface area, and MPFC deactivation.

DISCUSSION

In order to better understand the neural signature of SCA, we first determined whether there were brain-cognition relationships unique to the aging process that predicted our measure of cognition or whether the same relationships persisted across adulthood. Contrary to our hypotheses (as summarized in Table 4), relationships between working memory performance and our structural and functional brain measures did not differ with age. At least when considering the neural measures examined in our study, SCA did not appear to result from brain-cognition relationships unique to older adulthood. Instead, SCA resulted from older adults maintaining the same brain-cognition relationships that occur throughout adulthood. The specific neural factors supporting good working memory performance across adulthood are detailed below.

It is well-known that older age is associated with reduced volume in frontal regions, including the DLPFC (Bergfield et al., 2010; Fjell, Walhovd, et al., 2009; Raz et al., 1997), but it has not been reported whether age-related volumetric differences in the DLPFC are due to differences in cortical thickness, cortical surface area, or both. In the present study, we found that age was negatively associated with DLPFC cortical thickness in the left hemisphere, but there were no significant age relationships with right DLPFC cortical thickness or DLPFC surface area in either hemisphere. Following the radial unit hypothesis, which posits that the cortex is composed of columns of developmentally-related cells (Rakic, 1988; Rakic, 2000), our findings suggest that age-related differences in DLPFC structure are primarily driven by a loss of cells within DLPFC radial columns, rather than a loss in the number of DLPFC columns.

Compared to the abundance of studies examining how brain volume relates to cognition in aging, less is known about the relationship between cortical surface area and cortical thickness in aging. Although cortical thinning has been cited as a neuropathological process in Alzheimer's disease (Dickerson, Bakkour, et al., 2009; Dickerson, Feczko, et al., 2009), in the present study of healthy adults, age-related differences in left DLPFC cortical thickness were unrelated to our

cognitive measure. Instead, left DLPFC surface area was positively associated with working memory across adulthood. These findings suggest that working memory performance is largely unaffected by age-related structural differences in the DLPFC. Rather, it appears that adults who have developed greater DLPFC surface area, particularly in the left hemisphere, will continue to perform better on working memory tasks into older age.

A common, although not universal, finding in the literature is that, during cognitive challenge tasks, older adults show a shift from posterior to anterior activation (PASA) and increased bilateral activation (HAROLD) compared to younger adults, and there is some evidence to suggest that these functional differences may facilitate cognitive performance. Our findings did not follow these patterns. Namely, task-related activation within our region of interest, the DLPFC, decreased with age in both hemispheres, DLPFC activation shifted from being bilateral among the younger adults to being left-lateralized among the older adults, and bilateral DLPFC activation was associated with better working memory performance across the age groups. Further in contrast with the HAROLD and PASA models, there was no evidence that older age was associated with activation increases in regions outside of the DLPFC, as the positive age relationships found in the whole-brain fMRI analysis were not truly age-related increases in activation but rather age-related decreases in deactivation.

Our finding that older age was associated with less task-related activation is not an unprecedented result and is corroborated by the literature. Reduced frontal activation among older adults compared to younger adults has been reported including in studies of selective attention (Solbakk et al., 2008), speeded response preparation (Vallesi, McIntosh, & Stuss, 2009), probabilistic learning (Fera et al., 2005), recognition memory (Brassen & Buchel, 2009; Gutchess et al., 2007), and executive functioning (Rosano et al., 2005). Some previous studies of working memory have found that older age was associated with less activation within a structurally-defined DLPFC ROI. In Rypma and D'Esposito (2000), bilateral DLPFC activation was found

among younger adults during a working memory task, and, in comparison, older adults showed less DLPFC activation in both right and left DLPFC ROIs. Similarly, Rypma, Prabhakaran, Desmond, and Gabrieli (2001) found that, compared to younger adults, older adults showed less DLPFC activation, driven by age differences within the right DLPFC in particular. Unfortunately, we cannot compare our findings of greater left-lateralization in aging with these studies, as neither directly tested for laterality effects.

From our findings, SCA, as defined as good working memory ability, appears to refer to older adults who are able to maintain the greater and more bilateral DLPFC activation seen among the young. Brain aging as it relates to working memory and related cognitive processes may diverge from the HAROLD and PASA patterns. It may be that there are not functional changes that come online in aging to compensate for (or even attempt to compensate for) a declining working memory system. Alternatively, our findings may differ at least somewhat from previous studies that found the HAROLD and PASA patterns, as, unlike most functional MRI studies, we examined activation within a structurally-defined ROI, making our measurements independent of age-related structural differences. We also cannot rule out the possibly that our results may have been influenced by altered hemodynamic response in aging, particularly as we did not measure or control for resting cerebral blood flow. However, measuring the contrast between the BOLD signal response to the 2-back condition minus the 1-back condition as we did makes it more likely that our fMRI findings truly reflect age differences in task-related response rather than neurovascular differences (D'Esposito, Deouell, & Gazzaley, 2003).

In addition to DLPFC structure and function, we examined how function in the DMN, specifically the MPFC, related to SCA. While deactivation measured based on the MPFC ROI was not associated with aging, a whole-brain analysis revealed a small cluster within the medial frontal gyrus for which older age was associated with reduced deactivation. This discrepancy is

likely related to differences in imaging analysis methods. For the MPFC ROI analysis, deactivation was calculated by measuring the percentage of voxels deactivated across the entire structurally-defined ROI mask, whereas the whole-brain analysis results reflect a relatively smaller cluster for which the mean fit coefficient is more negative among the young adults (M = -.21, SD = .23) than among the middle-aged (M = -.05, SD = .17) and older adults (M = .07, SD = .25). In addition, our structurally-defined MPFC ROI and the small cluster obtained from the whole-brain analysis are not entirely overlapping in space, likely contributing to the discrepancy. Nevertheless, findings of age-related reductions in MPFC deactivation are consistent with previous studies (Lustig et al., 2003; Persson et al., 2007; Sambataro et al., 2010), none of which conducted their analyses using a structurally-defined MPFC ROI.

With respect to the relationship between MPFC deactivation and cognition, we found that greater MPFC deactivation, as measured across the entire MPFC ROI, was positively associated with working memory performance across adulthood, consistent with the findings of Sambataro (2010). However, the observed age-associated reductions in deactivation within the functionally-defined medial frontal gyrus cluster were not related to performance. Thus, the observed age effects did not appear to be deleterious to performance, rather overall MPFC deactivation predicted performance across age groups. Thus, as far as MPFC deactivation, SCA appears to result from maintaining the same greater deactivation—better performance relationship throughout adulthood.

In functional connectivity analyses, we showed that, throughout adulthood, the DMN is apparent even during task performance. In line with previous studies finding that older adults have weaker DMN functional connectivity during task performance (Andrews-Hanna et al., 2007; Sambataro et al., 2010), we found a trend for an age-associated reduction in MPFC-PC functional connectivity. However, unlike in Sambataro et al. (2010) and Andrews-Hanna et al. (2007), MPFC-PC functional connectivity was not associated with working memory performance. The

fact that the age relationship was only at a trend level and that a performance relationship was not found may have been contributed to by a difference in methodology between our study and these previous studies. While we measured the functional correlations within a structurally-defined MPFC ROI, Sambataro et al. used a whole-brain analysis approach and Andrews-Hanna et al. used a functionally-defined MPFC ROI.

The most novel aspects of the present study are our use of multivariate statistical techniques to explore the relative contribution and inter-relationships of the examined neural measures in predicting SCA. When considering all of the examined neural variables within the same model, activation within the right DLPFC was found to be the strongest predictor of working memory performance, followed closely by deactivation within the MPFC. We were somewhat surprised that the DLPFC laterality index was not also revealed as one of the strongest predictors, but this is likely contributed to by the fact that the right DLPFC activation and DLPFC laterality index variables are somewhat redundant with one another. It was also interesting that no structural measure was found to be among the strongest predictors, suggesting that functional measures are more important than structural measures in predicting SCA. It should be noted, however, that although they were not the strongest predictors and did not get included in the final LASSO model, the DLPFC laterality index and left DLPFC surface area variables were next in line to enter the LASSO model, suggesting that these variables do play a contributing, albeit smaller, role in promoting good working memory. As no age X brain interaction variables were found to be important predictors, this again argues against the idea that unique neural factors give rise to SCA. Analyzing the data in this fashion to reveal right DLPFC activation and MPFC deactivation as the most important contributors to SCA is particularly informative for possible brain-based interventions. Specifically, intervention efforts aimed at maintaining or improving cognition among older adults should target these aspects of the neural system, particularly as right DLPFC activation, and to some extent MPFC deactivation, are altered in aging.

Using another multivariate technique, partial least squares regression, we were able to determine the combination of neural variables that was most predictive of our measure of SCA. Results from this analysis show that being younger, having greater right and left DLPFC activation, less left-lateralized (i.e. more bilateral) DLPFC activation, larger global surface area, larger DLPFC surface area (particularly in the left hemisphere), and greater MPFC deactivation is a combination that promotes good working memory performance. This analysis highlights the importance of thinking of the brain as being a system whose components work together to achieve a cognitive function. Again, the lack of importance of age X brain interaction variables indicates that the different aspects of the neural system work together in a similar manner across adulthood. Although components of the system may change in the aging brain (e.g., DLPFC activation decreases), there is no indication that the components of the neural system begin to work together in a different manner to compensate for such changes. In other words, there is no indication that some components begin to take on a more important role or that other components come to take on a lesser role in supporting performance.

