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SUCCESSFUL COGNITIVE AGING: IMPLICATIONS OF EARLY ALZHEIMER'S
DISEASE DETECTION, LIFESTYLE CHOICES, AND ENVIRONMENTAL FACTORS

BY

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DISSERTATION

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Abstract

The question as to why one seventy-year-old has Alzheimer's disease and another continues to work productively carries with it profound societal implications. Determining the antecedents in one's life which shape his or her cognitive aging trajectory may allow for an increase in those who remain healthy and productive throughout senescence, which would alleviate multiple socioeconomic and emotional burdens. In the current report, a series of studies are documented aimed at understanding and promoting successful cognitive aging, defined as 1) the early detection and ultimate prevention of Alzheimer's disease, and 2) maximizing cognition in healthy older adults who are free of dementia. In studying these effects, particular emphasis has been given to the hippocampal memory system, given the impact aging and Alzheimer's disease has on the hippocampus. Turning to the empirical work, chapter two describes the use of a new memory task in young, healthy older, and very mild Alzheimer's disease participants to further delineate the cognitive manifestations of the earliest part of the disease. The data from this study support a multi-factorial model of aging, whereby the memory deficits in the earliest stages of Alzheimer's disease are qualitatively distinct than those from healthy aging. Chapter three uses principal components analysis to demonstrate that relational memory tasks developed in our lab, which could be considered non-traditional hippocampal based tasks, do indeed cluster with historic hippocampal based tasks such as delayed word-list recall, and that these newly developed tasks strongly relate to hippocampal structure. Chapters four and five then use these relational memory tasks to study the structure and function of the hippocampal memory system in aging as a function of history of mild traumatic brain injury (chapter four) and cardiorespiratory fitness and physical activity levels (chapter five). The results from chapter four indicate the combination of an early life mild traumatic brain injury and aging is associated with

smaller hippocampal volumes and worse memory relative to participants with no brain injury. Chapter five demonstrates the neuroprotective effects of maintaining cardiorespiratory fitness and engaging in an active lifestyle by illustrating benefits from these variables to memory performance and pathways in the hippocampal memory system. The implications and interrelatedness of these studies on successful cognitive aging is discussed in chapter six, including a discussion on future directions.

For my mother

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Chapter 1: Introduction

The study of cognitive aging affords opportunities for significant improvements in the public health and socioeconomic realms, along with making important advances to science. The demographic in many countries is shifting towards an aging population. Along with this shift, there is the likelihood that cases of neurodegenerative diseases such as Alzheimer's disease (AD) will increase, causing enormous burdens on nations' health systems. Furthermore, the inability of older adults to continue to work and live independently creates strain on the socioeconomic infrastructure of a country, along with intense emotional burdens for family members and caregivers. For these reasons, the identification of factors that promote successful cognitive aging is a crucial task for those performing research in the cognitive neuroscience of aging.

Successful cognitive aging (heretofore referred to as "successful aging") can have a myriad of meanings; for the purposes of this endeavor, it refers to two complimentary ideas. The first is the notion of living one's entire life free from any neurodegenerative disorders such as AD. Secondly, within those who are "cognitively normal" and have no neurodegenerative disease, successful aging refers to minimizing any cognitive decline typically deemed "normal" for one's age. The series of experiments described here seeks to promote these two goals via two methods. In terms of not developing clinical AD, the focus is on cognitive tasks that can identify AD in its earliest stages. This affords the best opportunity for any type of intervention to be successful. (Note: the term "clinical AD" is used here to denote the condition in which an individual is demonstrating noticeable cognitive problems, with "preclinical AD" referring to the situation in which one has underlying AD pathology with no neuropsychological deficits). With regard to maximizing cognitive abilities even in those deemed cognitively normal, an approach centered on the idea that lifestyle/environmental factors interact with the aging process to

produce various outcomes is pursued. It is of course the case that lifestyle/environmental factors interact with the probability that one will develop AD, but in the current series of reports, this approach was only used in older adults without clinical AD.

Given its susceptibility to aging and AD, plus its sensitivity to a wide variety of environmental effects, the primary brain system under investigation here is the hippocampus and its interactions with the adjacent medial temporal (MTL) cortex, subcortical structures (e.g., amygdala, striatum, thalamus), and neocortex in the service of cognition; together these regions collectively give rise to the hippocampal memory system. This introduction provides further motivation for focusing on the hippocampal memory system to meet the two goals for the study of successful aging listed above, as well as what cognitive framework is used to represent hippocampal-based cognition; this introduction concludes with a brief description of the individual experiments.

Vulnerable neural systems in aging

The biological aging process does not affect all brain regions and systems equally, leaving some areas largely spared, while others undergo multiple deleterious transformations. For instance, sensory areas such as primary visual cortex have minimal volume loss across the lifespan, and show the least amount of AD pathology, even in the end stages of AD (Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010; Yankner, Lu, & Loerch, 2008). In contrast, there are several networks and regions more susceptible to the aging process. One clear example of this is the prefrontal cortex (PFC), which is the site of demonstrable changes stemming from multiple factors. Vascular pathology in the white matter, as detected by white matter hyperintensities on T2 or FLAIR magnetic resonance images, microbleeds, and other subtle vascular lesions are common in aging and preferentially impact the PFC (Jagust, 2013;

Wen & Sachdev, 2004). Moreover, there are substantial changes to the morphology of the dorsolateral PFC (dlPFC) with regard to dendritic branching and synapse loss; specifically, animal models suggest that thin dendritic spines in the dlPFC are lost during aging, and given their highly plastic nature, may underlie working memory deficits in aging (Morrison & Baxter, 2012). These changes occurring in the PFC likely underlie the substantial volume loss that is noted in the PFC in longitudinal MRI studies of aging humans (Raz et al., 2005, 2010).

One brain network that is vulnerable to aging involves the PFC and its connections with posterior cingulate cortex (PCC) and parietal lobe, collectively forming the default-mode network (DMN; Buckner, Andrews-Hanna, & Schacter, 2008; Greicius, Krasnow, Reiss, & Menon, 2003). Similar to the PFC, the parietal lobe undergoes some structural volume loss with aging (Raz et al., 2005), but with respect to the DMN, functional MRI (fMRI) and positron emission tomography (PET) studies have been more informative in characterizing the transformations in this network due to aging. In older adults, it has been observed that these areas display less activity overall and show less coordinated activity between the individual regions; the latter finding may be particularly important in speaking to the network disruption that occurs with aging (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008). The regions of the DMN, particularly PCC and medial parietal lobe, are also the first to harbor the amyloid beta ($A\beta$) pathology associated with AD, and these regions typically show the densest accumulation of $A\beta$ (Buckner, 2004; Kennedy et al., 2012). PET studies have routinely detected $A\beta$ in living humans diagnosed with AD, and recent studies have documented the existence of $A\beta$ in older adults showing no signs of cognitive impairment, which may be indicative of preclinical AD (Kennedy et al., 2012; Mintun et al., 2006; Rodriguez et al., 2012; Sperling et al., 2011). Thus, several areas

of the neocortex, particularly those involved in higher order cognition, are vulnerable to the aging processes, whereas sensory areas are predominantly spared.

Moving deeper into the brain, the totality of evidence indicates that nearly all subcortical regions shrink with aging, including the thalamus, putamen, and nucleus accumbens; the only exception may be the caudate nucleus, where data have been equivocal (Fjell & Walhovd, 2010; Fjell et al., 2013; Raz et al., 2005). One subcortical region that displays a wide variety of pathological and morphological changes due to aging is the hippocampus, along with the adjacent MTL cortex (Jagust, 2013; Small, Schobel, Buxton, Witter, & Barnes, 2011). Through autopsy studies, it is now clear that, irrespective of having a diagnosis of AD, hyperphosphorylated tau lesions in the form of neurofibrillary tangles (NFTs) occur in nearly all older adults (Bennett, Wilson, Boyle, Buchman, & Schneider, 2012; Braak, Thal, Ghebremedhin, & Del Tredici, 2011; Price et al., 2009). The topographical pattern of these NFTs follows a strict pattern such that, in those without a diagnosis of AD, they are limited to the MTL, specifically in the transentorhinal area, entorhinal cortex, and hippocampus; in those afflicted with AD, the density of tangle formation in these areas is greater, and they are also found in neocortical regions (Braak & Braak, 1991; Mesulam, 2000). This predilection that NFTs display for the MTL underscores this region's distinct vulnerability to this neurological aging process. Moreover, these NFTs are detrimental to cognition in not just AD patients, but also those without any obvious cognitive impairment (Bennett et al., 2012; Guillozet, Weintraub, Mash, & Mesulam, 2003).

There are several other age-related structural and metabolic changes that occur within the hippocampus and entorhinal cortex. Similar to the dlPFC, synapse loss occurs in the hippocampus in both aging and AD, but in the hippocampus it is the large and complex synapses,

such as perforated synapses or multisynaptic boutons, which are vulnerable to the aging process, and this synapse loss likely interferes with the ability to encode and retrieve complex information (Morrison & Baxter, 2012). The dentate gyrus of the hippocampus may be specifically susceptible to age-related changes in those without AD. Neurogenesis occurs in the dentate gyrus, and in the rodent the rate of neurogenesis declines precipitously with age (Kempermann, 2008). Until recently it was assumed that a similar drastic decline in neurogenesis occurred in the human; however, recent evidence indicates that only a modest slowing of new neuron birth may take place in the aged human (Spalding et al., 2013). Nonetheless, it is clear that neurogenesis does decline somewhat with advancing age, and this in turn may be a contributor to deficits in hippocampal based cognition later in life. In addition to the reduction in neurogenesis, it is also clear that the basal metabolism of the dentate gyrus, as measured by cerebral blood volume, is reduced with age (Small, Chawla, Buonocore, Rapp, & Barnes, 2004). Interestingly, there seems to be a distinction within the areas of the MTL and subfields of the hippocampus with regard to which regions are differentially affected by aging and AD. Whereas the dentate gyrus shows this decline in basal metabolism in healthy older adults with a sparing of the entorhinal cortex, it is the entorhinal cortex and CA1 region of the hippocampus that are most affected in AD, highlighting one of the multiple pieces of evidence suggesting AD is qualitatively distinct from aging (Mueller & Weiner, 2009; Small et al., 2011).

These reductions in hippocampal health likely undergird functional and structural MRI findings in older adults with respect to the hippocampus. Regarding fMRI, there are several noteworthy observations in the aging literature. One consistent result during memory paradigms comparing young and healthy older adults is a reduction in the blood oxygenation level dependent (BOLD) signal during successful memory (encoding or retrieval) for older adults

(Daselaar, Fleck, Dobbins, & Madden, 2006; Gutchess et al., 2005). A recent longitudinal study that scanned the same older adults at different time points confirmed this finding (Persson et al., 2012). Perhaps surprisingly, fMRI studies utilizing memory paradigms with individuals who have amnestic mild cognitive impairment (aMCI), a potential precursor stage to AD, paradoxically show increased activity in the hippocampus; once an individual reaches the AD stage however, there is a decrease in activity (Dickerson et al., 2005; Sperling et al., 2010). This hyperactivity in aMCI seems to be maladaptive, as ameliorating it through pharmacological intervention improves memory (Bakker et al., 2012). These results underscore the inherent difficulties in interpreting whether a larger or smaller BOLD signal is indicative of better brain function, and this problem is compounded in aging and disease (D'Esposito, Deouell, & Gazzaley, 2003). Finally, in addition to alterations in overall activity in the hippocampus, important variability also exists with respect to the functional connectivity between the hippocampus and its major input via the entorhinal cortex. Yassa and colleagues report that the degree of functional connectivity between the dentate gyrus and entorhinal cortex predicted performance on a pattern separation task in older adults (Yassa, Mattfeld, Stark, & Stark, 2011).

These fMRI findings must also be interpreted with regard to volumetric differences which occur in aging and AD. Similar to the PFC, structural MRI studies of aging typically (but not always) indicate reductions in hippocampal volume with age when only considering healthy older adults (Erickson et al., 2011; Raz et al., 2010; but see Head, Snyder, Girton, Morris, & Buckner, 2005, for null result). A recent report indicates that the loss of hippocampal tissue does not occur linearly with advancing age across the entire lifespan, but instead demonstrates a period of relative stability into the sixth decade, with volumetric loss beginning after that and at an accelerated pace compared to other subcortical regions (Fjell et al., 2013). In AD,

hippocampal volume loss is observed consistently and in much greater magnitude than in older adults free of neurodegenerative disorders; in fact, hippocampal volume is a very strong and reliable differentiator among healthy aging and mild AD, particularly when combined with cortical thickness measures (Dickerson et al., 2011; Dickerson et al., 2009; Head et al., 2005).

It is important to note that the volume loss that takes place in the hippocampus and other areas of the brain due to aging reflects at least two different processes, depending on whether an individual has a neurodegenerative disorder such as AD. In older adults free of AD or similar disorders, the loss of neurons due to aging is minimal, suggesting that the volume reductions are due to neuronal shrinkage, white matter lesions, synapse loss, and other deletions in the neuropil; however, in AD, there is substantial loss of gray matter and neuron death (Burke & Barnes, 2006; Jagust, 2013; Salat, Kaye, & Janowsky, 1999; Small et al., 2011). Thus, the volume loss in AD is due in part to neuron death, which is not the case in older adults without any neurodegenerative disorder. This distinction is important to keep in mind when considering what interventions may be efficacious in aging and AD, as well as characterizing the distinct cognitive phenotypes that may arise due to these two conditions.

In sum, certain regions and networks of the brain are more vulnerable to the processes of aging than others. Brain regions responsible for complex cognition and behavior such as the dlPFC or lateral parietal cortex undergo more substantial changes than primary visual or motor cortex. Nearly all subcortical regions show steady or accelerated volumetric declines, and the hippocampus and entorhinal cortex change dramatically with age due to a plethora of mechanisms acting in healthy aging as well as AD. This is not to say the hippocampus is necessarily more affected by aging than a region such as the dlPFC, but the multitude of influences on the aged hippocampus present multiple targets for intervention; this notion coupled

with the observed sensitivity of the structure with regard to a host of lifestyle/environmental factors and medical conditions make it an ideal candidate for the study of successful aging.

Hippocampus as a target for the study of successful aging

An obvious reason why the hippocampus would be a suitable target for the study of successful aging is that it is vulnerable to aging processes. This is particularly true with regard to the early identification of AD, given that tau pathology begins in the MTL and then spreads to the hippocampus, and hippocampal volume loss occurs early on in the process (Braak & Braak, 1991). Moreover, episodic memory complaints are typically the major cognitive deficit in AD (Weintraub, Wicklund, & Salmon, 2012). This suggests focusing on the hippocampus in order to detect AD at the earliest stages; however, this does not mean the early detection of AD should center exclusively on the hippocampus and memory. Neocortical A β potentially builds in a dormant fashion before tau pathology accrues, appearing first in the preclinical stage of the disease (Sperling et al., 2011). Plus, neuropsychological research indicates breakdowns in attentional control and inhibition to be excellent predictors of AD in its earliest stages (Balota et al., 2010; Hutchison, Balota, Duchek, 2010; Tse, Balota, Moynan, Duchek, & Jacoby, 2010). These issues are further discussed in the final section of this chapter, and in chapter two.

With respect to how modifiable lifestyle/environmental factors interact with aging, there are several indications that the hippocampus is an excellent model to study given its exquisite sensitivity to these factors, owing in part to its disproportionate capacity for plasticity. For instance, the dentate gyrus of the hippocampus is one of two known brain regions where neurogenesis occurs in mammals, the other area being the olfactory bulb (Ming & Song, 2011, though see Bergmann et al., 2012, for evidence that neurogenesis does not occur in the olfactory

bulb of humans). The recent discovery that, unlike rodents, neurogenesis continues at a high rate throughout the lifespan, coupled with the notion that new neurons are highly plastic and broadly recruited into hippocampal networks suggests that neurogenesis may play a larger role in hippocampal based cognition in the human than previously thought (Clark et al., 2012; Ming & Song, 2011; Spalding et al., 2013; van Praag et al., 2002). This has important implications for the study of lifestyle/environmental factors influencing hippocampal health and cognition late in life, given that research in animal models demonstrates that a number of factors such as aerobic exercise and nutrition can modulate the rate of neurogenesis (van Praag, 2009).

Beyond the specific realm of neurogenesis, the structure of the hippocampus in late adulthood (and even in young and middle-aged adults) is moderated by a host of lifestyle/environmental factors. The role of traumatic brain injury (TBI), and physical activity & cardiorespiratory fitness and the hippocampus are detailed in chapters four and five respectively, and are not discussed in depth further here. However, to highlight the responsiveness of hippocampal structure to modifiable factors, and thus speak to its candidacy as a prime target for intervening in aging, the moderation of hippocampal structure due to other mechanisms deserves brief mention (for review see Fotuhi, Do, & Jack, 2012). Studies investigating aging and cardiovascular or metabolic syndromes have reported atrophy specific to the hippocampus due to obesity, hypertension, and type 2 diabetes (Jagust, Harvey, Mungas, & Haan, 2005; Korf, White, Scheltens, & Launer, 2004, 2006). The link between hippocampus and cardiovascular mechanisms is furthered by a recent finding in the nutrition literature. Amnestic MCI patients with high levels of homocysteine who took B-vitamins for an extended period of time suffered less hippocampal volume loss than those in the placebo group (Douaud et al., 2013). These cardiovascular factors likely relate to the sensitivity of the hippocampus to hypoperfusion and

hypoxia/anoxia, as studies report those with cardiac arrest have evident hippocampal tissue loss, with one study finding it is the only brain region consistently implicated in hypoxic related atrophy (Di Paola et al., 2008; Fujioka et al., 2000; Petito, Feldmann, Pulsinelli, & Plum, 1987). Two other factors unrelated to blood flow or metabolism that can reduce hippocampal size are clinical depression and chronic alcohol abuse (Agartz, Momenan, Rawlings, Kerich, & Hommer, 1999; Videbech & Ravnkilde, 2004). On a more positive note, it has been demonstrated that extensive cognitive training or learning, such as that conducted by London taxi drivers in training or medical students studying for a certification exam, has been shown to increase hippocampal size (Draganski et al., 2006; Woollett & Maguire, 2011). Finally, it should be noted that the hippocampus is by no means the only area where the size of the region can be modified by any of the above factors. For instance, the students studying for their medical examination in the study by Draganski and colleagues had the largest gains in neocortical areas, and as will be evident in chapter five, physical activity modifies other brain regions besides the hippocampus. However, what does seem unique is that the hippocampus is implicated and amenable to change due to a wide array of lifestyle/environmental factors, as well as medical conditions, and it is this property, coupled with its vulnerability to aging process that makes it an attractive target for the study of successful aging.

