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Characterizing the age-related decline of memory monitoring: Neuroimaging and genetic approaches

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Characterizing the age-related decline of memory monitoring: Neuroimaging and genetic approaches

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Dissertation

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas at Austin

May, 2011

Dedication

For my Mémère, with love.

Acknowledgements

First and foremost, I'd like to thank my parents, Steve and Connie Pacheco, who from the earliest age made sure I knew that "because" was an inadequate answer to the question "why". My mom showed through her example what it is to be a strong, caring, intelligent woman. And my dad was always just a few steps ahead of me, making sure I was equipped with the tools to do anything on my own. You were right, Dad, units conversion is a useful skill! Thank you both for fostering my sense of curiosity, encouraging my creativity, and always being my biggest cheerleaders!

I have been fortunate to work closely with wonderful scientists and mentors. Thank you to my advisor, David Schnyer, your guidance, support and advice has turned me into a more critical thinker. Thank you to my collaborators Todd Maddox, Chris Beevers and John McGeary, your insight has helped to make this a more interesting project. Thank you to my committee members, Andreana Haley and Carole Holahan, for your interest in my research and the time you have dedicated to it. A special thanks to Jeanette Mumford, your patience with my statistical questions has not gone unnoticed. Lastly, a big thank you to the Schyner Lab and collaborators, Emily Knight, Logan Trujillo, Peter Clasen Marissa Gorlick, and especially all of the undergraduate research assistants who have contributed to this work: Natalie Dailey, Sara Dholakia, Catherine Faig, Lauren Fanty, Megan Forbes, Sarah Greene, Cassandra Jacobs, Brittany Nix, Maria Olivares, and Caitlin Tenison.

If it's true what they say, and you are judged by the company you keep, then I will be judged extremely well. Thank you to all of my wonderful friends: Ryan O'Donnell and Chelsea Brewer, for putting up with my shenanigans at home. Jim Giddings, Stacey Harper, Danielle Kachapis, and Melanie Najarian, for your years of unending friendship, no matter how far apart we have gone. My Boston-based gang, Valerie Carr, Nathanael Hevelone, Julie Kong, Vihann Kong, Chris Player, Allison Stevens, Alexandra Zaleta, and the rest of my super best friends, thank you for your never-ending supply of hilarity. And finally to all of my Austin friends, especially Nanci Argueta, Akram Bakkour, Matt Brooks, Thad Czuba, Tyler Davis, Brian Glass, Lisa Dawn Hamilton, Cari Goetz, Dean Kirson, Emily Luther, Laura Marusich, Ross Otto, Cindy Stappenbeck, Kyle Walsh, Darrell Worthy, all the Ovenmitts, and Beer Is On The House teammates. I really could not imagine going through this grad school thing with a better group of people. Thank you for a wonderful and unforgettable 4 years!

And lastly, Austin, TX. Thank you for providing an incredible backdrop for this journey. In 2007, I left Boston nervous and unsure, but Austin has been the most wonderful city and home.

Hook 'em!

Characterizing the age-related decline of memory monitoring: Neuroimaging and genetic approaches

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Memory monitoring, or the ability to accurately assess one's memory retrieval success, is known to be declined for older adults. The behavioral decline has been well explored, and is specific to tasks of source monitoring; tasks involving item memory monitoring do not show age-related deficits. This study attempts to further characterize the decline by exploring neuroanatomical contributions to the decline, and genetic influences that may explain performance variability in older adults. Older adults were genotyped for the serotonin transporter (5-HTTLPR) gene, and those that are carriers of the low-expressing allele demonstrate the expected age-related decline of source monitoring performance when compared to younger adults. Interestingly, older adults who lack this allele did not display any decline in performance when compared to younger adults. Neuroanatomical correlates of task performance indicate that prefrontal regions in the inferior and lateral cortices support accurate source memory monitoring, likely through their role in the proper selection of memory cues and inhibition of irrelevant information. This relationship suggests that age-related atrophy occurring in

these structures could be responsible for the performance deficits on source memory monitoring tasks. There was no direct relationship seen between genotype for the 5-HTTLPR gene and cortical volumes, however diffusion tensor imaging shows that older adults who carry this allele have altered connections between the medial temporal lobe, responsible for memory retrieval, and prefrontal cortex, which monitors the retrieval process. Through stronger connections of critical networks, older adults who lack the 5-HTTLPR short allele may be able to compensate for the age-related atrophy seen in the prefrontal cortex. Functional results further indicate that the older adult non-carriers recruit inferior and lateral frontal regions to a greater extent than the older adult carriers during accurate memory monitoring. These results begin to suggest a neuroprotective mechanism for the 5-HTTLPR genotype, wherein some older adults may be able to postpone the expected decline of memory monitoring by retaining the ability to recruit essential inferior frontal structures through more organized white matter pathways.

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Chapter 1: Introduction

OVERVIEW

In order to examine the basis of episodic memory monitoring changes that occur during healthy aging, one must first begin with a basic understanding of memory systems, and the process of monitoring memory retrieval. There are multiple memory systems in the brain, and the current proposal focuses on the declarative, and more specifically the episodic domain of memory. Healthy aging imposes many changes on both cognitive function and neuroanatomical structure, both of which contribute to the overall decline observed in memory monitoring. In younger adults a neural network supporting memory monitoring has been uncovered, however many of the critical structures are known to undergo significant age-related changes. As the brain ages, atrophy is shown to be prominent in the frontal lobes which are a critical component to memory monitoring processes, and is a primary focus in understanding the underlying neural network in older adults. With this work I explore the age-related changes seen in brain function and structure as it relates to memory monitoring. Other biological effects are likely to influence memory monitoring performance as well. Recently, serotonin systems have become a target of intervention for memory related disorders, such as Alzheimer's disease and amnesia, indicating that the amount of available serotonin has a positive impact on memory function. Genetic influences that may impact the memory monitoring process are explored for both older and younger adults. Additionally, I examine the relationship that the serotonin transporter gene, 5-HTTLPR, has on memory performance through the lifespan.

Figure 1

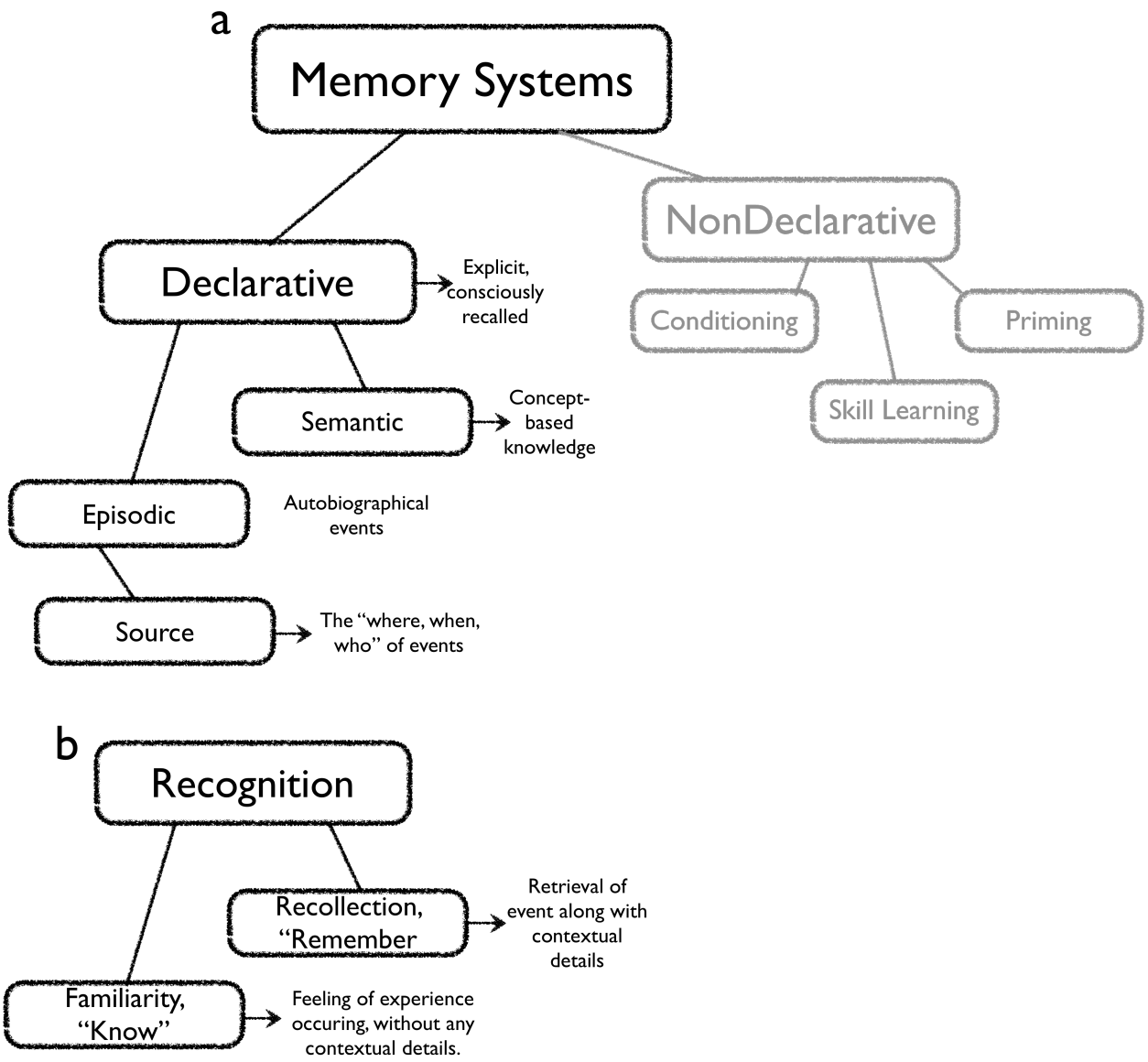


Figure 1. Overview of Memory System Organization

Panel **a** shows the Declarative and Non-declarative memory systems and panel **b** shows the subcomponents of Recognition memory.

METAMEMORY

Memory performance shows significant age-related declines, particularly in declarative memory, which is explicit memory that can be consciously stated (See Figure 1 for an overview of memory systems). Declarative memory can be further subdivided into semantic and episodic memory (Tulving 1987). Semantic memory is concept-based knowledge (i.e., what is the capitol of France?), and has not been the domain of much age-related decline. In contrast, episodic memory is memory for autobiographical events. These are generally accompanied by clear and coherent contextual information of the event (e.g., where it was, when it happened, who was there). Memories for the contextual information is called source memory, and both episodic and source memory are worse in older adults than they are in younger adults.

The framework for memory monitoring proposed by Nelson and Narens (1990) describes memory processes as engaging two levels: the *object* level and the *meta* level. For processes of memory retrieval, the object level contains retrieved, or target information. The meta level contains information relevant to the context and task goals associated with the current retrieval effort. Memory monitoring mechanisms serve to assess the information retrieved at the object level relative to that at the meta level in order to determine the extent of relevance and validity to the current tasks – this process is used to assess the potential for accuracy of retrieved information. Johnson and colleagues built upon this to develop a framework specifically for source monitoring (Johnson, Hashtroudi et al. 1993), which could either involve discriminating between two different external sources (e.g., something said by person A or person B) or discriminating between two different internal sources (e.g., something I thought or something I said). Following the original model by Nelson and Narens, Johnson suggests

that these monitoring judgments are made based on the specific characteristics of the memories retrieved and whether they fit logically into the criteria imposed by the task at hand. For example, a memory that contains large amounts of perceptual, spatial, and/or temporal detail is judged likely to be a memory that came from an external source. Source monitoring can also capitalize on the amount of match between a retrieved memory and the activated schema for the source. An example that will become relevant to the work presented here is that if the auditory quality in a memory matches your working schema for a specific person's voice, then you will attribute the statement to that person (Johnson, Hashtroudi et al. 1993). Episodic memories, more so than other memories, are rich with contextual and feature details, and clues from these details can be used to influence the assessment of retrieval accuracy. Successful monitoring of episodic retrieval requires proper selection of key details while disregarding irrelevant information. Populations prone to difficulties with this type of inhibition will likely demonstrate difficulty with memory monitoring.

MEMORY PATTERNS IN AGING

Models of cognitive aging indicate that older adults do not show deficits in their semantic memory ability (Zacks, Hasher et al. 2000). Likewise, many studies have shown older adults perform at similar, or better, levels of memory monitoring accuracy as younger adults do in response to semantic memory tasks (Perlmutter 1978; Pliske and Mutter 1996; Marquie and Huet 2000). In contrast, older adults have shown a decline in memory monitoring accuracy for tasks involving episodic information, source information, and associative memory (Kelley and Nairne 2003; Dodson and Krueger 2006; Dodson, Bawa et al. 2007). Successful episodic monitoring relies more heavily on specific contextual information, which older adults may not be able to access. Based on

the frameworks proposed for source monitoring, these missing details would make it difficult to accurately determine where a specific memory took place, and if it was a logical response to the current query.

Retrieval of episodic memories requires the combination of many contextual details into one salient scene. Older adults are susceptible to failures in recombining feature details, and are prone to mistakenly combine features from one event with features from other events (Kroll, Knight et al. 1996; Henkel, Johnson et al. 1998; Koutstaal, Schacter et al. 2001). This recombination error can result in salient, but incorrect, memories and produce highly confident feelings of accuracy (Dodson and Krueger 2006). In other words, the age-related decline of memory monitoring may be a result of an inaccurate assessment of the actual contents of memory stores and a reliance on more familiarity of information and events. It may be that older adults are not simply remembering less but are misremembering more (Dodson and Krueger 2006; Dodson, Bawa et al. 2007). The distinction here is that older adults are more likely to make salient and convincing false memories of past events and to feel highly confident about their accuracy.

A dissociation between recognition memory performance and memory monitoring ability has been demonstrated in older adults (Dodson, Bawa et al. 2007). The study investigated three groups of 24 subjects each: the young group (age range = 18-26), the young-delay group (age range = 18-26) and the older group (age range = 61-76). Participants were presented with a study and a test phase, in which they were aware of the upcoming memory test. During the study phase, subjects were allowed to view and hear 80 different statements, each read by one of two speakers. This was followed by a short 5-minute filler task, after which the younger and older adult groups completed the

test phase. The young-delay group returned 24 hours later to complete the test phase. During the test phase participants were shown a combination of new statements and statements used in the previous phase, and asked to identify them as *new* or *old*. A subsequent question asked them to rate how confident they were in their previous response on a scale of 50% (guessing) to 100% (certain). A calibration score was calculated for memory monitoring ability based on the accuracy for each confidence rating. Perfect calibration is reflected when 60% of the statements rated 60 were answered correctly. In this same manner, subjects were asked to identify the speaker of each sentence from two given choices and rate their confidence. The results from the recognition task (*new*/*old*) showed that there was no difference between the three groups on their recognition accuracy (all groups close to ceiling), nor on the accuracy of the judgments about their recognition performance. In contrast, the source memory recognition of the young group was significantly better than either the young-delay or the older group, which both performed similarly (Figure 2). Interestingly, there was no significant difference between the young group and the young-delay group on their monitoring accuracy, whereas the older adults were significantly worse. These results show that poor source memory monitoring is not simply a result of poor source memory ability. The participants in the young-delay group seemed aware of their inability to recognize the correct answer, whereas the older adults were less aware (Dodson, Bawa et al. 2007). High-confidence errors, or times when participants were highly confident about their memory success (ratings of 80, 90 and 100), but had answered incorrectly, were more common in the older adults than in either of the younger adult groups. Further, this was not a result of skewed responding as all groups used the entire rating scale to the same degree (Dodson, Bawa et al. 2007).

Figure 2

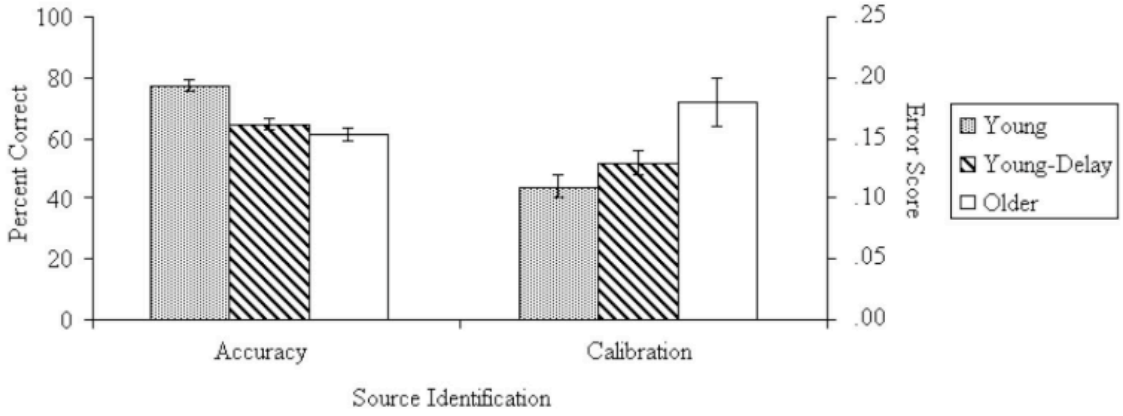


Figure 2. Dissociation of Source Memory Performance and Monitoring.

Conditional source and calibration error scores for the young, young– delay, and older groups in Experiment 1. Error bars represent the standard error of the mean. Figure and caption taken from Dodson, Bawa, et al. (2007)

Source memory monitoring displays signs of specific age-related declines, which is consistent with several theories of cognitive aging. With a decreased ability to properly inhibit irrelevant information from invading their initial attempts at memory retrieval, older adults are less likely to accurately assess their retrieval for episodic memories, particularly source memory, which requires combination of many details. In addition, because of an over-reliance on familiarity, older adults may be more likely to believe their false memories, without the ability to realize that they may not be correct.

EFFECTS OF AGE ON COGNITION

Healthy aging imposes many changes, which can be seen in a variety of domains of cognitive performance, neural functioning, and neuroanatomy. One of the most popular theories of cognitive aging is the *processing-speed theory*, which indicates that

the cognitive deficits of older adults are a result of reduced speed of processing (Salthouse 1996; Dennis and Cabeza 2008). Behaviorally, cognitive slowing, or reductions in response reaction time, are among the most commonly reported age-related declines and have shown to correlate considerably with deficits in accuracy on cognitive tasks (Shimamura 1994). According to Salthouse (1996), there are two mechanisms by which reductions in processing speed can disrupt cognitive performance. In one mechanism, increased amount of time spent on early processing events subsequently restricts time available for later processing events. A second mechanism postulates that the results of the earlier processing stages can ultimately be lost or forgotten when the later processing stages are completed. Each of these mechanisms can act independently or jointly to reduce accuracy of cognitive performance with advanced age.

Another popular theory of cognitive aging is the *resources deficit theory*, which suggests that there is a decrease in the amount of attentional resources available for cognitive processes. In accordance with this theory, older adults show larger deficits as task demands are increased (Craik and Byrd 1982; Kane, Hasher et al. 1994; Dennis and Cabeza 2008). Additionally, when younger adults are deprived of attentional resources, by subjecting them to a task requiring dual-attention, they show declines in cognitive performance similar to those seen in older adults under full attention (Jennings and Jacoby 1993; Anderson, Craik et al. 1998). It could be that deficits seen in source monitoring ability arise from the increases in task demands. Older adults may not have the needed resources to successfully monitor salient contextual details.

A third theory of cognitive aging is the *inhibition deficit theory*, which attributes cognitive decline to failures of inhibitory control (Hasher and Zacks 1988; Dennis and Cabeza 2008). The lack of inhibitory control seen in older adults can result in inclusion of

irrelevant information in working memory, which in turn can impair processes of episodic memory encoding and retrieval (Dempster 1992; Zacks, Hasher et al. 2000). Initial attempts at memory retrieval produce many cues, or memory products, from which to select and elaborate upon. The presence of irrelevant cues included during source retrieval increases the chances of selecting an inappropriate choice, but could result in more prominent, albeit incorrect monitoring outcomes. Together, these three theories of cognitive aging can be applied broadly and provide a basis for the general types of declines and changes that can be seen across domains with increasing age.

A theory of aging specific to the domain of memory is the *recollection deficit theory*. This theory applies specifically to declarative memory, a branch of memory systems dedicated to remembering things that can be consciously recalled and explicitly stated (See Figure 1 for an overview of memory systems). Recognition memory can be discussed in terms of memory for items or for source, which is the specific information associated with the "where, when and who" of an event. Recognition is comprised of two separate processes; recollection, which involves retrieval of an event along with its specific contextual details, or familiarity, which is the mere feeling that an event occurred without any accompanying details (Brown and Aggleton 2001; Eichenbaum, Yonelinas et al. 2007). The *recollection deficit theory* specifically attributes the deficits seen in recognition memory to a decline of recollection performance (Yonelinas 2002; Dennis and Cabeza 2008). The *remember-know* paradigm is primarily used to distinguish recollection from familiarity (Tulving 1985). In this paradigm, subjects are instructed to distinguish their responses as those they remember (implies recollection) and those they know (implies familiarity). It has been shown in older adults that recognition memory deficits are driven by large deficits in the recollection process (Jennings and Jacoby 1993;

Davidson and Glisky 2002; Yonelinas 2002). Because recollection memory involves strong associations between the main and contextual elements of an event, it is thought that this recollection deficit is also behind the age-related declines seen in source memory (Johnson, Hashtroudi et al. 1993). Aging is associated with a host of cognitive changes, including general slowed processing speed, reduced attention, or a lack of ability to discern relevant from irrelevant information. Problems with each of these can lead to specific problems on basic cognitive tasks.

EFFECTS OF AGE ON NEUROANATOMY

In order to fully explore the above theories of cognitive aging it is important to understand the anatomical and functional changes that healthy aging imposes on the brain itself. As with any other organ, the brain and its various systems deteriorate as a function of healthy aging. Overall, changes in cortical brain volume are seen throughout the lifespan, but the decline increases after age 50. Similarly, the ventricles begin enlarging at increased rates after the age of 70 (Raz, Lindenberger et al. 2005; Dennis and Cabeza 2008). However, the rate of atrophy is not constant across areas of the cortex; structural imaging studies have revealed a pattern of atrophy that identifies the frontal lobes as a major contributor to age-related changes (Pfefferbaum, Adalsteinsson et al. 2005; Raz, Lindenberger et al. 2005; Dennis and Cabeza 2008). After the frontal lobes, parietal regions show the next largest rate of atrophy in older adults, whereas the temporal and occipital regions show the smallest rate (Kemper 1994; Resnick, Pham et al. 2003). The cerebral cortex is the sheet of gray matter tissue, comprised of neuronal cell bodies, that surrounds the deeper subcortical white matter, comprised of neuronal axons. Morphological measurements of these structures have also shown that frontal regions show prominent age-related changes. Cortical thickness, or distance between the

outermost gray matter surface and the gray matter/white matter boundary has shown to change in the prefrontal cortex during middle age (the 5th and 6th decades; Salat, Buckner et al. 2004). The subcortical white matter has been explored using measures of diffusivity, quantification of the amount of free diffusion of water molecules through the tissue. The neuronal axons that make up this tissue should prohibit much of the diffusion when they are organized in a highly structured fashion. Measures of white matter diffusivity have shown a specific age-related decline in frontal regions, while posterior regions appear relatively preserved (Salat, Tuch et al. 2005; Zahr, Rohlfing et al. 2009). In addition, the development of white matter hyperintensities (WMH), which are thought to arise from both vascular and neural pathologies, are more prevalent in the frontal lobes in older adults (Dennis and Cabeza 2008).

Tasks like the Wisconsin Card Sorting Task are known to be mediated by frontal regions, and performance on these tasks have been negatively correlated with age (Shimamura 1994; Bugg, Zook et al. 2006), prefrontal cortex volume, and the number of WMHs in the frontal lobes (Gunning-Dixon and Raz 2003). Additionally, measures of frontal white matter microstructure (e.g., fractional anisotropy values, apparent diffusion coefficient) have been linked with processing speed, reasoning, and memory tasks. Together, the general pattern of age-related atrophy and performance on cognitive tasks implicate the frontal lobes as important regions of age-related change.

Along with the structural changes, patterns of brain activity across the age span have highlighted the importance of the frontal lobes by showing a decrease in occipital activation that is directly linked to an increase in prefrontal activation (Grady, Maisog et al. 1994; Davis, Dennis et al. 2008). This posterior-anterior shift in aging, dubbed PASA by Davis et al. (2008), has been explained as compensation for visual processing deficits

by the recruitment of prefrontal regions involved in higher cognitive processes. In the original observation of this pattern, older adults were matched with younger adults on accuracy but showed significantly reduced reaction times (Grady, Maisog et al. 1994). Contributing to the concept of functional compensation, Cabeza et al. (2002; 2004) developed a model of hemispheric asymmetry reduction of older adults (HAROLD model) after observing a general pattern of increased bilateral activation for a variety of functional tasks. The increased bilateral activation is mostly a result of increases in prefrontal and parietal activation of older adults. The HAROLD model can be showcased by the results of a verbal and spatial working memory task. In younger adults, activation is primarily left lateralized for verbal working memory and right lateralized for spatial working memory. Reuter-Lorenz et al. (2000) showed that older adults displayed patterns of anterior bilateral activation for both types of tasks.

Two competing mechanisms for this bilateralization in aging have been proposed: compensation and dedifferentiation. Increased bilaterality helps to counteract age-related neurocognitive deficits through the engagement of additional neural resources to maintain task performance reflecting compensation to the deleterious affects of aging (Cabeza, Grady et al. 1997). Older adults who display this bilateral pattern are faster at responding than adults who do not. Additionally, the older adults with bilateral activation did not show behavioral differences when compared with younger adults. These findings support the theory of increased recruitment for compensation, associating bilateralization with enhanced cognitive performance (Reuter-Lorenz, Jonides et al. 2000). Although less support has been found for the dedifferentiation theory, decreases in lateralization may merely be byproducts of aging, a reversal of the differentiation process that occurs in development (Li and Lindenberger 1999). Dedifferentiation suggests that the decreases in

lateralization may not serve any functionally beneficial role. In other words, certain regions begin to lose their task specificity with advancing age. In support of this view, cognitive measures become increasingly more inter-correlated as people get older (Baltes and Lindenberger 1997). This intercorrelation has been interpreted as a movement away from groups of distinct cognitive capacity and into a fluid general ability (Cabeza 2002).

Undoubtedly, there are numerous effects from healthy aging that can influence the cognitive process. Previous work has demonstrated that there are reliable age-related structural and functional changes in the frontal lobes, and these have been associated with widespread cognitive declines experienced with advancing age.

NEURAL ARCHITECTURE OF MEMORY MONITORING

A coordinated neural network has been proposed for assessment of episodic memory contents that is consistent with the proposed cognitive framework. This network includes structures in the medial temporal lobe (MTL; Schnyer, Nicholls et al. 2005; Chua, Schacter et al. 2006), parietal lobe (Maril, Simons et al. 2003; Chua, Schacter et al. 2006), and prefrontal cortex (PFC; Wagner, Maril et al. 2001; Kikyo, Ohki et al. 2002; Maril, Simons et al. 2003; Schnyer, Verfaellie et al. 2004; Schnyer, Nicholls et al. 2005; Chua, Schacter et al. 2006; Chua, Schacter et al. 2009) The literature is rich with studies showing medial temporal lobe contributions to accurate memory retrieval. The process of recognition memory can be separated into recollection and familiarity (see Figure 1b for an overview), and there is a dissociation in the neural structures that support the dual-processes. The hippocampus and posterior parahippocampal gyrus have been shown to be active for items that were recollected, whereas the anterior parahippocampal gyrus and entorhinal cortex are active during item recognition based on familiarity (Ranganath and Rainer 2003; Daselaar, Fleck et al. 2006).

The prefrontal cortex (PFC) has been shown to play many strategic roles in mediating the retrieval process. The ventral medial prefrontal cortex (VMPC) supports accurate monitoring and evaluation of episodic memory retrieval (Moscovitch and Winocur 2002), shown through lesion studies (Schnyer, Verfaellie et al. 2004) as well as fMRI analysis (Schnyer, Nicholls et al. 2005; Chua, Schacter et al. 2006; Modirrousta and Fellows 2008). Using fMRI, Schnyer and colleagues (2005) showed activation in the VMPC for accurate episodic monitoring judgments irrespective of retrieval success. Damage to the VMPC has previously been linked to the prevalence of confabulations (Gilboa, Alain et al. 2006), described as an inability to monitor the contextual appropriateness of retrieved memories, and thus the role of the VMPC appears to be tightly coupled with the ability to monitor one's memory retrieval, or the "felt-rightness" of one's memory (Moscovitch and Winocur 2002).