Some limitations should be considered in interpreting our results. First, we defined SCA based on performance on a measure of working memory. While working memory is an important cognitive domain in which older adults experience decline, SCA is clearly a multi-faceted construct that is broader and more complex than can be captured by a single cognitive domain. Future studies should examine SCA in a broader fashion such as by defining SCA based on performance on a comprehensive cognitive battery. In addition, as with all cross-sectional studies, our conclusions regarding age-related changes are limited. To truly understand what neural factors promote SCA and how brain-cognition relationships might remain the same or change as individuals age, a longitudinal design including repeated measurements of brain factors and cognition is needed. Further, although we clearly did not find evidence for age X brain interactions in our ROI analyses, it is possible that we were unable to detect true interaction

effects in our whole-brain fMRI analysis. We used the AFNI program 3dRegAna to explore, in a whole-brain fashion, whether there were regions where the relationship between task-related BOLD signal and working memory performance differed by age. While 3dRegAna is a widely used method for such an analysis, its limitation is that it is fairly strict, meaning that to find a significant cluster of interaction, it is often the case that the brain-cognition relationship must be in opposite directions in different age groups. 3dRegAna is less successful at picking up, for example, regions where there might be a brain-cognition relationship in one age group but no association within another age group. Thus, we cannot be certain that there are not regions outside of our DLPFC ROI that might show this sort of interaction effect. Finally, a possible limitation of the present study was our choice to combine data from different study samples, including data that was originally collected for purposes other than the present analyses. This has the potential to bias our findings. First, some participants from the original studies were excluded from the present study due to incomplete data, primarily because of poor image quality. Second, there was the potential for systematic differences in the data related to differences in the studies under which the data was collected. However, this did not appear to significantly affect the results, as the only variable that differed by study was MPFC cortical thickness, a variable that was not related to age or working memory.

In summary, the present study is one of the first to examine neural correlates of SCA by investigating brain structure, task-related activation and deactivation, and functional connectivity within the same sample of young, middle-aged, and older adults. Instead of finding that unique neural relationships emerge in aging to give rise to SCA as we expected, we found that the same neural factors work together in a similar manner across adulthood to support cognition, despite age-related changes among individual components of the system. Task-related activation, task-related deactivation, and brain structure were all found to be important to SCA but to varying degrees.

Our results could be extended in the future by applying similar multi-modal imaging and multivariate statistical approaches to additional studies of SCA, with the goal of understanding how components of the neural system work together to promote good performance in other cognitive domains and/or how the neural system supports good cognition longitudinally. Given that studies using paradigms other than working memory tasks have found evidence for age-related functional differences consistent with the HAROLD and PASA patterns, it would be interesting to apply our methodologies to understand how the neural system might work differently in younger and older adults when these functional pattern differences are apparent. It could be, for example, that among younger adults, brain structure and function are equally important in supporting cognition. Whereas among older adults showing the HAROLD and/or PASA pattern, function may play a greater role than structure, as the age-related functional differences might be compensating for comprised brain structure. In addition to examining such possibilities within the context of SCA, it will also likely prove important to investigate these sorts of questions within cognitively-compromised older adult populations, such as individuals with Mild Cognitive Impairment or Alzheimer's disease. Doing so could lead to a better understanding of how the neural system breaks down and results in age-related cognitive impairment. Brain-based interventions aimed at preventing, or at least slowing, the deterioration of the neural system could then use this information to determine when (i.e. at what stage in progression of the neural changes) and where (i.e. on what aspect of the neural system) to intervene.

REFERENCES

Abdi, H. (2010). Partial least squares regression and projection on latent structure regression (PLS Regression). *WIREs Computational Statistics, 2*, 97-106.

Andrews-Hanna, J. R., Snyder, A. Z., Vincent, J. L., Lustig, C., Head, D., Raichle, M. E., & Buckner, R. L. (2007). Disruption of large-scale brain systems in advanced aging. *Neuron, 56*(5), 924-935.

Beason-Held, L. L., Kraut, M. A., & Resnick, S. M. (2009). Stability Of Default-Mode Network Activity In The Aging Brain. *Brain Imaging Behav, 3*(2), 123-131.

Bergfield, K. L., Hanson, K. D., Chen, K., Teipel, S. J., Hampel, H., Rapoport, S. I., . . . Alexander, G. E. (2010). Age-related networks of regional covariance in MRI gray matter: reproducible multivariate patterns in healthy aging. *Neuroimage, 49*(2), 1750-1759.

Blair, J. R., & Spreen, O. (1989). Predicting premorbid IQ: A revision of the national adult reading test. *The Clinical Neuropsychologist, 3*(2), 129-136.

Boes, A. D., Mehta, S., Rudrauf, D., Van Der Plas, E., Grabowski, T., Adolphs, R., & Nopoulos, P. (2011). Changes in cortical morphology resulting from long-term amygdala damage. *Soc Cogn Affect Neurosci*, 1-8.

Brassen, S., & Buchel, C. (2009). Structure–function interactions of correct retrieval in healthy elderly women. *Neurobiol Aging, 30*, 1147-1156.

Brodtmann, A., Puce, A., Darby, D., & Donnan, G. (2009). Regional fMRI brain activation does correlate with global brain volume. *Brain Res, 1259*, 17-25.

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci, 1124*, 1-38.

Buckner, R. L., & Vincent, J. L. (2007). Unrest at rest: default activity and spontaneous network correlations. *Neuroimage, 37*(4), 1091-1096; discussion 1097-1099.

Bugg, J. M., Zook, N. A., DeLosh, E. L., Davalos, D. B., & Davis, H. P. (2006). Age differences in fluid intelligence: contributions of general slowing and frontal decline. *Brain Cogn, 62*(1), 9-16.

Bunea, F., She, Y., Ombao, H., Gongvatana, A., Devlin, K., & Cohen, R. (2011). Penalized least squares regression methods and applications to neuroimaging. *Neuroimage, 55*(4), 1519-1527.

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol Aging, 17*(1), 85-100.

Cherbuin, N., Anstey, K. J., Reglade-Meslin, C., & Sachdev, P. S. (2009). In vivo hippocampal measurement and memory: a comparison of manual tracing and automated segmentation in a large community-based sample. *PLoS ONE, 4*(4), e5265.

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. [Research Support, U.S. Gov't, P.H.S.]. *Comput Biomed Res, 29*(3), 162-173.

D'Esposito, M., Deouell, L. Y., & Gazzaley, A. (2003). Alterations in the BOLD fMRI signal with ageing and disease: a challenge for neuroimaging. *Nat Rev Neurosci, 4*(11), 863-872.

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage, 9*(2), 179-194.

Damoiseaux, J. S., Beckmann, C. F., Arigita, E. J., Barkhof, F., Scheltens, P., Stam, C. J., . . . Rombouts, S. A. (2008). Reduced resting-state brain activity in the "default network" in normal aging. *Cereb Cortex, 18*(8), 1856-1864.

Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S., & Cabeza, R. (2008). Que PASA? The posterior-anterior shift in aging. *Cereb Cortex, 18*(5), 1201-1209.

Depp, C. A., & Jeste, D. V. (2006). Definitions and predictors of successful aging: a comprehensive review of larger quantitative studies. *Am J Geriatr Psychiatry, 14*(1), 6-20.

Desikan, R. S., Segonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., . . . Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage, 31*(3), 968-980.

Dickerson, B. C., Bakkour, A., Salat, D., Feczko, E., Pacheco, J., Greve, D. N., . . . Buckner, R. L. (2009). The cortical signature of Alzheimer's Disease: Regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. *Cereb Cortex, 19*(3), 497-510.

Dickerson, B. C., Feczko, E., Augustinack, J. C., Pacheco, J., Morris, J. C., Fischl, B., & Buckner, R. L. (2009). Differential effects of aging and Alzheimer's disease on medial temporal lobe cortical thickness and surface area. *Neurobiol Aging, 30*(3), 432-440.

Dickstein, D. L., Kabaso, D., Rocher, A. B., Luebke, J. I., Wearne, S. L., & Hof, P. R. (2007). Changes in the structural complexity of the aged brain. *Aging Cell, 6*(3), 275-284.

Drag, L. L., & Bieliauskas, L. A. (2010). Contemporary review 2009: cognitive aging. [Review]. *J Geriatr Psychiatry Neurol, 23*(2), 75-93.

Efron, B., Hastie, T., Johnstone, I., & Tibshirani, R. (2004). Least angle regression. *The Annals of Statistics, 32*(2), 407-451.

Esposito, F., Aragri, A., Pesaresi, I., Cirillo, S., Tedeschi, G., Marciano, E., . . . Di Salle, F. (2008). Independent component model of the default-mode brain function: combining individual-level and population-level analyses in resting-state fMRI. *Magn Reson Imaging, 26*(7), 905-913.