Relational memory as a tool for testing hippocampal function

There are numerous levels at which the status of the hippocampus can be assessed in aging. Thus far, the discussion has focused primarily on analyzing the structure of the hippocampus, as ascertained predominantly by MRI in humans, along with fMRI techniques to analyze cerebral blood volume and the BOLD response. Another way to test the status of the hippocampus is to devise cognitive tasks based on what is a primary function of the structure,

and evaluate performance on these tasks as a function of age and lifestyle factors. This approach will be utilized in the current research, using the cognitive phenomenon of relational memory as a behavioral manifestation of the functioning of the hippocampal memory system. The rationale for this choice is described in part in chapters two and three; here additional information is given to provide further reasoning as to why using this framework will be fruitful in the study of successful aging.

Since the influential report of Scoville & Milner (1957) identifying the profound amnesia of patient HM following resection of the MTLs due to intractable epilepsy, it has been known that the MTL plays a critical role in memory in humans. Over the last several decades, considerable research has been conducted in order to ascertain the specific type(s) of memory that the MTL gives rise to, as well as to understand the various contributions of the hippocampus proper versus the MTL cortex (e.g., perirhinal, parahippocampal, entorhinal). A large body of research with patient HM and similar MTL amnesic patients has revealed a wide array of spared and impaired domains of memory that can thus be considered dependent or independent of the MTL. It was very apparent from early research with these patients that they were densely impaired on tasks assessing declarative memory, which required participants to remember word lists or pictures, and that this decrement was exacerbated at longer delays (Milner, Corkin, & Teuber, 1968). It was also clear that previously acquired semantic memories were intact, but acquiring new semantic information was very difficult and expressed in a hyperspecific manner (Eichenbaum & Cohen, 2001). Furthermore, it seemed that these patients could carry on a conversation over a short period of time, and memory deficits were less apparent or non-existent at short delays (Wickelgren, 1968).

The areas of memory that were spared in those with MTL damage provided further insight into the cognitive role that the MTL plays. Broadly speaking, MTL amnesic patients show normal cognition in four areas of memory (Eichenbaum & Cohen, 2001). These patients are able to learn general skills like mirror reading, as well as habitual learning, where one must learn a series of repetitive responses, such as on the serial response task (Cohen & Squire, 1980; Nissen & Bullemer, 1987). Additionally, MTL patients display normal conditioning, so long as it is “delay conditioning” and there is no interval between the conditioned and unconditioned stimuli; finally, repetition priming, such as word-stem completion, has been found to be unimpaired in these patients (Gabrieli et al., 1995; Graf, Squire, & Mandler, 1984). There are a few inferences that can be gleaned from this pattern of spared and impaired memory. First, while some of the tasks in which the MTL patients were unimpaired are characterized by slow, incremental learning (e.g., skill learning), other tasks or paradigms show rapid memory acquisition, such as conditioning. This indicates that while the hippocampus is typically associated with rapid learning, this type of fast acquisition of some knowledge can still occur in the absence of the hippocampus. One distinction between the tasks the MTL patients were impaired on and those where they showed no impairment was that the latter tasks were characterized mainly by implicit memory, that is, people generally learn the tasks without conscious awareness. This distinction along with some of the findings described above has led to the idea that the MTL contributes to explicit, long-term memory, and memory outside of this domain is independent of the MTL (Squire, 1992).

However, work by Chun & Phelps (1999) reported that MTL patients were impaired in implicit memory for contextual information. Moreover, similar conclusions were drawn from research by Ryan and colleagues (2000) who employed eye-tracking to study the nature of the

memory deficit in MTL amnesia (Ryan, Althoff, Whitlow, & Cohen, 2000). This study revealed healthy participants implicitly made eye-movements to areas of scenes displayed on a computer screen where changes in the relationship between objects and locations occurred, but patients did not exhibit this effect. Together, these data suggest that the implicit/explicit distinction of MTL based memory to be inaccurate. The Ryan et al., study also reported that the amnesic patients displayed a pattern of eye-movements indicative of intact item based memory, and that the deficit was in memory for the relations amongst items and spatial locations in a scene. This distinction between intact item based memory but impaired memory for relational information in amnesia is an example of a deficit predicted by relational memory theory.

The major idea undergirding relational memory theory (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001) is that the hippocampus processes the relations amongst constituent elements of an event or scene, and binds them in a flexible manner in the service of memory and future inference. An example of the hippocampus performing relational memory would be its encoding and/or retrieval of an event such as this morning's breakfast, which took place at specific time, at a distinct location, involving a certain food, and potentially in the presence of others. The hippocampus binds these individual representations (place, time, Cheerios, etc.) into a memory. Importantly, the representation of the individual elements for the event is largely hippocampal-independent, with memory for single elements of an event typically relying on the MTL cortex, and the permanent residence of those elements likely in neocortical regions. Thus, relational memory theory makes predictions differentiating individual parts of the MTL and their contributions to memory; specifically memory for single elements being in the purview of the MTL cortex (principally perirhinal), whereas memory for the relations between those elements invokes the domain of the hippocampus. This prediction has been borne out in humans utilizing a

convergence of cognitive neuroscience methods including eye-tracking, fMRI, and behavioral studies with MTL patients (Konkel, Warren, Duff, Tranel, & Cohen, 2008; Ryan et al., 2000; Staresina & Davachi, 2009). Additionally, it has become clear that the involvement of the hippocampus in relational memory is not limited to long time lags between encoding and retrieval. Studies involving healthy participants and fMRI, as well as patients with hippocampal damage have reported a role for the hippocampus in relational memory on timescales typically associated with the construct of working memory (e.g. several seconds). These ideas are further expounded upon throughout this document, particularly in the introduction sections of chapters two and three. In summarizing all of this information, it seems evident that an excellent way to assess the function of the hippocampal memory system with respect to cognition is through paradigms that stress relational processing and thereby maximally engage the hippocampus.

Finally, as the word “system” implies, the hippocampal memory system involves many more structures than the hippocampus. It is indeed the hippocampus that is the critical hub performing the relational computations amongst different elements, but it does so as part of a whole brain network that contributes to relational memory. For instance, the hippocampus processes multimodal information, and as such it receives inputs from disparate cortical sites that process unimodal information. Moreover, various goals and states partially comprise relational memories, and the hippocampus has access to the brain regions (e.g. PFC) that underlie goal driven behavior.

In addition to the various brain regions contributing to the information that is relationally processed by the hippocampus, PFC, parietal lobe, and other subcortical structures interact with the hippocampus in service of aiding encoding and retrieval. One example of this at encoding is the phenomenon of “cue specification,” which refers to deep and elaborate encoding of an

element such that its representation is orthogonal to other items when passed along to the hippocampus; it is thought that the ventrolateral PFC has a major role in this function (Dobbins, Foley, Schacter, & Wagner, 2002). At retrieval, portions of the dorsolateral, ventrolateral, and medial PFC make contributions including cue specification and monitoring hippocampal output for a match with current goals (see Simons & Spiers, 2003, for review). Also, fMRI studies have continually observed activity in the posterior parietal cortex during successful memory retrieval, which may reflect attentional contributions, information held in a temporary buffer, and/or the accumulation of evidence in line with a retrieval goal (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Wagner, Shannon, Kahn, & Buckner, 2005). Additionally, several subcortical structures interact with the hippocampus during all phases of memory processing. One well known example would be the amygdala interacting with the hippocampus to influence consolidation of certain types of memories (McGaugh, 2000). Furthermore, the major output of the hippocampus, the fornix, connects to the mammillary bodies and the thalamus, and damage to these regions causes a similar amnesic impairment to hippocampal damage (Carlesimo, Lombardi, & Caltagirone, 2011; Kopelman, 1991). Lastly, though sometimes thought to have an antagonistic relationship with the hippocampus (Poldrack et al., 2001), the striatum seems to also positively interact with the thalamus and hippocampus in the service of declarative or relational memory (Aggleton, 2012; Scimeca & Badre, 2012).

Thus the hippocampus is the critical structure for relational/declarative memory due to its processing capabilities that allow it to rapidly integrate information from a variety of brain structures and bind that information into a representation for future use in a flexible manner, and without a hippocampus, a person would not be capable of relational memory. However, this process is carried out in concert with a network of brain regions. In this regard, relational

memory provides an excellent vehicle in assessing successful aging, in that it taps into the hippocampal memory system, but since it is aided by areas such as the PFC, it affords the possibility to be informative with regard to the functioning of these structures as well.

To conclude, given its distinct vulnerability to aging and AD coupled with its plastic responsiveness to many lifestyle/environmental factors, the hippocampus provides an excellent structure to study successful aging. This assessment will take place utilizing relational memory as a framework for understanding hippocampal-based cognition in aging and disease, as well as structural and functional MRI indices of brain health. The final portion of this introduction provides an overture of the individual experiments carried out in this pursuit, providing context for their inclusion.

Prelude

Chapters 2-5 entail reports on four completed experiments aimed at the study of successful aging, with chapter six providing a discussion of the experiments, with a focus on the inter-relatedness of the studies, and ideas for future directions.

Chapter two describes a study involving young adults, healthy older adults, and individuals with very mild AD, with the main goal of creating a paradigm based on the ideas of relational memory theory that could aid in discriminating healthy aging from the earliest stages of AD. In this investigation we created a novel task expected to evoke relational processing. I view this study in what I hope to be a line of investigation based on establishing cognitive tasks sensitive to preclinical AD (i.e. the condition in which individuals harbor A β and tau, but do not show cognitive deficits on current neuropsychological tasks). To that end, this would be the first study in this line, demonstrating this paradigm is sensitive to the earliest stages of those with

clinical AD. Data were collected on ninety participants, and the results indicate memory impairments in healthy aging and very mild AD to be dissociable. Namely, healthy older adults were less accurate overall compared to young adults, but those with very mild AD were less accurate compared to their age-matched peers, and also showed an additional memory impairment centered on a sensitivity to interference. The results suggest memory impairments in AD to be a product of what is seen in aging, along with an additional factor likely due to a disease state.

In terms of the pursuit of understanding what lifestyle/environmental factors interact with the aging process, **chapter three** can be thought of as a proof of principle that the relational memory tasks developed in our laboratory and subsequently used in the next experiments to study aging actually relate to the hippocampus and classical neuropsychological tests associated with hippocampal function. Additionally, the results of this study also inform the debate as to the type of memory processes that rely on similar cognitive constructs and brain regions, largely divorced from an aging perspective. In this study, 109 participants, ages 18-83, participated in a battery of cognitive tasks which included neuropsychological tasks linked to the hippocampus (e.g., delayed recall), multiple tasks predominantly relying on other cognitive constructs outside of declarative or relational memory, and then two relational memory tasks developed in our lab, which have varying delay periods and stimulus domains. One task required participants to remember pairs of faces and scenes, while the other asked individuals to memorize the spatial locations of abstract objects. The neuropsychological data were analyzed using principal components analysis, with the hypothesis that the two relational memory tasks would cluster with the two delayed recall tasks, indicating their performance relied on a similar cognitive construct; this was indeed the case. Also, structural brain imaging data were available for all of

these participants, and the component associated most strongly with these memory tasks was correlated with hippocampal structure.

The remaining two studies use one of the relational memory tasks validated above to investigate what lifestyle/environmental factors interact (positively or negatively) with brain health and relational memory. All older adults in these studies were screened for dementia, and excluded if they had a diagnosis of a neurodegenerative disorder, mild cognitive impairment, or scored below a certain value on the Mini Mental Status Exam. Thus, the population of older adults here is considered cognitively normal, though it is possible, if not likely, that some of these individuals are in the preclinical stages of AD, given the protracted development of the clinical manifestations of AD.

Chapter four describes a recently published study measuring the effects of mild traumatic brain injury (mTBI) on the aging process by using a face-scene relational memory task in conjunction with fMRI, and also measuring the volume of subcortical structures. This study reports that, compared to age- and education-matched peers, those who sustained mTBI early in life and are now in their 40s to 60s performed worse on the face-scene relational memory task, had smaller bilateral hippocampal volumes, and had less neural activity for successful memory in neocortical regions (Monti et al., 2013). Young adults who had an mTBI were not different on any of these measures compared to their peers, suggesting that it is the combination of aging plus a previous brain injury that acts to produce worse outcomes later in life.

Chapter five details an investigation into how cardiorespiratory fitness and/or physical activity may be associated with better relational memory (tested with our face-scene task), volume of subcortical structures, and brain activity. These data are pre-test data from the Fit and

Active Seniors Trial (FAST), which is a six-month exercise and nutrition intervention. Data were analyzed from 130 older adults, with the results indicating fitness and physical activity beneficial for the volume of the thalamus, which in turn predicted better performance on the face-scene relational memory task. This boost in performance may occur due to hippocampal-thalamic-medial PFC interactions, as larger thalamus volume was associated with more medial PFC activity for correct rejections. These results add to the burgeoning literature indicating the importance of physical activity and fitness to brain health in late adulthood.

Chapter 2: Very mild Alzheimer's disease is characterized by increased sensitivity to mnemonic interference

Abstract

Early pathology and tissue loss in Alzheimer's disease (AD) is concentrated in the hippocampus, a brain region that has recently been implicated in relational processing irrespective of delay. Thus, tasks that involve relational processing will especially tax the hippocampal memory system, and should be sensitive to even mild dysfunction typical of early AD. Here we used a short-lag, short-delay memory task previously shown to be sensitive to hippocampal integrity in an effort to discriminate cognitive changes due to healthy aging from those associated with very mild AD. Young adults, healthy older adults, and individuals with very mild AD ($N = 30$ for each group) participated in our investigation, which entailed attempting to find an exact match to a previously presented target among a series of stimuli that varied in perceptual similarity to the target stimulus. Older adults with very mild AD were less accurate than healthy older adults, who, in turn, were impaired relative to young adults. Older adults with very mild AD were also particularly susceptible to interference from intervening lure stimuli. A measure based on this finding was able to explain additional variance in differentiating those in the very mild stage of AD from healthy older adults after accounting for episodic memory and global cognition composite scores in logistic regression models. Our findings suggest that cognitive changes in early stage AD reflect aging along with an additional factor potentially centered on sensitivity to interference, thereby supporting multifactorial models of aging.

Introduction

Episodic memory impairments across long retention intervals are generally described as the chief cognitive symptom of those with early Alzheimer's disease (AD; Weintraub, Wicklund, & Salmon, 2012). This deficit maps on to the first site of tau pathology in early AD, which occurs in the transentorhinal cortex of the medial temporal lobe (MTL) before spreading to the entorhinal cortex and then the hippocampus (Braak & Braak, 1991). Consequently, neuropsychological tests of delayed episodic memory, such as delayed recall of word lists or narratives, have been relied on for the diagnosis of AD. However, recent studies evaluating the function of the hippocampal memory system have shown that hippocampus is necessary for relational processing irrespective of delay (Hannula, Tranel, & Cohen, 2006; Olson, Page, Moore, Chatterjee, & Verfaellie; Piekema, Kessels, Mars, Petersson, & Fernández, 2006; Warren, Duff, Tranel, & Cohen, 2011; Watson, Voss, Warren, Tranel, & Cohen, 2013) suggesting that tasks requiring on-line relational processing may be helpful in discriminating healthy aging from the earliest stages of AD. Here we report an investigation testing the hypothesis that a task requiring ongoing, rather than long-term, relational memory processing can discriminate healthy aging from very mild AD.

Early neuropsychological research in amnesic patients with hippocampal damage such as HM seemed to reveal a focal cognitive deficit in which newly learned declarative information could not be recalled only minutes later. In contrast, simple information could be recalled normally after shorter delays (e.g., a few seconds) and non-declarative information could be learned and retained normally (Cohen & Squire, 1980; Corkin, 1968; Graf & Schacter, 1985; Milner, Corkin, & Teuber, 1968; Sidman, Stoddard, & Mohr, 1968; Wickelgren, 1968). Further neuropsychological work and research with animal models of amnesia led to the conclusion that

the major contribution of the hippocampus to cognition was supporting the encoding and explicit retrieval of declarative information in a long-term memory system (e.g., Squire, 1992). However, converging evidence from neuropsychological investigations of hippocampal amnesic patients and functional neuroimaging of healthy adults suggests that this description of hippocampal function is incomplete. In the last decade, it has been shown that if newly learned information is relational (i.e., the relationships among individual elements must be processed: Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001), then the hippocampus is engaged irrespective of delay. For instance, hippocampal patients are impaired at remembering relational information at delays of only a few seconds (Hannula et al., 2006; Watson et al., 2013). These reports complement findings from neuroimaging studies in which hippocampal activity was observed when novel or relational information needed to be maintained over delays of approximately ten seconds (i.e., the timescale of working memory; Hannula & Ranganath, 2008; Ranganath & D'Esposito, 2001).

Perhaps even more intriguing are the findings detailing impaired performance of hippocampal amnesic patients on what might typically be termed perceptual tasks, in which the participant must make comparisons among several simultaneously-presented stimuli in order to, for example, decide which stimulus does not match the others. Critically, these tasks impose no delay and all of the information needed to correctly respond to a trial is in front of the participant. For example, patients with hippocampal damage were impaired in making discriminations between scenes (Lee, Buckley, et al., 2005; Lee, Bussey, et al., 2005), and research employing functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) has provided complimentary evidence for a role attributed to the hippocampus in the processing and discrimination of complex visual scenes (Lee, Scahill, &

Graham, 2008; Riggs et al., 2009). Similar deficits in simultaneous comparison of multiple single objects have been reported in patients with MTL damage including hippocampus and nearby cortical regions (Barense, Gaffan, & Graham, 2007) and patients with focal hippocampal damage have impairments in the ability to separate or integrate visual information about single objects (Warren, Duff, Jensen, Tranel, & Cohen, 2012).

One report particularly germane to the current study found that patients with hippocampal damage were impaired while performing a complex visual search task (Warren et al., 2011). In the task, participants sought a target matching a centrally-positioned sample item. The surrounding search array was composed of objects that had parametrically manipulated levels of similarity to the target. Items were composed of three sections filled with distinctive designs expected to provoke relational processing, and sections were manipulated to create lure items that matched the sample and target items to varying degrees (i.e., zero, one, or two matching features; see Figure 2.1). In this study, Warren and colleagues (2011) monitored eye movement behavior during visual search by hippocampal amnesic patients and healthy comparison participants. The authors found that in addition to reduced rates of target detection (despite no imposed delay) the patients' representation of the target stimulus degraded as a function of the number of fixated lures. Hippocampal patients and healthy comparisons alike had longer fixations to items resembling the target. However, whereas this effect was robust throughout search in the comparison participants, for hippocampal patients this effect was seen only for lures viewed shortly after (re)viewing the target stimulus. The duration of their fixations to lures resembling the target decreased the more lures they fixated without having re-sampled the central sample item, which suggests a fading of the internal representation of the target during visual search (Warren et al., 2011).

Taken together, these data suggest a critical role for the hippocampus in relational binding and comparison irrespective of delay (Voss et al., 2011; Warren et al., 2012). Thus, if the essence of hippocampal function is not necessarily memory for declarative information at long delays, but rather relational binding and memory at any delay (even a delay of just several saccades), then tests assessing these processes may be able to detect dysfunction of the hippocampus, thereby providing tools sensitive to the earliest stages of AD. In the current study, we used a behavioral paradigm inspired by Warren et al., (2011) that proved sensitive to hippocampal dysfunction. Data were collected from young adults, healthy older adults, and participants with very mild AD in an effort to isolate effects related to aging versus those due to the earliest stages of AD. Given the effects found in Warren et al. (2011) with hippocampal amnesic patients, we hypothesized this task would be sensitive to the earliest changes that occur within the hippocampus due to very mild AD.