Prior work has delineated the lateral prefrontal cortex into separable regions, whereby the dorsolateral prefrontal cortex monitors and aids in selection of goal-relevant information that is maintained by the ventrolateral prefrontal cortex (Wagner, Maril et al. 2001). Further, the inferior frontal gyrus (IFG) has been implicated in cue specification, a process that involves specific comparisons between the retrieval cue and the characteristics of the possible source, which can help to trigger memory contents and aid in memory judgments (Wagner, Gais et al. 2001; Dobbins, Foley et al. 2002; Kikyo, Ohki et al. 2002; Buckner 2003). The IFG has also been implicated in the process of semantic selection, which involves choosing between closely competing alternatives (Hirshorn and Thompson-Schill 2006). In studies of memory monitoring the IFG is specific to monitoring processes, and is not recruited for successful recall. This has been shown in

fMRI studies using both feeling-of-knowing paradigms (Kikyo, Ohki et al. 2002) and confidence ratings (Chua, Schacter et al. 2006).

In one study, Chua et al., (Chua, Schacter et al. 2006) recruited a group of 20 young subjects (age range = 20-33) and collected confidence ratings associated with a face-name recognition fMRI paradigm. During each study phase pictures of 4 faces were shown accompanied with a name. Participants were instructed to learn the face-name pair for a subsequent memory test. A delay of approximately 5 minutes separated the study phase from the test phase, where subjects were shown a previously seen face along with 3 name choices (recognition), and asked to select the correct name. Immediately following this selection subjects were asked to rate their confidence in their answer, as either high or low. The task was presented using a mixed block/event-related design type, interleaving the study and test phases, and presenting many "blocks" of this pattern. In total, each subject was shown 120 stimuli during the course of the experiment. Functional activation analysis compared the confidence rating trials to the recognition trials in order to uncover differential activation for memory monitoring processes. A neural network including medial and lateral parietal regions and right orbital frontal regions was revealed for the confidence rating trials. In addition, they compared high confidence trials to low confidence trials, revealing a network of limbic structures – hippocampus, parahippocampal gyrus, amygdala, thalamus, cingulate, and medial prefrontal cortex – whose activation modulated confidence levels. These results demonstrate a unique network for monitoring processes that is different from the structures used for strict recognition memory (Chua, Schacter et al. 2006).

Much attention has been placed on the MTL for its role in the encoding, storage, and retrieval of memories, this evidence suggests that PFC plays an important role in

assessment and monitoring at the retrieval stage. Additionally, the inferior and lateral PFC regions support the identification, selection, and inhibition of contextual details of episodic memory. This is a critical component for memory monitoring, and individuals who are unable to recruit these regions, will likely show impairments with accurate monitoring.

While this network of regions associated with memory monitoring has been relatively well studied in young adults, to date there has been little work investigating the functional neuroanatomy of the age-related changes in memory monitoring abilities. One recent study (Chua, Schacter et al. 2009), investigated the neural basis of confidence ratings for both younger and older adults. Both groups showed similar patterns of activation for low-confidence items greater than high-confidence items, namely in a fronto-parietal network. However, only younger adults showed any activation for items of high-confidence greater than low-confidence. These results suggest that older adults maintain their mechanisms of uncertainty (low-confidence greater than high-confidence), but have an altered mechanism for high-confidence items. According to this study, and in agreement with others (Kelley and Nairne 2003; Dodson and Krueger 2006; Dodson, Bawa et al. 2007; Dodson, Bawa et al. 2007), older adults are prone to more high-confidence errors, or moments when they are very sure but are subsequently wrong. These high-confidence errors are thought to be caused by older adults tendency to recombine inaccurate contextual details into salient events, leading to higher feelings of confidence (Dodson and Krueger 2006; Dodson, Bawa et al. 2007). This study suggests that older adults experience an alteration in the neural network responsible for high-confidence monitoring, and thus have a tendency towards a greater number of high-confidence mistakes than younger adults.

Older adults undergo many changes that may affect their memory monitoring ability. Cognitively, these adults have more difficulty with cue selection or inhibition of extraneous information, which can lead to improper assessment of memory contents. Recombining contextual details into inaccurate episodic memories can lead older adults to have significantly high feelings of confidence in their memories, despite their inaccuracy. Neuroanatomically, the inferior and lateral regions of the prefrontal cortex support these processes of inhibition and selection, but are prime regions of age-related atrophy and change. Older adults may have trouble recruiting these regions during memory monitoring, which may be the cause of their decreased performance.

GENETIC CONTRIBUTIONS TO BRAIN STRUCTURE AND MEMORY FUNCTIONING

Beyond brain function, research from twin studies suggests that genetic factors account for as much as 50% of the variability seen in memory performance (Sabb, Burggren et al. 2009). In their recent meta-analysis, Sabb et al. (2009) explored models of the phenotypes "memory" and "intelligence" based on current candidate gene literature. They uncovered several, albeit small, contributions from candidate genes to these phenotypes. Particularly in older adults, where individual variability in cognitive performance is so large, the contributions of these candidate genes could prove informative. While sometimes conflicting, Sabb et al. (2009) note that there have been reported effects of the serotonin transporter gene (5-HTT) on memory performance.

Serotonin systems and their controlling genetics, have been a recent target for treatment of memory disorders, including both amnesia and Alzheimer's disease (Perez-Garcia and Meneses 2008), offering evidence for a potential mediating relationship between serotonin levels and memory functioning. Findings have shown that enhancing brain serotonin activity improved memory in animals (Haider, Khaliq et al. 2006) and in

normal older adults, patients with AD (Porter, Lunn et al. 2003; Schmitt, Wingen et al. 2006) and patients with schizophrenia (Levkovitz, Ophir-Shaham et al. 2003). There have been studies linking the serotonin receptor genotype (5-HT2a) to memory performance, showing that heterozygotes for the 5-HT2a gene had poorer performance on tasks that involved 30 minute delayed recall (Wagner, Gais et al. 2001; de Quervain, Henke et al. 2003; Koppel and Goldberg 2009). Additionally, there is evidence from positron emission tomography that older adults have a reduced number of serotonin receptors in the prefrontal cortex and medial temporal lobe (Sheline, Mintun et al. 2002). These studies highlight the possible relationship between serotonin levels and memory performance and indicate that this could have an impact for older adults, who tend to show a decline in serotonin receptors in neural structures that are crucial for memory function. Further understanding the role serotonin has in memory performance of older adults could help to identify additional causes for the variety of individual differences seen in that population.

The serotonin transporter, 5-HTT, is ultimately responsible for determining the duration and intensity of serotonin communication with post-synaptic receptors and targets. This communication is regulated by controlling the reuptake of serotonin to the presynaptic neuron for recycling or degradation after serotonin release. Importantly, the efficiency with which the 5-HTT returns serotonin to the presynaptic neuron appears to be influenced by a polymorphism of the serotonin transporter linked promoter region (5-HTTLPR) polymorphism. This common deletion polymorphism results in 2 variants: a short (S) allele and a long (L) allele. The presence of one or two S alleles, rather than two copies of the L allele, is associated with reduced transcriptional efficiency that putatively results in significant decreases (approximately 50%) in serotonin reuptake (Caspi,

Sugden et al. 2003; Hu, Oroszi et al. 2005). While the 5-HTTLPR genotype has been typically studied in relation to mood disorders, we have presented a number of reasons to think it may impact memory function.

Correlations between 5-HTTLPR and structural aspects of the neural network involved in memory monitoring have been demonstrated. Recent work from our lab has shown that development of the white matter microarchitecture along a tract connecting the MTL to PFC is significantly affected by genotype for the 5-HTTLPR serotonin transporter gene (Pacheco, Beevers et al. 2009). Importantly, there is a strong relationship between the number of low-expressing 5-HTTLPR alleles and the measure of fractional anisotropy of the frontal portion of the uncinate for a population of healthy adolescent and college-aged women. Further, 5-HTTLPR genotype has been shown to modulate the association of lateral prefrontal cortex volume and cognitive control mechanisms associated with shifting attention away from emotionally salient but irrelevant stimuli (Beevers, Pacheco et al. 2009). Carriers of the short allele show an association of lateral PFC volume and biased attention. This process of focusing attention away from irrelevant stimuli has been shown to be crucial for successful memory monitoring and is declined for older adults. The connection between 5-HTTLPR and these cortical structures could be important in the investigation of memory monitoring. These structural findings, coupled with the influence of serotonin on memory performance, indicate that there may be an influence of this genotype on memory monitoring ability. To date, there has been no investigation integrating 5-HTTLPR genotype and age related declines in metamemory functioning.

SUMMARY

In sum, healthy aging imposes many changes to critical brain regions and pathways that support the memory monitoring process. The goal of this project is to further understand the relationship between functional activation, structure changes, and biological influences that are related to the well-characterized behavioral difference in memory monitoring ability of older adults. In order to reach this goal I have designed and implemented an item and source memory task, in which participant's responses indicate their level of confidence in their choice. The task is designed to increase the need for careful cue selection and inhibitory control by using two competing sources. Using fMRI, I will explore the underlying neural network of accurate memory monitoring, focused on activation in lateral and inferior PFC regions, known to be crucial to selection and inhibition processes. I will explore the contributions of regional brain volume, particularly of the PFC and temporal lobe, and the effects on accurate memory monitoring. Lastly, I will include 5-HTTLPR status, and begin to explore the effects of this gene on memory monitoring performance in older adults. As this gene is known to have an effect on PFC structure, I expect to see some influence in memory monitoring as well.

Chapter 2: Methods

This chapter includes method and data collection information that is common to all the presented studies. In general, the presented studies relied on the same cognitive task and data collection methods. Subjects were enrolled in either the younger group (between 18 and 30 years old) or the older group (over 60 years old). Older adults underwent an extensive neuropsychological battery to ensure they were free from memory or other cognitive impairments. All subjects, young and old, underwent a scanning session where both structural and functional scans were collected. During the functional scans participants engaged in a memory monitoring task modeled after Dodson, et. al (2007). Saliva samples were collected at the scan session, or at another time, from which genotype for the 5-HTTLPR, and other commonly examined genes, were determined.

PARTICIPANTS

Participants were recruited from the greater Austin community, were all right-handed, healthy individuals and were paid $25 per hour for participating in the imaging session. All participants were free from psychological and neurological illness, none were taking medications with known central nervous system effects, and all were screened for contraindications to MRI. Each subject provided written informed consent approved by the Institutional Review Board at the University of Texas at Austin. Individuals enrolled in the older group underwent a comprehensive neuropsychological battery during an initial visit, separate from the imaging session. The battery of tests was designed to assess general intellectual ability (Weschler Adult Intelligence Scale Third Edition Vocabulary, Information, Similarities, Arithmetic, and Letter-Number Sequencing subtests: Wechsler

1997), memory (California Verbal Learning Test: Delis, Kramer et al. 1987; Weschler Memory Scale Third Edition Logical Memory and Visual Reproduction subtests: Wechsler 1997), mood (Geriatric Depression Scale: Brink, Yesavage et al. 1982), and executive functioning and mental flexibility (Stroop Color-Word Test: Stroop 1935; Wisconsin Card Sorting Task: Heaton 1981; Trail Making Test A&B, Controlled Oral Word Association: Lesak 1995). The tests were administered in a single two-hour session, in the same basic order to all subjects. The standard, age appropriate, published norms were used to calculate standardized scores for each subject. All older adults who were consistently greater than 1 SD below normal performance across each neuropsychological domain we excluded from the study. Table 1 shows all subjects neuropsychological scores, including raw scores (or WAIS standardized where appropriate) and a standard z-score for each test administered. Table 1 also includes group means for the specific subsample used in each analysis reported in the remaining chapters.

Table 1. Neuropsychological test scores by subject.

	Demographics				Working Memory			
Subject	Age	Education	Gender	5-HTTLPR Genotype	Digits Total Score	Letter/Number Sequencing	WAIS-III Arithmetic	WAIS-Working Memory Index
1	62	18	F	L/L	15 (1.7)	13 (1.0)	10 (0.0)	115 (0.9)
2	64	22	M	L/S	9 (-0.2)	14 (1.3)	13 (1.0)	111 (0.6)
3	64	18	F	L/S	18 (2.5)	15 (1.7)	16 (2.1)	141 (2.6)
4	65	20	M	L/S	19 (2.5)	15 (1.7)	16 (2.1)	144 (2.8)
5	61	16	M	L/S	9 (-0.2)	10 (0.0)	11 (0.3)	99 (-0.2)
6	65	18	F	n/a	19 (2.5)	18 (2.5)	13 (1.0)	144 (2.8)
7	76	13	F	n/a	10 (0.0)	14 (1.3)	11 (0.3)	109 (0.5)
8	61	16	F	L/L	10 (0.0)	13 (1.0)	10 (0.0)	106 (0.3)
9	72	16	F	S/S	17 (2.5)	14 (1.3)	11 (0.3)	124 (1.4)
10	62	18	M	L/L	14 (1.3)	17 (2.5)	14 (1.3)	130 (1.9)
11	81	18	F	L/L	10 (0.0)	9 (-0.2)	7 (-1.0)	92 (-0.7)
12	79	14	F	L/S	9 (-0.2)	13 (1.0)	13 (1.0)	109 (0.5)
13	61	20	M	L/L	18 (2.5)	17 (2.5)	13 (1.0)	139 (2.5)
14	64	16	F	L/L	11 (0.3)	10 (0,0)	13 (1.0)	108 (0.4)
15	76	18	F	L/S	10 (0.0)	9 (-0.2)	14 (1.3)	106 (0.3)
16	75	17	M	L/S	11 (0.3)	13 (1.0)	15 (1.7)	117 (1.0)
17	72	18	F	L/S	18 (2.5)	14 (1.3)	16 (2.1)	139 (2.5)
18	74	12	M	L/S	10 (0.0)	9 (-0.2)	16 (2.1)	109 (0.5)
19	61	18	M	L/S	11 (0.3)	13 (1.0)	11 (0.3)	109 (0.5)
20	60	12	M	L/S	9 (-0.2)	13 (1.0)	11 (0.3)	106 (0.3)
21	65	13	M	L/L	10 (0.0)	11 (0.3)	13 (1.0)	108 (0.4)
22	70	19	M	L/L	12 (0.7)	10 (0.0)	12 (0.7)	108 (0.4)
23	68	13	F	L/L	11 (0.3)	3 (-2.7)	5 (-1.7)	78 (-1.6)
24	60	18	M	L/S	9 (-0.2)	8 (-0.6)	16 (2.1)	106 (0.3)
25	64	14	M	L/S	8 (-0.6)	8 (-0.6)	12 (0.7)	95 (-0.4)
26	60	18	F	L/S	7 (-1.0)	8 (-0.6)	9 (-0.2)	88 (-0.9)

Table 1 continued.

27	68	18	M	L/S	9 (-0.2)	9 (-0.2)	10 (0.0)	95 (-0.4)
28	63	16	F	L/S	12 (0.7)	14 (1.3)	9 (-0.2)	109 (0.5)

Average Scores

	Age	Education	Gender	5-HTTLPR Genotype	Digits Total Score	Letter/Number Sequencing	WAIS-III Arithmetic	WAIS-Working Memory Index
Total Sample								
				9 L/L; 16				
OA	67	16.7	14F/14M	L/S; 1 S/S	11.96 (0.64)	11.93 (0.78)	12.14 (0.74)	112.29 (0.70)
CAR	67	16.8	7F/10M		11.47 (0.5)	11.71 (0.60)	12.88 (1.0)	112.18 (0.70)
NC	66	16.8	5F/4M		12.33 (0.76)	11.44 (0.89)	10.78 (0.26)	109.33 (0.50)
fMRI Sample								
				6 L/L; 13				
OA	68	16.5	9F/11M	L/S; 1 S/S	11.55 (0.52)	11.25 (0.60)	11.90 (0.66)	109.55 (0.52)
CAR	68	16.5	6F/9M		11.43 (0.49)	11.57 (0.56)	12.71 (0.94)	111.43 (0.65)
NC	68	16.5	3F/4M		11.83 (0.58)	10.50 (0.72)	10.00 (0.00)	105.17 (0.22)
Morphometry Sample								
				7 L/L; 15				
OA	67	16.4	11F/12M	L/S; 1 S/S	11.70 (0.54)	11.35 (0.60)	12.00 (0.69)	110.35 (0.57)
CAR	67	16.3	6F/9M		11.20 (0.41)	11.33 (0.48)	12.67 (0.93)	110.33 (0.58)
NC	67	16.4	4F/3M		11.71 (0.54)	10.43 (0.60)	10.43 (0.14)	105.57 (0.24)
DTI Sample								
				9 L/L; 12				
OA	67	16.6	8F/14M	L/S; 1 S/S	11.41 (0.48)	11.41 (0.65)	12.09 (0.70)	109.73 (0.53)
CAR	68	16.5	3F/10M		10.7 (0.29)	11.38 (0.50)	13.00 (1.02)	110.00 (0.55)
NC	64	16.6	5F/4M		12.6 (0.85)	11.75 (1.04)	11.25 (0.41)	111.50 (0.65)
Behavioral Sample								
				7 L/L; 14				
OA	67	16.5	10F/12M	L/S; 1 S/S	11.52 (0.50)	11.19 (0.57)	11.95 (0.68)	109.48 (0.51)
CAR	68	16.5	6F/9M		11.43 (0.49)	11.57 (0.56)	12.71 (0.94)	111.43 (0.65)
NC	67	16.4	4F/3M		11.71 (0.54)	10.43 (0.60)	10.43 (0.14)	105.57 (0.24)

Table 1 continued.

	Executive Function						
Subject	Trails A Time	Trails B Time	Stroop Interference	FAS	WCST Categories	WCST Errors	WCST Perseveration
1	39 (0.27)	72 (-0.24)	-7.8 (-0.8)	46 (0.33)	n/a	n/a	n/a
2	33 (-0.24)	132 (1.32)	-12.4 (-1.4)	42 (0.00)	1 (-2.14)	63 (-1.70)	45 (-1.90)
3	37 (0.10)	42 (-1.02)	10.2 (1.0)	47 (0.41)	6 (0.80)	11 (0.400	5 (0.30)
4	20 (-1.33)	69 (-0.32)	20.5 (2.0)	52 (0.83)	n/a	n/a	n/a
5	40 (0.35)	58 (-0.60)	-1.2 (-0.17)	40 (-0.17)	6 (0.80)	12 (0.50)	8 (0.30)
6	21 (-1.24)	34 (-1.23)	12.5 (1.2)	46 (0.33)	6 (0.82)	8 (1.00)	5 (0.70)
7	36 (-0.63)	58 (-1.22)	-2.1 (-0.4)	42 (0.00)	0 (-1.86)	98 (-1.90)	56 (-1.50)
8	36 (0.02	50 (-0.81)	2.4 (0.2)	31 (-0.91)	6 (0.80)	8 (0.60)	6 (0.30)
9	36 (-0.35)	50 (-0.85)	9.0 (0.8)	31 (-0.91)	6 (1.24)	31 (0.50)	13 (1.00)
10	35 (-0.07)	50 (-0.81)	-2.1 (-0.4)	43 (0.08)	6 (0.80)	12 (0.30)	6 (0.30)
11	37 (-0.91)	91 (-0.74)	-2.3 (-0.4)	31 (-0.54)	3 (-0.35)	69 (-1.10)	40 (-0.90)
12	33 (-0.79)	62 (-1.14)	-7.8 (-0.8)	36 (-0.50)	6 (2.03)	16 (2.50)	7 (2.50)
13	19 (-1.41)	65 (-0.42)	6.1 (0.6)	45 (0.25)	6 (0.80)	19 (-0.10)	9 (0.00)
14	46 (0.86)	113 (0.83)	3.6 (0.2)	48 (0.50)	5 (0.21)	50 (-1.300	18 (-0.50)
15	44 (-0.18)	77 (-0.84)	-0.3 (-0.2)	55 (1.07)	6 (2.03)	9 (2.50)	6 (2.10)
16	60 (0.72)	109 (-0.21)	7.5 (0.6)	35 (-0.58)	6 (2.03)	8 (2.50)	5 (2.50)
17	24 (-1.15)	58 (-0.74)	1.0 (0.0)	48 (0.50)	6 (1.24)	10 (1.30)	6 (1.00)
18	44 (0.18)	93 (-0.25)	4.2 (0.4)	30 (-0.45)	6 (1.24)	11 (2.50)	6 (2.50)
19	37 (0.10)	47 (-0.89)	-1.2 (-0.2)	41 (-0.08)	6 (0.80)	9 (0.50)	6 (0.30)
20	29 (-0.57)	101 (0.51)	6.6 (0.6)	46 (0.83)	6 (0.80)	7 (1.80)	4 (1.50)
21	21 (-1.24)	46 (-0.91)	-2.8 (-0.4)	35 (-0.58)	6 (0.80)	11 (1.50)	6 (1.30)
22	34 (-0.49)	55 (-0.78)	Color Blind	31 (-0.91)	Color Blind	Color Blind	Color Blind
23	43 (0.61)	87 (0.15)	22.8 (2.2)	30 (-0.99)	6 (0.80)	16 (1.00)	9 (0.80)
24	21 (-1.24)	36 (-1.17)	11.7 (1.0)	45 (0.25)	6 (0.80)	28 (1.50)	12 (1.90)
25	57 (1.78)	213 (3.42)	-2.1 (-0.4)	23 (-1.57)	6 (0.80)	13 (0.90)	5 (1.00)
26	33 (-0.24)	87 (0.15)	1.6 (0.0)	36 (-0.50)	0 (-2.73)	44 (-1.20)	17 (-0.60)
27	35 (-0.07)	71 (-0.26)	2.7 (0.2)	26 (-1.32)	6 (0.80)	19 (0.20)	11 (0.10)
28	42 (0.00)	19 (-1.2)	10.0 (0.8)	63 (1.74)	6 (0.80)	7 (0.90)	4 (0.70)

Table 1 continued.

	Average Scores						
	Trails A Time	Trails B Time	Stroop Interference	FAS	WCST Categories	WCST Errors	WCST Perseveration
Total Sample							
OA	35.43 (-0.26)	73.04 (-0.38)	3.34 (0.23)	40.14 (-0.10)	5.16 (0.57)	23.56 (0.62)	12.60 (0.63)
CAR	36.76 (-0.17)	77.88 (-0.27)	3.52 (0.25)	40.94 (-0.03)	5.31 (0.71)	18.63 (0.98)	10.00 (0.95)
NC	34.44 (-0.26)	69.89 (-0.42)	2.50 (0.15)	37.78 (-0.31)	5.43 (0.55)	26.43 (0.13)	13.43 (0.19)
fMRI Sample							
OA	34.40 (-0.40)	66.55 (-0.59)	4.76 (0.38)	39.35 (-0.15)	5.50 (0.82)	18.56 (0.99)	9.72 (0.96)
CAR	35.57 (-0.33)	66.93 (-0.59)	4.59 (0.36)	41.71 (0.05)	5.54 (0.91)	16.23 (1.23)	8.08 (1.22)
NC	31.67 (-0.57)	65.67 (-0.59)	5.25 (0.44)	33.83 (-0.61)	5.40 (0.57)	24.60 (0.38)	14.00 (0.30)
Morphometry Sample							
OA	35.30 (-0.29)	73.52 (-0.38)	4.75 (0.37)	39.30 (-0.16_	5.52 (0.79)	19.29 (0.88)	9.67 (0.88)
CAR	37.00 (-0.19)	76.67 (-0.32)	4.14 (0.31)	40.47 (-0.06)	5.57 (0.91)	16.00 (1.21)	7.86 (1.20)
NC	33.71 (-0.37)	72.43 (-0.38)	4.98 (0.40)	35.86 (-0.45)	5.33 (0.51)	28.83 (0.10)	14.67 (0.17)
DTI Sample							
OA	36.32 (-0.18)	79.41 (-0.23)	2.73 (0.17)	38.27 (-0.24)	5.53 (0.79)	21.63 (0.79)	11.68 (0.79)
CAR	37.62 (-0.13)	86.00 (-0.10)	2.86 (0.18)	38.62 (-0.20)	5.58 (0.94)	18.83 (1.18)	10.67 (1.15)
NC	34.13 (-0.18)	67.25 (-0.37)	3.19 (0.23)	38.63 (-0.28)	5.83 (0.70)	19.33 (0.33)	9.00 (0.37)
Behavioral Sample							
OA	34.95 (-0.34)	68.76 (-0.52)	4.71 (0.37)	39.76 (-0.12)	5.47 (0.79)	20.21 (0.87)	10.16 (0.88)
CAR	35.57 (-0.33)	66.93 (-0.59)	4.59 (0.36)	41.71 (0.05)	5.54 (0.91)	16.23 (1.23)	8.08 (.122)
NC	33.71 (-0.37)	72.43 (-0.38)	4.98 (0.40)	35.86 (-0.45)	5.33 (0.51)	28.83 (0.10)	14.67 (0.17)

Table 1 continued.

	Verbal IQ				Mood	
Subject	WAIS Information	WAIS Vocabulary	WAIS Similarities	Verbal IQ	GDS Score	GDS Rating
1	13 (1.00)	13 (1.00)	11 (1.00)	115	3.00	normal
2	16 (2.10)	16 (2.10)	13 (2.10)	122	17.00	mild depression
3	13 (1.00)	13 (1.00)	17 (1.00)	137	1.00	normal
4	15 (1.70)	15 (1.70)	13 (1.70)	138	7.00	normal
5	13 (1.00)	10 (0.00)	11 (0.00)	103	1.00	normal
6	15 (1.70)	14 (1.30)	11 (1.30)	134	7.00	normal
7	11 (0.30)	8 (-0.60)	8 (-0.60)	101	1.00	normal
8	11 (0.300	11 (0.30)	11 (0.30)	105	11.00	mild depression
9	11 (0.30)	11 (0.30)	12 (0.30)	116	11.00	mild depression
10	17 (2.50)	16 (2.10)	16 (2.10)	139	3.00	normal
11	13 (1.00)	12 (0.70)	10 (0.70)	100	8.00	normal
12	10 (0.00)	13 (1.00)	11 (1.00)	108	2.00	normal
13	14 (1.30)	17 (2.50)	18 (2.50)	143	1.00	normal
14	17 (2.50)	16 (2.10)	16 (2.10)	124	9.00	normal
15	12 (0.70)	12 (0.70)	10 (0.70)	106	4.00	normal
16	15 (1.70)	13 (1.00)	18 (1.00)	127	4.00	normal
17	17 (2.50)	17 (2.50)	12 (2.50)	139	1.00	normal
18	11 (0.30)	7 (-1.00)	12 (-1.00)	104	2.00	normal
19	16 (2.10)	14 (1.30)	16 (1.30)	122	0.00	normal
20	14 (1.30)	11 (0.30)	14 (0.30)	112	3.00	normal
21	15 (1.70)	11 (0.30)	15 (0.30)	115	2.00	normal
22	16 (2.10)	10 (0.00)	11 (0.00)	111	1.00	normal
23	14 (1.30)	14 (1.30)	15 (1.30)	101	7.00	normal
24	16 (2.10)	14 (1.30)	12 (1.30)	115	5.00	normal
25	13 (1.00)	11 (0.03)	14 (0.30)	105	9.00	normal
26	11 (0.30)	8 (-0.60)	12 (-0.60)	94	2.00	normal
27	11 (0.30)	13 (1.00)	11 (1.00)	102	1.00	normal
28	13 (1.00)	13 (1.00)	17 (1.00)	118	8.00	normal

Table 1 continued.