Eyler, L. T., Sherzai, A., Kaup, A. R., & Jeste, D. V. (2011). A review of functional brain imaging correlates of successful cognitive aging. *Biol Psychiatry, 70*(2), 115-122.

Fera, F., Weickert, T. W., Goldberg, T. E., Tessitore, A., Hariri, A., Das, S., . . . Mattay, V. S. (2005). Neural mechanisms underlying probabilistic category learning in normal aging. *J Neurosci, 25*(49), 11340-11348.

Fischl, B., & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. [Research Support, U.S. Gov't, P.H.S.]. *Proc Natl Acad Sci U S A, 97*(20), 11050-11055.

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., . . . Dale, A. M. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron, 33*(3), 341-355.

Fischl, B., Sereno, M. I., & Dale, A. M. (1999). Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *Neuroimage, 9*(2), 195-207.

Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Segonne, F., Salat, D. H., . . . Dale, A. M. (2004). Automatically parcellating the human cerebral cortex. *Cereb Cortex, 14*(1), 11-22.

Fjell, A. M., Walhovd, K. B., Fennema-Notestine, C., McEvoy, L. K., Hagler, D. J., Holland, D., . . . Dale, A. M. (2009). One-year brain atrophy evident in healthy aging. *J Neurosci, 29*(48), 15223-15231.

Fjell, A. M., Walhovd, K. B., Reinvang, I., Lundervold, A., Salat, D., Quinn, B. T., . . . Dale, A. M. (2006). Selective increase of cortical thickness in high-performing elderly--structural indices of optimal cognitive aging. *Neuroimage, 29*(3), 984-994.

Fjell, A. M., Westlye, L. T., Amlien, I., Espeseth, T., Reinvang, I., Raz, N., . . . Walhovd, K. B. (2009). High consistency of regional cortical thinning in aging across multiple samples. *Cereb Cortex, 19*(9), 2001-2012.

Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci, 8*(9), 700-711.

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M. C., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci USA, 102*(27), 9673-9678.

Grady, C. L., Maisog, J. M., Horwitz, B., Ungerleider, L. G., Mentis, M. J., Salerno, J. A., . . . Haxby, J. V. (1994). Age-related changes in cortical blood flow activation during visual processing of faces and location. *J Neurosci, 14*(3 Pt 2), 1450-1462.

Grady, C. L., Springer, M. V., Hongwanishkul, D., McIntosh, A. R., & Winocur, G. (2006). Age-related changes in brain activity across the adult lifespan. *J Cogn Neurosci, 18*(2), 227-241.

Greenwood, P. M. (2007). Functional plasticity in cognitive aging: review and hypothesis. *Neuropsychology, 21*(6), 657-673.

Greicius, M. (2008). Resting-state functional connectivity in neuropsychiatric disorders. *Curr Opin Neurol, 21*(4), 424-430.

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. *Proc Natl Acad Sci U S A, 100*(1), 253-258.

Grober, E., Sliwinski, M., & Korey, S. R. (1991). Development and validation of a model for estimating premorbid verbal intelligence in the elderly. *Journal of Clinical and Experimental Neuropsychology, 13*(6), 933-949.

Gutchess, A., Hebrank, A., Sutton, B. P., Leshikar, E., Chee, M. W. L., Chow Tan, J., . . . Park, D. C. (2007). Contexual interference in recognition memory with age. *Neuroimage, 35*(3), 1338-1347.

Hampson, M., Driesen, N. R., Skudlarski, P., Gore, J. C., & Constable, R. T. (2006). Brain connectivity related to working memory performance. *J Neurosci, 26*(51), 13338-13343.

Holt, D. J., Cassidy, B. S., Andrews-Hanna, J. R., Lee, S. M., Coombs, G., Goff, D. C., . . . Moran, J. M. (2011). An anterior-to-posterior shift in midline cortical activity in schizophrenia during self-reflection. *Biol Psychiatry, 69*(5), 415-423.

Horn, J. L., & Cattell, R. B. (1967). Age differences in fluid and crystallized intelligence. *Acta Psychol (Amst), 26*(2), 107-129.

Im, K., Lee, J. M., Lyttelton, O., Kim, S. H., Evans, A. C., & Kim, S. I. (2008). Brain size and cortical structure in the adult human brain. *Cereb Cortex, 18*(9), 2181-2191.

Insel, K., Morrow, D., Brewer, B., & Figueredo, A. (2006). Executive function, working memory, and medication adherence among older adults. *J Gerontol B Psychol Sci Soc Sci, 61*(2), P102-107.

Johnson, S. C., Saykin, A. J., Baxter, L. C., Flashman, L. A., Santulli, R. B., McAllister, T. W., & Mamourian, A. C. (2000). The relationship between fMRI activation and cerebral atrophy: comparison of normal aging and alzheimer disease. *Neuroimage, 11*(3), 179-187.

Kane, M. J., & Engle, R. W. (2002). The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: an individual-differences perspective. *Psychon Bull Rev, 9*(4), 637-671.

Kane, M. J., Hambrick, D. Z., Tuholski, S. W., Wilhelm, O., Payne, T. W., & Engle, R. W. (2004). The generality of working memory capacity: a latent-variable approach to verbal and visuospatial memory span and reasoning. *J Exp Psychol Gen, 133*(2), 189-217.

Kannurpatti, S. S., Motes, M. A., Rypma, B., & Biswal, B. B. (2010). Neural and vascular variability and the fMRI-BOLD response in normal aging. *Magn Reson Imaging, 28*(4), 466-476.

Kaup, A. R., Mirzakhanian, H., Jeste, D. V., & Eyler, L. T. (2011). A review of the brain structure correlates of successful cognitive aging. *J Neuropsychiatry Clin Neurosci, 23*(1), 6-15.

Kinsella, K., & He, W. (2009). An Aging World: 2008 U. S. C. Bureau (Ed.) *International Population Reports*

Koch, W., Teipel, S., Mueller, S., Buerger, K., Bokde, A. L., Hampel, H., . . . Meindl, T. (2010). Effects of aging on default mode network activity in resting state fMRI: does the method of analysis matter? *Neuroimage, 51*(1), 280-287.

Lehmann, M., Douiri, A., Kim, L. G., Modat, M., Chan, D., Ourselin, S., . . . Fox, N. C. (2010). Atrophy patterns in Alzheimer's disease and semantic dementia: a comparison of FreeSurfer and manual volumetric measurements. *Neuroimage, 49*(3), 2264-2274.

Lustig, C., Snyder, A. Z., Bhakta, M., O'Brien, K. C., McAvoy, M., Raichle, M. E., . . . Buckner, R. L. (2003). Functional deactivations: change with age and dementia of the Alzheimer type. *Proc Natl Acad Sci U S A, 100*(24), 14504-14509.

Lutz, W., Sanderson, W., & Scherbov, S. (2008). The coming acceleration of global population ageing. *Nature, 451*(7179), 716-719.

Madden, D. J., Bennett, I. J., & Song, A. W. (2009). Cerebral white matter integrity and cognitive aging: contributions from diffusion tensor imaging. *Neuropsychol Rev, 19*(4), 415-435.

Mevik, B. H., & Wehrens, R. (2007). The pls package: Principal component and partial least squares regression in R. *Journal of Statistical Software, 18*(2), 1-24.

Ostby, Y., Tamnes, C. K., Fjell, A. M., Westlye, L. T., Due-Tonnessen, P., & Walhovd, K. B. (2009). Heterogeneity in Subcortical Brain Development: A Structural Magnetic Resonance Imaging Study of Brain Maturation from 8 to 30 Years. *Journal of Neuroscience, 29*(38), 11772-11782.

Pakkenberg, B., & Gundersen, H. J. (1997). Neocortical neuron number in humans: effect of sex and age. *J Comp Neurol, 384*(2), 312-320.

Panizzon, M. S., Fennema-Notestine, C., Eyler, L. T., Jernigan, T. L., Prom-Wormley, E., Neale, M., . . . Kremen, W. S. (2009). Distinct genetic influences on cortical surface area and cortical thickness. *Cereb Cortex, 19*(11), 2728-2735.

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. *Psychol Aging, 17*(2), 299-320.

Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: aging and neurocognitive scaffolding. *Annu Rev Psychol, 60*, 173-196.

Persson, J., Lustig, C., Nelson, J. K., & Reuter-Lorenz, P. A. (2007). Age differences in deactivation: a link to cognitive control? *J Cogn Neurosci, 19*(6), 1021-1032.

Plassman, B. L., Langa, K. M., Fisher, G. G., Heeringa, S. G., Weir, D. R., Ofstedal, M. B., . . . Wallace, R. B. (2007). Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology, 29*(1-2), 125-132.

Raichle, M. E., & Mintun, M. A. (2006). Brain work and brain imaging. *Annu Rev Neurosci, 29*, 449-476.

Raichle, M. E., & Snyder, A. Z. (2007). A default mode of brain function: a brief history of an evolving idea. *Neuroimage, 37*(4), 1083-1090; discussion 1097-1089.

Rakic, P. (1988). Specification of cerebral cortical areas. *Science, 241*(4862), 170-176.