Materials and Methods

Participants

Sixty-four older adults, age range 62-94, were recruited to participate from the Charles F. and Joanne Knight Alzheimer's Disease Research Center (Knight ADRC). Of the 64 participants recruited, 30 were healthy older adults and 34 had very mild AD. The presence and severity of Alzheimer's disease was assessed using the Washington University Clinical Dementia Rating (CDR) Scale (Morris, McKeel, Fulling, Torack, & Berg, 1988; Morris, 1993). The CDR is a 90-minute interview assessment conducted by a trained clinician that assesses the patient and collects information from family members to determine changes in cognition and function. The CDR employs a scale with the values 0, 0.5, 1, 2, and 3, mapping on to no AD, very mild AD,

mild AD, moderate AD, and severe AD, respectively. The CDR has been shown to be particularly sensitive to detecting the earliest stages of AD, is highly reliable (Burke et al., 1988), and has a very high concordance with a neuropathological diagnosis of AD confirmed at autopsy, even in individuals with a CDR of 0.5 (Berg et al., 1998; Storandt, Grant, Miller, & Morris, 2006).

Several participants with AD ($N = 7$) had difficulty completing the task and those sessions were terminated before completion. Participants were included in the study if they completed more than half of the experiment's main phase test trials (≥ 22 of 42 total trials); this criterion excluded an additional four participants with very mild AD. Three individuals with very mild AD completed more than half the experiment and thus their data were retained for analysis; all other data presented here reflect complete test sessions. Thus, the final numbers of participants in the older adult groups were as follows: healthy older adults (CDR 0) = 30, very mild AD patients (CDR 0.5) = 30. To further dissociate the effects of aging from very mild AD, 31 young adults from the Urbana-Champaign community, aged 19-28, completed the experiment. One participant's data were discarded due to a very low accuracy level (d' value more than three standard deviations less than the group mean), leaving the final number of participants in this sample at 30. All participants signed informed consent documents and this experiment was approved by the institutional review boards of Washington University and the University of Illinois at Urbana-Champaign. Participants were monetarily compensated for their participation.

The AD group was significantly older than the healthy older adult group (see Table 2.1 for demographic information). Therefore, all comparisons involving the healthy older adult group and AD patients either included age as a covariate, or when analyses also involved young

adults, a separate confirmatory analysis was conducted on the older adult samples including age as a covariate to partial out the effect of age on any findings of AD status.

Table 2.1

Participant Demographics

Variable	Young	CDR 0	CDR 0.5
N	30	30	30
% female	50%	53%	47%
Age	21.7 (2.1)	71.3 (6.7)	76.1 (7.6)
MMSE	-	28.7 (1.2)	27.1 (2.3)

Procedure

We employed a task that required participants to maintain an internal representation of a target stimulus while attempting to find an exact match to that target when viewing a series of highly similar objects presented on a computer display. The experiment was conducted using Presentation software (Neurobehavioral Systems, <http://www.neurobs.com/>). Figure 2.1 displays an example of the stimuli and an example trial. The stimuli used here were novel, computer-generated objects as used in Warren et al. (2011). Each stimulus was composed of three distinct sections that together formed a circular object, with each section containing a unique, novel design (i.e., a “feature”). Three different, distinctive features were available for each section, yielding a total of 27 unique stimuli that were used throughout the experiment.

Prior to participating in the actual experiment, participants completed four practice trials that were structured identically to those in the actual experiment, with different stimuli. The full experiment contained 42 trials. During a trial, participants were presented with a sample target stimulus at the top of the display and instructed to study the stimulus. After studying the item,

the participant pressed a button that initiated a search sequence. During this phase of the trial, the target stimulus disappeared from the top of the display and the first potentially matching stimulus appeared at the bottom of the display. Participants were instructed to indicate whether the stimulus at the bottom of the display was an exact match with the studied sample by pressing one of two keyboard keys indicating “yes” or “no.” During a trial, participants saw ten serially presented stimuli; each stimulus was presented 300 ms after the previous match/mismatch response. Nine of the stimuli presented during each trial were *lures*, and their similarity to the target (“feature overlap”) was parametrically varied such that a lure could share zero, one, or two identical features with the target. One of the ten stimuli shown was the *target*, that is, an exact match to the sample item. To maximize interference and engage the MTL memory system, on most trials (36 of 42) the target was the sixth, eighth, or tenth object presented. These 36 *critical trials* were split evenly between the different target position conditions (i.e., target at ordinal positions six, eight, and ten). Additionally, an equal number of stimuli presented throughout the critical trials shared zero, one, or two features with the target stimulus. In the six remaining trials, the target was the second item and all subsequently presented items on these trials shared no features with the target; these *catch trials* were introduced in order to keep participants from learning to reject all items shown early in a trial without evaluating them.

Example trial and stimuli

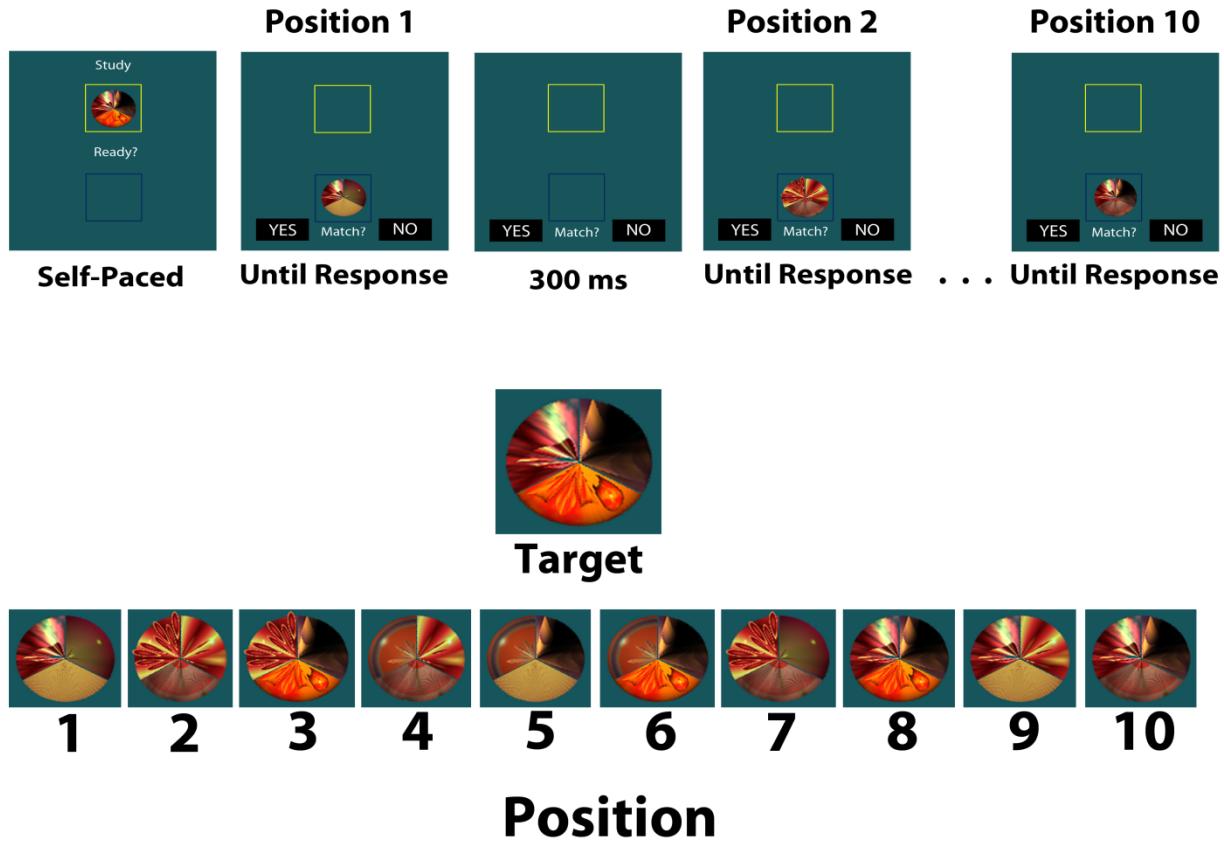


Figure 2.1: Top panel: Example timing and sequence of a trial. Participants study the target item and press a button to initiate the search sequence. At each position they make a decision as to whether the presented item is an exact match to the target item. There are ten stimuli presented sequentially on each trial. Bottom panel: Shows target and the ten stimuli shown during the search sequence of this trial. The stimulus at position eight is the match to the target. Stimuli at positions four, five, and six represent feature overlap levels zero, one, and two, respectively.

Data analysis

Both accuracy and response time (RT) measures were analyzed to evaluate performance on this task. A signal detection approach was utilized to assess accuracy, and d' values were calculated for each participant at each of the three possible target positions; catch trials were not

included in any analyses. The d' measure was derived by calculating the hit rate and false alarm (FA) rate at (ordinal) positions six, eight, and ten; these d' values are heretofore referred to respectively as d'_{6} , d'_{8} , and d'_{10} . In the case of a hit rate of 1 or an FA rate of 0, d' values were calculated by using $1-(1/2N)$ and $1/2N$ respectively, with N equaling the number of trials contributing to the analysis (Green & Swets, 1966). When only assessing the hit rate or FA rate individually, the raw values were used. In addition to the d' measure, a FA rate was calculated across the trials for each participant at each level of feature overlap. To assess how the FA rate changed as the trial unfolded, levels representing the stages of the trial were formed by combining positions 2-4, 5-7, and 8-10 into “early,” “middle,” and “late” in trial, respectively, forming the factor “trial stage.” Responses to items at position one were discarded, as response times on these trials were much longer than responses to items at the other nine positions across all populations, likely reflecting a task-switching cost between the study phase and the test phase.

Prior to statistical analysis of the RT measures, the RT data were trimmed in the following manner. Only correct responses were considered for the RT analysis, and RTs shorter than 250 ms or longer than 6000 ms were discarded; this resulted in the removal of 2.6% of all data. Following this initial pruning of the data, values that were three standard deviations greater than an individual’s mean were discarded, resulting in the additional removal of 1.8% of the remaining data set. To account for overall age- and dementia-related changes in RT, which can mislead the interpretation of group \times condition interactions (Faust, Balota, Spieler, & Ferraro, 1999) the trimmed RTs for each participant were standardized by transforming them into z scores using each participant’s overall trimmed mean and standard deviation; all statistical analyses were performed on the standardized RT data which are referred to as zRT. The main zRT measure focused on correct rejections so as to analyze zRT across the groups as a function of

feature overlap and trial stage. zRT to the target was conducted in a separate analysis so as to not directly compare "yes" and "no" responses.

After these initial analyses, we also tested whether task performance could successfully discriminate healthy aging (CDR 0) from very mild AD (CDR 0.5), compared to the classification results to those achieved by using standard neuropsychological measures. Several hierarchical logistic regression analyses were conducted that used data from this task along with two composite scores derived from the extensive neuropsychological testing administered to the participants of this study: an episodic memory score and a global cognition score. The episodic memory composite score was composed of an average of scores from: the sum of the three free recall trials on the Selective Reminding Task (Grober, Buschke, Crystal, Bang, & Dresner, 1988), Paired Associate Learning from the Wechsler Memory Scale (WMS; Wechsler & Stone, 1973), and immediate recall from WMS Logical Memory. The global cognition score was composed of the averaged scores on the above tests making up the episodic memory score, plus averaged scores from tests which formed three other composites: semantic memory, working memory, and visual spatial function. The semantic memory composite score included scores from the Information subtest on the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1955), Boston Naming Test (Goodglass, 1983), and Animal Naming (Goodglass, 1983). The working memory composite score was composed of WMS Mental Control, Digit Span Forward and Digit Span Backward, and Letter Fluency for S and P (Thurstone & Thurstone, 1949). The visual spatial composite included the WAIS Block Design and Digit Symbol subtests, and Trail Making A and B (Armitage, 1946). Information pertaining to the factor structure for these neuropsychological tests and their relation to AD and healthy aging has been previously reported (Johnson, Storandt, Morris, Langford, & Galvin, 2008).

The episodic memory composite was included in the logistic regression analysis because of the voluminous literature on declines in episodic memory and early AD (Salmon, 2000). The inclusion of a global cognition composite was due to the impairments on multiple cognitive domains that have been observed in early AD, deficits that can powerfully discriminate between healthy aging and AD (Johnson et al., 2008; Johnson, Storandt, Morris, & Galvin, 2009). The variable chosen (post hoc) for inclusion from the new task described in this report was d'_{10} , based on the finding to be reported here of declining accuracy as a function of trial stage associated with very mild AD (see Results). Composite scores were chosen as a comparison to our task rather than any individual neuropsychological sub-task based on the amount of data informing the measures from our task being larger than that collected on any individual neuropsychological test. Consequently, direct comparisons between this task and an individual neuropsychological task may be unfair, as the latter measure may be noisier. In all logistic regression analyses, age was entered as a factor due to age differences between the two groups. Neuropsychological data were available for 51 of the 60 CDR 0 and CDR 0.5 participants (CDR 0, $N = 24$; CDR 0.5, $N = 27$), and thus the logistic regression analyses only included these participants.

In the logistic regression analyses, age and one of the composite scores were entered in step one to establish the variance associated with these measures, and then d'_{10} was entered to determine if this carried any unique explanatory power; two separate models were run for episodic memory and global cognition. Finally, the reverse analysis was completed where age and d'_{10} were entered, followed by episodic memory or global cognition.

Results

Study time analysis

Since the study phase on each trial was self-paced, it is possible that this may have differed between groups, and that those who spent longer observing the object would do better on the task. To assess this, we compared the mean study time for the three groups in a one-way ANOVA; study time data for one young adult was unavailable due to a computer error. This analysis indicated a main effect of group, $F(2, 86) = 29.00, p < .001$, which was driven by the young adult group studying the sample item for shorter periods of time ($M = 6.4$ s, $SD = 1.9$ s) than the CDR 0 ($M = 14.65$ s, $SD = 6.3$ s), $t(57) = 6.76, p < .001$, and CDR 0.5 groups ($M = 13.75$ s, $SD = 4.3$ s), $t(57) = 8.45, p < .001$. There was no difference in study time between the two older adult groups, $t(58) = .65, p = .52$. Also, given that the young adults studied the sample item for the shortest duration, but performed most accurately in the task (see below), it is unlikely that the results here are due to speed-accuracy tradeoffs during the study phase.

Accuracy Measures

Figure 2.2 displays the d' values as a function of group and position. Overall, young adults were more accurate than healthy older adults, who were in turn more accurate than those with very mild AD; also, the very mild AD group showed declining accuracy as position increased. The mixed effect ANOVA revealed a main effect of group, $F(2, 87) = 44.86, p < .001$, as well as a significant group \times position interaction, $F(4, 174) = 5.95, p < .001$. Across all positions, young adults ($M = 3.29, SD = .48$) were more accurate than the CDR 0 participants ($M = 2.75, SD = .79$), $t(58) = 3.21, p = .002$, who in turn had better signal detection than the CDR 0.5 group ($M = 1.64, SD = .75$), $t(58) = 5.58, p < .001$. The interaction reflected differential

effects of the position factor between the two older adult groups. Specifically, the CDR 0 group showed an increase in accuracy from d'_6 ($M = 2.59, SD = .95$) to d'_8 ($M = 2.86, SD = .76$), $t(29) = 2.39, p = .02$, whereas the CDR 0.5 group displayed significant decreases in accuracy when comparing d'_6 ($M = 1.83, SD = .91$) or d'_8 ($M = 1.71, SD = .80$) to d'_{10} ($M = 1.39, SD = .79$), $t(29) = 4.32, p < .001$, and, $t(29) = 2.64, p = .01$, respectively. Furthermore, the differences in signal detection across position were attributable to changes in the FA rate for the CDR 0 group, but changes in the hit rate for the CDR 0.5 group. The CDR 0 group's FA rate decreased significantly from position six ($M = .07, SD = .07$) to position eight ($M = .03, SD = .05$), $t(29) = 2.9, p = .01$. For the CDR 0.5 group, a declining hit rate largely contributed to the decrease in d' , as there was a reliable difference in the hit rate from position six ($M = .67, SD = .22$) to position ten ($M = .56, SD = .22$), $t(29) = 2.8, p = .002$., whereas the FA rate from position six ($M = .11, SD = .09$) to position ten ($M = .13, SD = .09$) only increased modestly, $t = 1.6, p = .12$. Table 2.2 provides detailed descriptive statistics for all groups. Visual inspection of the data suggested that in contrast to the other two groups, the CDR 0.5 group may have a linear decrease in d' across the three levels of position; this was confirmed by a group \times position interaction for the linear term, $F(2,87) = 11.54, p < .001$. This interaction was not an effect of differing age between the CDR 0 and CDR 0.5 group, because a separate 3×2 ANCOVA with the two older groups (and age as a covariate) yielded the same result, $F(1,57) = 14.01, p < .001$.