Average Scores

	WAIS Information	WAIS Vocabulary	WAIS Similarities	Verbal IQ	GDS Score
Total Sample					
OA	13.68 (1.25)	12.61 (0.89)	13.11 (0.89)	116.29	4.68
CAR	13.35 (1.14)	12.41 (0.82)	13.24 (0.82)	115.76	4.59
NC	14.44 (1.52)	13.33 (1.14)	13.67 (1.14)	117.00	5.00
fMRI Sample					
OA	13.40 (1.15)	12.30 (0.78)	13.05 (0.78)	113.95	4.05
CAR	13.21 (1.09)	12.21 (0.75)	12.93 (0.75)	114.57	3.64
NC	13.83 (1.28)	12.50 (0.85)	13.33 (0.85)	112.50	5.00
Morphometry Sample					
OA	13.61 (1.23)	12.48 (0.84)	13.13 (0.84)	114.87	4.61
CAR	13.20 (1.09)	12.13 (0.72)	13.00 (0.72)	113.93	4.00
NC	14.29 (1.46)	13.00 (1.03)	13.71 (1.03)	114.14	5.57
DTI Sample					
OA	13.77 (1.29)	12.73 (0.92)	13.18 (0.92)	115.14	5.05
CAR	13.31 (1.12)	12.31 (0.77)	12.85 (0.77)	113.85	5.08
NC	14.63 (1.59)	13.50 (1.20)	14.13 (1.20)	119.13	4.63
Behavioral Sample					
OA	13.57 (1.21)	12.48 (0.84)	13.19 (0.84)	114.43	4.29
CAR	13.21 (1.09)	12.21 (0.75)	12.93 (0.75)	114.57	3.64
NC	14.29 (1.46)	13.00 (1.03)	13.71 (1.03)	114.14	5.57

Table 1 continued.

	Memory Function								
Subject	CVLT Trials 1-5	CVLT Imm. Recall	CVLT Cued Recall	CVLT Delayed Recall	CVLT Delayed Cued Recall	WMS-III logical mem imm recall	WMS-III logical mem 30 min recall	Visual Reproduction Immediate	Visual Reproduction Delay
1	64 (66)	14 (1.50)	15 (1.5)	15 (1.5)	15 (1.0)	12 (0.7)	12 (0.7)	6 (-1.3)	9 (-0.2)
2	50 (59)	8 (0.00)	10 (0.0)	10 (0.5)	12 (0.5)	13 (1.0)	12 (0.7)	9 (-0.2)	10 (0.0)
3	71 (73)	16 (2.00)	16 (1.5)	16 (1.5)	16 (1.5)	15 (1.7)	16 (2.1)	10 (0.0)	14 (1.3)
4	47 (55)	12 (1.00)	11 (0.5)	13 (1.5)	13 (1.0)	14 (1.3)	17 (2.5)	9 (-0.2)	12 (0.7)
5	42 (49)	9 (0.00)	10 (0.0)	11 (1.0)	10 (0.0)	8 (-0.6)	8 (-0.6)	12 (0.7)	10 (0.0)
6	55 (57)	12 (1.00)	13 (0.5)	13 (0.5)	13 (0.5)	14 (1.3)	14 (1.3)	15 (1.7)	12 (0.7)
7	48 (53)	8 (0.00)	10 (-0.5)	7 (-0.5)	10 (-0.5)	10 (0.0)	12 (0.7)	7 (-1.0)	9 (-0.2)
8	51 (53)	15 (2.00)	15 (1.5)	13 (0.5)	14 (1.0)	9 (-0.2)	12 (0.7)	12 (0.7)	13 (1.0)
9	51 (56)	15 (1.50)	15 (1.5)	13 (1.0)	14 (1.0)	10 (0.0)	13 (1.0)	13 (1.0)	15 (1.7)
10	64 (74)	13 (1.50)	13 (1.0)	14 (2.0)	15 (2.0)	15 (1.7)	13 (1.0)	8 (-0.6)	14 (1.3)
11	47 (57)	12 (1.50)	14 (1.5)	14 (1.5)	14 (1.5)	13 (1.0)	15 (1.7)	9 (-0.2)	10 (0.0)
12	63 (68)	14 (1.5)	15 (1.5)	15 (1.5)	13 (0.5)	7 (-1.0)	17 (2.5)	10 (0.0)	14 (1.3)
13	56 (66)	12 (1.00)	14 (1.5)	11 (1.0)	14 (1.5)	12 (0.7)	15 (1.7)	13 (1.0)	13 (1.0)
14	49 (51)	10 (0.00)	13 (0.5)	12 (0.5)	14 (1.0)	14 (1.3)	16 (2.1)	11 (0.30)	7 (-1.0)
15	55 (60)	9 (0.00)	12 (0.5)	11 (0.5)	13 (0.5)	7 (-1.0)	9 (-0.2)	8 (-0.6)	9 (-0.2)
16	58 (70)	13 (2.00)	14 (2.0)	14 (2.0)	14 (2.0)	14 (1.3)	14 (1.3)	12 (0.7)	19 (2.5)
17	68 (73)	15 (1.50)	14 (1.0)	16 (2.0)	16 (1.5)	16 (2.1)	17 (2.5)	16 (2.1)	16 (2.1)
18	53 (65)	13 (2.00)	13 (1.5)	12 (1.5)	13 (1.5)	7 (-1.0)	3.00	13 (1.0)	18 (2.5)
19	57 (67)	10 (0.50)	13 (1.0)	10 (0.5)	12 (0.5)	14 (1.3)	13 (1.0)	14 (1.3)	15 (1.7)
20	55 (65)	13 (1.50)	12 (1.0)	13 (1.5)	13 (1.0)	15 (1.7)	15 (1.7)	9 (-0.2)	15 (1.7)
21	34 (40)	7 (-0.50)	9 (-0.5)	9 (0.0)	9 (-0.5)	9 (-0.2)	12 (0.7)	8 (-0.6)	13 (1.0)
22	29 (38)	7 (0.00)	9 (0.0)	6 (-0.5)	8 (-0.5)	5 (-1.7)	6 (-1.3)	9 (-0.2)	11 (0.30)
23	62 (64)	14 (1.50)	15 (1.5)	13 (0.5)	14 (1.0)	11 (0.3)	9 (-0.2)	7 (-1.0)	11 (0.30)
24	41 (48)	9 (0.00)	12 (1.0)	7 (-0.5)	12 (0.5)	14 (1.3)	16 (2.1)	13 (1.0)	11 (0.30)
25	28 (34)	5 (-1.00)	7 (-1.0)	6 (-1.0)	8 (-0.5)	12 (0.7)	11 (0.3)	7 (-1.0)	9 (-0.2)
26	42 (44)	13 (1.00)	13 (0.5)	14 (1.0)	13 (0.5)	13 (1.0)	13 (1.0)	11 (0.30)	11 (0.3)
27	63 (73)	14 (2.00)	13 (1.0)	13 (1.5)	12 (0.5)	13 (1.0)	12 (0.7)	16 (2.1)	17 (2.5)
28	72 (74)	16 (2.00)	16 (1.5)	16 (1.5)	16 (1.5)	15 (1.7)	15 (1.7)	13 (1.0)	17 (2.5)

Table 1 continued.

	Average Scores								
	CVLT Trials 1-5	CVLT Imm. Recall	CVLT Cued Recall	CVLT Delayed Recall	CVLT Delayed Cued Recall	WMS-III logical mem imm recall	WMS-III logical mem 30 min recall	Visual Reproduction Immediate	Visual Reproduction Delay
Total Sample									
OA	52.68 (59.00)	11.71 (0.96)	12.71 (0.84)	12.04 (0.88)	12.86 (0.79)	11.82 (0.62)	12.75 (1.09)	10.71 (0.28)	12.61 (0.88)
CAR	53.88 (60.76)	12.00 (1.03)	12.71 (0.84)	12.35 (1.03)	12.94 (0.82)	12.18 (0.74)	13.00 (1.27)	11.47 (0.53)	13.59 (1.21)
NC	50.67 (56.56)	11.56 (0.94)	13.00 (0.94)	11.89 (0.78)	13.00 (0.89)	11.11 (0.40)	12.22 (0.79)	9.22 (-0.21)	11.22 (0.41)
fMRI Sample									
OA	52.30 (59.25)	12.10 (1.10)	12.95 (1.00)	12.20 (0.98)	12.85 (0.83)	11.30 (0.45)	12.55 (1.08)	11.35 (0.50)	13.45 (1.15)
CAR	54.79 (61.93)	12.50 (1.18)	13.07 (1.04)	12.71 (1.18)	13.14 (0.89)	11.93 (0.65)	13.00 (1.32)	12.07 (0.73)	14.14 (1.39)
NC	46.50 (53.00)	11.17 (0.92)	12.67 (0.92)	11.00 (0.50)	12.17 (0.67)	9.83 (-0.02)	11.50 (0.55)	9.67 (-0.05)	11.83 (0.60)
Morphometry Sample									
OA	51.22 (57.70)	11.70 (0.96)	12.70 (0.87)	11.96 (0.85)	12.70 (0.76)	11.57 (0.53)	12.70 (1.10_	11.30 (0.47)	12.91 (0.98)
CAR	53.00 (60.07)	12.00 (1.03)	12.67 (0.90)	12.27 (1.03)	12.80 (0.80)	11.93 (0.65)	12.87 (1.25)	11.73 (0.61)	13.80 (1.28)
NC	46.86 (52.71)	11.00 (0.79)	12.71 (0.87)	11.14 (0.50)	12.43 (0.71)	10.43 (0.17)	12.14 (0.77)	9.86 (0.00)	11.14 (0.37)
DTI Sample									
OA	50.86 (58.09)	11.27 (0.89)	12.45 (0.86)	11.59 (0.84)	12.55 (0.77)	11.27 (0.44)	12.27 (0.96)	10.36 (0.17)	12.45 (0.82)
CAR	51.00 (59.15)	11.08 (0.85)	12.08 (0.81)	11.38 (0.88)	12.23 (0.69)	11.38 (0.46)	12.31 (1.08)	11.15 (0.43)	13.31 (1.10)
NC	51.13 (56.50)	11.50 (0.88)	12.88 (0.88)	11.63 (0.69)	12.88 (0.81)	10.88 (0.33)	11.88 (0.68)	9.25 (-0.21)	11.38 (0.46)
Behavioral Sample									
OA	52.14 (58.86)	12.00 (1.05)	12.95 (0.98)	12.19 (0.95)	12.90 (0.83)	11.43 (0.49)	12.71 (1.13)	11.33 (0.49)	13.14 (1.05)
CAR	54.79 (61.93)	12.50 (1.18)	13.07 (1.04)	12.71 (1.18)	13.14 (0.89)	11.93 (0.65)	13.00 (1.32)	12.07 (0.73)	14.14 (1.39)
NC	46.86 (52.71)	11.00 (0.79)	12.71 (0.87)	11.14 (0.50)	12.43 (0.71)	10.43 (0.17)	12.14 (0.77)	9.86 (0.00)	11.14 (0.37)

Table 1

INCLUSION/EXCLUSION CRITERIA

The specific inclusion criteria were:

1) Between the ages of 18-30 (for the younger group) and above the age of 60 (for the older group). The onset of age-related cognitive decline varies from person to person, but has been linked to the 5th or 6th decade (ages 40-50). To ensure the exclusion of any persons already experiencing any of these effects the upper limit for the young adult group was set well below a typical age of onset. Additionally, to ensure that we will observe age-related effects in our older group, the lower age limit was set above the age of onset.
2) Right-hand dominant. There is an unpredictable neuroanatomical structure in persons who are left-hand dominant (i.e., language areas can be localized to either the left hemisphere or to the right hemisphere, whereas language areas are localized only to the left hemisphere in right-hand dominant persons); such variance would impair our ability to localize functional results from an fMRI analysis.
3) Native English speakers. Participants were fluent in English because the entire set of stimuli, instructions, and neuropsychological tests are written in English, and must be fully understood in order to be effective. In addition, there is evidence that shows neuroanatomical differences in persons who have learned English as a second language, in an attempt to keep the sample as "neurologically similar" as possible, non-native speakers were not included.

Specific exclusion criteria were:

1) Current medical problems, or past neurological or psychological problems. Participants who have experienced a stroke, seizure, extended loss of consciousness, extreme head injury, or other neurological disorder were excluded. Additionally, anyone undergoing current medical treatment for a serious illness was excluded. Neuroimaging results are sensitive to these past incidents, and current medication interactions.
2) Currently taking medications known to interact in the central nervous system. These medications include antidepressants and anti-anxiety medications, as well as others that will interfere with normal brain chemistry.
3) Contraindication for MRI. Persons who have any contraindication for MRI were excluded; this includes any ferromagnetic metal anywhere in their body, cardiac pacemakers, some tattoos, and anything else that is potentially dangerous for use in an MRI environment. All subjects were screened both over the phone at initial contact, and again prior to the scanning session at the imaging center. See Appendix C for a copy of the MR screening form.
4) Currently pregnant, or possibly pregnant. MRI is not currently performed on women who are pregnant, except in the case of extreme medical emergency, and thus anyone who is pregnant or potentially pregnant was excluded. Female subjects were asked to provide the date of their last menstrual period in order to confirm their status.

5) Self report of claustrophobia. Due to the extremely small size of the MRI scanner, any person who indicated that they have experienced claustrophobia or anxiety in small spaces was excluded.
6) Extremely poor vision or hearing. Subjects with glasses and hearing aids were excluded on a case-by-case basis. All subjects needed to be able to see comfortably in the MRI scanner, without their own glasses. We were able to provide a pair of MR-safe glasses as needed, but extreme vision deficits were hard to correct. Similarly, hearing aids were not allowed in the scanner, but the subject needed to be able to hear well enough to both perform the task, and communicate with the researchers for safety purposes. Subjects who cannot meet these criteria were excluded.

EXPERIMENTAL PROCEDURES

Prior to coming in for their initial appointment, all participants were screened over the phone to ensure that they qualify given the exclusion and inclusion criteria. At the onset of their initial visit a demographics and health history screen was administered to all participants. This questionnaire includes questions pertaining to years of education, occupation, ethnicity, smoking and drinking history, current prescription medications, previous surgeries and hospitalizations, as well as personal and familial history with certain major health issues (e.g., stroke, seizure, cancer, dementia, motor disorders).

The initial visit for the older adult group was primarily for the comprehensive neuropsychological battery. The tests were all administered in a single session in the following order: California Verbal Learning Test, Geriatric Depression Scale, WAIS-III Information subtest, WASI-III Arithmetic subtest, WAIS-III Vocabulary subtest,

California Verbal Learning Test delayed recall, WMS-III Logical Memory subtest, Stroop, Trail Making Test A&B, WAIS-III Similarities subtest, Controlled Oral Word Association, WAIS-III Digit Span subtest, WMS-III Logical Memory delayed-recall, WMS-III Visual Reproduction subtest, WAIS-III Letter/Numbering Sequencing subtest, Wisconsin Card Sorting Task computerized version, WMS-III Visual Reproduction delayed-recall.

The initial session for the younger adults was the imaging session, for the older adults this was their second session. At the beginning of the imaging session subjects completed a metal screen, approved by both the Imaging Research Center and the Institutional Review Board, to further ensure that there were no contraindications for MRI.

At this point, subjects were ready to begin scanning. The complete scan session lasted between 90 and 120 minutes and consisted of a combination of functional and structural scans. Scans were generally run in the following order: Localizer 1, Localizer 2, Hi-resolution structural scan, Functional study phase 1 (scanner not running), Function test phase 1, Functional study phase 2 (scanner not running), Function test phase 2, Hi-resolution structural scan, Functional study phase 3 (scanner not running), Function test phase 3, Functional study phase 4 (scanner not running), Function test phase 4, DTI scan.

Most subjects provided a saliva sample for genotyping (complete procedures listed below) at the completion of their scanning session. As the study progressed, some subjects provided saliva samples at the completion of their neuropsychological session. In some cases, saliva was collected in a separate session entirely.

IMAGE ACQUISITION

All scanning was performed on The University of Texas at Austin Imaging Research Center's whole body 3T GE MRI scanner with an 8-channel phase array head coil. Head motion was minimized with foam inserts and a forehead strap. Stimuli were viewed utilizing a back projection screen and a mirror mounted on the top of the head coil. MRI compatible audio headphones were used for presentation of auditory stimuli, and prior to the scan all subjects confirmed adequate hearing to a test recording. Additionally, MR safe glasses were provided as needed. Responses were collected with a single 4-button MR compatible optical transmission device, held in the participants' right hand.

Structural image acquisition

At least one high-resolution T1-weighted SPGR structural image data sets (TR = 9.7, TE = 4, flip angle = 10 degrees, slice thickness = 1.4 mm, 134 slices, FOV = 25cm and matrix size = 256x256 mm) was collected on each participant for the anatomical coregistration with functional imaging datasets and for the morphological analysis of cortical thickness and subcortical volume measurement. The SPGR scans have been empirically optimized for high contrast between GM and WM, and GM and cerebrospinal fluid (CSF).

Diffusion MRI were collected using single shot echo planar imaging, and a twice-refocused spin echo pulse sequence, optimized to minimize eddy current-induced distortions (GE 3T, TR/TE=12000/71.1, B=1000, 128x128 matrix, 3mm (0-mm gap) slice thickness, 1 T2 + 25 DWI). Forty-one slices were acquired and the diffusion tensor and fractional anisotropy were calculated on a voxel by voxel basis using conventional reconstruction methods in FSL.

Functional image acquisition

Functional EPI images using a parallel imaging approach with GRAPPA reconstruction were collected utilizing whole head coverage with slice orientation to reduce artifact (approx 20 degrees off the AC-PC plane, TR = 2 sec., TE = 30 msec., 31 axial slices oriented for best whole head coverage, acquisition voxel size = 3.125 X 3.125 X 3 mm with a .3 mm inter-slice gap). The first four EPI volumes were discarded to allow scans to reach equilibrium.

GENOTYPING

Saliva samples were collected for 22 of the older adults. Genomic DNA was isolated from buccal cells using a modification of published methods (Lench, Stanier et al. 1988; Meulenbelt, Droog et al. 1995; Spitz, Moutier et al. 1996; Freeman, Powell et al. 1997). The cheeks and gums were rubbed for 20 seconds with three sterile, cotton-tipped wooden swabs. The swabs were placed in a 50-ml capped polypropylene tube containing lysis buffer (500 µl of 1 M Tris-HCl; 200 mM disodium ethylene diaminetetracetic acid (EDTA), pH 8.0; 500 µl of 10% sodium docecyl sulfate; and 100 µl of 5 M sodium chloride). The subjects then rinsed out the mouth vigorously with 10 ml of bottled water for 20 seconds, and added this to the 50-ml tube. The tubes were stored at 4°C or less until the DNA was extracted. Polymerase chain reaction (PCR) was used for DNA amplification. The DNA was then cut using restriction digest, and the resulting fragments were used to identify the presence of a long or short allele on the 5-HTTLPR gene. Participants were characterized by the number of short 5-HTTLPR alleles present: 0, 1, or 2.

COGNITIVE TASK

A two-part memory task was used to assess memory monitoring of item and source recognition (for a schematic see Figure 3, based on a task by Dodson, Bawa et al. 2007). Part one was a study phase that was performed while the subject was in the scanner. Images were not collected during study in order to minimize the interference of scanner noise with the auditory presentation of task stimuli. Each individual study phase consisted of a series of 24 sentences, presented in a self-paced manner, read aloud by either a male or female speaker. The sentences were presented visually in the center of the screen with a photograph of the speaker presented above each sentence, and the speakers name presented clearly below their picture. Simultaneously, the sentence was presented aurally through headphones, read by either Kim, the female voice, or Dan, the male voice. Subjects were asked to provide a plausibility judgment during this phase, as proof that the sentences were being read and encoded. The sentences were all taken from the trivia book *Salted Peanuts* (McKenzie 1976), and are similar to the following example:

Eighty four percent of a raw apple is water.

The study phase was immediately followed by a test phase where twenty of the original sentences seen at study were presented, excluding the first and last two to account for primacy and recency effects. Additionally, 10 never before seen sentences were intermixed as recognition foils for a total of 30 test sentences. During the test phase, participants were presented with a test sentence and asked whether this sentence was presented in the study phase (old) or if it is a new sentence. Participants responded with one of four choices in order to indicate their old/new judgment and confidence level - *Certainly Old, Probably Old, Probably New,* and *Certainly New*. Subjects were trained prior to the task to use *Certainly* only when the answer came to mind easily, and

Probably on items they were less sure of or were guessing. Once the item recognition question was answered, the same sentence appeared again with prompts asking whom the speaker of the sentence was. Again, there were four answer choices that reflected the participant's response and confidence level: *Certainly Dan, Probably Dan, Probably Kim,* and *Certainly Kim*. In between every trial a visual fixation was presented (black cross on a white background) for 3, 5, or 7 seconds, randomly distributed. Also intermixed throughout the entire run were 10 control conditions. A string of x's was used as the functional control; one of the x's appeared in red and the participants indicated if the red x was on the *left* or *right* of the screen. This control involves visual search through a string of text and response, but lacks any memory or monitoring component. The ordering of conditions through the test run was determined randomly, but held constant for all subjects. The ordering of sentences presented during the study phase was determined randomly and varied for each subject at time of scanning.

Figure 3

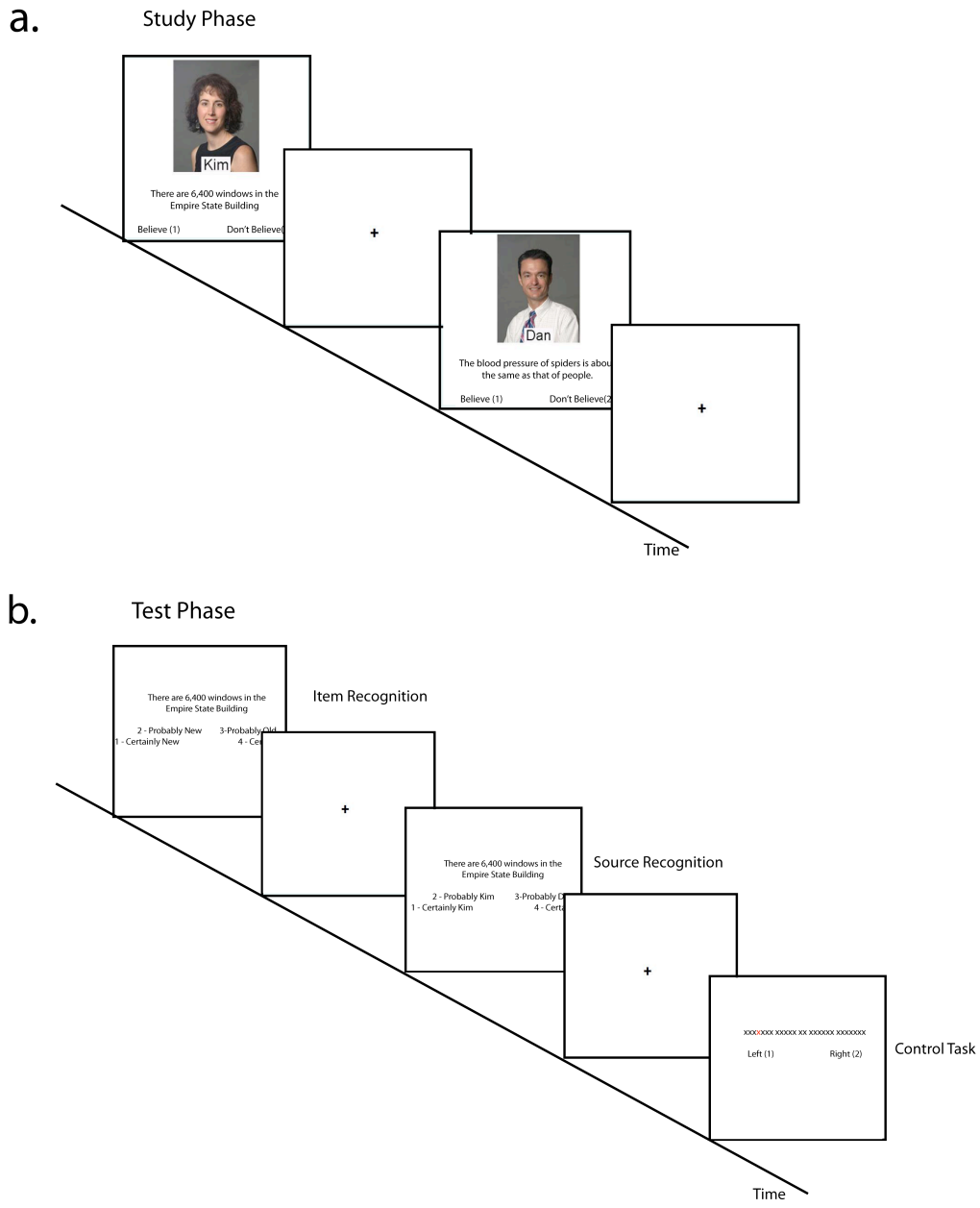


Figure 3. Schematic of Cognitive Task.

Panel **a.** depicts the study phase, during which the scanner will not be running. Subjects will see a total of 24 unique sentences per run, each separated by a variable fixation cross (3,5,or 7 seconds). Panel b. depicts the test phase, when the scanner will be running. Subjects will see 20 of the previous sentences and 10 new sentences. Included in this phase are 10 control tasks.

SUMMARY OF COLLECTED DATA

In total, 28 older adults and 20 younger adults were recruited for these studies. However, not each subject had a complete data set. Some subjects are missing scan data, either because of problems with collection (i.e., too much motion, insufficient time at scan block, subject requested to stop scanning). In each age group three subjects were excluded from the fMRI analysis: one subject in each group for extreme head motion during scanning, and two others for failure to respond during a significant portion of the task. Some subjects are missing genotype information because they could not be reached to provide a saliva sample, or the saliva sample they did provide could not be analyzed. Some subjects are missing memory monitoring accuracy scores because they did not use the full rating scale and an accuracy rate could not be calculated. The data that was collected for each subject is summarized in Appendix A.

BEHAVIORAL ANALYSIS

Behavioral responses from the fMRI task were classified according to both recognition success (correct new/old designation, correct source identification) as well as monitoring accuracy (correct determination of retrieval success). For each subject, all runs of the task were combined for analysis of behavioral responses. Each item recognition response was classified as either a true hit, true miss, false alarm or correct rejection, and a total item memory percentage was calculated, regardless of confidence rating, as: (True Hit – False Alarm) / Total Items. The source recognition responses were classified as either correct or incorrect, for all of the sentences reported as *Old*, and the source memory percentage was calculated for each subject as the proportion of correct items to total items.

To explore the accuracy of monitoring judgments, we used the percentage correct for all responses given a *Certainly* distinction. Prior to the task subjects were trained to

use this option to indicate they were highly confident, and to use the *Probably* option when they were less confident. Given this response structure, the lower-confidence answers likely contain moderate amounts of guessing, whereas the higher-confidence responses should reflect their confidence in being correct. For any individual subject, if they are accurately monitoring their source retrieval then the percentage correct for the higher-confidence response should be high.

Additionally, throughout each test phase there are 10 control conditions, where subjects report which side of the screen the colored "x" is on. These responses were scored for accuracy and used only for exclusionary purposes, any subject getting less than 70% of these conditions in a single run was excluded (for that run) on the premise of either lack of attention or understanding of the entire task. For this study, all of the subjects met this criteria.

Responses from the study phase of the task were only used to ensure that subjects were responding consistently, indicating attention and participation in this phase. Any subject who had a significant lack of responding during an individual run was excluded from analysis of the test phase for the coordinating run.

fMRI DATA ANALYSIS

Functional data analysis was primarily done using tools available through the software package FSL version 4.1 (FMRIB's Software Library, http://www.fmrib.ox.ac.uk/fsl/). Images were first motion corrected and then a high pass filter of 60 sec was used to remove low frequency drift components. Data was then resampled and spatially smoothed with a 5mm full width half maximum Gaussian kernel and rescaled to a mean signal value of 100. Finally, mean functional images for each subject were spatially normalized into the MNI (Montreal Neurological Institute)

standard brain template in order to obtain conversion matrices to apply for higher-level statistical analysis. For each run of the memory monitoring task there were a total of four cognitive conditions included in the model: Accurate Recognition (AccRec), Accurate Source (AccSrc), Inaccurate Recognition (InaccRec) and Inaccurate Source (InaccSrc). These conditions are the result of collapsing across confidence strength (e.g., High-confidence Accurate Source and Low-confidence Accurate Source were combined to form Accurate Source). This was necessary because not all participants used the full response scale which resulted in too few, or no, trials of certain types. It should be noted that these conditions are based on monitoring accuracy, and not solely on memory performance. For example, AccSrc contains responses that were rated as high confidence and answered correctly, as well as responses that were rated with low confidence and answered incorrectly. In contrast, InaccSrc contains all responses inaccurately monitored, including those responses rated with high-confidence and answered incorrectly as well as responses rated with low-confidence and answered correctly, or all responses inaccurately monitored. Also modeled were fixation (FIX), control (CONT) task conditions and and the individual run's motion parameters.