Rakic, P. (2000). Radial unit hypothesis of neocortical expansion. In G. R. Bock & G. Cardew (Eds.), *Novartis Foundation Symposium 228: Evolutionray Developmental Biology of the Cerebral Cortex* (pp. 30-45): John Wiley & Sons Ltd.

Raz, N., Gunning, F. M., Head, D., Dupuis, J. H., McQuain, J., Briggs, S. D., . . . Acker, J. D. (1997). Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. *Cereb Cortex, 7*(3), 268-282.

Reichstadt, J., Depp, C. A., Palinkas, L. A., Folsom, D. P., & Jeste, D. V. (2007). Building blocks of successful aging: a focus group study of older adults' perceived contributors to successful aging. *Am J Geriatr Psychiatry, 15*(3), 194-201.

Reuter-Lorenz, P., & Cappell, K. A. (2008). Neurocognitive Aging and the Compensation Hypothesis. *Current Directions in Psychological Science, 17*(3), 177-182.

Reuter-Lorenz, P. A., Jonides, J., Smith, E. E., Hartley, A., Miller, A., Marshuetz, C., & Koeppe, R. A. (2000). Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. *J Cogn Neurosci, 12*(1), 174-187.

Rosano, C., Aizenstein, H., Cochran, J., Saxton, J., De Kosky, S., Newman, A. B., . . . Carter, C. S. (2005). Functional neuroimaging indicators of successful executive control in the oldest old. *Neuroimage, 28*(4), 881-889.

Rowe, J. W., & Kahn, R. L. (1987). Human aging: usual and successful. *Science, 237*(4811), 143-149.

Rypma, B., & D'Esposito, M. (2000). Isolating the neural mechanisms of age-related changes in human working memory. *Nat Neurosci, 3*(5), 509-515. doi: 10.1038/74889

Rypma, B., Prabhakaran, V., Desmond, J. E., & Gabrieli, J. D. (2001). Age differences in prefrontal cortical activity in working memory. [Research Support, U.S. Gov't, P.H.S.]. *Psychol Aging, 16*(3), 371-384.

Saad, Z. S., Reynolds, R. C., Argall, B. D., Japee, S., & Cox, R. W. (2004). SUMA:an interface for surface-based intra- and inter-subject analysis with AFNI *Proceedings of the 2004 IEEE International Symposium on Biomedical Imaging, Arlington, VA* (pp. 1510-1513). New York: IEEE.

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychol Rev, 103*(3), 403-428.

Salthouse, T. A. (2004). What and When of Cognitive Aging. *Current Directions in Psychological Science, 13*(4), 140-144.

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. *Neurobiol Aging, 31*(5), 839-852.

Seghier, M. L. (2008). Laterality index in functional MRI: methodological issues. [Review]. *Magn Reson Imaging, 26*(5), 594-601.

Solbakk, A., Fuhrmann Alpert, G., Furst, A. J., Hale, L. A., Oga, T., Chetty, S., . . . Knight, R. T. (2008). Altered prefrontal function with aging: Insights into age-associated performance decline. *Brain Res, 1232*, 30-47.

Spreng, R. N., Wojtowicz, M., & Grady, C. L. (2010). Reliable differences in brain activity between young and old adults: a quantitative meta-analysis across multiple cognitive domains. *Neurosci Biobehav Rev, 34*(8), 1178-1194.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia, 47*(10), 2015-2028.

Sullivan, E. V., & Pfefferbaum, A. (2006). Diffusion tensor imaging and aging. *Neurosci Biobehav Rev, 30*(6), 749-761.

Tae, W. S., Kim, S. S., Lee, K. U., Nam, E., & Kim, K. W. (2008). Validation of hippocampal volumes measured using a manual method and two automated methods (FreeSurfer and IBASPM) in chronic major depressive disorder. *Neuroradiology, 50*, 569-581.

Thomsen, T., Specht, K., Rimol, L. M., Hammar, A., Nyttingnes, J., Ersland, L., & Hugdahl, K. (2004). Brain localization of attentional control in different age groups by combining functional and structural MRI. *Neuroimage, 22*(2), 912-919.

Tibshirani, R. (1996). Regression shrinkage and selection via the Lasso. *Journal of the Royal Statistical Society. Series B (Methodological), 58*(1), 267-288.

Uylings, H. B., & de Brabander, J. M. (2002). Neuronal changes in normal human aging and Alzheimer's disease. *Brain Cogn, 49*(3), 268-276.

Vallesi, A., McIntosh, A. R., & Stuss, D. T. (2009). Temporal preparation in aging: A functional MRI study. *Neuropsychologia, 47*, 2876-2881.

Wechsler, D. (1997). *WAIS-III administration and scoring manual* (3rd ed.). San Antonio, TX: The Psychological Corporation.

West, R. L. (1996). An application of prefrontal cortex function theory to cognitive aging. *Psychol Bull, 120*(2), 272-292.

Wilson, R. S., Beckett, L. A., Barnes, L. L., Schneider, J. A., Bach, J., Evans, D. A., & Bennett, D. A. (2002). Individual differences in rates of change in cognitive abilities of older persons. *Psychol Aging, 17*(2), 179-193.

Ylikoski, R., Ylikoski, A., Keskivaara, P., Tilvis, R., Sulkava, R., & Erkinjuntti, T. (1999). Heterogeneity of cognitive profiles in aging: successful aging, normal aging, and individuals at risk for cognitive decline. *Eur J Neurol, 6*(6), 645-652.

TABLE 1: Sample Characteristics

	Entire Sample	**By Age Group**			
	(N=64)	**Young** (n = 26)	**Middle** (n = 19)	**Old** (n = 19)	**One-Way ANOVA / Chi-Square comparing Age Groups**
Age *Mean (SD)*	46.1 (15.8)	30.2 (5.5)	48.7 (6.5)	65.5 (4.5)	$F_{2,61}$ = 227.1; p < .0005*
Gender *# of Participants*					
Female	40	13	13	14	
Male	24	13	6	5	X^2_2 = 3.0, p = .22
Education *Mean (SD)*	15.5 (2.3)	15.4 (2.4)	14.5 (1.8)	16.5 (2.5)	$F_{2,61}$ = 3.8, p = .03*
Ethnicity *# of Participants*					
Caucasian	51	20	15	16	
Hispanic	4	3	0	1	
African American	3	0	2	1	
Asian/Pacific Islander	2	0	1	1	
Other	4	3	1	0	X^2_8 = 8.8, p = .36
Estimated Verbal IQ *Mean (SD)*	115.1 (6.2)	113 (5.6)	116.9 (6.8)	116.0 (5.9)	$F_{2,55}$ = 2.29, p = .11