Accuracy at target positions

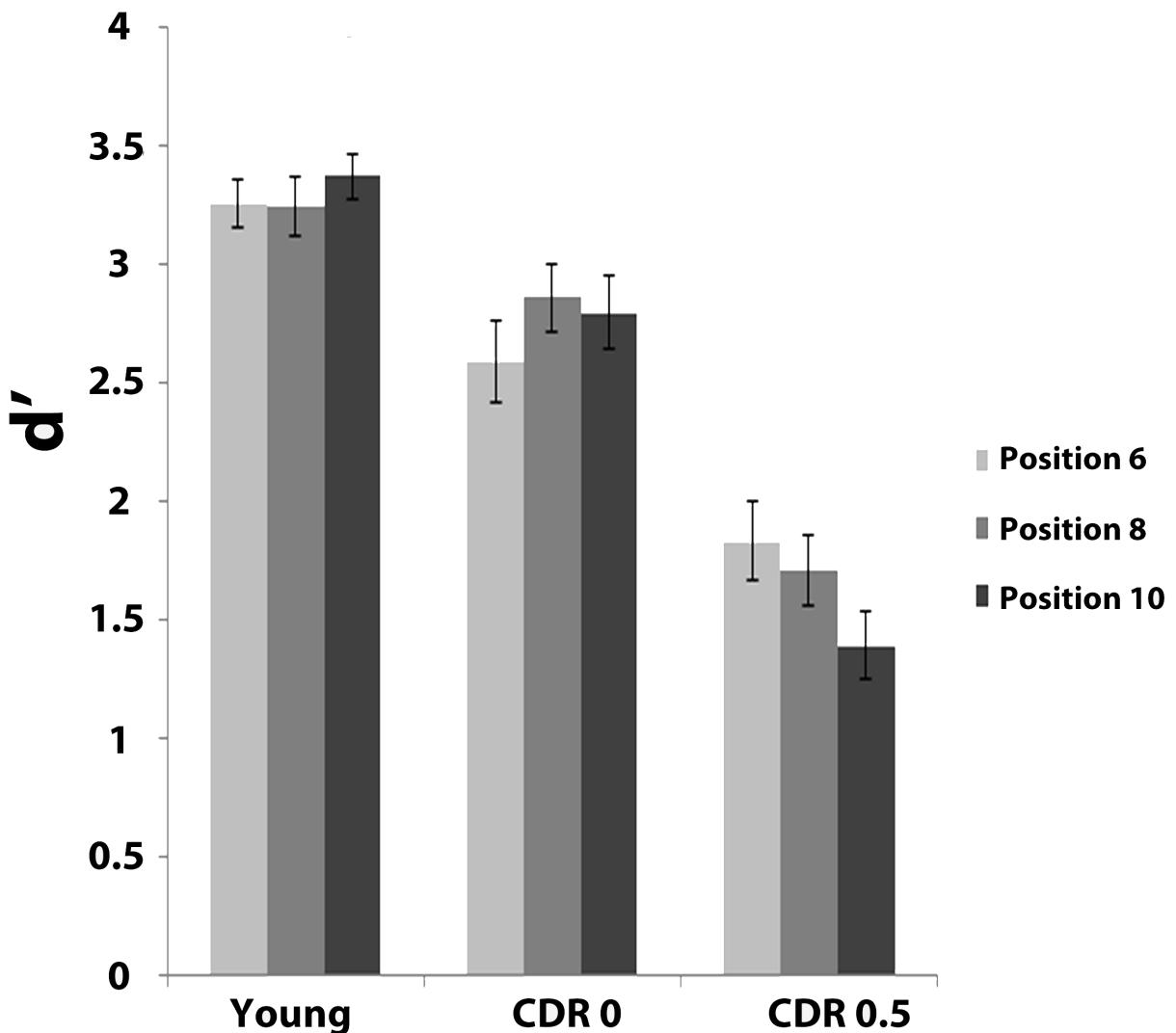


Figure 2.2: Accuracy as assessed by d' values. Error bars represent \pm one s.e.m.

Table 2.2
Accuracy at target locations

Position Variable	<u>Young</u>			<u>CDR 0</u>			<u>CDR 0.5</u>		
	6	8	10	6	8	10	6	8	10
Hit rate									
<i>M</i>	.92	.91	.92	.81	.83	.82	.67	.66	.56
<i>SD</i>	.09	.12	.11	.20	.17	.21	.22	.21	.22
False alarm rate									
<i>M</i>	.03	.02	.01	.07	.03	.04	.11	.13	.13
<i>SD</i>	.04	.04	.02	.07	.05	.04	.09	.10	.09
d'									
<i>M</i>	3.3	3.2	3.4	2.6	2.9	2.8	1.8	1.7	1.4
<i>SD</i>	.54	.69	.53	.95	.76	.84	.91	.80	.79

Accuracy data at each of the three possible target positions. CDR = Clinical Dementia Rating
 CDR 0 = no dementia; CDR 0.5 = very mild Alzheimer's disease

Analysis of the FA rate data from positions 2-10 indicated that young adults had the lowest FA rate followed by the CDR 0 group and the CDR 0.5 group. While all groups had increases in their FA rate as feature overlap increased (see Table 2.3 for detailed descriptive statistics), the effect of increasing feature overlap on FA rates was larger for the CDR 0 compared to young adults, and this pattern was exacerbated when comparing the CDR 0.5 group to the CDR 0 group. FA rates were entered into a $3 \times 3 \times 3$ mixed-measures ANOVA with group as a between-subjects factor and feature overlap (zero, one, or two) and trial stage (early, middle, and late) as within-subject factors. The effects of feature similarity, age, and CDR status were evident in main effects of feature overlap, $F(2,174) = 213.22, p < .001$ and group, $F(2, 87) = 42.05, p < .001$, and these were qualified by a feature overlap \times group interaction, $F(4,174) = 25.53, p < .001$. In order to further pursue the nature of this interaction, we conducted a 3×2 mixed-measures ANOVA with the factor of feature overlap and group (young adult and CDR 0), which produced a significant interaction, $F(2, 116) = 13.55, p < .001$ due to the two groups showing no difference in FA rate at feature overlap level zero (mean difference in FA rate =

.004), $t(58) = 1.78, p = .08$, but more FAs for the CDR 0 group at feature overlap level one (mean difference in FA rate = .02), $t(58) = 3.45, p = .001$, and this difference became larger at feature overlap two (mean difference in FA rate = .07), $t(58) = 3.75, p < .001$ (Table 2.3). This pattern of disproportionate increases in the FA rate per group when feature overlap increased was also apparent in a similar 3×2 ANCOVA comparing the CDR 0 and CDR 0.5 groups with age as a covariate, $F(2, 114) = 6.17, p = .003$. Here, the CDR 0.5 group had a significantly higher FA rate compared to the CDR 0 group at each level of feature overlap, but this difference became larger as feature overlap increased (mean difference in FA rates between CDR 0 and CDR 0.5 after adjusting for age: feature overlap level zero = .03; feature overlap level one = .06; feature overlap level two = .08; all t values > 3 , all p values $< .003$; Figure 2.3). Finally, a main effect of trial position was observed, $F(2, 174) = 7.77, p = .001$ due to a general increase in FAs during the middle portion of a trial ($M = .07, SD = .07$) compared to the early ($M = .06, SD = .06$), $t(89) = 4.15, p < .001$, and the late portions of trials ($M = .06, SD = .07$), $t(89) = 2.21, p = .03$.

False alarms by feature overlap

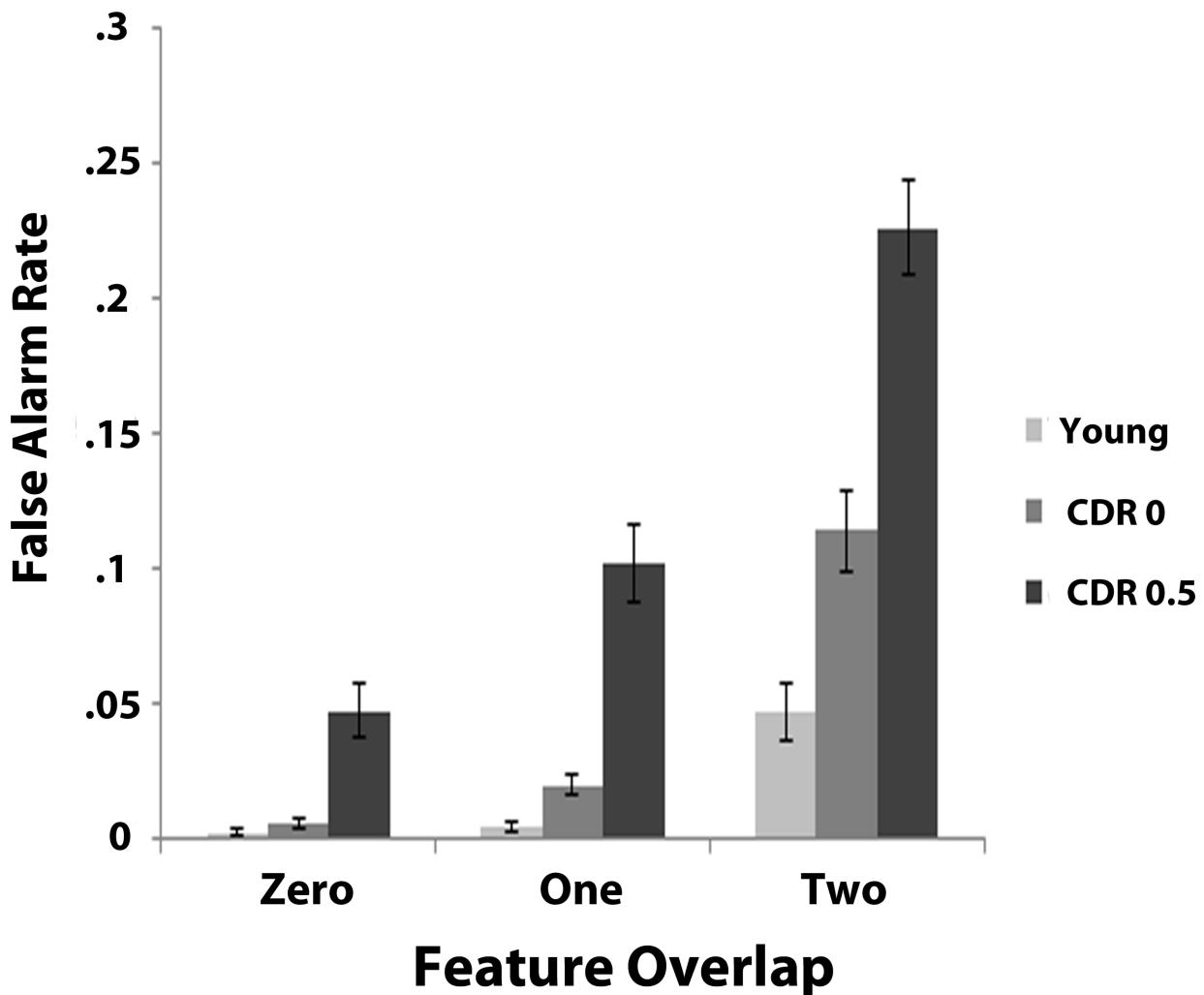


Figure 2.3: False alarm (FA) rate as a function of feature overlap with the target and trial stage
Error bars represent \pm one s.e.m.

Table 2.3
False alarm rate by feature overlap and trial stage M (SD)

Trial Stage	Feature Overlap		
	<u>Zero</u>	<u>One</u>	<u>Two</u>
Young			
Early	.00 (.00)	.00 (.01)	.04 (.06)
Middle	.00 (.00)	.00 (.02)	.05 (.06)
Late	.00 (.01)	.01 (.02)	.05 (.05)
CDR 0			
Early	.00 (.01)	.02 (.03)	.10 (.09)
Middle	.00 (.02)	.02 (.04)	.14 (.11)
Late	.01 (.03)	.02 (.04)	.10 (.08)
CDR 0.5			
Early	.03 (.04)	.10 (.10)	.22 (.10)
Middle	.06 (.06)	.11 (.08)	.25 (.12)
Late	.05 (.06)	.11 (.09)	.22 (.14)

Note: False alarm rates listed as .00 are due to rounding, as each group had some false alarms at each level of feature overlap and trial stage, accounting for cases where the mean is listed as zero but the standard deviation is greater than zero. Early refers to positions 2-4, Middle 5-7, Late 8-10. CDR = Clinical Dementia Rating CDR 0 = no dementia; CDR 0.5 = very mild Alzheimer's disease

Standardized RT data

Standardized RT data (zRT) of correct rejections were analyzed in $3 \times 3 \times 3$ mixed-measure ANOVA as described for the analysis of FA rates. zRT for all groups became longer as feature overlap increased; however, the patterns differed for the groups, indicated by main effects of feature overlap, $F(2, 174) = 583.38, p < .001$, and group, $F(2, 87) = 15.12, p < .001$, and a feature overlap \times group interaction, $F(4, 174) = 17.34, p < .001$. For both the young and CDR 0 groups, zRTs across feature overlap levels zero, one, and two were best fit with a quadratic term (young adults: $F(1, 29) = 19.12, p < .001$; CDR 0: $F(1, 29) = 20.28, p < .001$). This was due to a larger difference in zRT between feature overlap one and two compared to

zero and one (Table 2.4; Figure 2.4). The CDR 0.5 participants produced a linear increase in zRT across the three levels of feature overlap, $F(1,29) = 111.72, p < .001$, this increase was approximately equal between feature overlap level zero and one, and one and two, as indicated by the non-significant test for the quadratic term, $F(1,29) = .03, p = .86$ (Figure 2.4). An ANCOVA on the data from the older two groups with age as a covariate confirmed this interaction was not due to the difference in age between the two older groups, $F(2,114) = 13.48, p < .001$.

Response time data by feature overlap

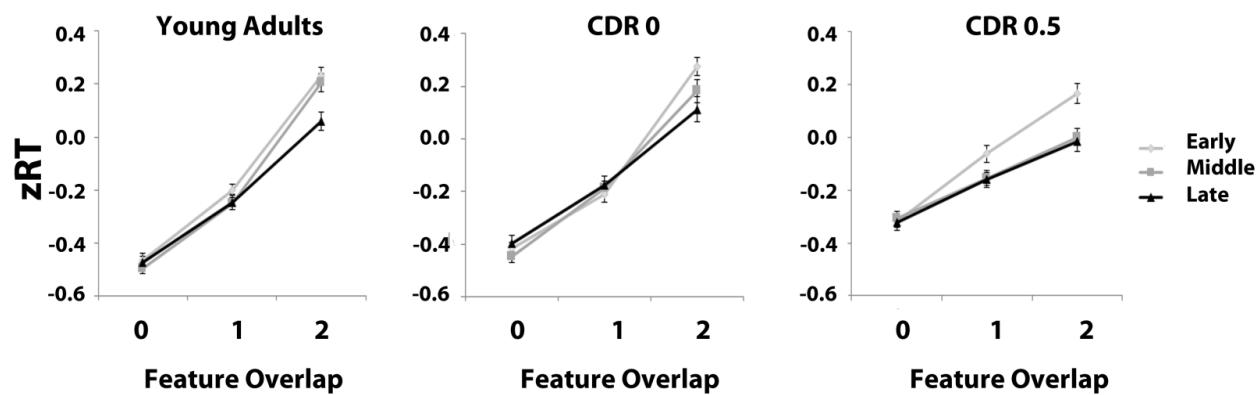


Figure 2.4: Standardized response time (zRT) data as a function of feature overlap with the target and trial stage for young, CDR 0 and CDR 0.5 participants. Error bars represent \pm one s.e.m.

Table 2.4
 zRT for correct rejections by feature overlap and trial stage M (SD)

Trial Stage	Feature Overlap		
	<u>Zero</u>	<u>One</u>	<u>Two</u>
Young			
Early	-.47 (.14)	-.20 (.12)	.23 (.17)
Middle	-.49 (.11)	-.25 (.12)	.21 (.19)
Late	-.47 (.14)	-.25 (.16)	.06 (.19)
CDR 0			
Early	-.42 (.14)	-.21 (.16)	.27 (.19)
Middle	-.45 (.11)	-.19 (.14)	.18 (.24)
Late	-.40 (.16)	-.18 (.19)	.11 (.26)
CDR 0.5			
Early	-.32 (.13)	-.06 (.18)	.17 (.21)
Middle	-.31 (.15)	-.15 (.15)	.00 (.18)
Late	-.32 (.17)	-.16 (.16)	-.02 (.20)

Early refers to positions 2-4, Middle 5-7, Late 8-10. CDR = Clinical Dementia Rating CDR 0 = no dementia; CDR 0.5 = very mild Alzheimer's disease

The initial three-way ANOVA also indicated a main effect of trial stage, $F(2, 174) = 7.44, p = .001$ and a feature overlap \times trial stage interaction, $F(4, 348) = 9.08, p < .001$. zRTs became shorter for all groups as trial stage increased, but this was not true for all levels of feature overlap. The interaction was due to zRTs decreasing for feature overlap level two from the early to middle stage of the trial, $t(89) = 3.0, p = .004$ and from the middle to late stage of the trial, $t(89) = 2.79, p = .006$. While the three-way interaction was non-significant, $F(8, 348) = 1.53, p = .14$, group status did appear to influence the relationship between feature overlap level two and trial stage. Given that feature overlap two represented the most difficult condition, we investigated possible group differences at this level, and conducted a 3 (group) \times 3 (feature overlap) ANOVA on the zRT data for feature overlap two. This analysis indicated a marginally significant group \times trial stage interaction when testing for a quadratic effect for trial stage, $F(2,$

$87) = 2.66, p = .08$. As shown in Figure 2.5 this pattern is quite systematic, in that for the healthy younger adults there is a reliable difference between both the early and middle positions and the late position, $t(29) = 3.3, p = .003$, and $t(29) = 2.79, p = .01$ respectively, with no difference between the early and middle positions, $t(29) = .61, p = .55$. Turning to the older adults, response times seemed to linearly decrease across the trial positions. While there is no reliable difference between early and middle positions, $t(29) = 1.41, p = .17$, and middle and late positions, $t(29) = 1.4, p = .17$, the difference between early and late positions was significant, $t(29) = 2.27, p = .03$. For the CDR 0.5 individuals there is a reliable decrease between the early positions and both the middle, $t(29) = 3.19, p = .003$, and the late $t(29) = 3.25, p = .003$ positions. Thus, the increase in response latency for the high two-feature overlap items systematically changed across positions across groups, with a relatively late effect for the young adults, more linear increase for the CDR 0 individuals, and a relatively early effect for the CDR 0.5 individuals (see Figure 2.5).

Feature overlap two: zRT by trial stage

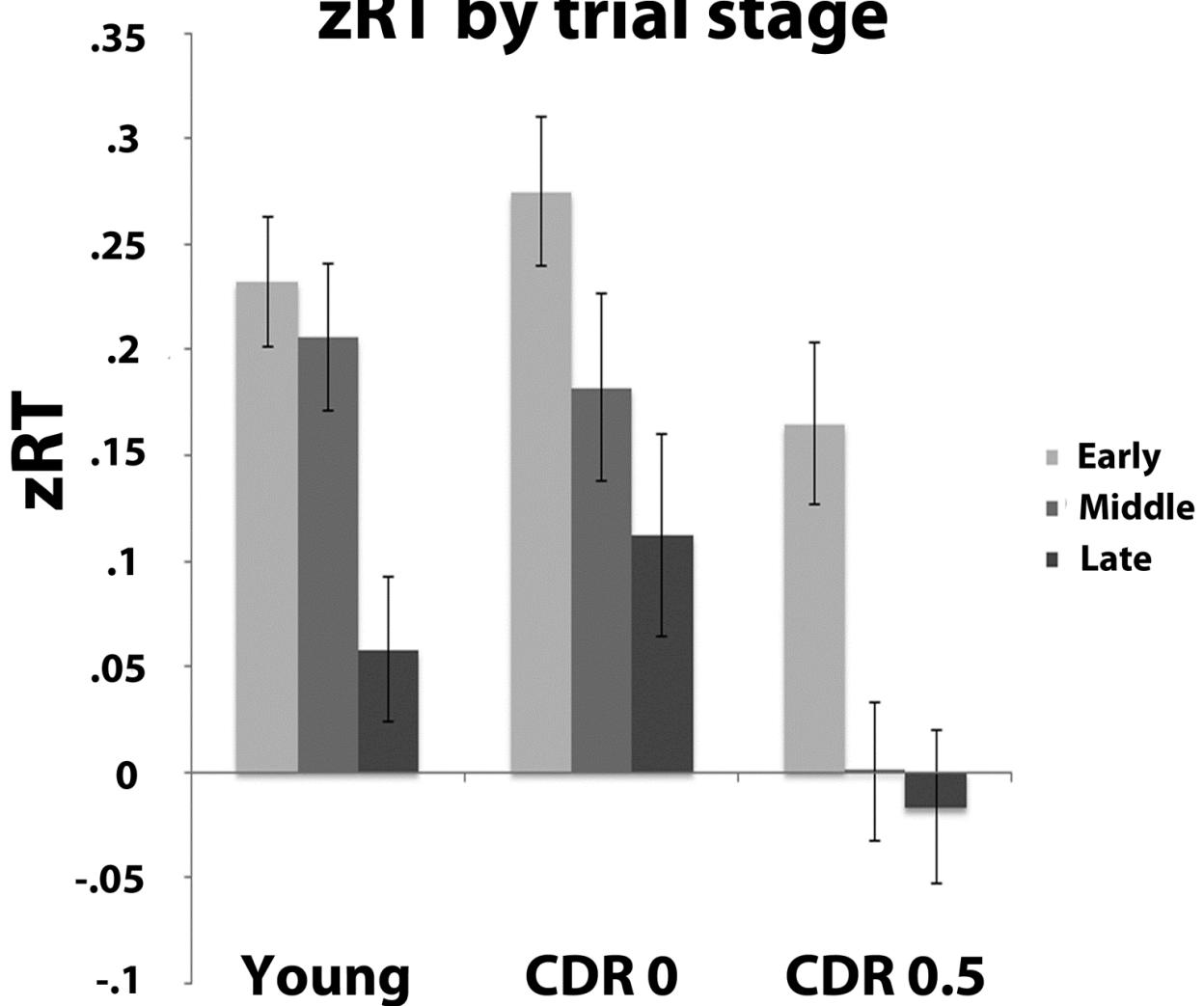


Figure 2.5: Differential decrease in standardized RTs for groups across trial stage at level two of feature overlap. Error bars represent \pm one s.e.m.