Individual events were modeled as a canonical hemodynamic response and its first-order temporal derivative. The resulting least squares parameter estimates, reflecting mainly the height of the modeled hemodynamic response for each condition were then contrasted for each subject. Contrasts from individual subject runs were then combined into a second level contrast analysis for each subject using a fixed effects model in order to combine data across all 3 runs. Finally, spatially normalized contrast maps were tested at a 3rd level in order to examine group effects. All group analysis utilized the FLAME (FMRIB's Local Analysis of Mixed Effects) approach in FSL with appropriate correction for multiple comparisons. The more general, omnibus contrasts, (e.g., Source Memory, a

combination of AccSrc and InaccSrc, versus CONT) were corrected for multiple comparison using a clustering approach where clusters were determined by $Z > 2.3$ and a corrected cluster significance threshold of $P = 0.05$ (Worsley 2001). A small volume correction was used for more specific contrasts examining the effects of genotype, where the tested volume was restricted to those regions showing significant activation in the AccSrc and InaccSrc, versus CONT contrast ($p < .05$ corrected).

STRUCTURAL ANALYSIS

The FreeSurfer (http://surfer.nmr.mgh.harvard.edu) software package was used for analysis of structural images, and has been described, applied, and validated in a number of publications (Dale, Fischl et al. 1999; Fischl, Sereno et al. 1999; Fischl and Dale 2000; Fischl, Salat et al. 2002; Fischl, Salat et al. 2004; Salat, Buckner et al. 2004; Salat, Greve et al. 2009). T1-weighted images of the brain were examined in two primary ways: a) surface based reconstruction resulting in measures of cortical thickness; b) volume based analysis of specific parcellated and segmented units utilizing a probabilistic atlas approach. Cortical thickness measurements were obtained by reconstructing representations of the gray/white matter and gray matter/CSF boundaries (Dale, Fischl et al. 1999). This method uses intensity and continuity information from the entire MR volume to generate surface models. Cortical thickness is then determined by calculating the distance between the surfaces at all points on the cortical surface (Fischl and Dale 2000). All volumetric measures were examined as native volume and corrected for head size by dividing by the total cerebral volume. The measures of interest were generated through computerized reconstruction of the cortical surface. This multistep procedure includes intensity normalization to reduce spatial variation in signal intensity for a given tissue type, stripping of non-brain tissue, and WM labeling using a unique

segmentation procedure that employs both intensity and continuity constraints. The distance between the GM/WM boundary and the outer cortical surface was used to calculate cortical thickness at each point across the cortical mantle (Rosas, Liu et al. 2002; Salat, Buckner et al. 2004). Following cortical reconstruction and segmentation an algorithm was implemented that automatically assigns a neuroanatomical label to each voxel in an MR volume based on a probabilistic atlas of class statistics derived from a manually labeled training set (Fischl, Salat et al. 2002; Fischl, van der Kouwe et al. 2004). These techniques have been shown to be comparable in accuracy and reliability to manual labeling (Fischl, Salat et al. 2002). Volumetric measurements are automatically calculated from a variety of regional neural structures by counting the number of voxels within the labeled region.

All surfaces were checked thoroughly to ensure that the automated reconstruction was successful. When necessary, manual intervention was used to correct small defects. In total, 20 subjects required manual edits (11 older adults and 9 younger adults). The majority of the edits to the younger adults were the placement of control points to adjust the image intensity, whereas the majority of the edits to the older adults were the addition of white matter voxels that were excluded from the white matter surface.

ROI Analysis

Structural regions of interest (ROI) were generated from the automatic segmentation of cortical and subcortical structures for the whole brain. ROIs from the temporal and frontal lobes were used for analysis, because of their prominent role in memory retrieval. Figure 4 depicts those ROIs that were used for analyses. Cortical volume was calculated for these regions, which comprises the product of surface area and thickness of the ROI. Measures of cortical volume can be sensitive to slight changes in

both thickness and surface area that might be missed when looking at cortical thickness alone. These ROIs were correlated with source monitoring performance and genotype status. Regression analyses were also used to explore the associations of source memory monitoring accuracy and the cortical volumes in regions of the prefrontal cortex and medial temporal lobe.

Figure 4

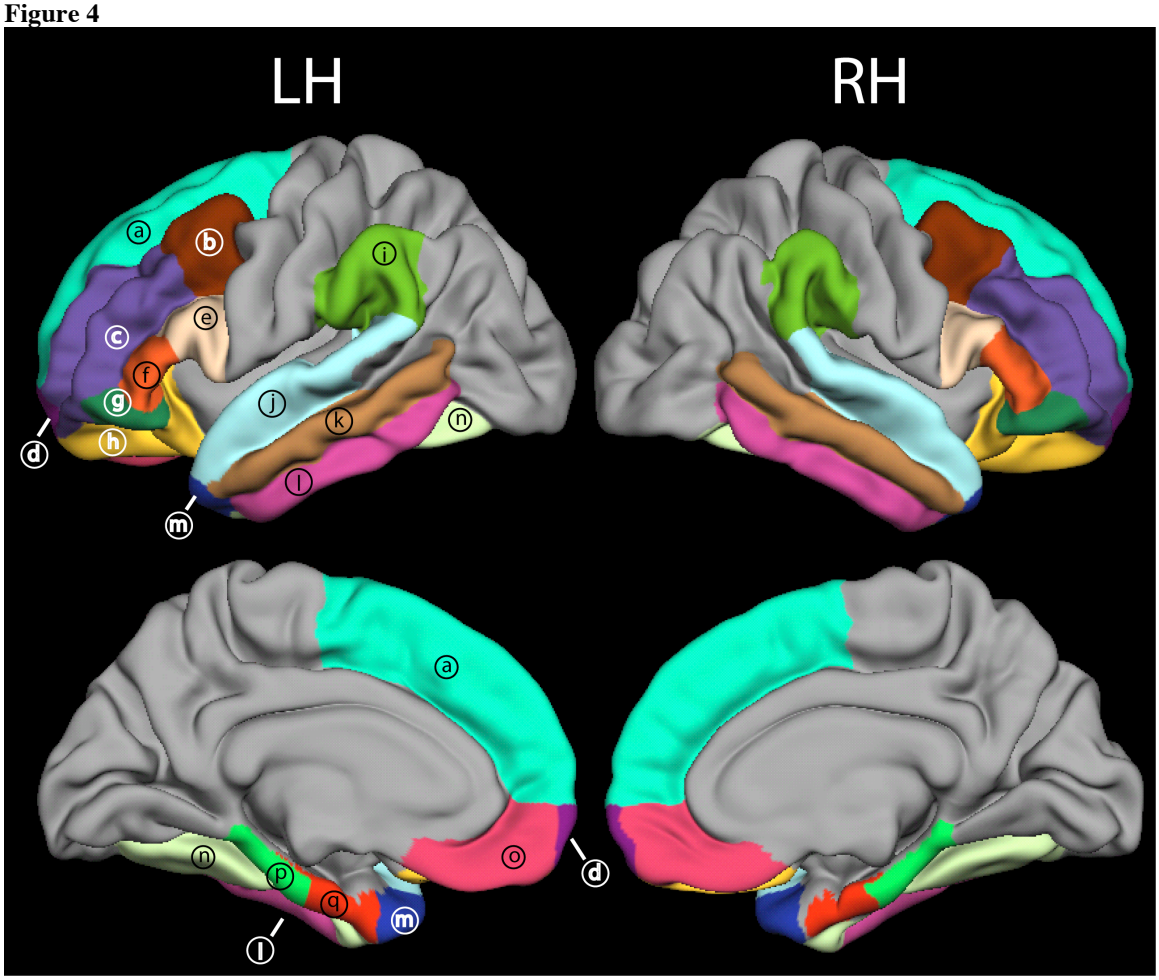


Figure 4. Volumetric ROIs of frontal and temporal lobes.

The 17 different ROIs from the frontal and temporal lobes are shown on both the left and right hemisphere. ROIs were generated automatically with the Freesurfer software, and selected based on their location in either the frontal or temporal lobe. ROIs in the frontal lobe are:
(a.) Superior Frontal Gyrus (b.) Caudal Middle Frontal (c.) Rostral Middle Frontal (d.) Frontal Pole (e.) Pars Opercularis (f.) Pars Triangularis (g.) Pars Orbitalis (h.) Lateral Orbital Frontal Gyrus and (o.) Medial Orbital Frontal Gyrus.
ROIs in the temporal lobe are:
(i.) Supramarginal Gyrus (j.) Superior Temporal Gyrus (k.) Middle Temporal Gyrus (l.) Inferior Temporal Gyrus (m.) Temporal Pole (n.) Fusiform Gyrus (p.) Parahippocampal Gyrus and (q.) Entorhinal Cortex

DIFFUSION TENSOR IMAGING ANALYSIS

Diffusion Tensor Imaging (DTI) data was processed by calculation of fractional anisotropy (FA), a measure of WM microstructure, for voxel-based and region of interest analyses (Pierpaoli and Basser 1996). Collected DTI volumes were motion corrected and averaged using FNIRT (FMRIB's Non-linear Image Registration Tool; http://www.fmrib.ox.ac.uk/fsl/fnirt/index.html) with mutual information cost function to first register each average for each direction to the first average of each similar direction and then register each direction to the T2 weighted DTI volume (no diffusion weighting, the volume with the least eddy current distortion). This procedure functions to correct for motion and eddy current distortions and has been demonstrated to perform robustly in registering volumes with different contrast properties, resulting in a significantly higher signal/contrast to noise volumes compared to averaging without such correction. The primary measure acquired from the DTI data for the proposed studies, fractional anisotropy (FA), is a calculated measure from DTI data that is dependent on the orientational coherence of the diffusion compartments within a voxel (Pierpaoli and Basser 1996). The three principal eigenvalues from the diffusion tensor of the DTI data are calculated, representing the diffusion coefficients along the three principal eigenvectors (vectors of diffusion orientation) and FA is computed as the variance of the three eigenvalues. FA analyses employed both whole brain voxel-based comparisons and ROI approaches. FA maps were first smoothed using a 4mm 3-dimensional Gaussian smoothing kernel to provide a more reliable estimate of FA at each voxel. Voxelwise statistical analysis of the FA data was carried out using TBSS (Tract-Based Spatial Statistics, Smith, Jenkinson et al. 2006). All subjects' FA data were then aligned into a common space using the nonlinear registration tool FNIRT (Andersson, Jenkinson et al. 2007; Andersson, Jenkinson et al. 2007), which uses a b-spline representation of the

registration warp field (Rueckert, Sonoda et al. 1999). Next, the mean FA image was created and thinned to create a mean FA skeleton, which represents the centers of all tracts common to the group. Each subject's aligned FA data was then projected onto this skeleton and the resulting data fed into voxelwise cross-subject statistics.

Chapter 3: Age-Related Changes in Memory Monitoring: an fMRI study

YOUNG VS OLD

Introduction

Healthy aging imposes many cognitive changes, which can account for performance differences when they are compared to younger adults. One theory, the *inhibition deficit theory*, attributes decline of working memory to failures of inhibitory control (Hasher and Zacks 1988; Dennis and Cabeza 2008). This lack of inhibitory control results in 'mental clutter' marked by the inclusion of irrelevant information into working memory (Dempster 1992; Zacks, Hasher et al. 2000). During source retrieval memory cues trigger the retrieval of a variety of information that gets stored temporarily in working memory and irrelevant information present could have a negative impact. Without adequate inhibition, working memory will be 'cluttered' with inaccurate or inappropriate retrieval products. This influx of potentially irrelevant information increases the difficulty of sorting through retrieval outcomes, as well as increases the likelihood of selecting the wrong outcome. Irrelevant information included during source retrieval could result in more prominent, albeit incorrect monitoring outcomes.

Another common cognitive change seen in older adults is the *recollection deficit theory*. This specifically attributes the deficits seen in recognition memory to a decline of recollection performance, or the ability to conjure coherent concrete episodes (Yonelinas 2002; Dennis and Cabeza 2008). Older adults tend to rely on the process of familiarity, or a feeling-of-experience rather than a concrete memory (Jennings and Jacoby 1993; Davidson and Glisky 2002; Yonelinas 2002). In this instance, when a cue is generated, normally triggering memory retrieval, only sparse information is brought up. With less

concrete information being brought to mind, it would be incredibly difficult to recreate an entire event, whereas a person may be able to get enough information to determine if something seems familiar without being able to place it in a concrete context. Because recollection memory involves strong associations between the main and contextual elements of an event, it is thought that this recollection deficit contributes to the age-related declines seen in source memory (Johnson, Hashtroudi et al. 1993).

A coordinated neural network has been proposed for assessment of episodic memory contents that is consistent with the proposed cognitive framework. The medial temporal lobe structures (i.e., parahippocampal cortex, entorhinal cortex, and hippocampus) are responsible for the retrieval of information from stored memories, and regions of the prefrontal cortex are responsible for mediating the retrieval process. The dorsolateral prefrontal cortex has been shown to aid in selection of goal-relevant information and ensuring that the retrieval results fit with the expectations (Wagner, Maril et al. 2001). The inferior frontal gyrus (IFG) has been implicated in cue specification, a process that can help to trigger memory contents and aid in memory judgments (Wagner, Gais et al. 2001; Dobbins, Foley et al. 2002; Kikyo, Ohki et al. 2002; Buckner 2003). The IFG has also been implicated in the process of semantic selection, which involves choosing between closely competing alternatives (Hirshorn and Thompson-Schill 2006). In studies of memory monitoring the IFG has been shown to be specific to monitoring processes, and is not recruited for successful recall (Kikyo, Ohki et al. 2002; Chua, Schacter et al. 2006). Not only are these lateral and inferior PFC regions crucial to memory monitoring, they support the processes that seem to contribute to the age-related performance decline. Older adults may have difficulty recruiting these regions, contributing to the decline in memory monitoring performance.

There have been relatively few published reports of the functional differences between older and younger adults for memory monitoring. In this study, I attempt to fill this gap by using a source memory task that is designed to increase the need for inhibitory control over extraneous information by using two competing sources. It is known that older adults struggle with this process of inhibition, and this task will exploit the performance differences between older and younger adults. Using fMRI, I explore the underlying neural network, and expect to see a dissociation of activation in lateral and inferior PFC regions, known to be crucial to selection and inhibition processes.

Methods

Methods were described in Chapter 2, however below are modifications specific to the fMRI portion of the study

Participants

Seventeen younger adults (YA) from the University of Texas at Austin community (5 male; mean age = 23.3 ± 3.4, age range = 19-30; 16 caucasian, 1 african american) and twenty-three older adults (OA; 12 male; mean age = 66.8 ± 6.3, age range = 60-81; 20 caucasian, 2 african american, 1 native american) were included in the final analysis. In each group three subjects were excluded from the final analysis: two subjects in each group for extreme head motion during scanning, and one other for failure to respond during a significant portion of the task, across all runs

Cognitive Task

A total of four study/test runs were administered per subject, however some runs were excluded for reasons of excessive head motion or absence of responding during the run. In total, there were 10 subjects with a complete set of 4 runs, 5 subjects with three useable runs, and 2 subjects with only two usable runs in the younger group. There were

16 subjects with a complete set of runs, 6 subjects with three useable runs, and 1 subject with 2 useable runs in the older group

Behavioral Results

The behavioral results for all runs were combined for each subject, and analyses were done to examine memory performance for item memory and source memory. Item memory was calculated as the number of the proportion of true hits minus false alarms to the total number of items. Source memory accuracy was calculated as the proportion of correctly identified speakers to the total number of items. Across the entire group of subjects, previous patterns of behavioral results were replicated (Dodson, Bawa et al. 2007), and are summarized in Table 2. A repeated measures ANOVA (see Table 3 for ANOVA results) was used to explore memory performance for memory type (item or source) between two groups (YA and OA). This revealed a significant main effect of memory type ($F(1,37)=247.54$, $p<0.001$) as well as a significant interaction of memory type x group ($F(2,37)=13.01$, $p<0.001$). There were no deficits for older adults during sentence recognition but they performed significantly worse on source memory recognition - two-tailed, two-sample t-tests showed significant overall reduction in source memory performance for older adults as compared to their younger counterparts (OA=64.9%, YA=75.5%, p=0.004, Figure 5a).

Table 2. Memory and Monitoring Accuracy Rates for All Groups.

				Memory Accuracy (SEM)		Memory Monitoring (SEM)	
Group	n	Mean Age (SD)	Age Range	Item	Source	Item	Source
YA	16	23.2 (3.4)	19-30	0.93 (0.01)	0.75 (0.02)	0.96 (0.01)	0.85 (0.03)
OA	23	66.8 (6.3)	60-81	0.94 (0.01)	0.65 (0.02)	0.97 (0.01)	0.74 (0.03)

Table 2

A similar analysis was done for memory monitoring accuracy. The accuracy rate for questions rated with high-confidence was used as a measure of memory monitoring accuracy for both item monitoring and source monitoring. The repeated measures ANOVA revealed a significant main effect of memory type ($F(1,37)=63.70$, $p<0.001$) as well as a significant interaction of memory type x group ($F(2,37)=7.76$, $p<0.01$). Confirmed by subsequent t-tests, older adults showed a significant decline in source memory monitoring when compared to the younger adults (OA=73.7% YA=84.7% p=0.017, Figure 5b).

Table 3. Repeated Measures ANOVA results for OA vs YA

	Mean Square	F(37)
Memory Performance		
Memory Type	1.094	247.54**
Memory Type x Group	0.058	13.01**
Monitoring Performance		
Memory Type	0.537	63.70**
Memory Type x Group	0.065	7.76*

*$p<0.01$; **$p<0.001$

Table 3

Figure 5

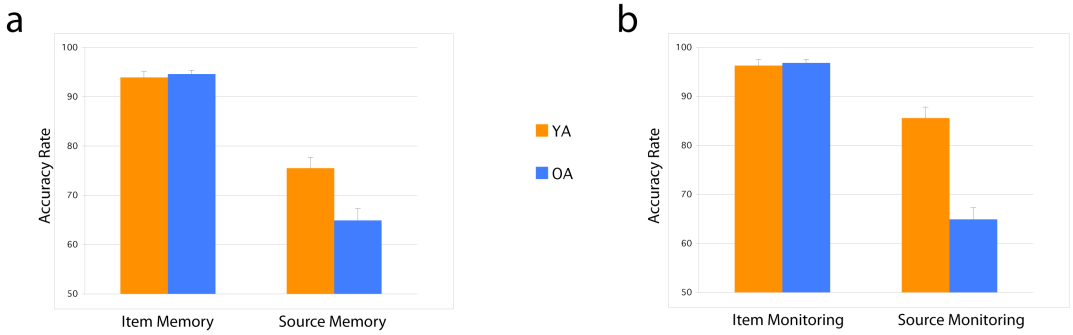


Figure 5. Accuracy rates for Item and Source Memory and Item and Source Monitoring.

Panel **a** shows the accuracy rates for YA (shown in orange) compared to OA (shown in blue) for both item and source memory. A significant interaction exists between memory type (item, source) and group (YA, OA). Panel **b** shows the accuracy rates for YA and OA for both item and source memory monitoring. A significant interaction exists here as well, OA is more decreased for source memory monitoring than YA.

fMRI results

Source Memory Network

While the participants performed the task described in Chapter 2, whole brain functional MRI were collected in order to explore the regions that are involved in this memory monitoring task. Initially, an omnibus test of source memory > control task (i.e., AccSrc + InaccSrc > CON) was performed in order to assess the task and how reliable it is at uncovering memory functioning. This initial contrast revealed a network of regions previously shown to be involved in source memory processes. These regions include areas of the lateral PFC and medial PFC (Stuss and Benson 1984; Shimamura 1994), MTL (Squire 1992; Cohen and Eichenbaum 1993), and parietal cortex (Buckner and Wheeler 2001; Rugg, Otten et al. 2002; Wagner, Shannon et al. 2005). This omnibus map was generated once for all subjects (YA and OA combined) and then again for the

younger adults alone. The results were were corrected for multiple comparison using a clustering approach where clusters were determined by $Z > 2.3$ and a corrected cluster significance threshold of $P = 0.05$ (Worsley 2001). This cluster-corrected map of the younger adults (shown in Figure 6, summarized in Table 4) was used in subsequent analyses as a small-volume correction mask to correct for multiple comparisons in contrasts using only the older adults.

Figure 6

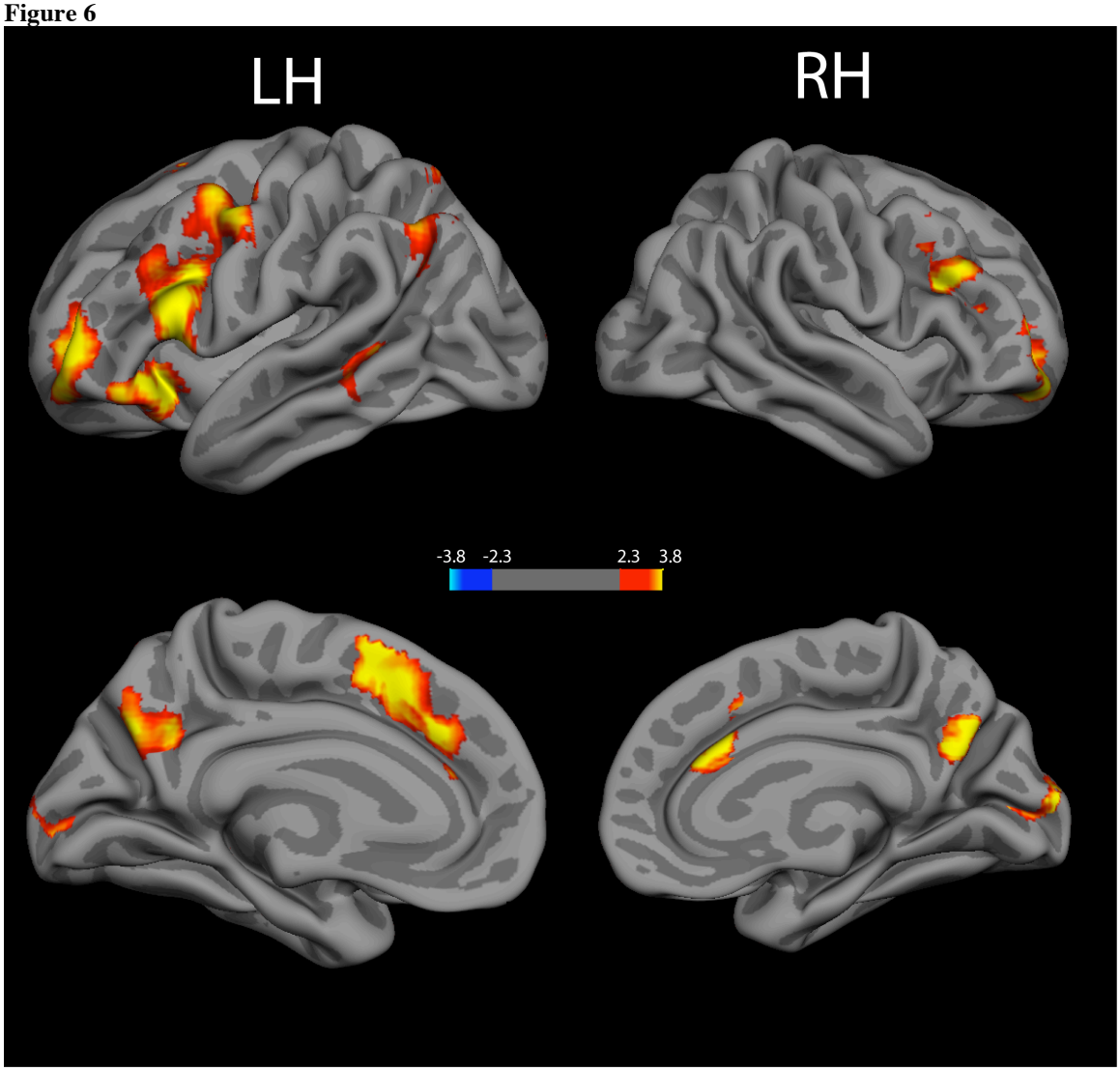


Figure 6. Source Memory Network for Younger Adults

Using an omnibus contrast looking at all the source memory questions, regardless of whether they were answered accurately or not, compared to the control task reveals a network of regions known to be involved in source memory. The regions that show significantly more activation for source memory than control task include: medial and lateral PFC, MTL, and parietal lobe. The images shown above have been corrected for multiple comparison using a clustering approach where clusters were determined by $Z > 2.3$ and a corrected cluster significance threshold of $P = 0.05$. The map of source memory was used in subsequent analyses, to constrain the statistical search as a means of limiting the multiple comparisons problem.

Table 4. Clusters of YA Source Memory Network

Brain Regions	Hemisphere	Voxels	Max Z-stat	x	y	z
Frontal Pole	L	536	5.27	-32	58	12
Paracingulate/Superior Frontal Gyrus	midline	463	4.8	-6	14	50
Inferior Frontal Gyrus - operculum/triangularis	L	162	4.15	-48	18	14
Frontal Orbital Cortex/Insula	L	117	4.07	-36	24	-6
Lateral Occipital Cortex/Angular Gyrus	L	40	4.2	-30	-66	56
Middle Frontal Gyrus/Precentral Gyrus	L	25	3.65	-48	-4	46

Voxels: number of activated voxels per cluster; Max Z-stat: maximum z statistic for each cluster; x, y, z are MNI coordinates for the peak of each cluster

Table 4

Source memory for YA compared to OA.

In order to determine changes in source memory between the younger (YA) and older adults (OA), a direct comparison was performed. This analysis combines all source memory items, both those answered accurately and inaccurately, and contrasts them against the control task. The direct comparison revealed no significant regions where younger adults had greater activation than older adults for source memory tasks, however bilateral regions of the anterior portion of the supramarginal gyrus were revealed as being more active for older adults than younger adults. This was significant to a level of $p < 0.05$ after using a cluster-based correction for multiple comparisons (Figure 7). Looking individually at the YA and OA maps of regions that are significantly more active for source memory compared to the control task, the significant difference seen between the two is driven by the slight deactivation of this region for YA as compared with the slight activation seen in the OA.

Figure 7

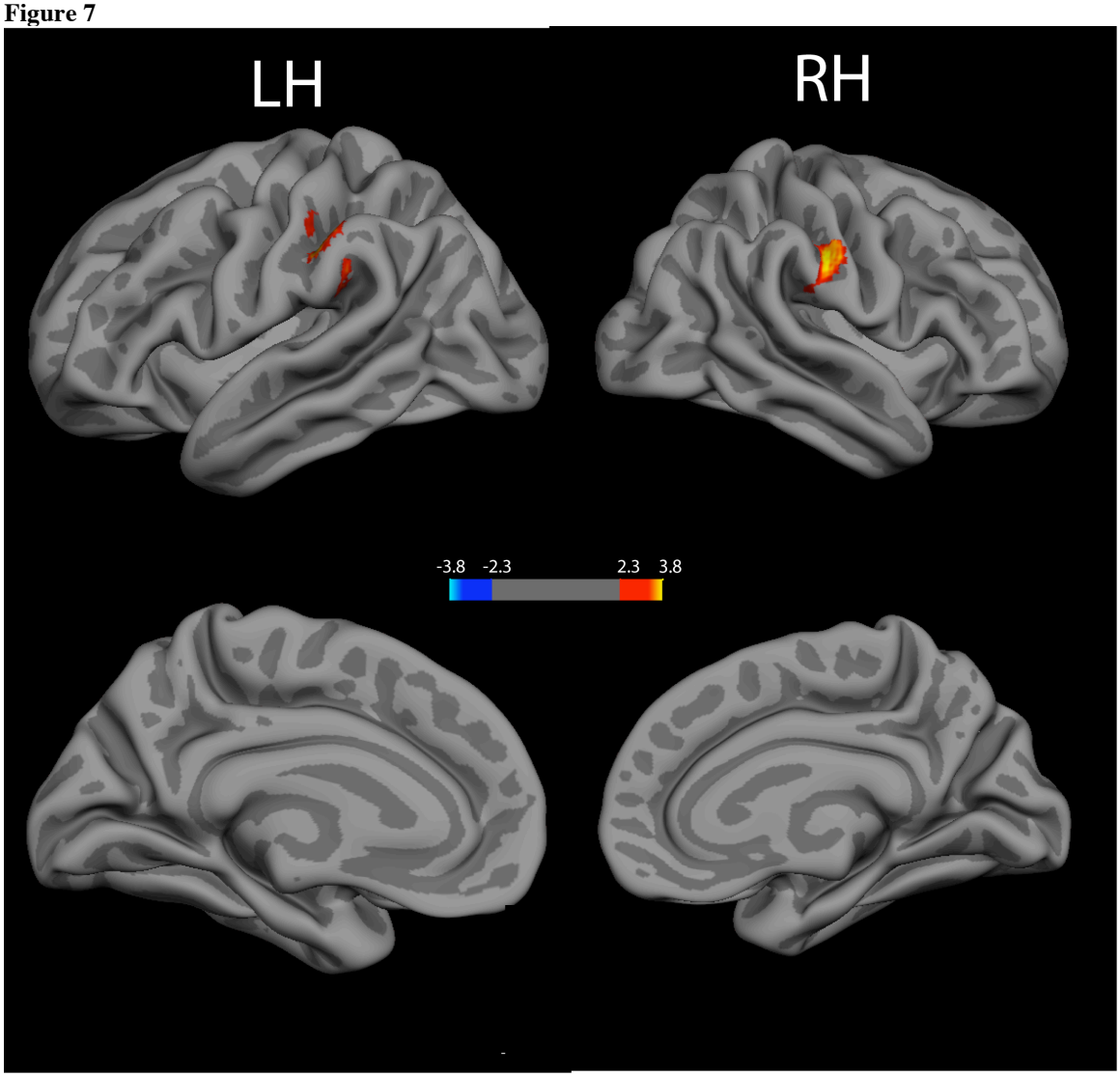


Figure 7. Regions of significantly greater activation in OA than YA for Source Memory.