* = p < .05

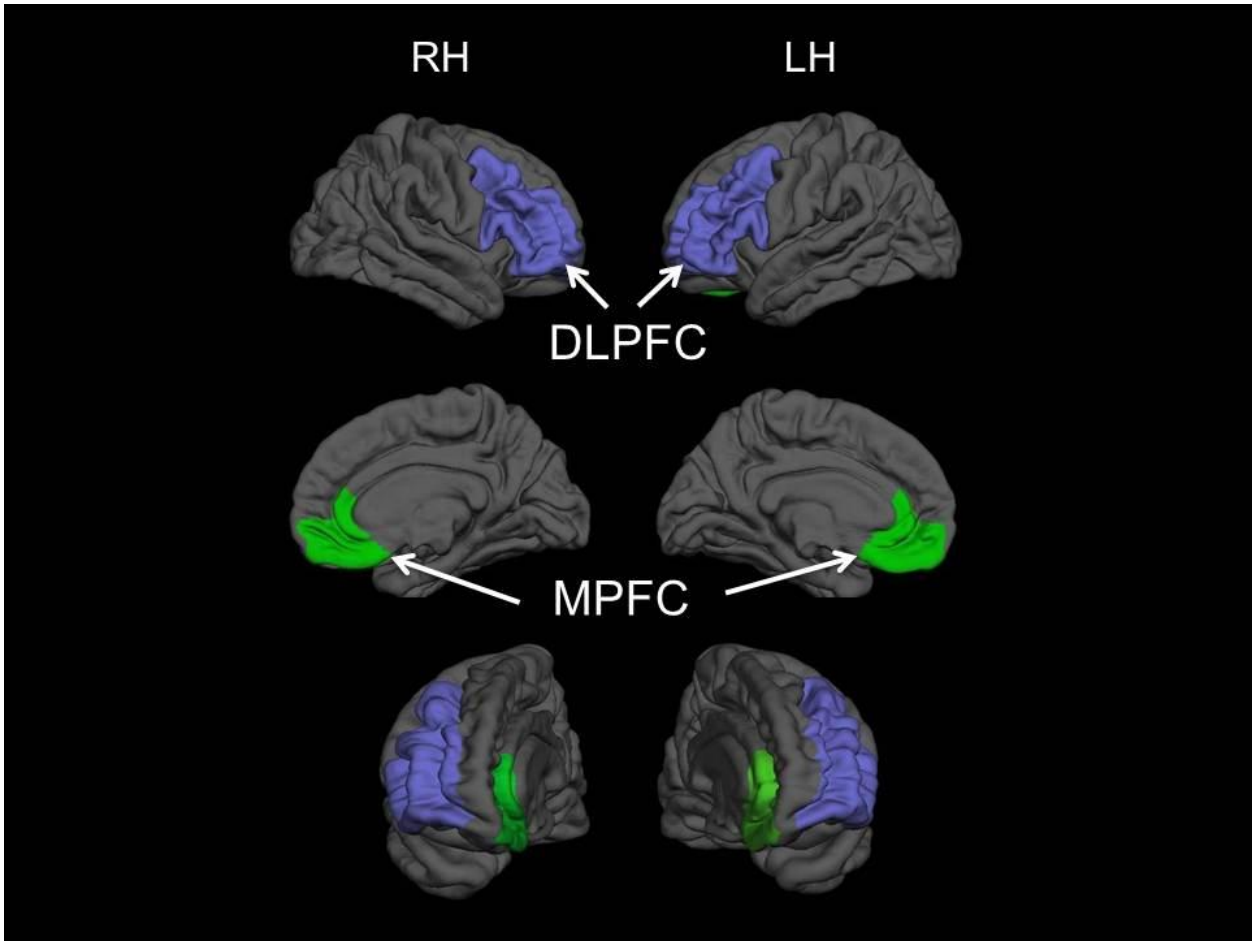
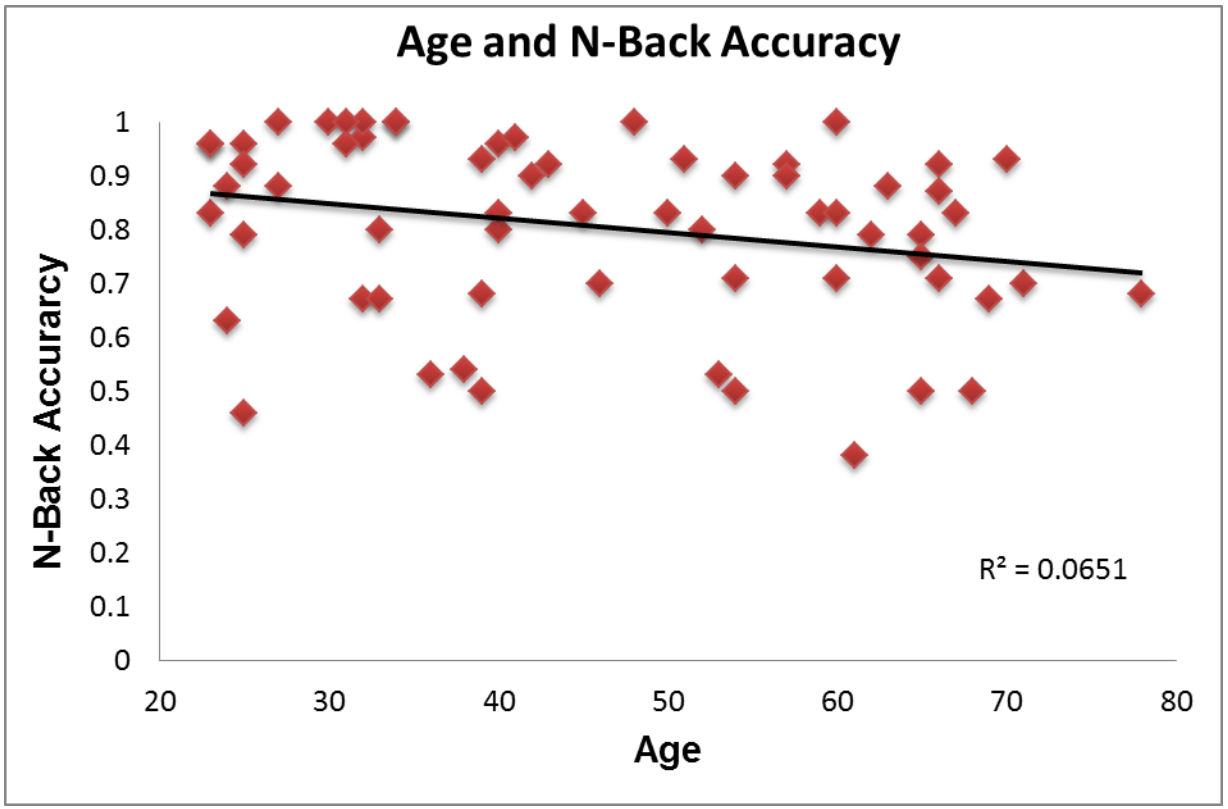
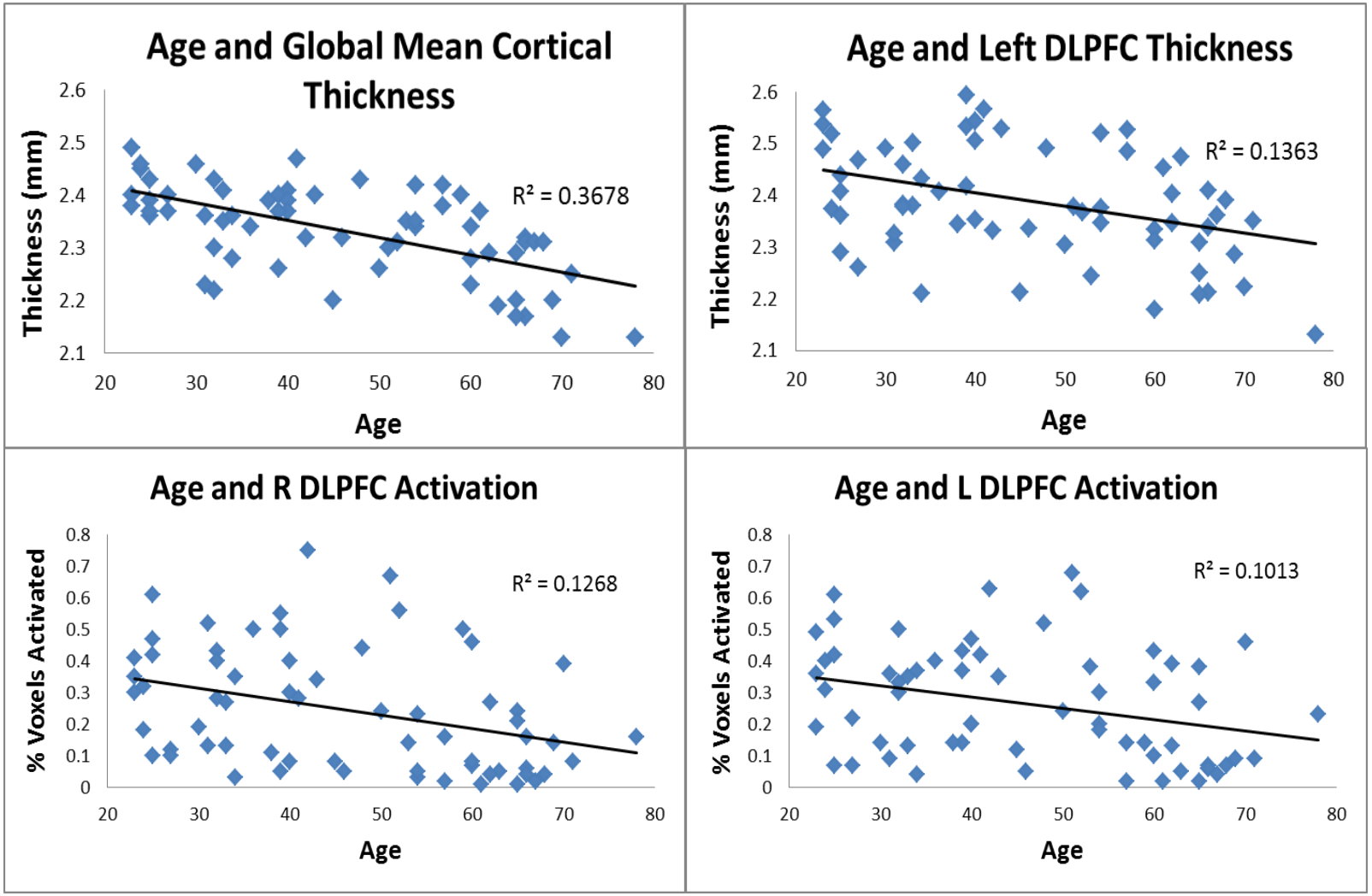


FIGURE 1: DLPFC and MPFC ROIs (shown on Freesurfer “fsaverage” Brain)