Logistic regression analysis

Logistic regression analyses revealed that a metric derived from the current task provided excellent discrimination between healthy older adults and those in the earliest stages of AD, surpassing discrimination performance using available standard neuropsychological measures.

The CDR 0 and CDR 0.5 groups were significantly different on the episodic memory composite $t(49) = 4.84, p < .001$, and the global cognition composite $t(49) = 4.46, p < .001$, with the CDR 0 group having higher scores on both measures. In the first analysis, age and the episodic memory composite score were entered in step one, and explained a significant amount of the variability in CDR status $\chi^2(2, N = 51) = 19.6, p < .001$. In step two, the inclusion of d'_{10} explained a significant amount of the residual variance $\Delta \chi^2(1, N = 51) = 9.4, p = .002$. A similar pattern emerged when entering the global cognition composite along with age as step one in a logistic regression model, as this explained a large proportion of variability in CDR status $\chi^2(2, N = 51) = 18.1, p < .001$. The inclusion of d'_{10} again explained a significant amount of residual variance $\Delta \chi^2(1, N = 51) = 10.8, p = .001$. When entering age and d'_{10} in step one however, the additional entry of either the episodic memory or global cognition composite scores only explained a marginally significant amount of variance. The initial model with age and d'_{10} was significant, $\chi^2(2, N = 51) = 25.8, p < .001$, and the inclusion of the episodic memory composite score in step two resulted in a marginally significant increase in the amount of variance explained, $\Delta \chi^2(1, N = 51) = 3.2, p = .08$; the inclusion of the global cognition composite, in a separate model, yielded a similar result, $\Delta \chi^2(1, N = 51) = 3.08, p = .08$. Thus, the discrimination performance in the most difficult condition appears to be particularly sensitive to the transition between healthy aging and the earliest stages of AD. Table 2.5 depicts the classification rates and effect sizes for the models.

Table 2.5
Logistic regression analyses predicting healthy aging vs. very mild Alzheimer's disease

1st step variables	CCR	R²	2nd step variable	CCR	R²
Age & episodic memory	70.6	.43	d' ₁₀	78.4	.58
Age & global cognition	74.5	.40	d' ₁₀	80.4	.58
Age & d' position ten	78.4	.53	episodic memory	78.4	.58
Age & d' position ten	78.4	.53	global cognition	80.4	.58

Episodic memory and global cognition refer to composite scores calculated from neuropsychological tests. CCR = correct classification rate; R² refers to Nagelkerke's R²

Discussion

In this study we employed a task sensitive to hippocampal function to assess changes in related cognitive abilities across the lifespan, and evaluated whether performance could distinguish healthy aging from very mild AD. Healthy aging was associated with reduced accuracy on this task. Subjects with very mild AD showed more marked impairment, both quantitatively and qualitatively, than the cognitively intact older adults. The AD-related impairment was coupled with an additional decrease, not seen in other older adults, in signal detection as a function of interference, specifically the number of intervening stimuli since the sample stimulus was presented. Classification (using logistic regression models) of CDR 0 vs. CDR 0.5 participants based on performance measures was highly accurate. Finally, while FA rates increased as a function of feature overlap with the target for all participants, FA rates increased more with feature overlap for healthy older adults than young adults, and for AD patients relative to healthy older adults. Together, these findings support the hypothesis that tasks assessing relational processing, even at short delays, are sensitive to the earliest stages of AD.

The results from the signal detection analyses are informative as to whether AD is an extreme along the trajectory of healthy aging or a qualitatively different state, as suggested by

multiplicative models of brain aging (Buckner, 2004). In addition to being less accurate overall, the d' data from the CDR 0.5 participants displayed a unique pattern characterized by decreasing accuracy as the number of interfering stimuli increased. This pattern of behavioral results indicates that AD carries with it an additional memory impairment that may be centered on sensitivity to interference. Therefore, these data suggest the cognitive manifestations of AD seem to be due to aging together with an additional factor due to a disease state.

Considering the neural substrates underlying these differences in task performance due to AD, it is likely that the hippocampus and possibly the MTL cortex are involved. In an eye-tracking version of an experiment using these stimuli, impairments in amnesic patients were only observed after a sufficient number of objects (greater than six) had been fixated, potentially indicating a degrading representation due to increased interference (Warren et al., 2011). Structural MRI studies of healthy aging and mild AD report that hippocampal volume and MTL cortical thickness correctly categorize individuals with a high level of accuracy, indicating substantial tissue loss in these regions occurs in the earliest stages of AD (Desikan et al., 2009; Dickerson et al., 2009; Head, Snyder, Girton, Morris, & Buckner, 2005). Given these anatomical findings and the observed decline in d' at longer latencies (similar to that observed in amnesic patients), the effect here may be related to hippocampal atrophy. This interpretation would be consistent with animal models that suggest deficits in the hit rate, which largely drove the decrease in d' observed here, are more related to hippocampal damage (Fortin et al., 2004).

The group differences in the FA rate data across the duration of a trial, where increasing feature overlap caused disproportionate increases in FA rates for the two older adult groups, could be attributable to several candidate mechanisms. For instance, atrophy in brain regions implicated in source monitoring and inhibition, such as the PFC, may play a role in the FA

effects since PFC volume decreases in healthy aging and this area is also damaged in AD (Dickerson et al., 2009; Mesulam, 2000; Raz et al., 2005). Additionally, FA rates on this task in both older adult groups may also partially be explained from a pattern separation framework centered on MTL integrity. Healthy older adults (relative to young adults) and amnestic mild cognitive impairment patients (relative to healthy older adults) are more likely to endorse highly similar lures as “old,” demonstrating a shift towards pattern completion, and mirroring the results observed here (Stark, Yassa, Lacy, & Stark, 2013; Yassa et al., 2010). From this perspective, the integrity of the perforant pathway and its associated structures may be important, as performance on pattern separation tasks is linked to these areas (Yassa, Mattfeld, Stark, & Stark, 2011).

The zRT data for the young and CDR 0 groups are intriguing because both of these groups remained as accurate in identifying the matching stimulus at position six as they were at position ten, but like the CDR 0.5 participants, both groups showed reduced zRTs to stimuli sharing two features with the target as the trial continued. This modulation of zRT by trial length was different for each of the three groups, with the CDR 0.5 group showing an early decrease in zRT, the young adults a late decrease, and the CDR 0 participants a gradual reduction in zRT (Figure 2.5). Since zRTs didn't decrease for all lure types, this effect is likely linked to the underlying mnemonic representation and decision making process, rather than generically faster responding at the end of a trial. Previous work using these stimuli while eye-movement data were recorded suggest that reduced viewing time to highly similar lures is indicative of reductions in the internal representation of the target, as the viewed stimulus provides less of a match with the individual's target representation and is thus easier to reject (Warren et al., 2011). Therefore, it is possible that all groups experienced some degradation of the internal representation of the target stimulus as more interference occurred, but the amount of

degradation that occurred in the young and CDR 0 groups was not enough to affect accuracy. It may also be that the zRT and d' metrics represent two different measures of the mnemonic representation of the target stimulus, as the zRT metric is composed solely of correct rejections, whereas the d' measure takes into account all responses.

The finding that the d'_{10} measure was able to further differentiate very mild AD from aging after accounting for episodic memory or global cognition is informative in defining the cognitive deficits of very early AD. It is conceivable that the memory demands in this task, particularly accuracy late in a trial, are more related to additional aspects of the cognitive construct of "episodic memory" and the presumed underlying neuropathology in the hippocampus than the traditional neuropsychological subtasks used to assess episodic memory (e.g. Logical Memory, Selective Reminding Task). Therefore, variance in performance between CDR 0 and CDR 0.5 participants in episodic memory that is not captured by traditional paper-and-pencil tests of memory may be detected here and in turn improves the classification rate.

Another possibility is that rather than being a milder phenocopy of a hippocampal amnesia, the earliest stages of AD may be marked by broader cognitive impairments, and this task may be sensitive to these additional deficits. For instance, a large body of evidence suggests that attentional processes decline in very early AD, including failures of inhibition and cognitive control (Balota et al., 1999; Budson, Daffner, Desikan, & Schacter, 2000; Monti, Weintraub, & Egner, 2010; Spieler, Balota, & Faust, 1996; Tse, Balota, Moynan, Duchek, & Jacoby, 2010; Watson, Balota, & Sergent-Marshall, 2001). Thus it is possible that the attentional demands in this paradigm, including sustained attention across the ten stimulus presentations on each trial, and inhibiting a "yes" response to stimuli that shared a majority of perceptual features with the target, caused the CDR 0.5 group to perform worse. This in turn may have carried unique

variance between the two older adult groups that improved classification beyond what was provided by the episodic memory or global cognition factor scores. The notion of cognitive manifestations of very mild AD extending beyond the domain of episodic memory meshes well with the full neuropathological picture of very mild AD, given that the earliest and greatest areas of amyloid deposition occur in the lateral and medial PFC and parietal lobe (Buckner, 2004). Moreover, metabolism dysfunction observed via [¹⁸F] fluorodeoxyglucose positron emission tomography in those with very early Alzheimer's disease is strongest in the posterior cingulate cortex, precuneus, and temporoparietal regions (Ewers, Sperling, Klunk, Weiner, & Hampel, 2011). Thus, given the multiple types and locations of pathology in very early AD, tasks that tax both the MTL system and its interaction with broader cortical networks may be more sensitive to the earliest stages of AD than domain-specific neuropsychological tasks. Future investigations could be designed to address this hypothesis by evaluating differences in the neuropsychological profiles of amnesic patients with focal hippocampal damage and patients with very mild AD.

In summary, we report results using a novel task for the discrimination of healthy aging from very mild AD. Healthy older adults were less accurate than young adults, and those with very mild AD showed further reduced accuracy, and additionally became less accurate as a function of interference. This effect was not observed in the young and healthy older adult groups, suggesting it may be an exclusive part of the cognitive phenotype in very mild AD, and indicates that this phenotype may be the product of both aging and an additional disease state. Furthermore, a metric derived from task performance explained additional variance in logistic regression models predicting CDR status after accounting for episodic memory or global cognition, suggesting this task may be uniquely sensitive to a portion of variance in the cognitive manifestation of very mild AD that is not captured by standard neuropsychological tasks.

Chapter 3: Relating hippocampus to relational memory processing across domains and delays

Abstract

Across various literatures within psychology and neuroscience, the hippocampus has been implicated in a diverse set of cognitive paradigms and domains, including spatial navigation and cognitive mapping, long-term memory especially for verbal materials, and relational memory regardless of study-test interval. Most studies assess hippocampal memory within the tradition of one or another of the separate literatures, making it difficult to know whether these studies all assess a similar underlying cognitive construct tied to the hippocampus, or if they tap multiple aspects of cognition to which the hippocampus contributes in qualitatively different ways. Here we directly tested the issue of hippocampal function by using principal component analysis on performance of 109 healthy adults on a battery of twelve cognitive tasks that included two traditional, long-delay neuropsychological tests of memory and two laboratory tests of relational memory, one spatial and one of visual object associations, that imposed only short delays between study and test. Also included were tests of semantic memory as well as other memory tasks and tests of executive function or processing speed not classically identified with hippocampal function. Structural MRI scans were available for a subset of participants ($N = 80$) for whom we were able to quantify the volume of the hippocampus and other subcortical regions. Results revealed that the twelve tasks clustered into four components; critically, the two neuropsychological tasks of long-term verbal memory and the two laboratory tests of relational memory loaded onto one component, suggesting that performance on these tasks relies on a similar cognitive construct. Moreover, bilateral hippocampal volume was strongly tied to performance on this component. Taken together, these data emphasize the critical contribution

the hippocampus makes to relational memory processing, and the commonality of relational memory demands across a broad range of tasks across multiple domains in various literatures.

Introduction

In studying the functional role of the hippocampus and related medial temporal lobe (MTL) structures, the fields of psychology and neuroscience are not wanting for paradigms or methods, as an impressive diversity of tests is apparent across the respective literatures. For example, countless investigations of hippocampal function in rodent models use one or another sensitive test of spatial memory, inspired largely by the ideas of cognitive mapping theory (O'Keefe & Nadel, 1978). By contrast, clinical investigation of hippocampal damage in humans historically involves testing memory at long delays, usually for verbal materials. For example, disproportionate impairments on the delayed test condition of the California Verbal Learning Test (CVLT) are often indicative of early clinical Alzheimer's disease, and also correlate with residual hippocampal tissue in amnesic patients, who are severely impaired on this task (Allen, Tranel, Bruss, & Damasio, 2006; Weintraub, Wicklund, & Salmon, 2012). The relationship between performance on tests like the CVLT or delayed recall of stories in the Logical Memory subtest of the Wechsler Memory Scale (WMS) and the integrity of the hippocampus is consistent with findings as far back as those with patient HM, who had grossly impaired memory at long delays but seemingly intact memory when delays were very short (Milner, Corkin & Teuber, 1968; Sidman, Stoddard & Mohr, 1968; Wickelgren, 1968).

Recently though, emerging findings in cognitive neuroscience indicate a critical role for the hippocampus in memory across even short delays. Hippocampal amnesic participants are impaired when they must process and remember the relationships between elements such as a

face with a scene or an object-location binding, thereby requiring relational memory, even when the delay between study and test is only several seconds (Hannula, Tranel, & Cohen, 2006; Olson, Page, Moore, Chatterjee, & Verfaellie, 2006; Pertzov et al., 2013; Watson, Voss, Warren, Tranel, & Cohen, 2013). Further, studies using a variety of stimuli indicate hippocampal/MTL-damaged patients perform more poorly on certain visual search tasks even with no experimenter-imposed delay; that is, patients are impaired even when all of the information necessary to correctly answer a trial remains present on the display for the participant, and the only delays are those occurring across successive saccades (Lee et al., 2005; Warren, Duff, Jensen, Tranel, & Cohen, 2012; Warren, Duff, Tranel, & Cohen, 2011). Finally, neuroimaging studies report hippocampal activity during encoding and maintenance at short delays for novel stimuli or for relations among items (Axmacher et al., 2007; Hannula & Ranganath, 2008; Olsen et al., 2009; Ranganath & D'Esposito, 2001; Ranganath, Cohen, & Brozinsky, 2005).

Viewing across the different literatures exploring hippocampal function, one gains an appreciation for the breadth of cognitive tasks that involve the hippocampus. But, how is the hippocampus involved in all of these disparate tasks? It is possible that the hippocampus makes a range of contributions to cognition by carrying out qualitatively different computations when, say, supporting memory for a word list after a long delay than when aiding in remembering a face-scene pair at short delays or when creating and maintaining representations that can distinguish among multiple similar stimuli. The possibility of multiple functional roles for the hippocampus would seem to be encouraged by recent findings critically implicating the hippocampus in functions less obviously related to those tapped by classical memory tasks, as in future imagining (Schacter et al., 2012), and aspects of language (Duff & Brown-Schmidt, 2012), decision-making (Gupta et al., 2009), and high-level perception (Lee, Yeung, & Barense, 2012).

The alternative possibility is that the hippocampus supports certain core memory computations or processes that can be invoked in common by multiple cognitive systems in service of a range of task performances. The idea that the hippocampus performs a common computation across these domains is in line with classifying memory systems, and the task performances they support, less by parameters such as conscious vs. non-conscious, short vs. long delay, or spatial vs. non-spatial, and instead focusing on the type of representations and information processing accomplished by a system (Eichenbaum, Otto, & Cohen, 1994; Henke, 2010; Cohen & Eichenbaum, 1993; Olsen, Moses, Riggs, & Ryan, 2012). Empirical data testing the possible commonality of the hippocampal contribution across different memory tasks are scant however, since most studies of hippocampal memory only include tasks from one tradition (e.g., in humans, long-delay verbal recall OR recollection responses in a recognition task OR non-verbal relational memory binding at short delays).

In the work reported here, we used multivariate analyses on data from a battery of cognitive tasks to test whether hippocampal involvement in a range of disparate paradigms reflects a common cognitive construct. More specifically, it tested the hypothesis that a critical commonality of hippocampal functioning is the use of relational memory representations and processing in supporting task performance. This hypothesis is based on relational memory theory (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001) and the suggestion that the hippocampus is critical for relational memory binding, creating memory representations of all manner of relations amongst the constituent elements of scenes or events, irrespective of temporal delay or stimulus modality, and for the flexible use of such representations in service of various cognitive demands and performance challenges.

The test battery used here included twelve tasks. Four in particular were deemed critical for testing the hypothesis. There were two delayed verbal recall tasks (California Verbal Learning Test (CVLT) and Logical Memory (LM) from the Wechsler Memory Scale). These are classic neuropsychological tests, with study-test intervals of 20-30 min, widely shown to be sensitive to memory impairment due to hippocampal dysfunction (Allen et al., 2006; Milner et al., 1968; Weintraub et al., 2012). These tasks also depend upon relational memory, for binding of the various commonly heard words to the specific temporal-spatial context of the experimental setting in the CVLT, and for binding together of the various pieces of the story, including actors, temporal sequence of events, and geographic setting in the LM. The test battery also included two relational memory tasks used regularly in our laboratory. One was a recognition memory test for face-scene pairings, with a delay between encoding and recognition of any given pair less than five min and as short as 30 s, based on a variant (Monti et al., 2013) of a task shown to be highly dependent on relational memory and hippocampal integrity (Hannula, Ryan, Tranel, & Cohen 2007; Hannula & Ranganath, 2009). The second was a spatial reconstruction task in which on each trial participants studied the spatial arrangement of a set of five novel stimuli and then had to reconstruct the array (objects in their locations) after just a four second delay, based on Watson et al., (2013; see Methods for further details on all tasks).