Bilateral portions of the anterior supramarginal gyrus show a significantly greater activation for the older adults, when comparing source memory to the control task. These results were corrected for multiple comparisons using a clustering approach where clusters were determined by $Z > 2.3$ and a corrected cluster significance threshold of $P = 0.05$. Looking further into the significant activations of each group separately, this result is driven by the slight deactivation of this region for the YA and the slight activation seen in the OA. This region doesn't actually appear to play a large role in the source memory process for either group, but upon direct comparison, it is a region that is recruited to a significantly greater degree in the OA when compared to the YA.

Accurate memory monitoring.

In order to assess the regions that are activated for accurate memory monitoring, various analyses were done with both individual groups alone and direct group comparisons. From the behavioral results of the task, every subject has one measure of source monitoring accuracy. Using the same whole brain group comparison of source memory as described above, each subject's accuracy was added as a covariate to the model which revealed regions whose activation correlates with monitoring accuracy. Each group (YA and OA) was processed separately and compared to each other. The OA group showed a region of the left PFC where activation was positively correlated with source monitoring accuracy. The resulting region includes IFG, namely the operculum, as well as some of the middle frontal gyrus.

More direct comparisons were made for the contrast of accurate monitoring responses compared to the control task. When processed individually, the YA group showed a network that contained much lateral prefrontal cortex, primarily along the middle frontal gyrus, as well as some portions of the medial cingulate cortex. A similar network of regions was revealed for the OA. When compared directly, there were no significant differences between the two groups. These functional results will be explored further in the following section, where some differences are found and more readily explained based on subjects genotype rather than age.

Taken together these results showcase the importance of the lateral and inferior PFC for accurate memory monitoring in this task. The two age groups do show a significantly different behavioral pattern for the task, unfortunately, the fMRI comparisons do not help to uncover a functional cause for this difference. Additional comparisons and analyses were attempted, but also resulted in no significant differences. These are further described in Appendix B.

CARRIERS VS NON-CARRIERS

Introduction

It has been shown that some of the individual variability seen in memory performance can be accounted for by genetics. The recent literature has identified the serotonin systems and their controlling genetics as targets for treatment of memory disorders (Perez-Garcia and Meneses 2008), suggesting that enhancing brain serotonin activity improved memory in animals (Haider, Khaliq et al. 2006) and in normal older adults, patients with AD (Porter, Lunn et al. 2003; Schmitt, Wingen et al. 2006) and patients with schizophrenia (Levkovitz, Ophir-Shaham et al. 2003). These studies highlight the possible relationship between serotonin levels and memory performance and implicate that this could have an impact for older adults, who tend to show a decline in serotonin receptors in neural structures that are crucial for memory function (Sheline, Mintun et al. 2002). Further understanding the role serotonin has in memory performance of older adults could help to identify additional causes for the variety of individual differences seen in that population.

The serotonin transporter, 5-HTT, is ultimately responsible for determining the duration and intensity of serotonin communication with post-synaptic receptors and targets. This communication is regulated by controlling the reuptake of serotonin to the presynaptic neuron for recycling or degradation after serotonin release. Importantly, the efficiency with which the 5-HTT returns serotonin to the presynaptic neuron appears to be influenced by a polymorphism of the serotonin transporter linked promoter region (5-HTTLPR) polymorphism. This common deletion polymorphism results in 2 variants: a short (S) allele and a long (L) allele. The presence of one or two S alleles, rather than two

copies of the L allele, is associated with reduced transcriptional efficiency that putatively results in significant decreases (approximately 50%) in serotonin reuptake (Caspi, Sugden et al. 2003; Hu, Oroszi et al. 2005). While the 5-HTTLPR genotype has been typically studied in relation to mood disorders, I have presented a number of reasons to think it may impact memory function.

Correlations between 5-HTTLPR and structural aspects of the neural network involved in memory monitoring have been demonstrated. Recent work from our lab has shown that development of the white matter microarchitecture along a tract connecting the MTL to PFC is significantly affected by genotype for the 5-HTTLPR serotonin transporter gene (Pacheco, Beevers et al. 2009). Importantly, there is a strong relationship between the number of low-expressing 5-HTTLPR alleles and the measure of fractional anisotropy of the frontal portion of the uncinate for a population of healthy adolescent and college-aged women. Further, 5-HTTLPR genotype has been shown to modulate the association of lateral prefrontal cortex volume and cognitive control mechanisms associated with shifting attention away from emotionally salient but irrelevant stimuli (Beevers, Pacheco et al. 2009). Carriers of the short allele show an association of lateral PFC volume and biased attention. This process of focusing attention away from irrelevant stimuli has been shown to be crucial for successful memory monitoring and is declined for older adults. The connection between 5-HTTLPR and these cortical structures could be important in the investigation of memory monitoring. These structural findings, coupled with the influence of serotonin on memory performance, indicate that there may be an influence of this genotype on memory monitoring ability. To date, there has been no investigation integrating 5-HTTLPR genotype and age related declines in metamemory functioning.

In this study, I examine the effects that the 5-HTTLPR genotype has on memory monitoring processes in older adults using an item and source memory task, in which participant's responses indicate their level of confidence in their choice. Using fMRI, I explore explore the effects of this gene on memory monitoring performance in older adults. As this gene is known to have an effect on PFC structure, I expect to see some influence in memory monitoring as well.

Methods

Participants

Twenty-two of the older adults were genotyped, resulting in 6 long allele homozygotes (L/L), 15 heterozygotes (L/S) and 1 short allele homozygote (S/S). These groups were further collapsed into short allele carriers (L/S and S/S; n = 16, 9 male, mean age = 67.1 ± 6.5, age range = 60-79; 19 Caucasian, 2 African American, 1 Native American) and non-carriers (L/L; n=6, 3 male, mean age = 66.5 ± 6.7, age range = 61-81). There were no significant group differences between carriers and non-carriers on age, education, or gender (all $F(1,21) > 1$).

Behavioral Results

In order to assess the effect that having one or more copies of the short 5-HTTLPR allele has on memory performance the older adult sample was further divided into carriers of the short allele (CAR) and non-carriers (NC), performance is summarized in Table 5. A repeated measures ANOVA was used to explore memory performance for memory type (item or source) between two groups (NC and CAR). This revealed a significant main effect of memory type ($F(1,22)=202.7$, $p<0.001$), however there was no significant interaction of memory type x group. There were no differences between the groups during sentence recognition but the older adult carriers performed significantly

worse on the source memory question - two-tailed, two-sample t-tests showed significant overall reduction in source memory performance for older adult carriers as compared to the non-carriers (CAR=73%, NC=60%, p=0.018 Figure 8a).

Table 5. Memory and Monitoring Accuracy Rates for All Groups.

				Memory Accuracy (SEM)		Memory Monitoring (SEM)	
Group	n	Mean Age (SD)	Age Range	Item	Source	Item	Source
YA	16	23.2 (3.4)	19-30	0.93 (0.01)	0.75 (0.02)	0.96 (0.01)	0.85 (0.03)
OA	23	66.8 (6.3)	60-81	0.94 (0.01)	0.65 (0.02)	0.97 (0.01)	0.74 (0.03)
Old NC	6	66.5 (6.7)	61-81	0.96 (0.01)	0.73 (0.04)	0.98 (0.01)	0.87 (0.03)
Old CAR	16	67.1 (6.6)	60-79	0.93 (0.01)	0.60 (0.02)	0.96 (0.01)	0.66 (0.04)

Table 5

The same analysis was done for the memory monitoring task. A repeated measures ANOVA revealed a significant interaction between carrier status (carrier, non) and monitoring type (item, source) ($F(2,20)=12.38$, $p=0.002$, Figure 8b). Subsequent t-tests indicated that having a short allele resulted in greater impairment for source monitoring (CAR: 66.2%; NC: 89.1%) with no differences in recognition monitoring. Additionally, comparisons between the younger adults and older adult non-carriers revealed that there are no significant differences between the either performance or monitoring of these two groups; older adult non-carriers have behavior rates equivalent to the younger adults (Table 5, Figure 8).

Table 6. Repeated Measures ANOVA results for CAR vs NC

	Mean Square	F(37)
Memory Performance		
Memory Type	0.903	202.795**
Memory Type x Group	0.016	3.696
Monitoring Performance		
Memory Type	0.344	50.30**
Memory Type x Group	0.085	12.38*

*p<0.005; **p<0.001

Table 6

Figure 8

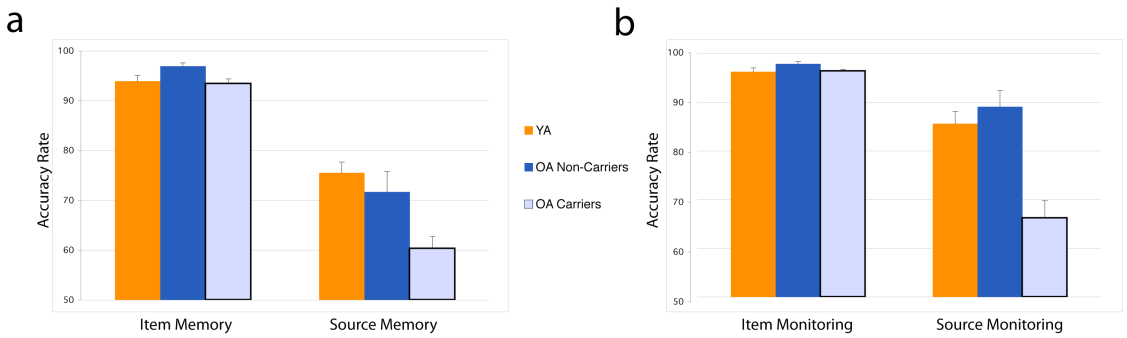


Figure 8. Accuracy rates for Item and Source Memory and Item and Source Monitoring.

Panel **a** shows accuracy rates for YA (shown in orange), OA-Non-carriers (shown in dark blue), and OA-carriers (shown in light blue) for item and source memory. Among the two OA groups, a significant interaction exists between memory and group, showing the OA-carriers are significantly worse at source memory. Similarly, panel **b** shows the accuracy rates for item and source memory monitoring. Again here, a significant interaction exists between memory and group. It should be noted that in panels **a** and **b** there is no significant difference between YA and OA-Non-carriers.

fMRI Results

Accurate Memory Monitoring

Behavioral analyses revealed a sharp difference in performance within the OA group, such that older adult carriers of the short 5-HTTLPR allele performed much worse than the older adults non-carriers. Because of this, I performed a whole brain analysis within the older group, comparing non-carriers (NC) to carriers (CAR) for accurate monitoring responses. It should be noted that accurate monitoring is irrespective of memory success; accurate monitoring includes both times when the subject felt highly confident and got the answer correct as well as times when the subject felt less confident and got the answer incorrect. The mask of source memory described above (shown in Figure 6) was used to constrain the statistical search and control for multiple comparisons. The resulting contrast revealed regions of the left lateral IFG (BA 44 and 45), the left dorsolateral PFC (BA 9), and the paracingulate gyrus that showed significantly more activation for non-carriers accurate monitoring responses than for the carriers (Figure 9). The resulting networks appear similar to those that were seen when the YA and OA groups were processed alone (Figure 10), indicating that the NC older adults may have been driving the results seen within the OA group. These results suggest that the NC older adults are recruiting the lateral PFC and paracingulate more than the CAR older adults are when making accurate monitoring judgments.

Figure 9

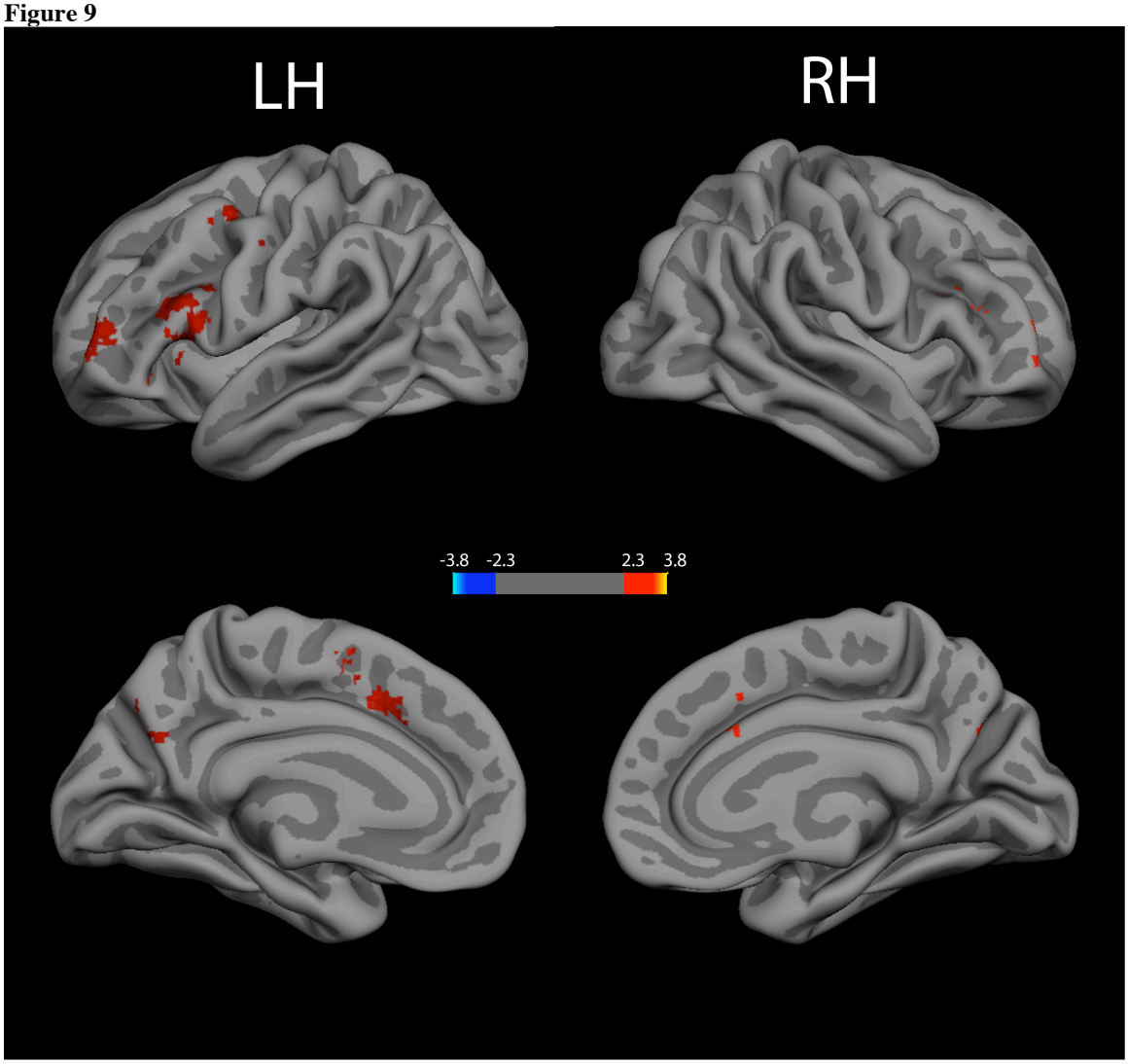


Figure 9. Regions of significantly greater activation for NC compared to CAR on Accurate Memory Monitoring.

Whole brain analysis within the older group, comparing non-carriers (NC) to carriers (CAR) for accurate monitoring responses. The mask of source memory was used to constrain the statistical search and control for multiple comparisons. The resulting contrast revealed regions of the left lateral IFG (BA 44 and 45), the left dorsolateral PFC (BA 9), and the paracingulate gyrus that show significantly more activation for non-carriers accurate monitoring responses than for the carriers. It should be noted that accurate monitoring is irrespective of memory success; accurate monitoring includes both times when the subject felt highly confident and got the source correct as well as times when the subject felt less confident and got the source incorrect.

Figure 10

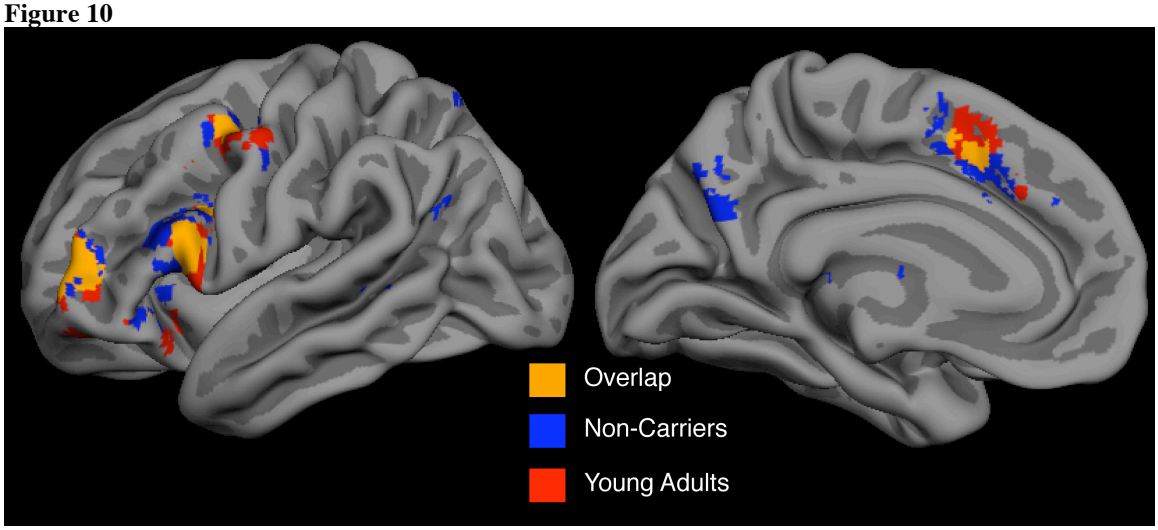


Figure 10. Regions of overlap between younger adults and older adult non-carriers.

Whole brain analysis within the younger group (shown in red) was done to uncover regions of significant activation for accurate memory monitoring. The regions revealed overlap to a great extent (shown in yellow) with the regions revealed for analyses comparing non-carriers (NC) to carriers (CAR) for accurate monitoring responses (shown in blue).

DISCUSSION

The primary goal of this study was to investigate the functional neural architecture of age-related changes in memory monitoring ability. Prior work has shown that older adults are worse at memory monitoring for episodic memory when compared to younger adults, however the literature is sparse when describing the neural correlates that correspond to these changes. Using the same task as in previous behavioral examinations of memory monitoring in aging, I replicated the expected behavioral results, showing that older adults are worse compared to younger adults at source memory and source monitoring, but show no deficits when it comes to item memory or monitoring. Looking at this task functionally, across all subjects, I was able to verify that

it assesses source memory as hoped; the network of regions identified for our source memory task are regions that are known to play a role in source memory. Further, I wanted to uncover regions that were specifically necessary for accurate source memory monitoring, and to identify functional differences between younger and older adults. Most results point to the lateral and inferior prefrontal cortex as being crucial for accurate source memory monitoring on this task, and indicate that older adults who are able to recruit this region perform better.

In addition to this, I began to explore specific biological contributions to the age-related deficits. By splitting the older subjects into groups based on their genotype for the serotonin transporter gene, I uncovered significant differences. Older adults who carry at least one copy of the short allele perform behaviorally worse than older adults who do not. Perhaps more interestingly, the older adults who lack a copy of the short allele perform at levels no different from younger adults. This initial result indicates that the complete older adult group was not as homogenous as originally thought, and our fMRI results were analyzed again using the two genotype groups separately for the older adults, rather than combining them in to one group. The functional results implicate that regions of the prefrontal cortex that are important for accurate memory monitoring are activated to a greater extent by older adult non-carriers than the older adult carriers. Taken together, the behavioral and functional results point to an interesting relationship between the 5-HTTLPR genotype and age-related deficits of source memory monitoring. Older adults who lack a copy of the short 5-HTTLPR allele perform behaviorally like younger adults, and show higher levels of activation in critical PFC regions, which is also consistent with young adults functional activation.

5-HTTLPR effects on source memory monitoring performance

Both older and young adults performed above 90% on item memory and item memory monitoring, as expected. The interesting group differences were seen for source memory. As previously shown, the older adults in this study showed deficits for both source memory accuracy and source monitoring accuracy as compared with younger adults. However, when the older adults were split into groups based on their genotype for the 5-HTTLPR gene, a significant group difference was revealed. Older adults who carry a copy of the short allele were significantly declined for both source memory and source memory monitoring as compared to the older adult non-carriers. Previous work by O'Hara et al., (2007) characterized an association of the 5-HTTLPR s-allele and poorer memory functioning in older adults. They reported a mediating effect of waking cortisol levels and measures of life stress on this association, factors that I did not measure in the current study. However, they do offer the suggestion that those individuals with an s-allele have an increased vulnerability to neurodegenerative processes, which could be consistent with our findings.

Missing from the O'Hara et al., (2007) analysis is a younger group for comparison, their analysis included only older adults. In the study presented here, I have compared both groups of older adults (carriers of the s-allele and non-carriers) to the group of younger adults. These comparisons resulted in no significant differences between younger adults and the older adult non-carriers. Given that there were no differences between the older adult non-carriers (NC) and the carriers (CAR) on age, gender, or education, the memory and monitoring effects aren't explained by any of these third-variable options. This result has some striking implications for older adults, that perhaps instead of the carriers being more susceptible, the homozygous long-allele genetic profile (L/L) may help older adults delay the normally observed age-related

decline. This protective property is likely not in a direct effect of the serotonin system on memory function, but could lie in the connections between genetic profile and brain structure or function. Prior work has shown that there is a relationship between the 5-HTTLPR genotype status and the white matter tract connecting medial temporal structures to prefrontal structures (Pacheco, Beevers et al. 2009). Perhaps it is due to a maintained ability to recruit crucial prefrontal regions that give older adult non-carriers an advantage over the carriers.

Functional Differences Between Younger and Older Adults

Source Memory

An initial goal of this study was to uncover the functional differences in older and younger adults that support the observed behavioral differences. Based on the behavioral findings, source memory was predicted to show more differences than item memory should. However, direct comparisons between the groups offered little along the lines of significant results. It should be noted, however, that our whole brain exploration of source memory combined both accurate and inaccurate memory responses, which perhaps made identifying regions of difference more difficult. If our task was more designed to assess strict accurate memory retrieval, instead of memory monitoring, we might have been able to uncover more of a difference. As it is, based on this task, it appears that older and younger adults are recruiting similar regions to perform general source memory tasks.

Memory Monitoring Accuracy

More importantly, the goal of this study was to uncover changes in the functional regions responsible for accurate memory monitoring. The task used was designed in a manner that requires a strict decision between two highly competing sources. During the

study phase of the task, subjects are presented numerous sentences spoken by one of only two difference speakers – Kim or Dan. At test, subjects are forced to recall the speaker. Many other source memory tasks include more source options, which allows for easier distinguishability. This task was designed in this manner to exploit older adults deficits of inhibitory control and difficulty making accurate cue selections (Zacks, Hasher et al. 2000).

Looking at both groups, young adults (YA) and older adults (OA) individually, memory monitoring accuracy showed correlations with neural activation of the lateral and inferior prefrontal cortex. These regions are known to play critical roles in inhibition of irrelevant details (Aron, Robbins et al. 2004; Nee, Wager et al. 2007), cue specification (Dobbins, Foley et al. 2002; Buckner 2003) and making choices between competing options (Eakin and Hertzog 2006; Hirshorn and Thompson-Schill 2006), which are necessary for success in this task. When the two groups, YA and OA, were contrasted directly, however, no significant differences were found, since both groups are activating similar regions.

Effects of 5-HTTLPR Genotype on Accurate Memory Monitoring

Once again, when the older adults were split based on their 5-HTTLPR genotype status, short allele carriers (CAR) and non-carriers (NC), significant differences were seen among the two groups. When looking at the contrast of accurate monitoring compared to baseline, as above, the same IFG and middle frontal regions were revealed. Looking within the CAR group alone, there are very few regions of significant activation that support accurate memory monitoring. These results indicate that there is little concordance in neural regions responsible for accurate memory monitoring for the CAR group, suggesting that the above result seen for OA combined is driven mainly by the NC

group. Further, there are little significant differences seen between the functional results of the YA and NC groups. This implies that older adult non-carriers are using these regions more during times of accurate monitoring than the carriers were. Taken with the behavioral findings, this implicates that the successful performance of the non-carrier group could be due to their recruitment of critical prefrontal structures. In contrast, the carriers perform much worse at memory monitoring, and also so a lack of recruitment of the PFC.

Summary

In summary, I suggest that there is an interesting effect of the 5-HTTLPR genotype in older adults. The lack of a short allele may be related to a lack of age-related decline for memory monitoring processes in older adults. Prior work has implicated the PFC as playing a crucial role in memory monitoring, and I have found the same. Regions of the left IFG and lateral PFC were shown to be involved in accurate memory monitoring for the entire group of older adults in this study. Interestingly, when carriers and non-carriers were compared directly, it was the non-carriers who showed significantly more activation in this region than the carriers. This result again indicates that the older adults who lack a short allele may be better suited to accurately assess memory retrieval by retaining an ability to recruit PFC regions during this task. While the benefit of the long-allele homozygous genotype may not be limited to this process, this study indicates that there is a benefit for older adults who lack a short allele of the serotonin transporter gene.

Chapter 4: Structural Correlates of Memory Monitoring in Older Adults

INTRODUCTION

The current study begins to explore the neural correlates of memory monitoring, which are expected to be in the prefrontal regions that support this process. Both memory monitoring ability and cortical volume of prefrontal regions are known to decrease with advancing age and here I will attempt to find associations between brain structure and behavioral performance.

Metamemory, or memory monitoring, is defined as one's ability to evaluate the current state of the memory system. This process involves both retrieval of accurate information, and determining whether this information is relevant to the context and task goals of the current memory effort (Nelson and Narens 1990). Episodic memories, which have shown specific age-related decline, require the combination of contextual (source) information with the feature details of the memory. For this reason, source memory monitoring relies more heavily on specific contextual information than item memory monitoring. Source monitoring judgments are made based on the specific characteristics of the memories retrieved and whether they fit logically into the criteria imposed by the specific question (Johnson, Hashtroudi et al. 1993). Successful monitoring of episodic retrieval requires proper selection of key details while disregarding irrelevant information. Older adults have shown difficulty with accurate source monitoring, and it may be due to deficits in selection of relevant information or inhibition of irrelevant information.

Healthy aging imposes many cognitive changes, which can account for performance differences when older adults are compared to younger adults. The

inhibition deficit theory attributes cognitive decline to failures of inhibitory control (Hasher and Zacks 1988; Dennis and Cabeza 2008). This lack of inhibitory control results in 'mental clutter' marked by the inclusion of irrelevant information into working memory (Dempster 1992; Zacks, Hasher et al. 2000). Irrelevant information included during source retrieval could result in more prominent, albeit incorrect monitoring outcomes. Another common cognitive change seen in older adults is *recollection deficit*, which specifically attributes the deficits seen in recognition memory to a decline of recollection performance, or the ability to conjure coherent concrete episodes (Yonelinas 2002; Dennis and Cabeza 2008). Older adults tend to rely on the process of familiarity, or a feeling-of-experience rather than a concrete memory (Jennings and Jacoby 1993; Davidson and Glisky 2002; Yonelinas 2002). Because recollection memory involves strong associations between the main and contextual elements of an event, it is thought that this recollection deficit contributes to the age-related declines seen in source memory (Johnson, Hashtroudi et al. 1993).