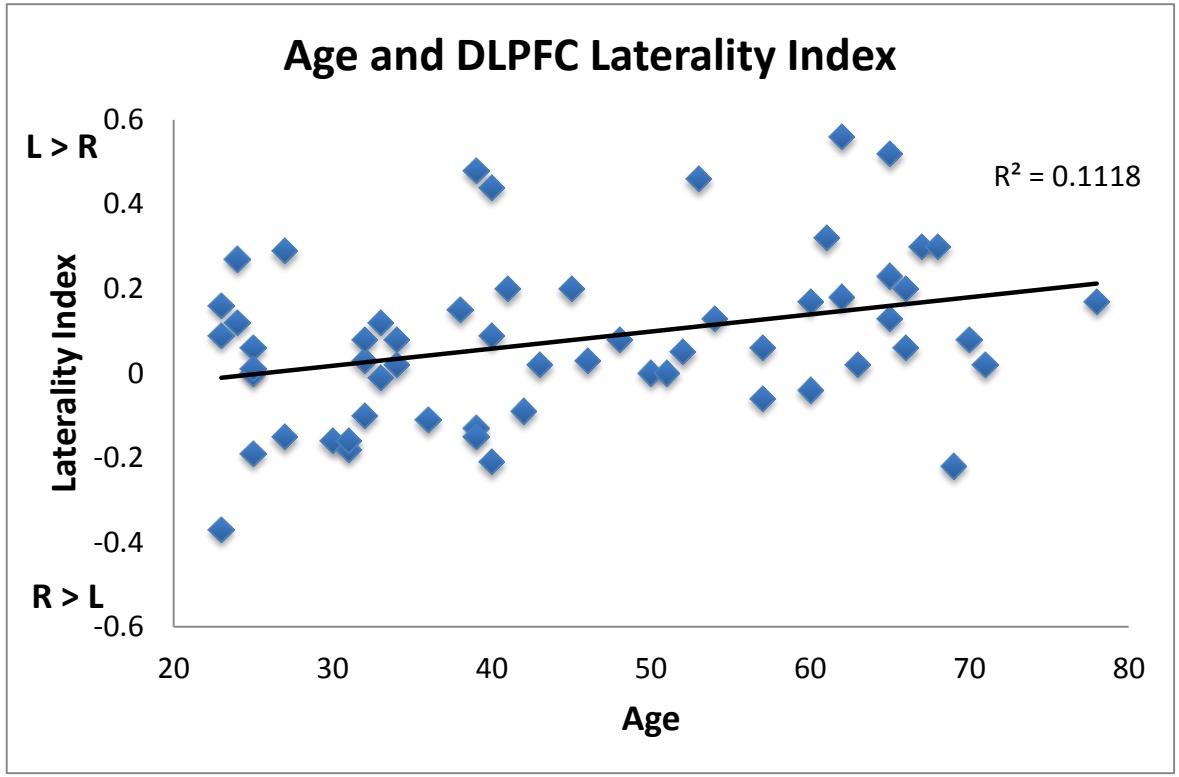
GRAPH 1: Relationship between Age and Working Memory Performance



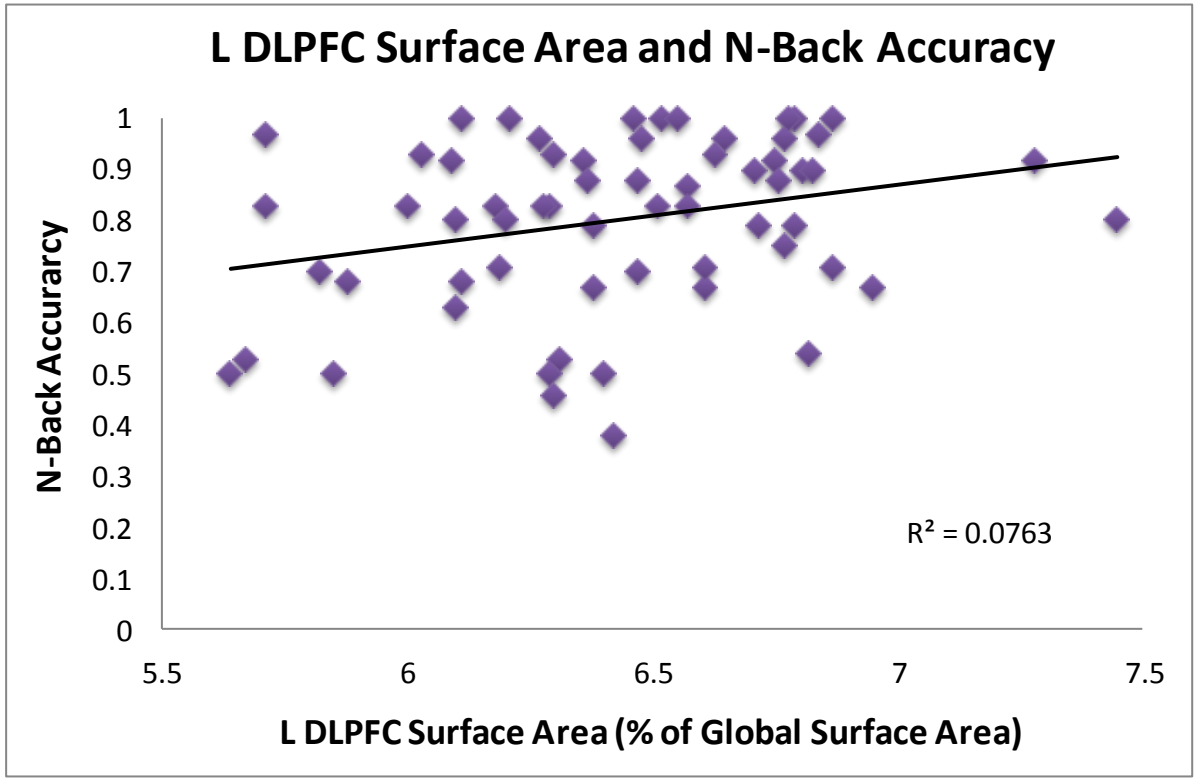
GRAPH 2: Negative Relationships between Age and Brain Variables

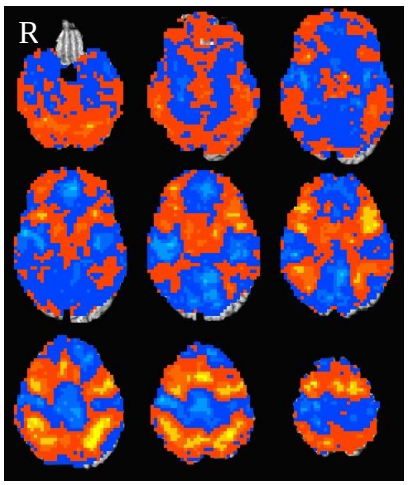


GRAPH 3: Positive Relationship between Age and DLPFC Laterality Index (*2- minus 1-back*)

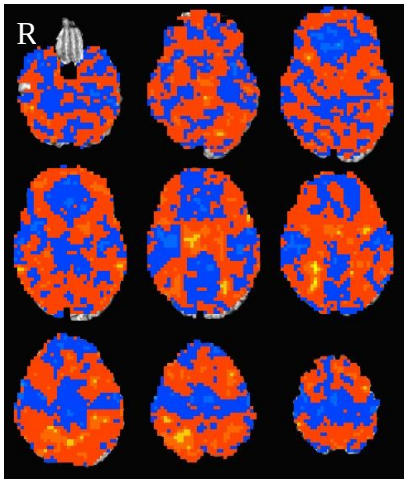


GRAPH 4: Relationship between Left DLPFC Surface Area (Adjusted for Global Surface Area) and Working Memory Performance

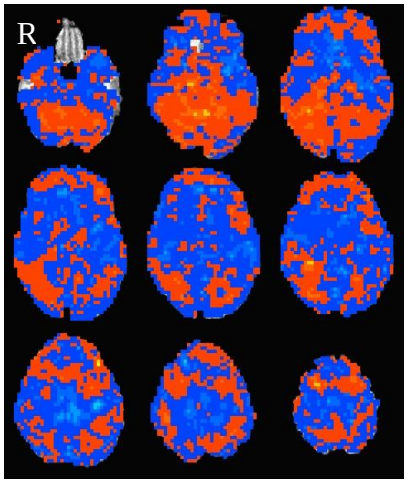




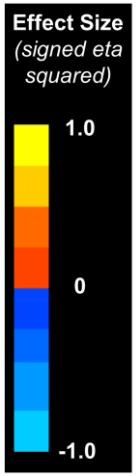
Young (n=26)

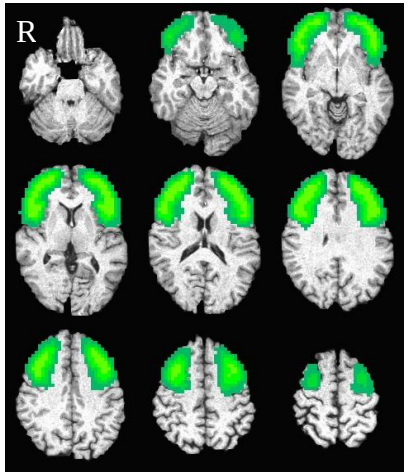


Middle (n=19)

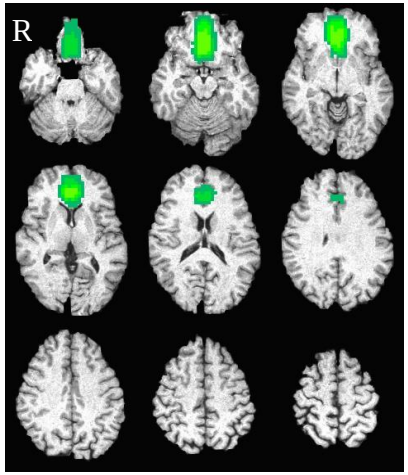


Old (n=19)