In addition to these tasks, we added memory tests of semantic memory, and memory tasks that do not create as high a challenge on relational memory processing, such as the n-back task and a spatial working memory task. Finally, to ensure we tested a wide-range of cognitive abilities, we included tasks of executive function and processing speed. To the extent that there is a commonality of hippocampal functioning based on the use of relational memory representations and processing in supporting task performance, we expected that performance on

the two traditional, longer-delay tests of verbal recall (CVLT and LM) and the two short-delay laboratory tasks (face-scene recognition paradigm and spatial reconstruction task) would load on one component in the principal components analysis, due to their common reliance on relational memory processing, despite involving different stimulus types, delay intervals, and response requirements. Furthermore, we expected performance on this component to be strongly tied to hippocampal volume.

Materials and Methods

Participants

One hundred thirty-five individuals participated as part of a multi-session study examining the effects of aging on brain and cognition across the lifespan. Data from participants aged 60 and older came from the pre-testing sessions of a cognitive training intervention, whereas the data from individuals below the age of 60 were collected for the purposes of obtaining a cross-sectional sample to study cognitive aging. Of the original 135 participants, data from 14 individuals were discarded due to chance performance on one of the tasks. Furthermore, an additional 12 participants' MRI data were not usable due to participant movement that rendered the images not suitable for subcortical segmentation. Thus, the final sample for the behavioral data contained 109 participants, with an age range of 18-83 ($M = 51.18$, $SD = 20.83$). Only a subsample of this larger group was used in relating behavioral measures to subcortical volumes (see below). The University of Illinois Institutional Review Board approved all procedures, and participants signed an informed consent document. All individuals were compensated monetarily for their time.

Cognitive tasks

A battery of twelve tasks assessing a variety of cognitive functions was used in this study, consisting of a mix of standard neuropsychological tasks and laboratory tasks. Participants completed the Trail Making Test A and B (Armitage, 1946) and the Digit Symbol Substitution Task (DSST) from the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981). An abbreviated version of the California Verbal Learning Test II (CVLT; Delis, Kramer, Kaplan, & Ober, 2000) was given that included the initial five learning trials (with a free recall after each reading of the word-list) and then a delayed free recall, which took place approximately 20 minutes later. Participants also completed Logical Memory (LM) Story B from the Wechsler Memory Scale (Wechsler & Stone, 1973) by listening to a reading of the story and immediately recalling all they can remember, and then participating in a delayed free recall approximately 30 minutes later. Two measures of category fluency were administered by having participants name as many fruits and vegetables as they could in one minute, and then naming as many animals in one minute.

A computerized N-back task consisting of lower case letters as stimuli and trials that included one- and two-back blocks was also given. Following 13 practice trials for the one-back condition, participants completed 100 trials broken into five blocks of 20 trials; the identical procedure, with practice, was repeated for the two-back blocks. There was also a task-switching paradigm where participants were required to respond to whether a presented number was odd or even, if presented on a pink background, or if it was above or below the value five, if presented on a blue background (Baniqued et al., 2013; Verstynen et al., 2012). This task was administered in three blocks, and each block had a practice session. First, participants completed back-to-back practice blocks of 24 trials each. In the first practice block, subjects only responded to stimuli on

blue backgrounds using a high/low judgment, and in the second block responded to stimuli on pink backgrounds using an odd/even judgment; participants were given feedback about their accuracy during these practice blocks. Participants then completed two identical blocks for data collection, with the only difference being there was no feedback given. The final block was a mixed condition where trials contained numbers on pink or blue backgrounds within a block in a randomly ordered fashion, and participants needed to make the appropriate judgment based on the color of the background. There was one, 32-trial practice block with feedback, followed by a 120-trial block with no feedback used for data collection.

Participants also completed a version of a spatial working memory paradigm previously used in our lab (Baniqued et al., 2013; Erickson et al., 2009, 2011). In this task, individuals were required to remember the location of dots on a computer screen. In the encoding phase of a trial, individuals studied the locations of two, three, or four dots for 500 ms. This was followed by a 3000 ms delay period where the screen was blank, after which one probe dot appeared on the screen and participants were instructed to indicate yes/no as to whether the probe dot occupied the same space as one of the dots in the encoding phase; participants were given 2000 ms to respond and trials were separated with a 1000 ms inter-trial-interval (ITI). Following 24 practice trials, participants completed the actual experiment that contained 40 trials for each set-size, presented in an intermixed fashion.

Finally, two relational memory tasks developed in our lab were used in this study. The first was a task where individuals had to remember pairs of faces and scenes reported in Monti et al., (2013). This task was conducted during a functional MRI session; data relating to brain activity were not considered in this report and will be reported elsewhere. The task was divided into three separate runs, with 24 encoding and 24 recognition trials in each run; the encoding and

recognition phases were separated by a 20-second rest period. Encoding and recognition trials consisted of the presentation of a scene for 2000 ms followed by a face overlaid on the scene for an additional 2000 ms. A fixation cross was displayed during the ITI, which was jittered and ranged from 2000-12000 ms (Figure 3.1). Participants completed a practice session outside the scanner before proceeding. On each encoding trial, participants made a yes/no judgment indicating whether the individual depicted “fit” with the scene; this was an arbitrary decision to elicit deep encoding. At recognition two trial types were presented, “intact” face-scene pairs, which were the identical face-scene combinations presented during encoding, and “re-pair” trials, created by recombining a previously displayed face and scene that were not shown together at encoding. Hence, all stimuli were equally familiar at recognition, and the task had to be completed via relational memory. Participants made a yes/no judgment as to whether the pair displayed was an exact match of a pair shown at encoding, with twelve trials from each trial type composing the recognition phase of a run.

The second task was a computerized version of a spatial reconstruction (SR) task reported in Watson et al., (2013). On each trial, participants studied the arrangement of five novel line-drawings (Figure 3.2). Study-time was self-paced and participants were instructed to use the mouse to click on each image during study. Following the study phase, a 4000 ms delay occurred where participants saw a blank screen; after this period a self-paced test phase began. In the test phase, stimuli appeared aligned at the top of the screen and participants used the mouse to click and drag them into where they thought they were positioned in the study phase; trials were separated with a 2000 ms ITI. Participants completed three practice trials and 15 trials for data collection.

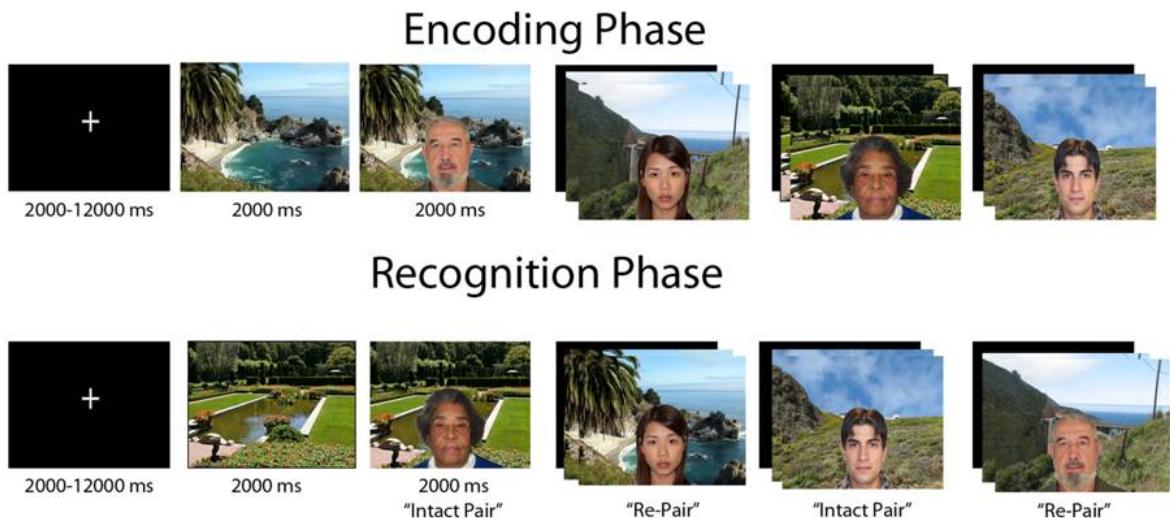


Figure 3.1: Example trials from encoding and recognition phase of face-scene task. The two phases were separated by a 20 s break.

Example trial from SR Task

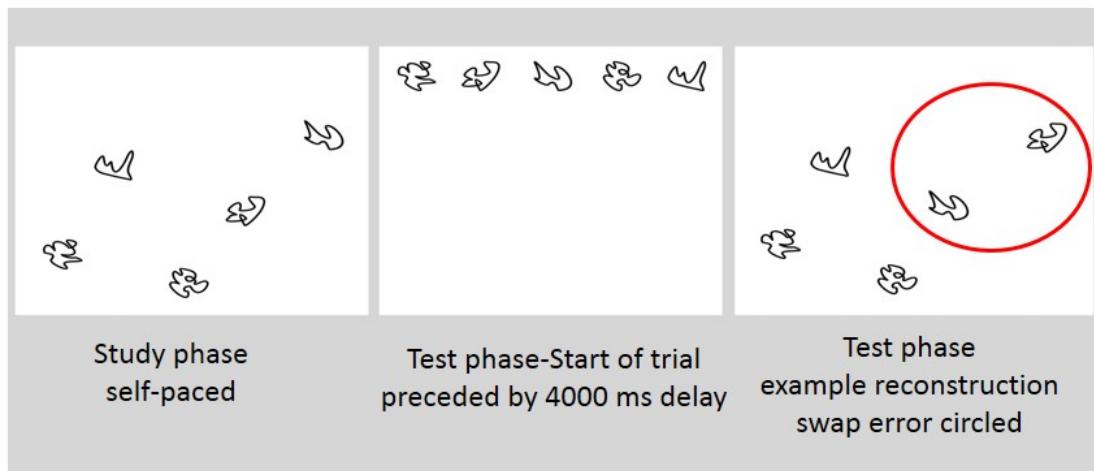


Figure 3.2: Example trial from SR task. Left panel shows example study phase. A 4000 ms blank screen separated the study and test phase. The right panel shows an example of a participant's reconstruction; note the swap error, indicated by the red circle.

Behavioral Measures

One measure for each task was selected for the PCA. For Trail Making Test A and B, the dependent variable used was time to accurately complete each task. For the DSST, the dependent measure was number of correct symbols completed in two minutes. The numbers of animals and fruits & vegetables named, excluding repetitions, were entered to assess performance on these two tasks. Overall accuracy on the spatial working memory task was used as the measure for this task. Cost measures for the N-back and task-switching task were selected for these paradigms. In the N-back task, accuracy on the one-back condition was subtracted from accuracy on the two-back condition to create a cost measure of accuracy. A global switch cost for accuracy was calculated to evaluate performance on the task-switching paradigm; we derived this by subtracting accuracy from the first two blocks (non-switch) from accuracy of the third (switch block), with more negative values indicating more difficulty with task switching¹.

Delayed recall from both the CVLT and LM tasks was selected as the variable of interest for the analysis of these tasks. The selection of delayed recall from both of these tasks was due to the long-standing finding that delayed recall from these types of measures is severely impaired in hippocampal amnesic patients and related to hippocampal volume (Allen et al., 2006) and thus, provides a benchmark with which to compare the relational memory tasks. In the face-scene task, a d' value was collected for each individual by using the overall hit rate and false alarm (FA) rate; in the event a participant had a hit rate of one or an FA rate of zero, these values were calculated by using $1-(1/2N)$ and $1/2N$ respectively, with N equaling the number of trials going into the analysis, in order to calculate d'.

¹ Choosing overall two-back accuracy as the measure from the N-back task or local switch cost for the task switching task yielded the same qualitative results in the PCA reported in the Results

For the SR task, the dependent variable was the proportion of pairwise object-location bindings that the participant erroneously “swapped” during the reconstruction phase (see Figure 3.2; Watson et al., 2013). Conceptually, a swap occurs when a participant places two objects in spatial locations that were previously occupied in the study phase, but not by the specific objects placed by the individual. Operationally, a swap is calculated as occurring when the sign of the x and y components of the vector representing the spatial relationship between two objects switch from the study to test phase. A swap error is recorded as a binary event, and the final metric is the number of swap errors divided by the number of possible pairwise relations in a trial (which was held constant in this experiment). The rationale for choosing the swap measure as the main metric for analysis stems from previous work in our lab and others indicating swap errors disproportionately occur in hippocampal amnesic patients due to the high relational demand entailed in remembering two or more object-location bindings (Pertzov et al., 2013; Watson et al., 2013).

Behavioral data analysis

To understand which tasks rely on similar cognitive constructs, principal components analysis (PCA) was utilized for dimension reduction. Prior to conducting the PCA, any task where a high value represented poorer performance was reverse-scored to simplify interpretation. These above twelve measures were entered into a PCA using a varimax rotation and components with initial eigenvalues larger than 1.0 were extracted (Kaiser, 1958). All reported eigenvalues and loadings are after varimax rotation. Measures loading on a component with a value greater than 0.5 were deemed to significantly contribute to that component. A metric for each component was created by averaging the standardized scores of the tasks that significantly

contributed to that component; these values, as well as the scores on the individual subtasks, were used in correlational and regression analyses comparing cognition to brain structure.

Structural MRI acquisition

Structural images were acquired with a T1-weighted 3D magnetization prepared rapid gradient echo imaging (MPRAGE) protocol of 192 contiguous sagittal slices collected in an ascending manner parallel to the AC-PC line [TR = 1900 ms; TE = 2.26 ms; flip angle = 9°; FOV = 256*256 mm; voxel size = 1 × 1 × 1 mm].

Subcortical volume measures

Automated segmentation of the hippocampus, striatum (caudate and putamen), and amygdala was performed using Freesurfer (v 5.3); details of the subcortical segmentation process utilized by Freesurfer are available in (Fischl et al., 2002). We chose the striatum and amygdala as additional regions to compare with task performance, since both are subcortical structures implicated in learning and memory. An automated measure of intracranial volume (ICV), which is comparable to manual tracing, was obtained for each participant via Freesurfer using the methods described in Buckner et al., (2004). This measure of estimated ICV was used to correct subcortical volume for head size by regressing each ROI volume onto ICV in order to obtain a slope (b) for the relationship between an ROI and ICV. The resulting slope was then used to normalize each ROI for head size via the following formula: normalized volume = raw volume – b (ICV - mean ICV); this correction has been used in multiple studies reporting subcortical volume measures (Erickson et al., 2009; Head, Rodriguez, Kennedy, & Raz, 2008; Raz et al., 2005).

Only MR data from middle-aged and older adults were included in the subcortical volume analyses. We chose to only include this age range due to the somewhat bimodal distribution of age in our sample. The age range of young adults ($N = 29$) in our sample was 18-29, and all other participants ($N = 80$) were in the 40-83 age range. Moreover, the distribution of young adults was mostly college-aged students $M = 21.3$, $SD = 2.8$, whereas those in the older group represented a more continuous sample $M = 62.0$, $SD = 12.0$. The rationale for excluding the young adults in the MR analyses relates to the idea that the size of brain structures in an 18-22 year-old is likely stable, and any variation in the size of a structure not meaningful; thus, including these values would introduce noise in the data. However, due to aging, the size of the subcortical regions begins to shrink by ones forties (Fjell et al., 2013), making the variation in size of a structure and its relationship to cognitive function much more meaningful. Finally, a family-wise Bonferroni correction for multiple comparisons for correlations between brain regions and components or brain regions and individual tasks was set at $p < .004$.

Results

Principal components analysis

The PCA extracted four components and contained a solution that explained 63.39% of the variance. As can be seen in Table 3.1, each of the twelve measures only loaded onto one component. Critically, the two measures from the relational memory tasks (SR and face-scene memory) loaded with the two canonical neuropsychological measures of hippocampal memory (CVLT and LM delayed free recall) to form a component (PC-2; $\lambda_2 = 1.95$) indicating performance on these tasks relies on a common cognitive construct. The largest amount of variance was explained by a component containing Trail Making Test A and B, as well as DSST (PC-1; $\lambda_1 = 2.34$). A third factor included the amount of animals named and the number of fruits

and vegetables named (PC-3; $\lambda_3 = 1.74$). Finally, the fourth factor included the measures from the N-back, spatial working memory, and task-switching tasks (PC-4; $\lambda_4 = 1.58$). Table 3.2 provides a correlation matrix containing all twelve tasks.

Table 3.1

Results from principal components analysis

Task	Components			
	PC-1	PC-2	PC-3	PC-4
Trails A	.85	.04	.04	.14
Trails B	.82	.25	.05	.20
DSST	.79	.26	.17	.12
CVLT	-.01	.68	.20	.13
LM	.13	.64	.06	-.06
Face-Scene	.13	.63	-.09	.21
SR	.34	.68	.07	.02
Animals	.17	.11	.87	.12
Fruits & Veg	.03	.07	.92	-.02
SPWM	.35	.17	.01	.64
Task Switch	.14	-.06	-.08	.75
N-back	.02	.16	.21	.68
% Variance	19.49%	16.22%	14.5%	13.13%

Abbreviations: PC = principal component; DSST = Digit Symbol Substitution Task; CVLT = California Verbal Learning Test; LM = Logical Memory; SR = spatial reconstruction task; Veg = vegetables; SPWM = spatial working memory task

Table 3.2**Correlation Matrix**

	Trials A	Trails B	DSST	CVLT	LM	Face-scene	SR	Animals	Fruits & Veg	SPWM	Task-switch	N-back
Trails A	-	.65***	.58***	.17	.17	.13	.27**	.18	.06	.29**	.26**	.16
Trails B		-	.65***	.22*	.28**	.28**	.41***	.20	.12	.45***	.25**	.20*
DSST			-	.18	.23*	.31**	.43***	.33**	.16	.38***	.13	.24*
CVLT				-	.28**	.24*	.39***	.18	.23*	.19*	.10	.13
LM					-	.24*	.29**	.13	.11	.05	.05	.14
Face-scene						-	.34***	.15	-.01	.28**	.11	.12
SR							-	.19*	.12	.26**	.02	.19
Animals								-	.68***	.16	.05	.22*
Fruits & Veg									-	.04	-.03	.11
SPWM										-	.31**	.31**
Task-switch											-	.23*
N-Back												-

* $p < .05$ ** $p < .01$ *** $p < .001$

Abbreviations: DSST = Digit Symbol Substitution Task; CVLT = California Verbal Learning Test; LM = Logical Memory; SR = spatial reconstruction task; Veg = vegetables; SPWM = spatial working memory task

Subcortical volumes: Correlation analyses

Hippocampal volume was significantly correlated with PC-1, $r(78) = .46, p < .001$, and PC-2, $r(78) = .41, p < .001$, and had a modest correlation with PC-3 that was non-significant after multiple comparison correction, $r(78) = .23, p = .03$. The amygdala significantly correlated with performance on PC-1, $r(78) = .37, p = .001$, and was moderately related to PC-2, $r(78) = .24, p = .03$. After multiple comparison correction, striatal volume was not significantly related to any components; however, it did display a relationship with PC-2, $r(78) = .31, p = .005$ and a modest link with PC-3, $r(78) = .27, p = .02$. Correlation values for all principal components and the three brain regions are reported in Table 3.3. To ascertain how performance on the four tasks putatively most reliant on the hippocampus related to the volume of that structure, correlations between the CVLT, LM, SR and face-scene tasks were conducted. Prior to multiple comparison correction, only hippocampal volume significantly correlated with performance on all four of the subtasks comprising PC-2; both the amygdala and striatum were positively related to the LM tasks, with striatal volume also correlating with the SR task (Table 3.4). However, after the conservative correction, only the SR task and hippocampal volume were significantly correlated.