Along with changes in cognition, aging has been associated with changes in the physical characteristics of the brain. As with any other organ, the brain and its various systems deteriorate as a function of healthy aging. Overall, changes in cortical brain volume are seen throughout the lifespan, but the rate of atrophy is not constant across areas of the cortex. The frontal lobes are a major site of age-related changes (Pfefferbaum, Adalsteinsson et al. 2005; Raz, Lindenberger et al. 2005; Dennis and Cabeza 2008). Morphological measurements of gray and white matter as well as cortical thickness, or the distance between the outermost gray matter surface and the gray matter/white matter boundary have all shown to change in the prefrontal cortex during middle age (the 5th and 6th decades; Salat, Buckner et al. 2004). Measures of the diffusion of water through white matter, such as mean diffusivity, have shown a specific

age-related decline in frontal regions, while posterior regions appear relatively preserved (Salat, Tuch et al. 2005; Zahr, Rohlfing et al. 2009). In addition, the development of white matter hyperintensities (WMH), which are thought to arise from both vascular and neural pathologies, are more prevalent in the frontal lobes in older adults (Dennis and Cabeza 2008). With the abundance of structural changes occurring within the frontal lobes due to advancing age, it follows that tasks which require the use of specific frontal regions should show a decline in function. For example, performance on tasks like the Wisconsin Card Sorting Task, known to be mediated by frontal regions, have been negatively correlated with age (Shimamura 1994; Bugg, Zook et al. 2006), prefrontal cortex volume, and the number of WMHs in the frontal lobes (Gunning-Dixon and Raz 2003). Previous work has demonstrated that there are reliable age-related structural changes in the frontal lobes, and these changes have been associated with widespread cognitive decline.

Regions of the prefrontal cortex that undergo these age-related changes have also shown to be important in memory monitoring. In terms of memory monitoring, regions of the prefrontal cortex have been shown to be involved in mediating the retrieval process. The lateral prefrontal cortex has been associated with selection of goal-relevant information and ensuring that the retrieval results fit with expectations (Wagner, Maril et al. 2001). The inferior frontal gyrus (IFG) has been implicated in cue specification, which can help to trigger memory contents and aid in in memory judgments (Wagner, Gais et al. 2001; Dobbins, Foley et al. 2002; Kikyo, Ohki et al. 2002; Buckner 2003). The IFG has also been implicated in the process of semantic selection, particularly when this selection involves choosing between closely competing alternatives (Hirshorn and Thompson-Schill 2006). In studies of memory monitoring the IFG has been shown to be specific to monitoring processes, and is not recruited for successful recall only (Kikyo, Ohki et al.

2002; Chua, Schacter et al. 2006). These processes, supported by the lateral PFC and IFG have shown a decline in older adults.(Zacks, Hasher et al. 2000) Not only are these lateral and inferior PFC regions crucial to memory monitoring, they support the processes that seem to contribute to the age-related performance decline.

Along with changes due to age, other biological factors may contribute to neural underpinnings responsible for individual differences in behavior. Correlations between 5-HTTLPR genotype and structural aspects of the neural network involved in memory monitoring have been demonstrated. Recent work from our lab has shown that development of the white matter microarchitecture along a tract connecting the MTL to PFC is significantly affected by genotype for the 5-HTTLPR serotonin transporter gene (Pacheco, Beevers et al. 2009). Importantly, there is a relationship between the number of low-expressing 5-HTTLPR alleles and the measure of fractional anisotropy of the frontal portion of the uncinate fasciculus across a population of healthy adolescent and college-aged women. Further, 5-HTTLPR genotype has been shown to modulate the association of lateral prefrontal cortex volume and cognitive control mechanisms associated with shifting attention away from emotionally salient but irrelevant stimuli (Beevers, Pacheco et al. 2009). Carriers of the short allele show an association between lateral PFC volume and attentional control. One aspect of attentional control, namely the process of shifting attention away from irrelevant stimuli is crucial for successful memory monitoring and is declined for older adults (Zacks, Hasher et al. 2000). The connection between 5-HTTLPR and cortical structures in prefrontal cortex could be important in the investigation of memory monitoring. These structural findings, coupled with the influence of serotonin on memory performance, indicate that there may be an influence of this genotype on memory monitoring ability.

A number of structural brain measures will be examined for this study. T1 weighted MRI will allow for the measurement of cortical thickness that will reveal the changing gray matter landscape; thinner cortex will have inherently less cell bodies, and presumably less dedicated real estate for neuronal functioning of a particular region. Regional cortical volumes will also be explored, which take in to account both the cortical thickness and surface area of a pre-defined region. Diffusion tensor imaging (DTI) will be used to characterize the white matter architecture and explore changes in white matter tracts that may also contribute to memory monitoring performance. These correlates will be explored while taking in to consideration normal age-related changes in the PFC, to uncover regions that are related to memory monitoring performance regardless of age. Relationships between neuroanatomical structure and 5-HTTLPR genotype, and the effect this relationship has on memory monitoring will also be explored. Using this approach we hope to more fully understand the neuroanatomical architecture that contributes to the age-related decline of source memory monitoring and to uncover any interactions that 5-HTTLPR genotype might have on the structure/function relationships.

MORPHOMETRY ANALYSIS

Methods

Methods about the task and structural analyses used were described in Chapter 2. To explore these associations in the current study, I used the same measure of source memory monitoring as described previously, obtaining an accuracy rate within each set of high-confidence rated responses, and used this score in models with a variety of morphological measures.

The FreeSurfer software package was used to generate accurate models of the gray matter/white matter boundary, and the gray matter/cerebrospinal fluid boundary for each subject. From these boundaries, cortical thickness was calculated for each vertex along the surface, yielding complete brain maps of cortical thickness measures for each subject. Additionally, the FreeSurfer software automatically labels cortical and white matter regions based on a probabilistic atlas. These labels, called parcellations, were used to look at the volumes and thickness of specific neuroanatomical regions of interest. Measuring cortical volume takes in to account both surface area and thickness of the region, so this measure can be sensitive to changes in both measures that would be missed by cortical thickness alone.

Participants

Seventeen younger adults from the University of Texas at Austin community (6 male; mean age = 23.2 ± 3.5 age range = 19-30; 16 caucasian, 1 african american) and twenty-two older adults (11 male; mean age = 67.3 ± 6.6, age range = 60-81; 19 caucasian, 2 african american, 1 native american) were included in the final analyses.

The group demographics differ slightly for analyses taking 5-HTTLPR genotype into consideration. For those analyses nine younger adults (5 male; mean age = 24.2 ± 3.7, age range = 19-30; 9 Caucasian) and twenty-one older adults (11 male; mean age = 67.4 ± 6.8 age range = 60-81; 18 caucasian, 2 african american, 1 native american). Within this sample, there were 6 younger adult carriers and 3 younger adult non-carriers, 14 older adult carriers and 7 older adult non-carriers.

Cortical thickness correlates with memory monitoring accuracy

For the entire sample of subjects (YA and OA), a whole brain analysis was performed using a general linear model (GLM) to identify regions where cortical

thickness is correlated to memory monitoring performance. Age was entered into the model as a regressor of no interest in order to control for the effects of age, as we would expect age to account for some variance in cortical thickness. In order to correct for multiple comparisons, a monte-carlo simulation test was done over 5000 iterations to correct for multiple comparisons. This simulation generates a distribution of the maximum cluster size, after 5000 random iterations. With the distribution of the maximum cluster size, multiple comparisons are corrected by setting the p-value of each resulting cluster from the original data to the probability of seeing a maximum cluster of that size during the simulation. The results of the monte carlo simulations retain the two regions (shown in Figure 11a) as statistically significant – the pars orbitalis region of the right inferior frontal gyrus (BA 47) and right lateral orbital frontal cortex (BA 11). An ROI from each of these regions was generated and mapped back to each individual subject. The mean thickness for each of these two ROIs was extracted, and scatter plots were generated, showing the significant positive relationship between cortical thickness and source monitoring accuracy (Figure 11b).

Figure 11

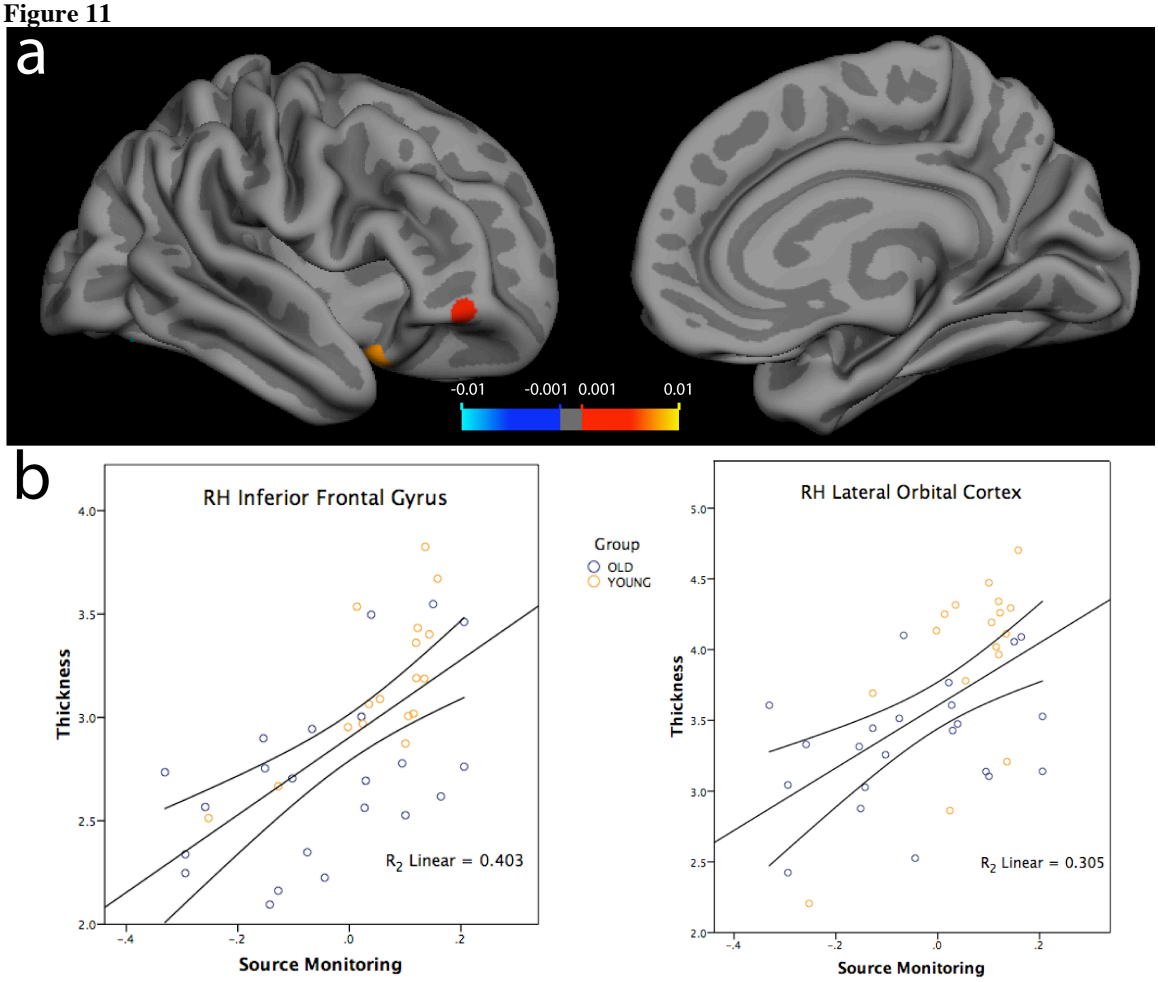


Figure 11. Regions of cortical thickness that correlate with source memory monitoring.

Using the entire sample of subjects, whole brain analysis was used to identify regions where cortical thickness was correlated with source memory monitoring performace, while controlling for effects of age. A monte carlo simulation was used to correct for multiple comparisons, and panel **a** shows the regions that survived this correction – the right pars orbitalis region of the inferior frontal gyrus (p<0.005) and the right lateral orbitofrontal cortex (p<0.01). There were no significant clusters in the left hemisphere. An ROI was generated from each of these resulting regions, mapped back on to each individual subjects' right hemisphere and the mean cortical thickness for each ROI was extracted. Scatter plots were generated from these values that show the correlation between mean cortical thickness and source monitoring performance, with 95% confidence intervals around the best-fit line, are shown in panel **b**

Additional analyses were done to uncover correlations between thickness and 5-HTTLPR status, as well as an interaction between accuracy and genotype, however these analyses yielded non-significant results. They are described more fully in Appendix B.

PFC Volumes Correlate With Source Monitoring

In order to assess the relationship of key prefrontal regions to performance on the memory monitoring task regional ROIs were created from FreeSurfer generated cortical parcellations. Using the entire sample of subjects, both old and young combined, there were a few regions of the PFC and MTL that showed correlations with memory monitoring accuracy, (ROIs shown in Figure 12, correlations summarized Table 7).

Figure 12

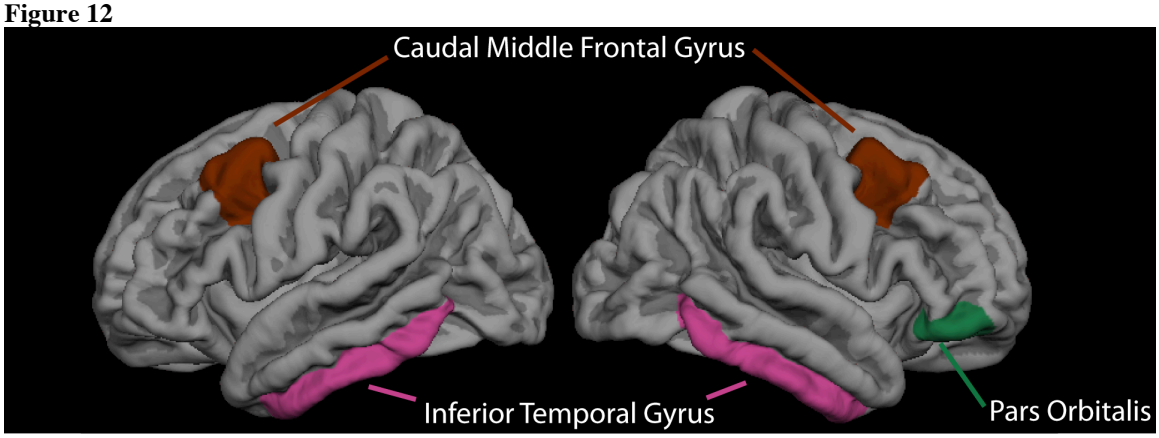


Figure 12. Anatomical ROIs associated with source memory monitoring.

Automatically generated ROIs from the FreeSurfer parcellation were used to extract gray matter volume from each individual subject. Shown above are the 5 regions that were significantly correlated with source memory monitoring performance.

The gray matter volume of the caudal middle frontal gyrus showed a significant positive correlation with source memory monitoring accuracy – those individuals with larger volumes in these regions performed better at the source monitoring task. There was

no relationship between the volume of the underlying white matter in these same regions and source monitoring performance. This effect was true for both the right and left hemispheres. A similar positive correlation was seen in the gray matter of the right orbitalis region of the inferior frontal gyrus, again with no relationship between the white matter volume and performance. One region of the temporal lobe, the inferior temporal gyrus, showed a positive correlation between both the gray and underlying white matter volumes with source monitoring accuracy. Additional analyses were performed to uncover regional volumes that correlate with genotype status, however these analyses were likely hindered by small sample sizes and did not yield any significant results. The analyses are summarized in Appendix B.

Table 7. Correlations between cortical volume and source memory monitoring accuracy.

Left Hemisphere ROI	Brodmann Area	$r_{(37)}$	Right Hemisphere ROI	Brodmann Area	$r_{(37)}$
Caudal Middle Frontal	46	0.365*	Caudal Middle Frontal	46	0.483**
Entorhinal	28/34	0.175	Entorhinal	28/34	-0.063
Fusiform	37	0.071	Fusiform	37	0.240
Inferior Temporal‡	20	0.331*	Inferior Temporal‡	20	0.391*
Lateral Orbital Frontal	47	0.219	Lateral Orbital Frontal	47	0.288
Medial Orbital Frontal	11	0.190	Medial Orbital Frontal	11	0.250
Middle Temporal	21	0.268	Middle Temporal	21	0.282
Parahippocampal	36	0.256	Parahippocampal	36	0.219
Pars Opercularis	44	0.166	Pars Opercularis	44	0.291
Pars Orbitalis	47	0.251	Pars Orbitalis	47	0.349*

Table 7 continued.

Left Hemisphere ROI	Brodmann Area	$r_{(37)}$	Right Hemisphere ROI	Brodmann Area	$r_{(37)}$
Pars Triangularis	45	0.150	Pars Triangularis	45	0.291
Rostral Middle Frontal	46	0.238	Rostral Middle Frontal	46	0.253
Superior Frontal	9	0.318	Superior Frontal	9	0.310
Superior Temporal	41/42	0.186	Superior Temporal	41/42	0.058
Supramarginal	40	0.150	Supramarginal	40	0.061
Frontal Pole	10	0.317	Frontal Pole	10	0.317
Temporal Pole	38	0.271	Temporal Pole	38	0.222

*p<0.05; **p<0.005 ‡ gray matter and underlying white matter

Table 7

Linear regression analyses examined the association between memory monitoring accuracy, 5-HTTLPR genotype, and cortical morphometry. Each PFC region was entered in to a separate regression model, as there were no effects seen when combining regions into one larger analysis. Regression results (summarized in Table 8) revealed that cortical morphometry and 5-HTTLPR carrier status separately predict memory monitoring accuracy. It should be noted that the negative beta values for genotype indicate that subjects with at least one s-allele have lower memory monitoring scores. Likewise, positive beta values for the ROI volume indicate that subjects with greater volumes have higher memory monitoring scores.

Table 8. Regression models predicting source memory monitoring accuracy from cortical morphometry and genotype.

	Unstandardized Coefficients		Standardized Coefficients			
	B	SE	ß	$t_{(27)}$	R^2	$F_{(1,27)}$
Right Pars Orbitalis					0.456	10.893**
Thickness	0.103	0.043	0.377	2.408		
Genotype	-0.144	0.052	-0.435	-2.779		
Right Orbital Frontal Cortex					0.496	12.813**
Thickness	0.177	0.061	0.482	2.890		
Genotype	-0.103	0.055	-0.312	-1.877		
Left Caudal Middle Frontal					0.502	12.579**
Volume	0.727	0.240	0.431	3.037		
Genotype	-0.202	0.048	-0.603	-4.255		
Right Caudal Middle Frontal					0.517	13.369**
Volume	0.753	0.235	0.449	3.210		
Genotype	-0.173	0.047	-0.516	-3.691		
Right Pars Orbitalis					0.366	7.201*
Volume	1.112	0.810	0.235	1.373		
Genotype	-0.160	0.057	-0.478	-2.789		
Left Inferior Temporal					0.364	7.145*
Volume	0.318	0.236	0.221	1.345		
Genotype	-0.171	0.055	-0.510	-3.103		

Table 8 continued.

	Unstandardized Coefficients		Standardized Coefficients			
	B	SE	ß	$t_{(27)}$	R^2	$F_{(1,27)}$
Right Inferior Temporal					0.420	9.047**
Volume	0.465	0.221	0.333	2.098		
Genotype	-0.157	0.053	-0.469	-2.952		

*p<0.005; **p<0.001

Table 8

These results align to reveal that both cortical thickness and cortical volume are predictive of source monitoring accuracy. The results overlap with the right orbitalis region of the IFG showing both thickness and volume effects. Right orbital frontal effects are seen only with cortical thickness, and caudal middle frontal and inferior temporal gyrus associations are only seen for cortical volume and not thickness.

DIFFUSION ANALYSIS

Fractional anisotropy was calculated for each subject based on their diffusion tensor data. Whole brain analyses were conducted using a tract-based spatial statistics (TBSS) method that first involves registering all subjects together in standard space and then making voxelwise comparisons between subjects. The program *Randomise* was used for permutation testing and the threshold-free cluster enhancement (TFCE) method was implemented for cluster thresholding. We also used a pathway of interest (POI) analysis to examine changes in FA specific to the uncinate fasciculus and other critical frontal-limbic pathways.

Participants

Twenty-two older adults (12 male; mean age = 67.0 ± 6.5, age range = 60-81; 21 caucasian, 1 african american) were included in the final analyses. Within this group there were 14 older adult carriers and 8 older adult non-carriers.

Associations between 5-HTTLPR and Fractional Anisotropy

Within the older adults, whole brain comparisons were done comparing carriers (CAR) of the short allele of the 5-HTTLPR gene and non-carriers (NC), to reveal regions where fractional anisotropy were significantly different. This uncovered two main regions of the white matter – the first within the right orbital frontal cortex along the inferior fronto-occipital tract and portions of the uncinate fasiculus, and the second within the left parietal cortex along the corticospinal tract and near the cingulum (Figure 13). In these regions the NC group had significantly higher FA values than the CAR group. A mask of this frontal region was made to extract mean FA values from each individual subject, a graph of group differences is shown in Figure 13.

Figure 13

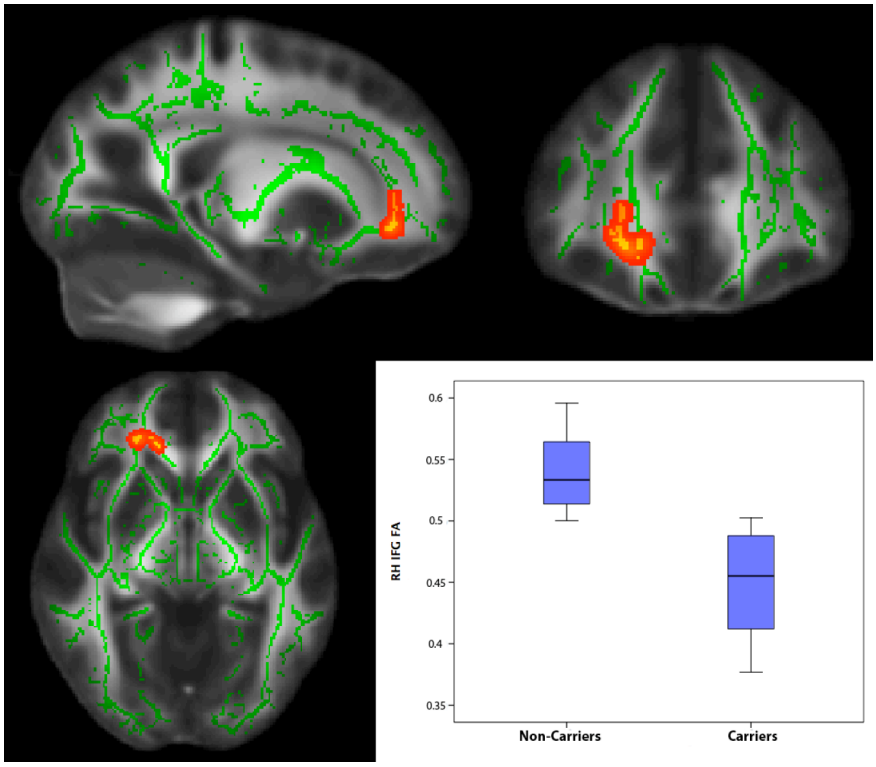


Figure 13. Fractional aniosotropy associated with 5-HTTLPR genotype.

Within the older adults, whole brain analysis was used to identify regions where fractional anisotropy is significantly different between 5-HTTLPR short allele carriers and non carriers. Three views of the brain (sagittal, coronal, and horizontal) are shown, with a mean FA map (in grayscale) the mean FA skeleton (in green) and the significant region (in heat scale). Full brain analysis was constrained to the white matter skeleton, and results were inflated for visualization purposes. The significant regions lie solely along the skeleton, shown in green. A binarized mask of this significant region was generated to extract mean FA values from each subject, and the resulting box plot shows the significant difference in mean FA between the non-carriers and carriers.

Prior work had uncovered a relationship between a frontal region of the uncinate fasiculus and the number of 5-HTTLPR short alleles (Pacheco, Beevers et al. 2009). In order to assess this in the current sample the same masks of the uncinate fasiculus were used to extract FA values from the older adult sample. ANOVA analysis reveals that

there is a significant reduction of FA ($F(1,15)$=6.648, p=0.022) in the frontal portion of the right uncinate fasiculus for the older adult carriers (shown in Figure 14).

Figure 14

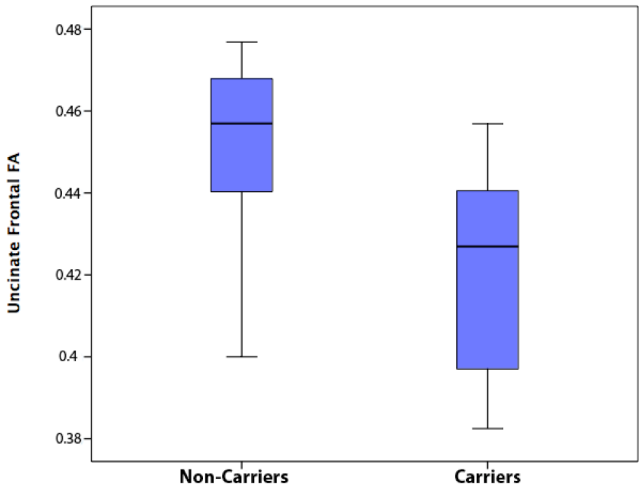


Figure 14. FA differences within the RH uncinate fasiculus for older adults.

The uncinate fasiculus was split into a frontal and a temporal region, for both hemisphere, and these masks were used to extracted FA values from each subject. ANOVA analysis revealed a significant difference in FA value for the frontal region of the right uncinate fasiculus when comparing 5-HTTLPR short allele carriers and non-carriers.

Additional analyses were done, namely trying to uncover regions where the FA values were associated with memory monitoring performance. These, however, did not yield any significant results and are described in more detail in Appendix B.

DISCUSSION

The primary goal of this study was to investigate the relationships between brain structure, 5-HTTLPR genotype and performance on a source memory monitoring task. It has been well documented that age-related brain atrophy has a primary focus on regions

of the frontal lobe (Raz, Lindenberger et al. 2005; Dennis and Cabeza 2008), and these regions are known to play a functional role in memory monitoring (Schnyer, Verfaellie et al. 2004; Chua, Schacter et al. 2006). Exploring the relationships between cortical structure and task performance can offer insight into the functional neuroanatomy associated with performance declines in aging. The results indicate that there are strong and independent associations between the volumes in specific cortical regions, genotype and source memory monitoring accuracy.

Based on multiple approaches to structural analysis, including cortical thickness and volume, the inferior frontal gyrus (IFG) has been identified as a key region of association between structure and behavioral performance. The IFG has been shown to be a critical component of the network thought to support memory monitoring (Wagner, Maril et al. 2001). It is involved in tasks that require inhibition (Wagner, Gais et al. 2001; Dobbins, Foley et al. 2002) and selection among competing choices(Hirshorn and Thompson-Schill 2006). These results suggest that it could be the age-related changes in the IFG underlying the memory monitoring performance declines seen in older adults.

Structural Morphometry Associated with Source Memory Monitoring Accuracy

It has been suggested that one of the changes in older adults that relates to memory monitoring is a loss of inhibitory control over retrieval results. As a result, older adults are prone to mistakenly combine features from one event with features from other events (Kroll, Knight et al. 1996; Henkel, Johnson et al. 1998; Koutstaal, Schacter et al. 2001). This recombination error can result in salient, but incorrect, memories and produce highly confident feelings of accuracy (Dodson and Krueger 2006) leading to declines of memory monitoring performance for source memory. The task used in this study requires the subject to distinguish between two competing sources, which requires

a large degree of inhibition of irrelevant information. A failure to adequately inhibit information can lead to extraneous information being present in working memory and causing distractions when trying to make accurate selections. This interference makes assessing memory performance more difficult.