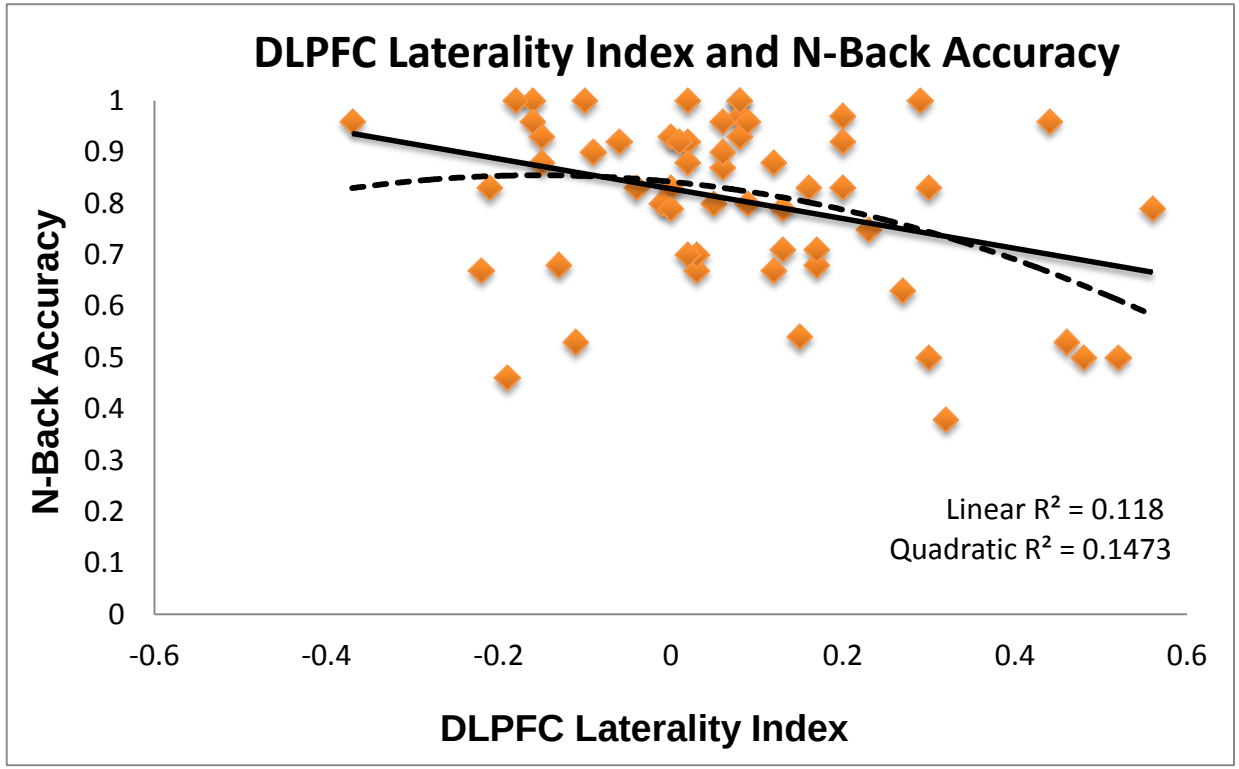
DLPFC ROI in Talairach



MPFC ROI in Talairach

FIGURE 2: Whole-Brain fMRI N-Back Group Analysis in Talairach Space (*2- minus 1-back*); Unthresholded

GRAPH 5: Relationship between DLPFC Laterality Index (*2- minus 1-back*) and Working Memory Performance



Age Main Effect

Performance Main Effect

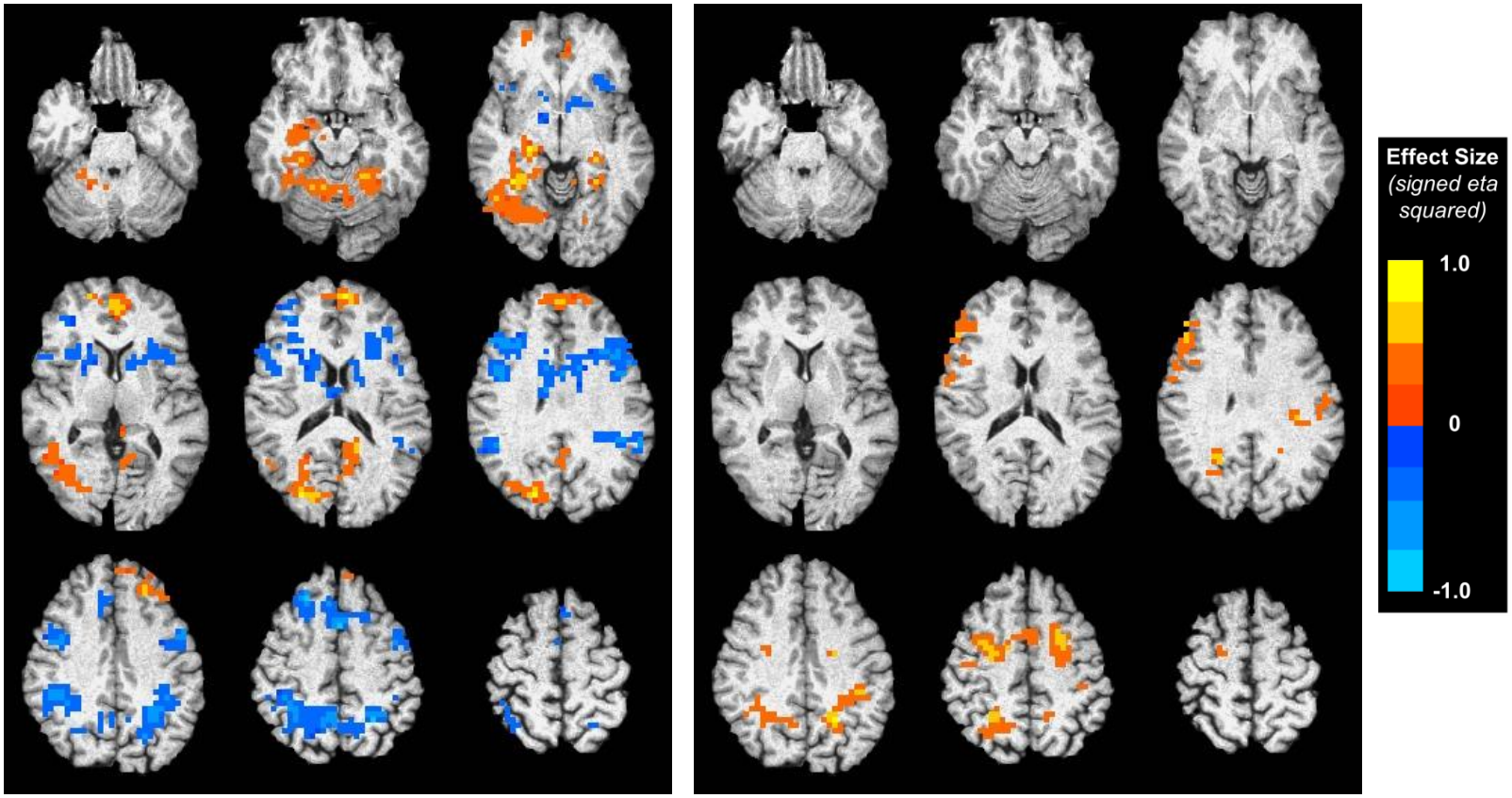


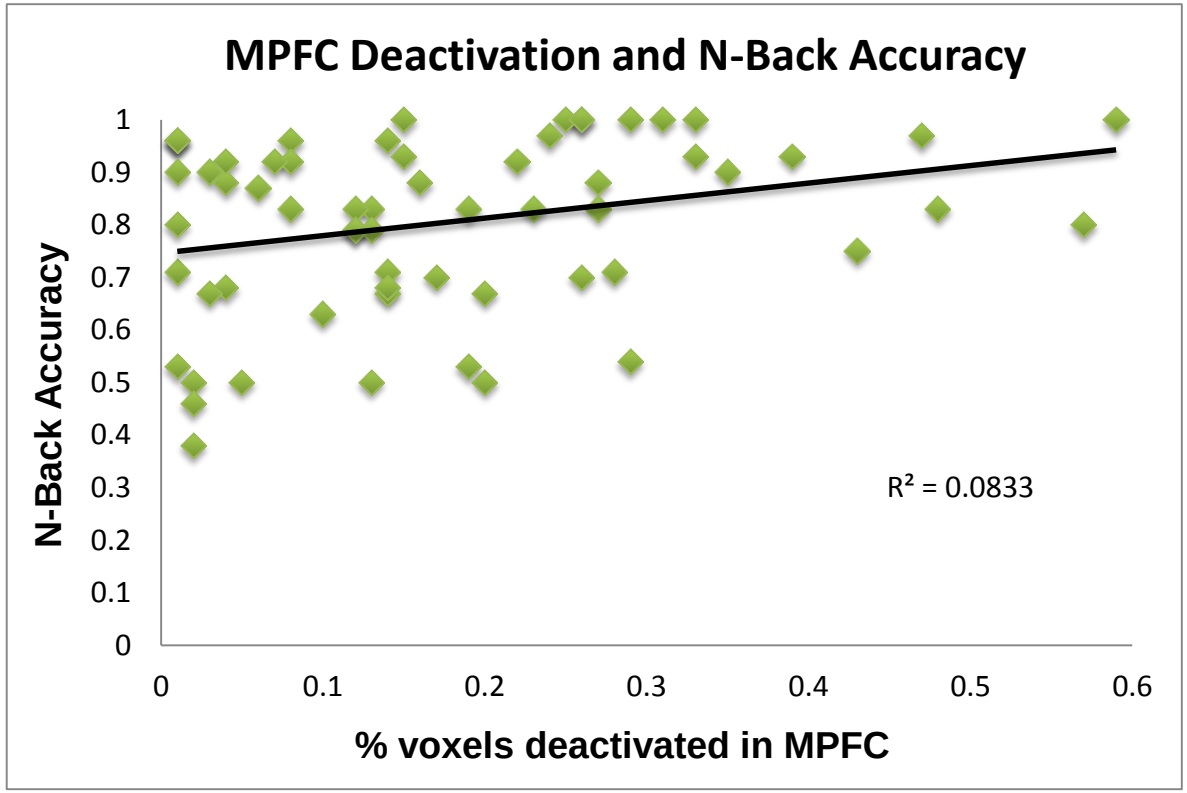
FIGURE 3: Whole-Brain fMRI 3dRegAna Results for the N-Back Task (*2- minus 1-back*) in Talairach Space; Significant Clusters