Table 3.3*Correlations between subcortical volume and components*

	<u>PC-1</u>	<u>PC-2</u>	<u>PC-3</u>	<u>PC-4</u>
Hippocampus	.46***	.41***	.25*	.20
Amygdala	.37***	.24*	.21	.12
Striatum	.17	.31**	.27*	.10

* $p < .05$ ** $p < .01$ *** $p \leq .001$

Abbreviations: PC = principal component; bolded numbers indicate significant after Bonferroni correction

Table 3.4*Correlations between hippocampal volume and RM subtasks*

	<u>CVLT</u>	<u>LM</u>	<u>Face-Scene</u>	<u>SR</u>
Hippocampus	.25*	.27*	.26*	.39***
Amygdala	.07	.27*	.20	.15
Striatum	.18	.27*	.17	.26*

* $p < .05$ *** $p \leq .001$

Abbreviations: CVLT = California Verbal Learning Test; LM = Logical Memory; SR = spatial reconstruction task; bolded numbers indicate significant after Bonferroni correction

Subcortical volumes: Regression analyses

Even though the striatum and amygdala were not significantly correlated with PC-2 after the Bonferroni correction, the r values indicate a potential relationship. Thus, we completed stepwise hierarchical linear regression models to understand the unique contribution of the three brain regions to performance on these memory tasks, and whether hippocampal volume displays the strongest relationship with PC-2, as predicted. In the first model, we entered striatal and amygdala volume in steps one and two, respectively, in order to see if adding hippocampal volume contributed in explaining a significant amount of the residual variance. The full results are presented in Table 3.5. In step one, striatal volume significantly explained 9.8% of the variance in PC-2 performance, $F(1,78) = 8.49, p = .005$; including amygdala volume in step two did not significantly improve the model, $\Delta R^2 = 1.8\%, F(1,77) = 1.6, p = .21$. In the last step, the addition of hippocampal volume explained 10.3% of the residual variance from the tasks comprising PC-2; this increase in explained variance was significant, $F(1,76) = 10.0, p = .002$. In the second model, we entered hippocampal volume first to test the idea that the inclusion of striatal or amygdala volume would not significantly contribute to the model. Entering hippocampal volume first to predict the PC-2 variable explained 17.2% of the variance, a highly significant amount, $F(1,78) = 16.15, p < .001$. The inclusion of striatal volume in step two produced a modest increase in R^2 , 3.4%, which was marginally significant $F(1,77) = 3.29, p = .07$; including the amygdala in step three did not improve the model, $\Delta R^2 = 1.3, F(1,76) = 1.32, p = .25$.

Table 3.5*Results from hierarchical linear regression analyses*Model 1

<u>Step</u>	<u>Brain structure</u>	<u>ΔR^2</u>	<u>F-value</u>	<u>p-value</u>
One	Striatum	9.8	8.47 (1,78)	.005
Two	Amygdala	1.8	1.60 (1,77)	.21
Three	Hippocampus	10.3	10.0 (1,76)	.002

Model 2

<u>Step</u>	<u>Brain structure</u>	<u>ΔR^2</u>	<u>F-value</u>	<u>p-value</u>
One	Hippocampus	17.2	16.15 (1,78)	< .001
Two	Striatum	3.4	3.29 (1,77)	.07
Three	Amygdala	1.4	1.32 (1,76)	.25

Beta coefficients (both models)

<u>Brain structure</u>	<u>Standardized beta</u>	<u>t-value</u>	<u>p-value</u>
Hippocampus	.46	3.16	.002
Striatum	.22	2.0	.05
Amygdala	-.17	1.15	.25

Discussion

From the principal components analysis, a clear component emerged indicating common variance in performance on delayed recall for the CVLT and LM tests, recognizing face-scene pairs, and reconstruction of the object-location relations amongst novel stimuli. Critically, the common variance in performance occurred despite the tasks being different in multiple ways: in the delay imposed between study and test (from 4 s to 30 min); the materials and domains tested (verbal, visual, spatial); and the response demands (verbal responses, button presses, spatial reconstruction with a computer mouse). We interpret the finding of common variance in performance occurring in the face of such disparities in the nature of the testing, in combination with their common association with structural measures of hippocampal volume, as suggesting that these tasks rely upon a common feature of hippocampal processing.

Consideration of the similarities and differences in the details of these multiple memory tasks permits some speculation about what the common denominator is that ties them to hippocampal processing. A critical factor in common among them is the demand placed on memory for the relations among elements (words with context, faces with scenes, objects with locations). Such a demand is consistent with the view that the hippocampus is central to relational memory binding for all manner of relations among the constituent elements of experience (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001; Eichenbaum, 2004; Konkel, Warren, Duff, Tranel, & Cohen, 2008).

By contrast, the length of study-test delay had little effect on which memory tasks clustered together, suggesting the traditional memory taxonomy centered on temporal distinctions may not be useful (Ranganath & Blumenfeld, 2005; Hannula, Tranel, & Cohen,

2006; Watson et al., 2013). Rather, with respect to principal component two, it seems the hippocampus has an active role in supporting memory performance for the tasks used here regardless of temporal delay. This idea is in line with several imaging and patient studies that find hippocampal involvement in memory tasks where delay between study and test are short and more similar to time courses typically associated with working memory (Hannula et al., 2006; Hannula & Ranganath, 2008; Olsen et al., 2009; Olson et al., 2006; Ranganath & D'Esposito, 2001). This finding may also have clinical relevance in that neuropsychologists may not need to impose long delays to assess hippocampal function for disorders such as Alzheimer's disease. Rather, valid and reliable tests with high demands on relational processing could be incorporated into neuropsychological batteries, potentially providing more data on hippocampal function in a shorter period of time.

One idea from the literature about hippocampal contributions to memory suggests that its role emerges only after a certain number of items to be encoded is exceeded; specifically, once immediate memory capacity (three-to-four objects) is surpassed, cortical regions can no longer support the representation and the hippocampus, with its greater capacity, must process and remember these items (see Jeneson & Squire, 2011). Given that the minimum number of items to remember in any task that loaded onto the relational memory factor was five, whereas tasks using smaller stimulus set sizes loaded onto other components, an argument based on memory span may seem plausible. However, we believe it is unlikely to explain these results. Previous work with a version of the SR task in amnesic patients indicated a similar rate of swap errors for two stimuli compared to five, indicating amnesic patients had difficulty remembering spatial relationships between just two objects (Watson et al., 2013). Similarly, Pertzov and colleagues (2013) found amnesic patients made swap errors when just three stimuli were presented, and

other relational memory paradigms employing a small number of stimuli or relations (one-to-three) have found impairments in amnesic patients (Hannula et al., 2006; Olson et al., 2006).

One memory task using a smaller set-size that did not cluster onto the component here presumably reflecting relational memory (PC-2), but has been shown to be sensitive to hippocampal integrity, was the spatial working memory (SPWM) paradigm (Erickson et al., 2009, 2011). This may have occurred because one can use multiple memory representations to solve this task. For instance, one could use relational memory processing to get a trial correct, but an alternate strategy would be to simply hold a single perceptual image of the study trial in mind during the delay phase. When the test probe appears, one would then only need to compute a match/mismatch with the stored perceptual image to answer correctly; this simpler strategy greatly reduces the relational load required to accurately answer a trial. Therefore, since one need not solely rely on relational memory processing on this task, its clustering with a non-hippocampal working memory task like the N-back seems appropriate, despite previous associations with hippocampal volume.

Furthermore, the finding that the SPWM task did not load with PC-2, which included swap errors from the SR task, speaks to the larger debate as to whether the hippocampus primarily performs spatial memory computations (O'Keefe & Nadel, 1978). If memory involving spatial information relied on a common cognitive ability, one would expect the SPWM and the SR tasks to load on the same component. However, the swap error rate from the SR task clustered with three other tasks that have no obvious spatial demands, whereas the SPWM task clustered with two non-spatial tasks that more heavily tax attentional processes that are potentially modulated by fronto-executive networks (Voss et al., 2010). Thus, rather than the hippocampus existing to preferentially deal in spatial memories, it seems that space is but one of

many domains that the hippocampus processes. Such an interpretation is consistent with research in rodents finding that hippocampal processing of time in the form of “time cells” that are akin to “place cells,” indicative of a non-preferential role for spatial processing within the hippocampus (MacDonald, Lepage, Eden, & Eichenbaum, 2011).

The other eight tasks in the analysis cleanly loaded onto three additional factors. PC-1 contained Trail Making Test A and B, as well as the DSST; based on the tasks comprising this component, it is possible that the common cognitive construct linking these tasks is processing speed, even though Trail Making Test B also contains elements of executive function (Lezak, Howieson, Loring, Hannay, & Fischer, 2004). The two tasks clustering with PC-3 (“fruits & vegetables” and “animals”) likely grouped together based on semantic knowledge being a critical component to success on these tasks. Finally, PC-4, which contained the N-back, task-switching, and spatial working memory tasks, may cluster together due to their reliance on executive functioning and/or the type of working or short-term memory computations aided by the PFC.

Though performance on the tasks comprising PC-2 was most strongly related to hippocampal volume, it was still the case that there was a modest, unique contribution from the striatum. While the hippocampus is likely a necessary component to successfully completing the tasks composing PC-2, it is of course the case that a network of brain structures, cortical and subcortical, supports performance on these tasks and any other psychological computation. Therefore, it is not surprising or unexpected that multiple brain regions relate to performance on all of these components, particularly the striatum and PC-2, given its recent appreciation in declarative memory retrieval (Scimeca & Badre, 2012). Approaching task performance with a network framework also aids in explaining the strong association with hippocampus and PC-1. To the extent this component represents a construct related to processing speed, it may be

expected that many brain regions correlate with this component, given the distributed nature of processing speed in the brain (Borghesani et al., 2013). Support for this idea comes from both the hippocampus and amygdala displaying high correlations with PC-1 performance. If it were the case though that PC-1 relies on many brain regions, it would seem striatum volume should also strongly correlate with PC-1 given the tasks composing that component involved motor processing. An alternate explanation still consistent with a network explanation may be that MTL structures have a contribution to the types of tasks in PC-1. This seems plausible when considering the Digit Symbol Substitution Task and the hippocampus, given performance on this task would be aided by the rapidity with which one can learn the nine arbitrary relations between the numbers and symbols, and future investigation of DSST performance and the MTL may be warranted.

To conclude, we report here that performance on four memory tasks differing substantially in the type of stimuli used, the delay imposed, and/or the modality of required response nonetheless clustered on a single component in principal component analysis, and moreover, was positively associated with bilateral hippocampal volume. In common among the tasks was a demand for relational memory processing, supporting the idea that relational memory is a core component of hippocampal processing that cuts across time delays, stimulus modalities, and cognitive domains.

Chapter 4: History of mild traumatic brain injury is associated with deficits in relational memory, reduced hippocampal volume, and less neural activity later in life¹

Abstract

Evidence suggests that a history of head trauma is associated with memory deficits later in life. The majority of previous research has focused on moderate-to-severe traumatic brain injury (TBI), but recent evidence suggests that even a mild TBI (mTBI) can interact with the aging process and produce reductions in memory performance. This study examined the association of mTBI with memory and the brain by comparing young and middle-aged adults who have had mTBI in their recent (several years ago) and remote (several decades ago) past, respectively, with control subjects on a face-scene relational memory paradigm while they underwent functional magnetic resonance imaging. Hippocampal volumes were also examined from high-resolution structural images. Results indicated middle-aged adults with a head injury in their remote past had impaired memory compared to gender, age, and education matched control participants, consistent with previous results in the study of memory, aging, and TBI. The present findings extended previous results by demonstrating that these individuals also had smaller bilateral hippocampi, and had reduced neural activity during memory performance in cortical regions important for memory retrieval. These results indicate that a history of mTBI may be one of the many factors that negatively influence cognitive and brain health in aging.

¹This chapter appears in its entirety (with the absence of the task figure, which is identical to Figure 3.1) in *Frontiers in Aging Neuroscience*, cited as, "Monti, J.M., Voss, M.W., Pence, A., McAuley, E., Kramer, A.F., & Cohen, N.J. (2013). History of mild traumatic brain injury is associated with deficits in relational memory, reduced hippocampal volume, and less neural activity later in life. *Frontiers in Aging Neuroscience*, 5:41, doi:10.3389/fnagi.2013.00041"

Introduction

A hallmark of cognitive aging is inter-individual variability, with some individuals in their seventh and eighth decades already experiencing Alzheimer's disease while others continue to be productive in their careers. Explaining this variability is a critical challenge for the field of cognitive aging. Understanding and predicting one's cognitive phenotype in middle-to-late adulthood is difficult due to the myriad of interacting factors that influence cognitive aging. The relationship between cognition and age is not a simple linear reflection of the number of years lived; rather, it is a complex process influenced by the passage of time, inherent and acquired neuroprotective factors (e.g., genetics and aerobic exercise), and the accumulation of events and processes with deleterious impacts on brain health, such as oxidative stress and hypertension (Fotuhi et al., 2009; Mesulam, 2000). An important factor thought to affect brain and cognitive aging that we know relatively little about are the effects of a history of TBI, as this may interact with aging processes to produce poorer outcomes (Moretti et al., 2012).

Research at the intersection of TBI and aging has historically focused on either the effects of repetitive head trauma, or how moderate-to-severe TBI (such as penetrating head injuries or injuries resulting in loss of consciousness greater than 30 minutes), influence an individual's cognitive aging trajectory. For instance, it is well-known that repeated head trauma, such as the type accumulated by a professional boxer, can lead to dementia later in life (Martland, 1928). More contemporary research has revealed that sustaining even a single moderate-to-severe TBI has negative implications on brain and cognition with advancing age. Research from Corkin and colleagues (1989) showed that those who suffered a penetrating brain injury in young adulthood displayed exacerbated cognitive decline with aging in a variety of cognitive domains, suggesting an interplay between early head trauma and the aging process. Complimentary evidence from

neuropathological data further bolsters the claim that a history of head trauma is associated with worse outcomes in brain health with advancing age. Johnson and colleagues quantified the amount of neurofibrillary tangles (NFTs) and amyloid-beta ($A\beta$) plaques in survivors of a TBI after they died years later of causes unrelated to the injury (Johnson et al., 2012). Compared to controls, those who had a TBI in their life displayed more widespread amyloid pathology that was fibrillary in nature, as well as a greater deposition of NFTs in patients under the age of 60. These data are consonant with epidemiological studies indicating moderate-to-severe TBI leads to an increased risk or the hastening of developing Alzheimer's disease (Plassman et al., 2000; Sullivan et al., 1987).

Only recently has attention shifted to whether cognitive aging is affected by mTBI or concussion, which is when a kinetic force to the head or body (causing the head to rapidly accelerate and decelerate) results in brief or no loss of consciousness, and cognitive deficits that seemingly resolve over the short term. Of the 1.7 million TBIs that occur annually, 75% are classified as mild TBI (Centers for Disease Control, 2003; Faul et al., 2010). Given the high prevalence of mTBI compared to moderate or severe TBI, investigation of how a history of mTBI impacts brain and cognitive health later in life may prove critical to understanding individual differences in cognitive aging. One line of studies investigating the effect of distal mTBI on cognitive aging examined former collegiate athletes that sustained mTBI's in college approximately thirty years earlier. Results showed deficits in declarative memory using neuropsychological tests when measured several decades after mTBI (De Beaumont et al., 2009; Tremblay et al., 2013). Compared to former college athletes without a history of mTBI, those who had sustained mTBI during their college career showed deficits in figural memory tasks, such as the Rey-Osterrieth Complex Figure. The poorer memory function was accompanied by

metabolic abnormalities within the medial temporal lobe (MTL) of the group with a history of mTBI, as well as greater cortical thinning in frontal, parietal, and temporal cortices, compared to the control group (Tremblay et al., 2013). Taken together, these studies indicate prior history of mTBI may exacerbate and/or accelerate age-related memory decrements and neural changes.

The current study examined the possible interaction of age and mTBI, combining behavioral assessment of relational (declarative) memory with structural and functional assessment of the hippocampus and the cortical regions with which it interacts. The focus here was on the hippocampal memory system (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001), based on converging evidence from several lines of work. The hippocampus has been shown to be greatly affected not only by age-related diseases (e.g. Alzheimer's disease, vascular dementia) but also by disease-free aging or so-called "healthy aging" (Jagust, 2013; Small et al., 2011). Longitudinal studies have consistently demonstrated hippocampal volumetric declines in older adults (Raz et al., 2005; 2010). Additionally, even in the absence of Alzheimer's disease, tau pathology is ubiquitously found in the entorhinal cortex and hippocampus in older adults (Bennett et al., 2012; Price et al., 2009), and the presence of this pathology relates negatively to memory performance (Bennett et al., 2012; Guillozet et al., 2003). Moreover, changes in basal metabolism occur within the hippocampus with aging and age-related diseases (for review, see Small et al., 2011).

Further, there is reason to believe the hippocampus is disproportionately affected by TBI; its physical location in the MTL makes it more vulnerable to impact forces, and it is also particularly susceptible to excitotoxic injury, which occurs in TBI (McAllister, 2011). Several MR studies in moderate-to-severe TBI populations have indicated significantly smaller hippocampal volumes within two years of the initial injury (Ariza et al., 2006; Bigler et al., 2002;

Hopkins et al., 2005). A study of pediatric TBI found reduced hippocampal and amygdala volumes at ten-year follow-up, which was true even for a group only sustaining mTBI (Beauchamp et al., 2011). Finally, animal models of mTBI reveal large apoptotic changes in the CA3 subfield of the hippocampus following experimenter-induced mTBI, second only to the anterior cingulate gyrus in magnitude of neuronal damage (Tashlykov et al., 2007). Taken altogether, the hippocampus would appear to be a particularly suitable target for detecting negative changes elicited by the combination of prior mTBI and aging. Here its status was assessed structurally, via measurement of volume of the hippocampus in comparison to other subcortical structures, and functionally, via examination of brain activation and memory performance during mnemonic challenge using functional magnetic resonance imaging (fMRI).