There have been many recent studies that have uncovered positive relationships with the inferior and lateral PFC volumes and cognitive processes. Elderkin-Thompson et al., (2008) compared regional volumes of the prefrontal cortex to performance on a variety of neuropsychological measures, including the Wisconsin Card Sorting Task and Controlled Oral Word Association. They observed increases in spontaneous responses during the WCST and COWA, indicating a lack of inhibition that was related to volume loss in the orbitofrontal cortex. Zimmerman et al., (2006) revealed an age-dependent positive relationship between the lateral frontal cortex volume and executive function. In this study, executive function was defined as performance on several neuropsychological tests including Digit Span backwards, Switching of Attention task part 2, Verbal Interference part 2, and the Maze Task. All of these executive function tasks require careful control of cognitive actions, including inhibition from interfering information. These results indicate that aging changes an individual's ability to plan and control cognitive actions and this ability is related to the amount of gray matter in the PFC.

In my sample, two regions of the inferior frontal cortex were directly associated with source memory monitoring, as revealed through whole brain analysis of cortical thickness. For these regions, thinner cortex was associated with lower source monitoring accuracy. Through regional volume measurements, significant positive relationships were found between the volumes of lateral and inferior prefrontal cortex and memory monitoring accuracy. While this suggests that greater amounts of PFC gray matter are required for success on source memory monitoring tasks, there has been disagreement

among the literature when relating lateral prefrontal thickness to cognitive performance. Some research shows that within older adults there is a negative relationship (i.e., greater regional volumes predict lower performance; Salat, Kaye et al. 2002; Elderkin-Thompson, Ballmaier et al. 2008). Other reports have suggested that the relationship varies with age, and report middle aged adults (in their 40s) as having a positive relationship between thickness and measures of episodic memory, while older adults (in their 60s) show a negative relationship (Gautam, Cherbuin et al.). And different yet, some studies indicate that disease prognosis has differing effects, with healthy older adults showing a negative relationship with tasks of executive function, but patients with Alzheimer's disease showing a positive one (Duarte, Hayasaka et al. 2006). These results, taken with my current study, strongly indicate that increased gray matter volume is associated with increases in source memory monitoring performance. This association is localized, both in our data and other studies, to regions known to play a significant role in inhibition of extraneous information and assessment of cognitive performance. I suggest that the declines seen in performance of older adults could be due to the age-related atrophy of crucial regions.

A recent study looked at the effects of source memory performance and cortical thickness to see if the relationship could be modulated by behavioral intervention. Engvig et al., (Engvig, Fjell et al. 2011) imposed an 8-week memory training on one group of older adults and compared cortical thickness and memory performance pre- and post-training with a group of controls. They discovered that after 8-weeks of training, older adults improved their source memory accuracy significantly, and also observed an increase in cortical thickness in the orbitofrontal cortex. The group that did not receive the training saw no such performance or thickness benefit. The implications of this result on our finding suggest, not only that there is a direct relationship between cortical

thickness of the orbital cortex and tasks involving source memory, but further suggest that this decline is reversible with additional cognitive training.

Behavioral findings revealed a relationship between genotype and performance, which may also be related to changes in IFG volume. The results from linear regression analysis indicate that there is an independent relationship between genetic status and source memory monitoring performance. As there were no direct relationships seen between gray matter morphometry and genotype, perhaps due to a small sample size, it is apparent that the number of short 5-HTTLPR alleles affects memory monitoring through a different mechanism.

Fractional Anisotropy Associations with 5-HTTLPR Genotype

In contrast to the lack of a relationship between cortical thickness and volume with 5HTTLPR genotype, results from DTI analysis indicate a significant effect of genotype on white matter structure. Previous research has demonstrated a relationship between the number of short 5-HTTLPR alleles and the fractional anisotropy of the white matter along a cortico limbic tract – the uncinate fasciculus (Pacheco, Beevers et al. 2009). It was suggested that the lower FA values along the UF were associated with a lower level of functional coupling between the PFC and amygdala that could be reflected in less regulated emotional responses since s-carriers are known to be at greater risk of mood disorders (Pacheco, Beevers et al. 2009). My current results converge in a frontal region of the right hemisphere, where the fractional anisotropy is lower for carriers of the s-allele than for non-carriers. The population used for this analysis was older than that of the previous study, but still show that the presence of one or more s-alleles is related to altered connectivity with pathways that are responsible for communication between limbic structures and prefrontal structures. These pathways are part of a network involved

in memory monitoring and likely help coordinate memory retrieval, dependent on the hippocampus and medial temporal lobe, with the memory monitoring in the prefrontal cortex. While there was no direct relationship between genotype status and any cortical morphometry measure, genotpye was observed to be an independent predictor of memory monitoring status. The results from the diffusion analysis suggest that the genotype effect could potentially be mediated through the white matter microarchitecture. The older adults who lack a copy of the short allele have been shown to perform better on source memory monitoring tasks compared to the carriers of a short allele. Whereas the age-related decline is thought to be mediated by normal atrophy of the PFC gray matter, perhaps the older adults who lack a short allele are able to maintain better communication between the hippocampus and PFC to compensate for the normal loss of gray matter.

The prior finding in adolescent adults was localized to the left hemisphere, whereas our finding with older adults is localized within the right hemisphere. While it may be possible that there is a hemisphere shift in this gene-white matter relationship that occurs with age, it is more likely that the differences lie in statistical power. Both studies suffer from a relatively small sample size, and with greater numbers a more bilateral pattern is thought to emerge. The two samples of subjects, adolescents and older adults, were not combined into a larger analysis, because the overall age differences in the sample would likely overrun any genetic effect that we could see.

Summary

The current study uncovered strong positive associations between both cortical thickness and cortical volume with source memory monitoring performance, as well as independent associations between 5-HTTLPR genotype and task performance. The results all converge to implicate the inferior frontal cortex as playing an important role in

predicting cognitive performance on a source memory monitoring task. These results indicate that the amount of gray matter is important to task performance, and it may be that the age-related decline in source monitoring accuracy is a result of the amount of normal atrophy that occurs within the inferior and lateral prefrontal. There was no direct relationship between genotype status for the 5-HTTLPR genotype and cortical morphometry, however an association between fractional anisotropy measures of the white matter and the number of short alleles was revealed. The microarchitecture of the white matter paths traveling into the prefrontal cortex are altered for subjects carrying one or more copies of the short allele. Taken together, these results suggest that the effect of genotype on source monitoring performance occurs through the relationship with white matter pathways. Older adults who do not carry a short allele of the 5-HTTLPR gene may be able to compensate for loss of gray matter volume in prefrontal regions by maintaining connections to the limbic structures when performing tasks that require accurate memory monitoring.

Chapter 5: General Discussion

The studies reported here were designed to characterize the age-related decline in memory monitoring performance by exploring the neuroanatomical and genetic contributions to the decline. A functional MRI task that required selection of one of two competing sources of previously learned material was used to better understand the functional neural correlates of the decline in performance for older adults. Looking at genetic contributions, a split was seen within the older adults as one genetic group maintained behavioral performance compared to younger adults. This group also showed greater activation for critical neural regions that was lacking in the other genetic group. This ability may arise from structured connections between key regions of the memory monitoring network, allowing for continued functional recruitment. It appears that this genetic group may have additional neuroanatomical benefits to help compensate for the normal age-related decline of source memory monitoring.

As expected, the behavioral results from this task replicated what has previously been well-documented in the literature, older adults are worse at both source accuracy and source monitoring when compared to younger adults. The metamemory task utilized in this work obtained confidence ratings to provide a measure of how well participants were able to monitor their memory retrieval. The competitive nature of the source selection in this task requires the ability to focus on relevant, while ignoring irrelevant information, and is a process known to be difficult for older adults (Dodson and Krueger 2006). Typically, through cue specification, people are able to trigger memory retrieval based on available information in working memory. This initiation of retrieval becomes increasingly difficult if working memory is cluttered with irrelevant information, which is likely what happens with older adults (Zacks, Hasher et al. 2000). When cue specification

fails, and irrelevant information is used to initiate memory retrieval, the resulting memories can often be salient and highly believable, albeit incorrect, which can lead to high feelings of accuracy in the face of failure (Johnson, Hashtroudi et al. 1993; Dodson and Krueger 2006).

One important issue that arises in work on cognitive aging is the large degree of variability of decline. Many investigators have tried to characterize this variability as potentially reflecting the early stages of cognitive decline due to dementia (Dickerson and Sperling 2005) or cardiovascular disease (Leritz, Salat et al.). One other important potential source of individual differences in cognitive aging is genetics. Evidence from twin studies suggests that up to 80% of the variance of general cognitive ability seen in older adults can be explained by genetics, and when looking at specific cognitive domains, up to 40% of the variance in memory performance has been shown to be related to genetics (Plomin, Pedersen et al. 1994). To explore the genetic contributions to changes in memory monitoring in aging, behavioral, functional and structural neural associations with the serotonin transporter gene polymorphism (5-HTTLPR) were examined.

The serotonin system has previously been tied to memory performance and changes in this system are seen in many memory disorders (for a review see, McEntee and Crook 1991). Recently, pharmacological enhancements of serotonin levels in the brain have shown to increase memory performance in animals as well as patients with both dementia and amnesia (Perez-Garcia and Meneses 2008). One aspect of the sertonin system that has been extensively studied are transporter molecules. Serotonin communication in the brain is controlled by the serotonin transporter (5-HTT), which is responsible for clearing the synapse and recycling serotonin into the presynaptic cell. A common genetic polymorphism in the 5-HTT gene (SLC6A4 located on chromosome

17q11.1-q12), the 5-HTTLPR, has received a lot of recent attention (Hariri and Holmes 2006). The 5HTTLPR polymorphism contains a variable repeat sequence in the promoter region and encodes two allelic forms – a short allele with 14 base pair repeats and a long allele with 16 repeats. The allele typescontribute to the amount of serotonin transported available at the synapse. Persons who have one or more short alleles have been shown to have less efficient re-uptake of serotonin. The 5-HTTLPR polymorphism has been studied a great deal in relation to mood disorders, often being though to represent genetic vulnerability to depression. Recent work has suggested that the polymorphism plays a role in the cognitive control of emotion, through effects on the white matter pathway that provides connection to control regions of the prefrontal cortex. Likewise, carriers of the short allele have shown reduced functional coupling between emotional response regions and prefrontal control regions (Heinz, Braus et al. 2005), as well as increased difficulty releasing attention from irrelevant stimuli (Beevers, Pacheco et al. 2009).

The genetic contribution to memory monitoring performance was evaluated within the older adults by comparing those that carry at least one copy of the short allele of the 5-HTTLPR gene and those who do not. The results indicate that older adult carriers of the short allele performed worse on both source memory and source monitoring aspects of the tasks relative to older adults who lacked a copy of the short allele. Further, the older adult non-carriers performed equivalent to younger adults (see Chapter 3, Figure 8). This result is consistent with the proposition that older adults who lack a short allele show significantly less decline in their memory monitoring ability than those who carry a short allele, who do show significant age-related decline. This protective property was further explored by examining neuroanatomical correlates of the source memory task.

Finding neuroanatomical properties that correlate with behavioral measures can be informative about the regions that are related to task performance. The results of the structural analysis indicated a strong relationship between the inferior frontal gyrus (IFG) and task performance; individuals who have less cortical volume or cortical thickness for these regions of IFG also show lower source memory monitoring accuracy. The IFG has shown to be involved in process of cue selection (Dobbins, Foley et al. 2002) and inhibition (Aron, Robbins et al. 2004), processes that are critical for successful performance of the task utilized here (Dobbins, Foley et al. 2002; Schnyer, Nicholls et al. 2005). The association between IFG volume and source memory monitoring performance further implies that reductions in IFG volumes due to age-related changes could be a contributing factor behind the decline in performance.

There was no apparent relationship between gray matter morphometry and 5-HTTLPR genotype. There was, however, a significant relationship between white matter microarchitecture and genotype. The current study replicated a previous result from our lab (Pacheco, Beevers et al. 2009), where a relationship was seen between the number of short alleles and the fractional anisotropy of the white matter pathway connecting medial temporal structures to the prefrontal cortex. This relationship was suggested to reflect a decreased functional coupling, corresponding to what has been shown in short allele carriers for tasks that involve emotional regulation. The lateral PFC has been involved in shifting attention away from irrelevant stimuli, and prior work from our lab has shown that this is more difficult for carriers of the short allele (Beevers, Pacheco et al. 2009). The process of memory monitoring requires similar inhibition of distracting information, and the lateral PFC may play a role in keeping irrelevant memory cues from invading the retrieval efforts of the MTL. Fractional anisotropy differences seen within the uncinate

fasciculus for short allele carriers may be reflective of better connectivity, which can aid in the inhibitory control of memory.

It is possible that genetics status offers the older adult non-carriers some protection against the age-related decline of memory monitoring monitoring as revealed through the effects of short alleles on brain structure and function. The non-carriers maintain more structured connections between the critical components of the memory monitoring network, which could contribute to better behavioral performance on source memory monitoring tasks. It could be that these older adult non-carriers are better able to compensate for age-related atrophy of the prefrontal regions by maintaining this stronger connection to the medial temporal lobe. Through this mechanism, those older adults who show a less structured white matter tract may be more hindered by loss of cortical matter. It could be the case that this relationship goes in a different direction, and the non-carriers maintain greater use of prefrontal regions through stronger white matter connections, which prevents the age-related atrophy. Evidence for this genetic-morphometry relationship was not seen in this study, however perhaps one would emerge with a larger number of participants.

The performance difference among the older adults was further characterized by comparing functional brain activation in older adult carriers to the non-carriers during accurate memory monitoring. This analysis revealed regions of the inferior and lateral prefrontal cortex that were significantly more active in adults without a short allele, than those that have one or more copies. This region was also significantly related to accurate memory monitoring within the younger participants alone. As discussed above, these regions have shown to be crucial in selection and inhibition processes during source memory monitoring. Both the younger adults and older adult non-carriers were able to recruit these regions to a greater extent when they were accurately monitoring their

memory retrieval, however the older adult carriers showed less activation in the inferior or lateral PFC. The inability to appropriately engage these regions, for the older s-allele carriers, suggests that they may have difficulty inhibiting irrelevant information and thereby are inappropriately selecting memory triggers that lead to inaccurate memory monitoring. It is likely that older adult carriers are more easily convinced into wrong source choices because of the failure to adequately select memory triggers.

The results of these studies are exciting, as they implicate a genetic profile that may offer some protection for older adults. Certainly, further explorations are required before any intervention or modification can be formally explored. I suggest that if we can further classify the behavioral processes that are most declined in older adults, like inhibition, then perhaps strategies can be developed to better engage these mechanisms. Older adults could be taught to pay specific attention to the extraneous cues that may leak in, and only use those that they distinctly can remember, and not those cues that seem less concrete. Similarly, if the mechanism of genetic influence can be further characterized, there are potential biochemical interventions that might increase the level of available serotonin at critical pathway development periods, or during crucial ages when declines of white matter and cortical volume begin.

While these results are potentially provocative, there are significant reasons to remain cautious about them. By far the biggest shortcoming of this work is the sample size. For whole brain analyses, either functional or structural, the group sizes are modest and they are even smaller when participants are split based on genotype. A greater number of subjects would increase statistical power and add to the strength and generalizability of the results. With respect to generalizability, another potential drawback of the current sample, is the high level of education in both our older and younger adults. Recruitment of a more representative sample should be considered to rule

out any third variable effects of education. Lastly, the near complete lack of genetic data from the younger adults leaves a few questions unanswerable. While the genetic relationships identified in the older adults is truly an exciting finding, it would be similarly interesting to see if these relationship exist already in the younger sample, or if they emerge only with increased age.

Moving forward, there are two lines of work that this project begets. First would be to try a different functional task, and see what neural support underlies other key components in the memory monitoring process. As it is, the current study worked to exploit the role of inhibition and cue selection in older adults. Alternative tasks could be designed to manipulate the amount of familiarity subjects have with specific items. Given their tendency to rely on familiarity over recollection, older adults may be susceptible to those manipulations as well. Additionally, monitoring can be explored in other realms of memory, word-pair associates, or semantic paradigms, to explore neural correlates for those tasks. Lastly, additional genetic contributions could begin to be explored in conjunction with the 5-HTTLPR polymorphism. It is not likely that the serotonin transporter gene works alone, and uncovering some other genetic interactions will certainly increase the understanding of the biochemical mechanism that appears to offer both neural and cognitive protection.

In summary, these results indicate that older adults who lack a short allele of the 5-HTTLPR genotype appear to show source monitoring abilities at levels equivalent to younger adults. While age-related atrophy is abundant in crucial inferior and lateral PFC structures, and related to normal age-related decline of source monitoring, older adult non-carriers may be able to compensate for this volume loss through stronger connections between the PFC and the medial temporal lobe. It is the case that older adult carriers show an inability to functionally recruit essential regions of the prefrontal cortex during

accurate memory monitoring, whereas the older adult non-carriers and younger adults show increased activation of inferior and lateral prefrontal cortex during the task. Taken together, these results begin to uncover a neuroprotective mechanism of the 5-HTTLPR genotype, wherein older adults may be able to prolong some cognitive abilities.

Appendix A: Summary of Data Collected

The following table summarizes the types of data available for each subject.

Subject	Genetics	Memory Monitoring Accuracy	# of useable T1 scans	Useable DTI	# of useable fMRI runs
Young Adults					
001	None	Yes	1	Yes	4
002	All	Yes	1	Yes	None
003	None	Yes	1	Yes	4
004	All	Yes	1	Yes	4
005	None	Yes	1	Yes	3
006	All	Yes	1	Yes	3
007	None	No	1	Yes	2
008	All	Yes	1	Yes	2
009	All	Yes	1	Yes	4
010	None	Yes	1	Yes	3
011	None	Yes	1	No	3
012	5HTTLPR	Yes	1	Yes	None
013	None	Yes	1	No	None
014	All	Yes	1	Yes	4
015	All	Yes	1	No	4
016	All	Yes	1	No	4

Subject	Genetics	Memory Monitoring Accuracy	# of useable T1 scans	Useable DTI	# of useable fMRI runs
Young Adults (continued)					
017	None	Yes	1	Yes	4
019	All	Yes	1	Yes	4
020	None	Yes	1	Yes	3
022	None	Yes	1	Yes	4
Older Adults					
001	5HTTLPR	No	2	Yes	None
002	5HTTLPR	No	2	Yes	None
003	All	No	1	No	3
004	All	Yes	2	Yes	4
007	All	Yes	2	Yes	4
009	BDNF, COMT	Yes	1	Yes	4
011	None	No	1	No	None
012	All	Yes	1	Yes	3
014	All	Yes	2	Yes	4
015	All	No	1	Yes	None
016	All	Yes	2	Yes	3
019	All	Yes	2	Yes	4
026	All	Yes	2	Yes	4

Subject	Genetics	Memory Monitoring Accuracy	# of useable T1 scans	Useable DTI	# of useable fMRI runs
Older Adults (continued)					
028	All	Yes	2	Yes	2
029	All	Yes	2	Yes	4
030	All	Yes	1	Yes	4
031	All	Yes	1	No	4
035	All	Yes	2	Yes	4
036	All	Yes	2	Yes	4
043	All	Yes	1	Yes	4
046	All	Yes	2	Yes	3
047	All	Yes	1	Yes	4
048	All	Yes	1	Yes	4
051	All	Yes	1	Yes	4
052	All	No	1	Yes	2
054	All	Yes	1	No	3
055	All	Yes	2	Yes	2
057	All	Yes	1	No	4

Appendix B: Non-Significant Analyses

This appendix contains descriptions of the various analyses that were attempted along the way, which did not yield any significant or conclusive results. While the above dissertation reflects a complete scientific story of results, it is not a comprehensive account of the entire investigation. Some of the original proposed analyses for this project did not work as planned, and they are described below. The most common problem encountered is due to small sample sizes, particularly when using genotype, and it would be interesting to look at this with a larger sample of older adults.

FMRI ANALYSES

Confidence levels

A main focus of the original proposal was to be able to look at differences in confidence ratings during memory monitoring. The task was designed to test this, by having subjects respond with either high- or low-confidence in their answer. The goal was to be able to directly contrast these items in an fMRI analysis. Once the data was fully collected it became obvious that this was going to be impossible. To be able to split responses up by confidence level, there would be eight resulting categories: StrongAccurateSource, WeakAccurateSource, StrongInaccurateSource, WeakInaccurateSource, StrongAccurateItem, WeakAccurateItem, StrongInaccurateItem, and WeakInaccurateItem. Unfortunately, the subjects were not reliably responding in all eight categories on each run. This is problematic from fMRI analysis standpoint, because FSL requires that each subject have the same number of EVs to be combined, and that none of those EVs be empty (empty EVs contain no timepoints). Initially, I began to discard any single run that had a missing EV, but this proved to be a large portion of the

data. In order to accurately process the functional results I had to collapse answer responses across confidence level, into: AccurateSource, InaccurateSource, AccurateItem, and InaccurateItem. Once this was done all data, except for 2 subjects, we retained.

It was primarily the WeakInaccurateItem responses that were unused, and certainly more of the Weak responses than Certain responses. Subjects had enough responses within the certain categories, and I was able to use those accuracy rates as a means of assessing memory monitoring.

Young vs Old

Another main focus of the original proposal included direct comparisons between young and old subjects for functional results, particularly of accurate memory monitoring. Direct comparisons of the older and younger adults produced very few regions of significant difference. Additionally, nothing remained when any correction for multiple comparison was done. Upon closer look at the Accurate Monitoring contrast, it appears that the older adult activations were being heavily driven by the older adults who lack a short allele. This pattern of activation was very similar to that of the younger adult group, which explains why there were no differences uncovered. The same small volume correction explained in the text, using the source memory map to constrain statistical search, was applied to direct YA and OA comparisons, but this did not help retain any statistically significant activation.

STRUCTURAL ANALYSES

Cortical Thickness

Looking at the scatter plots for the relationship between thickness and source memory monitoring accuracy, it looks as if the relationship is more apparent within the

older adults than within the younger adults. Analyses were tried with the older group alone, but there was no statistically significant relationship revealed. Statistical significance was only achieved with the addition of the younger subjects. This is likely due to the small sample size, and with more older adults, a significant relationship may emerge there without younger adults.

Similar analyses were run looking at regions where cortical thickness was associated with the number of short alleles. This was done using the number of short alleles as a regressor in the GLM model, and by doing a direct group comparison between carriers and non-carriers. No significant results were achieved, likely based on the very low numbers in these two groups. Particularly, there are very few non-carriers in the sample, finding a significant difference with a group of 6 is difficult. Also hindered by small sample size was any exploration into an interaction between genotype and thickness on source memory monitoring.

DTI Analysis

Whole brain analyses of regions where FA was related to source memory monitoring were performed. In order to test this, each subject's source monitoring score was entered as a regressor into the GLM model. While there were no statistically significant regions here, there were some "trends" seen when the statistical threshold was lowered to a very lenient level ($p>0.1$). Given this, some relationships may emerge with the addition of extra subjects.

Appendix C: MR Screening Form

University of Texas Imaging Research Center MRI Research Subject Screening Form

Date: ___ /___ /___ (Month / Day / Year) Exam Number: _____

Principal Investigator: _____ Level 2 User: _____

Name: _____ (Last / First / Middle Initial) Age: _____ Height: _____ Weight _____ lbs

Date of Birth: ___ /___ /___ (Month / Day / Year) Gender: ❑ Male ❑ Female Body part to be scanned: _____

Address: _____ (Street) Phone number: _____

_____ (City) _____ (State) _____ (Zip)

1. Have you had prior surgery or an operation (e.g., arthroscopy, endoscopy, etc.) of any kind? ❑Yes ❑No
   If yes, please indicate the date and type of surgery:

   Date: ___ /___ /___ (Month / Day / Year) Type of surgery: _____

   Date: ___ /___ /___ (Month / Day / Year) Type of surgery: _____

2. Have you had a prior MRI imaging study or examination? ❑Yes ❑No
   If yes, please specify:

   Body Part: _____ Date: ___ /___ (Month / Year) Facility: _____

   Body Part: _____ Date: ___ /___ (Month / Year) Facility: _____

   Body Part: _____ Date: ___ /___ (Month / Year) Facility: _____

3. Have you experienced any problem related to a previous MRI examination or MR procedure? ❑Yes ❑No
   If yes, please describe: _____
4. Have you had an injury to the eye involving a metallic object or fragment (e.g., metallic slivers ,shavings, foreign body, etc.)? ❑Yes ❑No
   If yes, please describe: _____
5. Have you ever been injured by a metallic object/foreign body (e.g., BB, bullet, shrapnel, etc.)? ❑Yes ❑No
   If yes, please describe: _____
6. Are you currently taking or have you recently taken any medication or drug? ❑Yes ❑No
   If yes, please list: _____
7. Are you allergic to any medication? ❑Yes ❑No
   If yes, please list: _____
8. Do you have a history of asthma, allergic reaction, respiratory disease, or reaction to a contrast medium or dye used for an MRI, CT, or X-ray examination? ❑Yes ❑No
9. Do you have anemia or any disease(s) that affects your blood, a history of renal (kidney) disease, renal (kidney) failure, renal (kidney) transplant, high blood pressure (hypertension), liver (hepatic) disease or seizures? ❑Yes ❑No
   If yes, please describe: _____

For female participants only: It is crucial that we find out whether there is any chance that you are pregnant.

10. Are you post menopausal? ❑Yes ❑No
11. Are you pregnant? ❑Yes ❑No
12. Do any of the following conditions apply:
    Has it been more than 28 days since your last menstrual period? ❑Yes ❑No
    Are you taking any type of fertility medication or are you having fertility treatments? ❑Yes ❑No
13. Are you currently breast feeding? ❑Yes ❑No

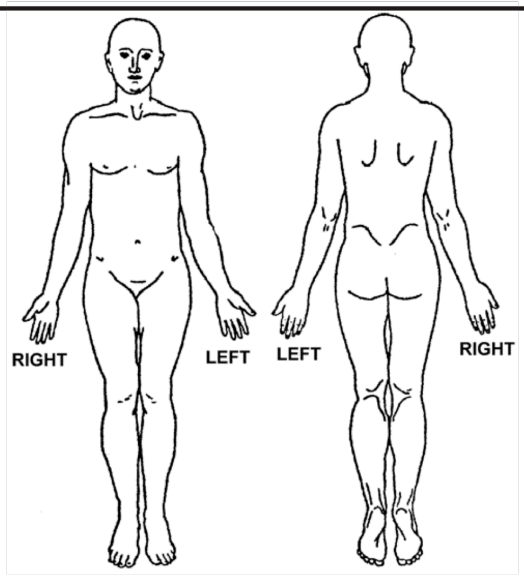
Subject Screening Form Version 090908/Luci

WARNING: Certain implants, devices, or objects may be hazardous to you and/or may interfere with the MR procedure (i.e., MRI, MR angiography, functional MRI, MR spectroscopy). Do not enter the MR system room or MR environment if you have any question or concern regarding an implant, device, or object. Consult the researcher BEFORE entering the MR system room. The MR system magnet is ALWAYS on.

Please indicate if you have any of the following:

- ❑Yes ❑No Aneurysm clip(s)
- ❑Yes ❑No Cardiac pacemaker
- ❑Yes ❑No Implanted cardioverter defibrillator (ICD)
- ❑Yes ❑No Electronic implant or device
- ❑Yes ❑No Magnetically-activated implant or device
- ❑Yes ❑No Neurostimulation system
- ❑Yes ❑No Spinal cord stimulator
- ❑Yes ❑No Internal electrodes or wires
- ❑Yes ❑No Bone growth/bone fusion stimulator
- ❑Yes ❑No Cochlear, otologic, or other ear implant
- ❑Yes ❑No Insulin or other infusion pump
- ❑Yes ❑No Implanted drug infusion device
- ❑Yes ❑No Any type of prosthesis (eye, penile, etc.)
- ❑Yes ❑No Heart valve prosthesis
- ❑Yes ❑No Eyelid spring or wire
- ❑Yes ❑No Artificial or prosthetic limb
- ❑Yes ❑No Metallic stent, filter, or coil
- ❑Yes ❑No Shunt (spinal or intraventricular)
- ❑Yes ❑No Vascular access port and/or catheter
- ❑Yes ❑No Radiation seeds or implants
- ❑Yes ❑No Swan-Ganz or thermodilution catheter
- ❑Yes ❑No Medication patch (Nicotine, Nitroglycerine)
- ❑Yes ❑No Any metallic fragment or foreign body
- ❑Yes ❑No Wire mesh implant
- ❑Yes ❑No Tissue expander (e.g., breast)
- ❑Yes ❑No Surgical staples, clips, or metallic sutures
- ❑Yes ❑No Joint replacement (hip, knee, etc.)
- ❑Yes ❑No Bone/joint pin, screw, nail, wire, plate, etc.
- ❑Yes ❑No IUD, diaphragm, or pessary
- ❑Yes ❑No Dentures or partial plates
- ❑Yes ❑No Tattoo or permanent makeup
- ❑Yes ❑No Body piercing jewelry
- ❑Yes ❑No Hearing aid *(Remove before entering MR system room)*
- ❑Yes ❑No Other implant _____
- ❑Yes ❑No Breathing problem or motion disorder
- ❑Yes ❑No Claustrophobia

Please mark on the figures below the location of any implant or metal inside of or on your body.