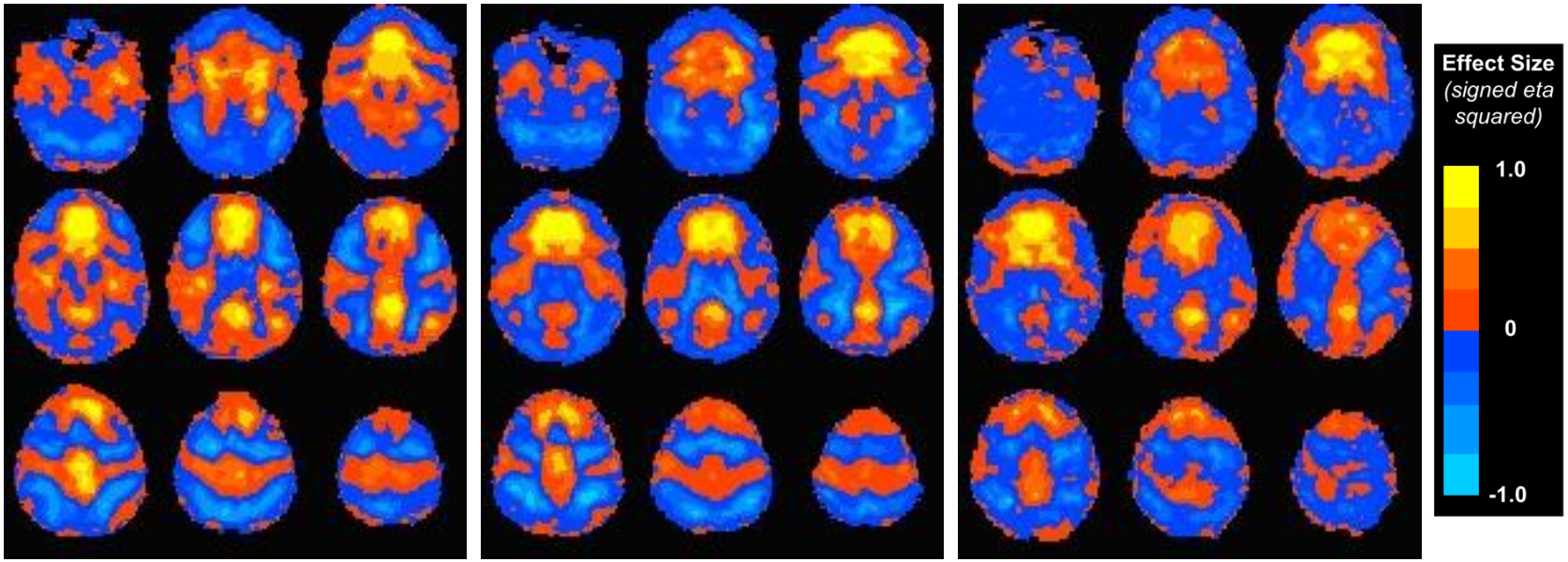
TABLE 2: Whole-Brain fMRI 3dRegAna Results for the N-Back Task (*2- minus 1-back*); Significant Clusters

Effect	***Cluster***	***# Voxels***	***Center of Mass***	***Mean Fit Coefficient (Eta^2)***	***Age Correlation (r)***	***Performance Correlation (r)***			
						All *(n=63)*	***Y*** *(n=26)*	***M*** *(n=19)*	***O*** *(n=18)*
Age	B Frontal / Cingulate / Caudate	842	-3.2 -14.5 +27.7	-.10	-.52**	.28*	.30	.17	.15
	R Occipital-Temporal	645	-20.3 +58.2 +0.3	.10	.44**	-.012	.23	.30	-.094
	B IPL and SPL	474	-2.0 +52.1 +43.3	-.11	-.55**	.33**	.35†	.26	.19
	Medial Frontal Gyrus	194	+4.2 -53.0 +20.2	.10	.49**	-.14	-.13	.25	-.10
	L PC / Cuneus / Precuneus	85	+7.5 +56.7 +16.6	.09	.42**	-.17	-.026	-.16	-.24
Performance	L IPL/Precuneus	131	+32.0 +44.3 +37.6	.09	-.41**	.51**	.61**	.34	.42†
	R SPL/Precuneus	122	-24.7 +59.9 +44.7	.10	-.36**	.50**	.62**	.32	.36
	R MFG/IFG	87	-47.8 -23.6 +24.7	.09	-.32*	.48**	.60**	.36	.21
	R MFG	83	-30.0 +6.0 +50.2	.11	-.15	.50**	.65**	.54*	.19
	L MFG	82	+16.2 +0.9 +48.2	.09	-.26*	.46**	.52**	.47*	.32
Age X Performance	No significant clusters								

†p< .10, *p <.05, **p <.01; R = right, L = left, B = bilateral, IPL = inferior parietal lobule, SPL = superior parietal lobule, PC = posterior cingulate, MFG = middle frontal gyrus, IFG = inferior frontal gyrus

GRAPH 6: Relationship between Deactivation within the MPFC ROI (*2- minus 1-back*) and Working Memory Performance





Young (n=26) Middle (n=19) Old (n=19)

FIGURE 4: Whole-Brain Functional Connectivity Maps Showing Functional Correlations between the PC Seed Region and Signal in All Other Voxels (n=64) in MNI Space; Unthresholded

TABLE 3: Variable Loadings on Component Resulting from PLS Regression

Variable (z)	***Loading on Component***
Age	-.34*
Global mean cortical thickness	.22
Global surface area	.27
Right DLPFC thickness	
Left DLPFC thickness	.15
Right DLPFC surface area	.25
Left DLPFC surface area	.27
DLPFC laterality index	-.33*
Right DLPFC activation	.38*
Left DLPFC activation	.30*
MPFC thickness	
MPFC surface area	.25
MPFC deactivation	.29
MPFC-PC seed functional connectivity	.24
Age x Global mean cortical thickness	.20
Age x Global surface area	-.11
Age x Right DLPFC thickness	.19
Age x Left DLPFC thickness	.17
Age x Right DLPFC surface area	
Age x Left DLPFC surface area	
Age x DLPFC laterality index	
Age x Right DLPFC activation	.14
Age x Left DLPFC activation	.16
Age x MPFC deactivation	
Age x MPFC-PC seed functional connectivity	

*Loadings $\geq$ |.30|

TABLE 4: Summary of Aim 1 Hypotheses and Results

Hypothesis	***Hypothesis Supported?***	***Result***
Y, **MA**, and **O**: ↑DLPFC cortical thickness and ↑DLPFC surface area = ↑working memory performance. Brain-cognition relationship will be significantly stronger in **O**.	Partially	↑Left DLPFC surface area = ↑N-back accuracy across ages. Right DLPFC surface area, left and right DLPFC thickness not associated with N-back accuracy.
O: Bilateral DLPFC activation = ↑working memory performance. **Y** and **MA**: Lateralized DLPFC activation = ↑working memory performance.	No	Bilateral DLPFC activation (not left-lateralized) = ↑N-back accuracy across ages. ↑Right DLPFC activation = ↑N-back accuracy across ages. Left DLPFC activation not significantly associated with N-back accuracy.
O: ↑MPFC deactivation = ↑working memory performance. **Y** and **MA**: No association.	Partially	↑MPFC deactivation (based on the structurally-defined MPFC) = ↑N-back accuracy across ages.
O: ↑Functional connectivity between DMN regions (MPFC and PC) = ↑working memory performance. **Y** and **MA**: No association.	No	Functional connectivity between MPFC and PC not associated with N-back accuracy.

Y = younger adults, **MA** = middle-aged adults, **O** = older adults, DLPFC = dorsolateral prefrontal cortex, MPFC = medial prefrontal cortex, DMN = default mode network, PC = posterior cingulate