IMPORTANT INSTRUCTIONS

Before entering the MR environment or MR system room, you must remove all metallic objects including hearing aids, dentures, partial plates, keys, beeper, cell phone, eyeglasses, hair pins, barrettes, jewelry, body piercing jewelry, watch, safety pins, paperclips, money clip, credit cards, bank cards, magnetic strip cards, coins, pens, pocket knife, nail clipper, tools, clothing with metal fasteners, & clothing with metallic threads.

Please consult the experimenter if you have any questions or concerns BEFORE you enter the MR system room

NOTE: You are required to wear earplugs or other hearing protection during the MR procedure to prevent possible problems or hazards related to acoustic noise.

I attest that the above information is correct to the best of my knowledge. I read and understand the contents of this form and had the opportunity to ask questions regarding the information on this form and regarding the MR procedure that I am about to undergo.

Signature of person completing form:_____ Date:___/___/___
Signature Month Day Year

Form completed by: ❑Subject ❑Relative _____ _____
Printed Name Relationship to subject

Form reviewed by:_____ _____
Signature Printed Name

Appendix D: Health and Demographic Form

COVER SHEET

Subject # ____ ____ ____ ____ ____

Name _____ _____
(First name) (Last name)

Phone Number: (___ ___ ___) ___ ___ ___-___ ___ ___ ___ (home)

(___ ___ ___) ___ ___ ___-___ ___ ___ ___ (work) EXT:

_____

(___ ___ ___) ___ ___ ___-___ ___ ___ ___ (other)

E-mail address: _____

Street Address

_____

_____

City _____ State _____ ZIP ___ ___ ___ ___ ___-___ ___ ___ ___

Approved for Behavioral?

Yes No

Notes

_____

Approved for MRI?

Yes No

Notes

_____

Initials_____ Date __ __ / __ __ / __ __ __ __ (M M / D D / Y Y Y Y)

Demographic and Health Questionnaire

Screened: Initials _____ Date __ __ / __ __ / __ __ __ __

Database: Initials _____ Date __ __ / __ __ / __ __ __ __

Double Checked: Initials _____ Date __ __ / __ __ / __ __ __ __

*** * Ask health questions first. If yes to any marked with asterisks, exclude the person and discontinue the interview. * ***

* * Have you ever had a stroke?

Yes **No**

If yes, when did it occur? Have you had more than one? Have you noticed differences in what you can and cannot do since your stroke?_____

_____

_____

*** * Have you ever been diagnosed with epilepsy?**

Yes No

If yes,
when?_____

_____

*** * Have you used cocaine, ecstasy, or any IV drugs that were not for medical purposes?** Yes No

* * Have you used LSD?

Yes No

If yes, how extensively, (i.e. how long and how much?)

_____ _____

Demographic Information

Date of Birth __ __ / __ __ / __ __ __ __ **Age** _____ **Handedness**_____

Ethnicity (Circle all that apply: African American, Asian, Caucasian, Hispanic, Native American, Other). If other, specify ethnicity_____ **Gender**_____

Occupation_____

Highest Level of education? (circle one: grade school, some HS, graduated HS, trade school, some college, BS/BA, some grad school, MS/MA, JD, PhD, MD, other) If other, explain:_____

Name and place of school? What area of Study?_____

_____

_____

Years of education (use HS 12; AA 14; BA 16; MA 18; Law 19; PhD/MD 20 or round down!!) _____

Are you a native English speaker?

Yes No

If no, at what age did you begin formal education in English?_____

_____

Are you fluent in any language(s) other than English?

Yes No

If yes, which one(s)?

_____

_

Health Information

Have you ever had a seizure?

Yes No

If yes, when? Do you still have them? How often did you have them?

Medications?_____

_____

_____

How often do you drink alcohol? (i.e. how many times per week/month/year?)_____

_____

How many drinks do you do drink at a time?_____

What do you normally drink?_____

◊ **Do you/have you ever had a drinking problem?**

Yes No

IF YES, EXPLAIN.

_____

_____

◊ **Do you have a learning disability?**

Yes No

If yes, did you need to be removed from the regular classroom and take special education classes? Please explain the details:

_____

_____

_____

Do you have a heart condition?

Yes No

If yes, when did the problems begin? What is your condition? Medications?_____

_____

_____

Do you have hypertension?

Yes No

If yes, when did the problems begin? What is your condition? Medications?_____

_____

_____

Have you ever had a heart attack?

Yes No

If yes, when? How many? Have you noticed differences in what you can and cannot do since your heart attack? _____

_____

_____

Have you ever had a psychological problem that required treatment? (This includes depression, anxiety, etc.)

Yes No

If yes, explain. Taking medications?_____

_____

_____

Have you ever had a head injury?

Yes No

Have you ever lost consciousness?

Yes No

If yes to either of the above:

Age	Circumstances	Lose consciousness? Y/N If Y, how long?	Hospitalized? Y/N If Y, how long?	Any noticeable changes? (includes headaches) Y/N If Y, explain.

Have you ever had a neurological disorder or any other problem with your brain or head? Yes No

If yes, explain: _____

_____

_____

_____

Have you ever had any surgeries (especially on the heart or head)?

Yes No

If yes:

Date	Reason	Amount of Time in hospital

Do you have any problems controlling your movements that would prevent you from being able to write or manipulate small objects?

Yes No

If yes, explain: _____

_____

_____

Diabetes?

Yes No

If yes, explain: _____

_____

_____

Vascular Disease?

Yes No

If yes, explain: _____

_____

_____

Cancer?

Yes No

If yes, explain: _____

_____

_____

Arthritis?

Yes No

If yes, explain: _____

_____

_____

Alzheimers?

Yes No

If yes, explain: _____

_____

_____

Parkinsons?

Yes No

If yes, explain: _____

_____

_____

Do you have any other serious illnesses?

Yes No

If yes, explain: _____

_____

_____

Do you smoke cigarettes/cigars/pipe?

Yes No

Did you ever smoke?

Yes No

If yes, how long have you/ did you smoke?_____

Number of packs/cigars/pipes per day/week ?

_____

When did you quit? (if applicable)_____

Are you seeing a health care practitioner for any current medical or psychological problems? Yes No

If yes, explain.

_____

_____

_____

Are you taking any medications for these problems or for any other reason (Including vitamins, aspirin, and other regularly taken medications)?

Yes No

If yes:

Med Name	Dosage	Prescribed? Y/N	Duration of Medication	Reason/Illness

Are you now, or have you ever taken estrogen and/or used hormone replacement therapy? Yes No

Do you wear glasses or contacts? (important for using goggles for fMRI studies.)

Yes No

If yes, circle all that apply: regular glasses, bifocals, trifocals, contacts

Are you: near-sighted or far-sighted? **(circle one)**

Are you color blind?

Yes No

If yes, explain: _____

_____

_____

Do you have cataracts?

Yes No

If yes, explain: _____

_____

_____

Subject Demo & Health Family History Add-on

Can you think of anyone in your family (living or deceased) that has (or has had) a neurological disorder such as Alzheimer Disease, Dementia, Parkinson's or Huntington's?

Yes No

If yes, detail: _____

_____

_____

_____

Mother?

Yes No

If yes, detail: _____

_____

_____

Father?

Yes No

If yes, detail: _____

_____

_____

Grandmother?

Yes No

If yes, detail: _____

_____

_____

Grandfather?

Yes No

If yes, detail: _____

_____

_____

Aunt or Uncle?

Yes No

If yes, detail: _____

_____

_____

Cousin?

Yes No

If yes, detail: _____

_____

_____

Your children?

Yes No

If yes, detail: _____

_____

_____

Your siblings?

Yes No

If yes, detail: _____

_____

_____

Can you think of anyone in your family (living or deceased) that has (or has had) any other serious illnesses that I haven't mentioned?

Yes No

If yes, please detail: _____

_____

_____

_____

_____

References

Anderson, N. D., F. I. Craik, et al. (1998). "The attentional demands of encoding and retrieval in younger and older adults: 1. Evidence from divided attention costs." Psychol Aging 13(3): 405-23.

Andersson, J. L. R., M. Jenkinson, et al. (2007). "Non-linear optimisation." from www.fmrib.ox.ac.uk/analysis/techrep.

Andersson, J. L. R., M. Jenkinson, et al. (2007). "Non-linear registration, aka Spatial normalisation." from www.fmrib.ox.ac.uk/analysis/techrep.

Aron, A. R., T. W. Robbins, et al. (2004). "Inhibition and the right inferior frontal cortex." Trends Cogn Sci 8(4): 170-7.

Baltes, P. B. and U. Lindenberger (1997). "Emergence of a powerful connection between sensory and cognitive functions across the adult life span: a new window to the study of cognitive aging?" Psychol Aging 12(1): 12-21.

Beevers, C. G., J. Pacheco, et al. (2009). "Prefrontal morphology, 5-HTTLPR polymorphism and biased attention for emotional stimuli." Genes Brain Behav.

Brink, T. L., J. A. Yesavage, et al. (1982). "Screening tests for geriatric depression." Clinical Gerontologist 1: 37-43.

Brown, M. W. and J. P. Aggleton (2001). "Recognition memory: What are the roles of the perirhinal cortex and hippocampus?" Nature Reviews Neuroscience 2: 51-61.

Buckner, R. L. (2003). "Functional-anatomic correlates of control processes in memory." J Neurosci 23(10): 3999-4004.

Buckner, R. L. and M. E. Wheeler (2001). "The cognitive neuroscience of remembering." Nat Rev Neurosci 2(9): 624-34.

Bugg, J. M., N. A. Zook, et al. (2006). "Age differences in fluid intelligence: contributions of general slowing and frontal decline." Brain Cogn 62(1): 9-16.

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

Cabeza, R., S. M. Daselaar, et al. (2004). "Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval." Cereb Cortex 14(4): 364-75.

Cabeza, R., C. L. Grady, et al. (1997). "Age-related differences in neural activity during memory encoding and retrieval: a positron emission tomography study." J Neurosci 17(1): 391-400.

Caspi, A., K. Sugden, et al. (2003). "Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene." Science 301(5631): 386-9.

Chua, E. F., D. L. Schacter, et al. (2006). "Understanding metamemory: neural correlates of the cognitive process and subjective level of confidence in recognition memory." Neuroimage 29(4): 1150-60.

Chua, E. F., D. L. Schacter, et al. (2009). "Neural basis for recognition confidence in younger and older adults." Psychol Aging 24(1): 139-53.

Cohen, N. J. and H. E. Eichenbaum (1993). Memory, Amnesia, and the Hippocampal System, MIT Press.

Craik, F. I. and M. Byrd (1982). Aging and cognitive deficits: The role of attentional resources. Aging and cognitive processes. F. I. Craik and S. Trehub. New York, Plenum: 191-211.

Dale, A. M., B. Fischl, et al. (1999). "Cortical surface-based analysis. I. Segmentation and surface reconstruction." Neuroimage 9(2): 179-94.

Daselaar, S. M., M. S. Fleck, et al. (2006). "Effects of healthy aging on hippocampal and rhinal memory functions: an event-related fMRI study." Cereb Cortex 16(12): 1771-82.

Davidson, P. and E. Glisky (2002). "Neuropsychological correlates of recollection and familiarity in normal aging." Cognitive, Affective and Behavioral Neuroscience 2(2): 174-186.

Davis, S. W., N. A. Dennis, et al. (2008). "Que PASA? The posterior-anterior shift in aging." Cereb Cortex 18(5): 1201-9.

de Quervain, D. J., K. Henke, et al. (2003). "A functional genetic variation of the 5-HT2a receptor affects human memory." Nat Neurosci 6(11): 1141-2.

Delis, D. C., J. H. Kramer, et al. (1987). California Verbal Learning Test: Adult Version Manual. San Antonio, The Psychological Corporation.

Dempster, F. N. (1992). "The rise and fall of the inhibitory mechanism: toward a unified theory of cognitive development and aging." Developmental Review 12: 45-75.

Dennis, N. and R. Cabeza (2008). Neuroimaging of healthy cognitive aging. Handbook of aging and cognition: Third edition. F. I. Craik and T. A. Salthouse. Mahwah, NJ, Erlbaum.

Dickerson, B. C. and R. A. Sperling (2005). "Neuroimaging biomarkers for clinical trials of disease-modifying therapies in Alzheimer's disease." NeuroRx 2(2): 348-60.

Dobbins, I. G., H. Foley, et al. (2002). "Executive control during episodic retrieval: multiple prefrontal processes subserve source memory." Neuron 35(5): 989-96.

Dodson, C. S., S. Bawa, et al. (2007). "Aging, metamemory, and high-confidence errors: a misrecollection account." Psychol Aging 22(1): 122-33.

Dodson, C. S., S. Bawa, et al. (2007). "Aging, source memory, and misrecollections." J Exp Psychol Learn Mem Cogn 33(1): 169-81.

Dodson, C. S. and L. E. Krueger (2006). "I misremember it well: why older adults are unreliable eyewitnesses." Psychon Bull Rev 13(5): 770-5.

Duarte, A., S. Hayasaka, et al. (2006). "Volumetric correlates of memory and executive function in normal elderly, mild cognitive impairment and Alzheimer's disease." Neurosci Lett 406(1-2): 60-5.

Eakin, D. K. and C. Hertzog (2006). "Release from implicit interference in memory and metamemory: older adults know that they can't let go." J Gerontol B Psychol Sci Soc Sci 61(6): P340-7.

Eichenbaum, H., A. P. Yonelinas, et al. (2007). "The medial temporal lobe and recognition memory." Annu Rev Neurosci 30: 123-152.

Elderkin-Thompson, V., M. Ballmaier, et al. (2008). "Executive function and MRI prefrontal volumes among healthy older adults." Neuropsychology 22(5): 626-37.

Engvig, A., A. M. Fjell, et al. (2011). "Effects of memory training on cortical thickness in the elderly." Neuroimage 52(4): 1667-76.

Fischl, B. and A. M. Dale (2000). "Measuring the thickness of the human cerebral cortex from magnetic resonance images." Proc Natl Acad Sci U S A 97(20): 11050-5.

Fischl, B., D. H. Salat, et al. (2002). "Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain." Neuron 33(3): 341-55.

Fischl, B., D. H. Salat, et al. (2004). "Sequence-independent segmentation of magnetic resonance images." Neuroimage 23 Suppl 1: S69-84.

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

Fischl, B., A. van der Kouwe, et al. (2004). "Automatically parcellating the human cerebral cortex." Cereb Cortex 14(1): 11-22.

Freeman, B., J. Powell, et al. (1997). "DNA by mail: an inexpensive and noninvasive method for collecting DNA samples from widely dispersed populations." Behav Genet 27(3): 251-7.

Gautam, P., N. Cherbuin, et al. "Relationships between cognitive function and frontal grey matter volumes and thickness in middle aged and early old-aged adults: The PATH Through Life Study." Neuroimage 55(3): 845-55.

Gilboa, A., C. Alain, et al. (2006). "Mechanisms of spontaneous confabulations: a strategic retrieval account." Brain 129(Pt 6): 1399-414.

Grady, C. L., J. M. Maisog, et al. (1994). "Age-related changes in cortical blood flow activation during visual processing of faces and location." J Neurosci 14(3 Pt 2): 1450-62.

Gunning-Dixon, F. M. and N. Raz (2003). "Neuroanatomical correlates of selected executive functions in middle-aged and older adults: a prospective MRI study." Neuropsychologia 41(14): 1929-41.

Haider, S., S. Khaliq, et al. (2006). "Long-term tryptophan administration enhances cognitive performance and increases 5HT metabolism in the hippocampus of female rats." Amino Acids 31(4): 421-5.

Hariri, A. R. and A. Holmes (2006). "Genetics of emotional regulation: the role of serotonin transporter in neural function." Trends Cog Sci 10(4): 182-191.

Hasher, L. and R. T. Zacks (1988). Working memory, comprehension, and aging: a review and a new view. The Psychology of Learning and Motivation. G. H. Bower. San Diego, CA, Academic Press. 22: 193-225.

Heaton, R. K. (1981). Wisconsin Card Sorting Test Manual. Odessa, FL, Psychological Assessment Resources, Inc.

Heinz, A., D. F. Braus, et al. (2005). "Amygdala-prefrontal coupling depends on a genetic variation of the serotonin transporter." Nat Neurosci 8(1): 20-1.

Henkel, L. A., M. K. Johnson, et al. (1998). "Aging and source monitoring: cognitive processes and neuropsychological correlates." J Exp Psychol Gen 127(3): 251-68.

Hirshorn, E. A. and S. L. Thompson-Schill (2006). "Role of the left inferior frontal gyrus in covert word retrieval: neural correlates of switching during verbal fluency." Neuropsychologia 44(12): 2547-57.

Hu, X., G. Oroszi, et al. (2005). "An expanded evaluation of the relationship of four alleles to the level of response to alcohol and alcholism risk." Alcohol Clin Exp Res 29(1): 8-16.

Jennings, J. M. and L. L. Jacoby (1993). "Automatic versus intentional uses of memory: aging, attention, and control." Psychol Aging 8(2): 283-93.

Johnson, M. K., S. Hashtroudi, et al. (1993). "Source Monitoring." Psychological Bulletin 114(1): 3-28.

Kane, M. J., L. Hasher, et al. (1994). "Inhibitory attentional mechanisms and aging." Psychol Aging 9(1): 103-12.

Kelley, M. R. and J. S. Nairne (2003). "Remembering the forgotten? Reminiscence, hypermnesia and memory for order." Q J Exp Psychol A 56(4): 577-99.

Kemper, T. (1994). Neuroanatomical and neuropathological changes during aging and in dementia. Clinical neurology of aging. M. Albert, Knoepfel, EJE. New York, Oxford University Press.

Kikyo, H., K. Ohki, et al. (2002). "Neural correlates for feeling-of-knowing: an fMRI parametric analysis." Neuron 36(1): 177-86.

Koppel, J. and T. Goldberg (2009). "The genetics of episodic memory." Cogn Neuropsychiatry 14(4-5): 356-76.

Koutstaal, W., D. L. Schacter, et al. (2001). "Dual task demands and gist-based false recognition of pictures in younger and older adults." Journal of Memory and Language 44: 399-426.

Kroll, N. E. A., R. T. Knight, et al. (1996). "Cohesion failure as a source of memory illusions." Journal of Memory and Language 35: 176-196.

Lench, N., P. Stanier, et al. (1988). "Simple non-invasive method to obtain DNA for gene analysis." Lancet 1(8599): 1356-8.

Leritz, E. C., D. H. Salat, et al. "Thickness of the human cerebral cortex is associated with metrics of cerebrovascular health in a normative sample of community dwelling older adults." Neuroimage 54(4): 2659-71.

Lesak, M. D. (1995). Neuorpsychological assessment (3rd Edition). New York, Oxford University Press.

Levkovitz, Y., O. Ophir-Shaham, et al. (2003). "Effect of L-tryptophan on memory in patients with schizophrenia." J Nerv Ment Dis 191(9): 568-73.

Li, S. C. and U. Lindenberger (1999). Cross-level unification: A computational exploration of the link between deterioration or neurotransmitter systems and dedifferentiation of cognitive abilities in old age. Cognitive neuroscience of memory. L. G. Nilsson and H. J. Markowitsch. Seattle, WA, Hogrefe & Huber: 103-146.

Maril, A., J. S. Simons, et al. (2003). "Feeling-of-knowing in episodic memory: an event-related fMRI study." Neuroimage 18(4): 827-36.

Marquie, J. C. and N. Huet (2000). "Age differences in feeling-of-knowing and confidence judgements as a function of knowledge domain." Psychol Aging 15(3): 451-60.

McEntee, W. J. and T. H. Crook (1991). "Serotonin, memory, and the aging brain." Psychopharmacology (Berl) 103(2): 143-9.

McKenzie, E. C. (1976). Salted Peanuts: 1800 Little Known Facts. New York, Signet.

Meulenbelt, I., S. Droog, et al. (1995). "High-yield noninvasive human genomic DNA isolation method for genetic studies in geographically dispersed families and populations." Am J Hum Genet 57(5): 1252-4.

Modirrousta, M. and L. K. Fellows (2008). "Medial prefrontal cortex plays a critical and selective role in 'feeling of knowing' meta-memory judgments." Neuropsychologia 46(12): 2958-65.

Moscovitch, M. and G. Winocur (2002). The frontal cortex and working with memory. Principles of frontal lobe function. D. T. Stuss and R. T. Knight. New York, Oxford University Press: 188-209.

Nee, D. E., T. D. Wager, et al. (2007). "Interference resolution: insights from a meta-analysis of neuroimaging tasks." Cogn Affect Behav Neurosci 7(1): 1-17.

Nelson, T. O. and L. Narens (1990). "Metamemory: A theoretical framework and new findings." The Psychology of Learning and Motivation 26: 125-173.

O'Hara, R., C. M. Schroder, et al. (2007). "Serotonin transporter polymorphism, memory and hippocampal volume in the elderly: association and interaction with cortisol." Mol Psychiatry 12(6): 544-55.

Pacheco, J., C. G. Beevers, et al. (2009). "Frontal-limbic white matter pathway associations with the serotonin transporter gene promoter region (5-HTTLPR) polymorphism." J Neurosci 29(19): 6229-33.

Perez-Garcia, G. and A. Meneses (2008). "Memory formation, amnesia, improved memory and reversed amnesia: 5-HT role." Behav Brain Res 195(1): 17-29.

Perlmutter, M. (1978). "What is memory aging the aging of?" Developmental Psychology 14: 330-345.

Pfefferbaum, A., E. Adalsteinsson, et al. (2005). "Frontal circuitry degradation marks healthy adult aging: Evidence from diffusion tensor imaging." Neuroimage 26(3): 891-9.

Pierpaoli, C. and P. J. Basser (1996). "Toward a quantitative assessment of diffusion anisotropy." Magn Reson Med 36(6): 893-906.

Pliske, R. M. and S. A. Mutter (1996). "Age differences in the accuracy of confidence judgments." Exp Aging Res 22(2): 199-216.

Plomin, R., N. L. Pedersen, et al. (1994). "Variability and stability in cognitive abilities are largely genetic later in life." Behav Genet 24(3): 207-15.

Porter, R. J., B. S. Lunn, et al. (2003). "Effects of acute tryptophan depletion on cognitive function in Alzheimer's disease and in the healthy elderly." Psychol Med 33(1): 41-9.

Ranganath, C. and G. Rainer (2003). "Neural mechanisms for detecting and remembering novel events." Nat Rev Neurosci 4(3): 193-202.

Raz, N., U. Lindenberger, et al. (2005). "Regional brain changes in aging healthy adults: general trends, individual differences and modifiers." Cereb Cortex 15(11): 1676-89.

Resnick, S. M., D. L. Pham, et al. (2003). "Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain." J Neurosci 23(8): 3295-301.

Reuter-Lorenz, P. A., J. Jonides, et al. (2000). "Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET." J Cogn Neurosci 12(1): 174-87.

Rosas, H. D., A. K. Liu, et al. (2002). "Regional and progressive thinning of the cortical ribbon in Huntington's disease." Neurology 58(5): 695-701.

Rueckert, D., L. I. Sonoda, et al. (1999). "Nonrigid registration using free-form deformations: application to breast MR images." IEEE Trans Med Imaging 18(8): 712-21.

Rugg, M. D., L. J. Otten, et al. (2002). "The neural basis of episodic memory: evidence from functional neuroimaging." Philos Trans R Soc Lond B Biol Sci 357(1424): 1097-110.

Sabb, F. W., A. C. Burggren, et al. (2009). "Challenges in phenotype definition in the whole-genome era: multivariate models of memory and intelligence." Neuroscience 164(1): 88-107.

Salat, D. H., R. L. Buckner, et al. (2004). "Thinning of the cerebral cortex in aging." Cereb Cortex 14(7): 721-30.

Salat, D. H., D. N. Greve, et al. (2009). "Regional white matter volume differences in nondemented aging and Alzheimer's disease." Neuroimage 44(4): 1247-58.

Salat, D. H., J. A. Kaye, et al. (2002). "Greater orbital prefrontal volume selectively predicts worse working memory performance in older adults." Cereb Cortex 12(5): 494-505.

Salat, D. H., D. S. Tuch, et al. (2005). "Age-related changes in prefrontal white matter measured by diffusion tensor imaging." Ann N Y Acad Sci 1064: 37-49.

Salthouse, T. A. (1996). "The processing-speed theory of adult age differences in cognition." Psychol Rev 103(3): 403-28.

Schmitt, J. A., M. Wingen, et al. (2006). "Serotonin and human cognitive performance." Curr Pharm Des 12(20): 2473-86.

Schnyer, D. M., L. Nicholls, et al. (2005). "The role of VMPC in metamemorial judgments of content retrievability." J Cogn Neurosci 17(5): 832-46.

Schnyer, D. M., M. Verfaellie, et al. (2004). "A role for right medial prefontal cortex in accurate feeling-of-knowing judgements: evidence from patients with lesions to frontal cortex." Neuropsychologia 42(7): 957-66.

Sheline, Y. I., M. A. Mintun, et al. (2002). "Greater loss of 5-HT(2A) receptors in midlife than in late life." Am J Psychiatry 159(3): 430-5.

Shimamura, A. P. (1994). "Neuropsychological perspectives on memory and cognitive decline in normal human aging." Seminars in Neurosciences 6: 387-394.

Smith, S. M., M. Jenkinson, et al. (2006). "Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data." Neuroimage 31(4): 1487-505.

Spitz, E., R. Moutier, et al. (1996). "Comparative diagnoses of twin zygosity by SSLP variant analysis, questionnaire, and dermatoglyphic analysis." Behav Genet 26(1): 55-63.

Squire, L. R. (1992). "Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans." Psychol Rev 99(2): 195-231.

Stroop, J. R. (1935). "Studies of interference in serial verbal reactions." Journal of Experimental Psychology(18): 643-662.

Stuss, D. T. and D. F. Benson (1984). "Neuropsychological studies of the frontal lobes." Psychol Bull 95(1): 3-28.

Tulving, E. (1985). "Memory and conciousness." Canadian Psychology 25: 1-12.

Tulving, E. (1987). "Multiple memory systems and consciousness." Hum Neurobiol 6(2): 67-80.

Wagner, A. D., A. Maril, et al. (2001). "Prefrontal contributions to executive control: fMRI evidence for functional distinctions within lateral Prefrontal cortex." Neuroimage 14(6): 1337-47.

Wagner, A. D., B. J. Shannon, et al. (2005). "Parietal lobe contributions to episodic memory retrieval." Trends Cogn Sci 9(9): 445-53.

Wagner, U., S. Gais, et al. (2001). "Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep." Learn Mem 8(2): 112-9.

Wechsler, D. (1997). Wechsler Adult Intelligence Scale - Third Edition. San Antonio, Harcourt Brace & Company.

Worsley, K. J. (2001). Statistical analysis of activation images. Functional MRI: An Introduction to Methods. P. Jezzard, P. M. Matthews and S. M. Smith. OUP.

Yonelinas, A. P. (2002). "The nature of recollection and familiarity: A review of 30 years of research." Memory and Language 46: 441-517.

Zacks, R. T., L. Hasher, et al. (2000). Human Memory. Handbook of Aging and Cognition, 2nd Edition. T. A. Salthouse and F. I. Craik. Mahwah, NJ, Erlbaum.

Zahr, N. M., T. Rohlfing, et al. (2009). "Problem solving, working memory, and motor correlates of association and commissural fiber bundles in normal aging: a quantitative fiber tracking study." Neuroimage 44(3): 1050-62.

Zimmerman, M. E., A. M. Brickman, et al. (2006). "The relationship between frontal gray matter volume and cognition varies across the healthy adult lifespan." Am J Geriatr Psychiatry 14(10): 823-33.