Functional assessment focused on relational memory, i.e., the ability to acquire and retain memory for arbitrary or accidental relations amongst the constituent elements of a scene, event, or experimental session (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001). Relational memory is critically dependent on the hippocampus (Hannula et al., 2006, 2007; Konkel et al., 2008; Ryan et al., 2000; Watson et al., 2013), and its successful expression engages the hippocampus and larger brain networks involving MTL-cortical (perirhinal, entorhinal, and parahippocampal cortex) and neocortical (principally, prefrontal and posterior parietal) regions (Cabeza et al., 2008; Cohen et al., 1999; Simons & Spiers, 2003; Staresina & Davachi, 2009; Wagner et al., 2005). The dependence of relational memory on both the hippocampus and large-scale brain networks make it a favorable target for the current investigation, with the prediction that individuals who had sustained mTBI several decades ago would show decrement in this form of memory and would show structural and functional brain aberrations in the brain regions and networks subserving relational memory.

Materials and Methods

Participants

Participants were administered a standardized questionnaire to ascertain if they had a history of mTBI. This questionnaire gathered information regarding the number of head injuries, approximate date(s), description of the event(s), and duration of symptoms (including loss of consciousness (LOC) and duration, confusion/disorientation, length of post-traumatic amnesia). Only those participants whose mTBIs were diagnosed by a medical professional and/or resulted in loss of consciousness were included in the mTBI groups. Additionally, in order to ensure all TBIs were categorized as "mild," any individuals who experienced a loss of consciousness greater than 30 minutes or post-traumatic amnesia longer than 24 hours were excluded from this study (American Congress of Rehabilitation Medicine, 1993). Finally, participants suffering an mTBI after the age of 25 were excluded from the study, as to isolate the combined effects of early mTBI and the aging process. A total of 22 participants met these criteria. For comparison, 22 age, gender, and education matched participants without a history of major head trauma were also included. All 44 participants in the final sample were screened for, and did not report, any alcohol abuse. Participants were categorized into two groups based on current age, with ages 20-29 years being classified as "young" and 40-69 years as "middle-aged." This yielded four experimental groups: young control (YC), young mTBI (YI), middle-aged control (MC), and middle-aged mTBI (MI; see Table 4.1). The two mTBI groups reported similar durations of LOC, which for both groups ranged from a few seconds to approximately five minutes, with one exception in the YI group of an individual reporting a duration of approximately 20 minutes. This study was approved by the University of Illinois Institutional Review Board, and all participants signed an informed consent document.

Table 4.1

Participant Demographics and Memory Performance: Mean (SD)

Variable	YC	YI	MC	MI
N	12 (5 female)	12 (5 female)	10 (6 female)	10 (6 female)
Age	22.3 (2.6)	22.4 (2)	52.5 (7.9)	52.9 (9.4)
Years of education	15.6 (.9)	15.4 (.52)	17.3 (3.6)	17.3 (3.9)
Number of mTBIs	-	1.3 (.62)	-	1.4 (.52)
Years since last mTBI	-	4 (3.1)	-	39 (12.6)
LOC	-	10	-	9
Hit rate	.81 (.18)	.84 (.08)	.85 (.1)	.73 (.13)
False alarm rate	.28 (.14)	.25 (.13)	.33 (.14)	.33 (.12)

mTBI = mild traumatic brain injury; LOC = loss of consciousness; YC = young control group; YI = young mTBI group; MC = middle-aged control group; MI = middle-aged mTBI group. Number of mTBIs refers to group average, the range for the YI group was 1-3, and the MI group 1-2. LOC identifies the number of participants who sustained an mTBI that resulted in LOC less than 30 minutes in duration. Hit rate and false alarm rate pertain to performance on the memory task.

Memory task

This task is identical to the face-scene task described in chapter three. Participants completed an event-related relational memory task during fMRI scanning where the goal was to form an association between a face and scene (Figure 3.1). The task consisted of 72 images of outdoor scenes and 72 images of faces, of which 36 were male and 36 were female. Further, 36 of the faces were of young people and the other 36 of elderly people. The task was divided into three separate runs, with 24 encoding and 24 recognition trials in each run; the encoding and

recognition phases were separated by a 20-second break. Encoding and recognition trials consisted of the presentation of a scene for 2000 milliseconds (ms), followed by a face overlaid on the scene for an additional 2000 ms. A fixation cross was displayed during the intertrial interval (ITI), which was jittered and ranged from 2000-12000 ms.

On each encoding trial, participants made a yes/no judgment indicating whether the individual depicted "fit" with the scene; this was an arbitrary decision to elicit deep encoding. At recognition two trial types were presented, "intact" face-scene pairs, which were the identical face-scene combinations presented during encoding, and "re-pair" trials created by recombining a previously displayed face and scene that were not shown together at encoding. Hence, all stimuli were equally familiar at recognition, and the task had to be completed via relational memory. Participants made a yes/no judgment as to whether the pair displayed was an exact match of a pair shown at encoding, with twelve trials from each trial type composing the recognition phase of a run.

A correct response to an intact pair was classified as a "hit," with an incorrect response categorized as a "miss;" a correct response to a re-pair trial was a "correct rejection," whereas an incorrect response was a "false alarm." A hit rate was derived for each participant by calculating the proportion of hits on trials with intact pairs, and a false alarm (FA) rate was obtained for each participant by finding the proportion of FAs on re-pair trials. Both the hit rate and false alarm rate were entered into 2×2 fixed effects ANOVAs with the factors of Age (young vs. middle-aged) and TBI history (control vs. mTBI).

Image acquisition

All images were collected on a Siemens Trio 3-Tesla full body magnet, using a 12-channel birdcage headcoil. Functional BOLD images were acquired parallel to the anterior commissure - posterior commissure (AC-PC) line with a T2*-weighted echo-planar imaging sequence of 35 contiguous axial slices collected in ascending fashion [repetition time (TR) = 2000 ms; echo time (TE) = 25 ms; BOLD volumes = 299; flip angle = 80°; field of view (FOV) = 220*220 mm; voxel size = 3.4 × 3.4 × 4 mm]. Structural images were acquired with a T1-weighted 3D magnetization prepared rapid gradient echo imaging (MPRAGE) protocol of 192 contiguous sagittal slices collected in an ascending manner parallel to the AC-PC line [TR = 1900 ms; TE = 2.26 ms; flip angle = 9°; FOV = 256*256 mm; voxel size = 1× 1 × 1 mm].

Subcortical volume analysis

Automated segmentation of subcortical regions was conducted using Freesurfer (v 5.1); details of the subcortical segmentation process utilized by Freesurfer are available in Fischl et al., (2002). The algorithm employed by Freesurfer for subcortical segmentation has been shown to have a very high correlation with manual tracing, particularly for the hippocampus, and has proven to be sensitive to volume differences between groups (Morey et al., 2009). The main regions of interest (ROIs) for which volumetric data was estimated were the left and right hippocampus; to assess the specificity of the effect of mTBI and aging on hippocampal volume, bilateral putamen, caudate, and thalamus volumes were also estimated. An automated measure of intracranial volume (ICV), which is comparable to manual tracing, was obtained for each participant via Freesurfer using the methods described in Buckner et al., (2004). This measure of estimated ICV was used to correct subcortical volume for head size by regressing each ROI

volume onto ICV in order to obtain a slope (b) for the relationship between an ROI and ICV. The resulting slope was then used to normalize each ROI for head size via the following formula:

normalized volume = raw volume – b (ICV - mean ICV); this correction has been used in multiple studies reporting subcortical volume measures (Erickson et al., 2009; Head et al., 2008; Raz et al., 2005). The normalized volumes for each ROI were then entered into 2×2 ANOVAs with Age and TBI history as factors.

Functional analysis

Preprocessing of the fMRI data was done using FSL 4.1.3 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The first three volumes of each run were removed prior to analysis. For each run of functional data, a 100-second temporal high pass filter was applied, and data were smoothed with a Gaussian kernel of full width at half-maximum at 6 mm^3 . Also, motion correction was applied using MCFLIRT. Non-brain structures from the structural scan were removed and the image was co-registered to the subject's mean functional scans and placed into Montreal Neurological Institute (MNI) template space.

Each participant's three runs of the memory task were analyzed individually using FSL's FEAT (version 5.98) function. The hemodynamic response was convolved with a double-gamma HRF function. The statistical model for the task contained three regressors from the encoding phase, corresponding to whether a face-scene pair was later correctly remembered, forgotten, or went on to be a re-pair trial, and then five regressors in the recognition phase, with four coding the outcome of a trial (hit, miss, false alarm, correct rejection) and a nuisance variable tracking trials that were not responded to. All eight regressors corresponded to the onset of the scene and had a duration of four seconds. This model was then regressed against the observed fMRI data

from each run. Analysis of each run consisted of creating contrasts from the events described above. Next, each contrast was averaged across an individual's three runs via a fixed effects analysis. Finally, group-level, mixed-effects analyses were conducted on data from the recognition phase, specifically looking at the contrasts of hits > correct rejections, hits > baseline, and correct rejections > baseline; these analyses were carried out using FSL's FLAME function with the variances for the two age groups estimated separately (Beckmann, Jenkinson, & Smith, 2003). The decision to investigate group differences for hits and correct rejections compared to baseline rather than relying solely on the hits > correct rejections contrast was due to both of these conditions likely having a high memory demand, given that the stimuli composing the foils at recognition have also been previously seen in the encoding phase; thus, it is possible that the hits > correct rejections contrast may remove a substantial amount of the BOLD signal in each individual, potentially masking group differences in neural processing. Therefore, the additional contrasts against baseline were also included for group comparison. The group level comparisons of the fMRI data were conducted via a 2×2 mixed effects ANOVA that considered between-subjects variance and contained the factors "Age" and "TBI history." Significant main effects or an interaction were followed up with pairwise group comparisons. Reported functional imaging findings are significant at a voxel activation threshold of $Z > 1.96$ ($p < .05$), and a family wise error cluster correction threshold of $p < .05$.

Results

The ANOVA investigating the proportion of hits indicated a significant interaction with age and TBI history [$F(1, 40) = 3.93, p = .05$]. Planned comparisons revealed that this interaction was driven by the MI group having a significantly lower hit rate than the MC group, [$t(18) = 2.37, p = .03$], whereas there was no difference between the young groups [$t(22) = .56, p$

$= .58]$ (Figure 4.1). There were no main effects of Age or TBI history for hit rate (all F 's < 1.4 , p 's $> .24$). The FA rate data indicated the observed effect was not due to differences in response bias between the middle-aged groups, as analysis of the FA rate data did not reveal an effect of TBI history [$F(1, 40) = .08, p = .78$] nor an Age \times TBI history interaction [$F(1, 40) = .12, p = .73$; see Table 1 for values]. Finally, there was no difference between age groups in the FA rate, [$F(1, 40) = 2.45, p = .13$].

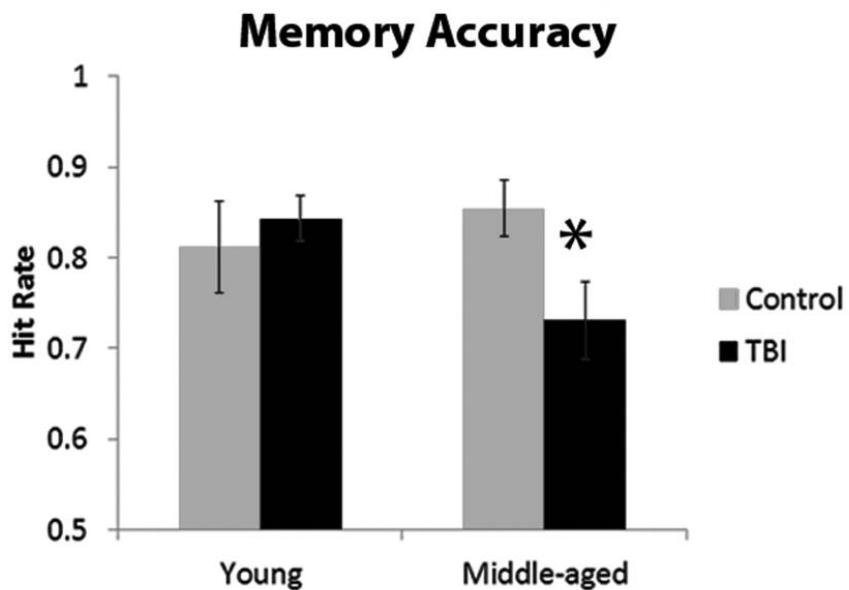


Figure 4.1: Behavioral data from memory paradigm, * $p < .05$. Error bars are \pm one standard error of the mean.

Estimation of hippocampal volume revealed main effects of TBI history for bilateral hippocampus, whereby the mTBI group had smaller hippocampal volumes: left hippocampus [$F(1, 40) = 7.18, p = .01$]; right hippocampus [$F(1, 40) = 5.29, p = .03$] (see Table 4.2 for mean volumes). In the right hippocampus there was a marginal Age \times TBI history interaction, [$F(1, 40) = 3.42, p = .07$]; this was not true of the left hippocampus, [$F(1, 40) = 1.00, p = .32$]. Also,

there was no main effect of Age in the left or right hippocampus (all F 's < 1.4 , all p 's $> .25$). To ascertain if the marginal interaction in the right hippocampus, and the main effects that occurred bilaterally, were due to the hypothesized combination of aging and mTBI, planned comparisons were performed contrasting the TBI history factor at each level of Age. For the right hippocampus, the observed effects were due to differences between the two middle-aged groups. The MI group had a significantly smaller right hippocampus compared to the MC group [$t(18) = 2.97, p < .01$], whereas there was no difference in hippocampus size between the two young groups [$t(22) = .32, p = .75$]. Similarly, in the left hippocampus, a difference existed between the two middle-aged groups indicating smaller left hippocampus for the MI group, $t [(18) = 2.65, p = .02]$, but no difference between the young adults [$t(22) = 1.19, p = .25$]. Hippocampal volume differences amongst the four groups are depicted graphically in Figure 4.2. The above finding of smaller subcortical tissue due to a combination of mTBI and aging seems specific to the hippocampus, as analyses of the left and right putamen, caudate, and thalamus did not show any effects of TBI history or interactions between Age and TBI history (all F 's < 1.4 , all p 's $> .24$; Table 4.2). There were large effects of Age for both the left [$F(1, 40) = 16.43, p < .001$] and right putamen [$F(1, 40) = 17.37, p < .001$], with the middle-aged groups having smaller volumes. There were trends for smaller left [$F(1, 40) = 3.34, p = .08$] and right [$F(1, 40) = 3.53, p = .07$] caudate nuclei in the middle-aged groups as well.

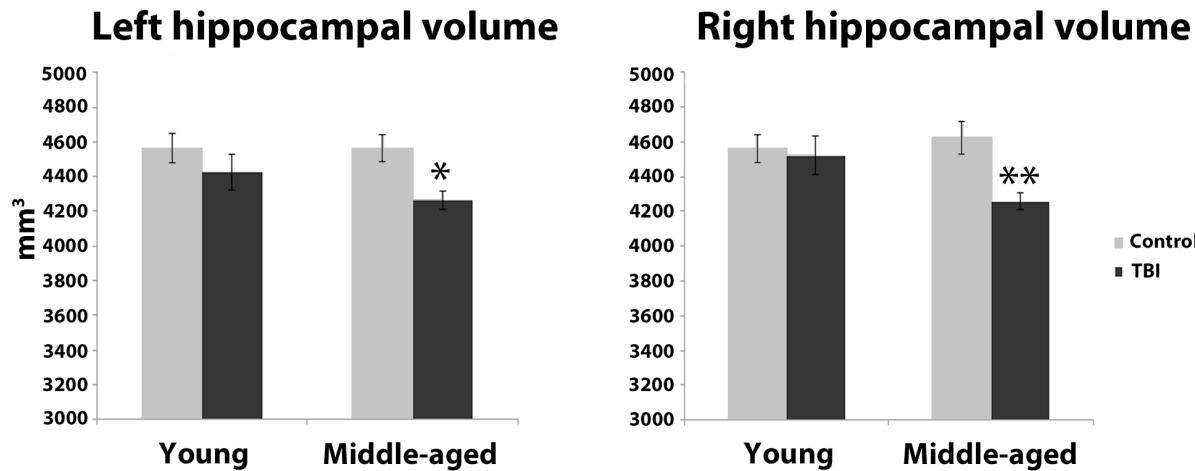


Figure 4.2: Hippocampal volume differences as a function of the combination of distal mTBI and aging. * p < .05, ** p < .01; error bars are \pm one standard error of the mean.

Table 4.2

Subcortical Volume Estimates: Mean (SD)

Region	YC	YI	MC	MI
Left Hippocampus	4561 (295)	4424 (269)	4563 (321)	4263 (158)
Right Hippocampus	4561 (283)	4521 (322)	4624 (353)	4258 (165)
Left Putamen	6321 (579)	6132 (575)	5710 (278)	5552 (393)
Right Putamen	5797 (572)	5657 (490)	5203 (455)	5059 (299)
Left Caudate	3769 (420)	3878 (338)	3573 (502)	3621 (369)
Right Caudate	3778 (394)	3843 (392)	3580 (431)	3604 (307)
Left Thalamus	7690 (549)	7659 (534)	7682 (945)	7290 (493)
Right Thalamus	7726 (523)	7691 (380)	7711 (606)	7454 (634)

YC = young control group; YI = young mTBI group; MC = middle-aged control group; MI = middle-aged mTBI group. Values are reported in mm³ and are corrected for intracranial volume.

In the fMRI data, the group-level ANOVA on the contrast of hits > correct rejections at recognition revealed a significant interaction with activity in multiple areas of the prefrontal cortex (Figure 4.3 A-B). To determine if this interaction was due to differences specific to the

middle-aged group, consistent with our hypothesis, follow-up contrasts were formed comparing TBI history at each level of Age. The contrast of brain activation between the young adult groups yielded no significant effects in either direction. However, reduced neural activity in multiple regions of the PFC was found for the MI group relative to the MC group (Figure 4.3 C-E), including the right inferior frontal gyrus, right medial PFC (mPFC), bilateral frontopolar cortex, and middle and superior frontal gyri. Additional pairwise comparisons revealed that this interaction was also due in part to the YI group having more activity than the MI group in PFC and parietal regions.

In an effort to more fully understand any group differences in the BOLD response during relational memory recognition, each participant's contrasts of hits > baseline and correct rejections > baseline were analyzed at the group level. With regard to the analysis of hits > baseline, once again a significant interaction indicated a differential BOLD signal between the groups in the PFC (Figure 4.4 A-B). In similar fashion to the hits > correct rejection analysis, pairwise comparisons were conducted between the TBI groups at both levels of Age. There were no significant differences between the two young groups, but the comparison of the middle-aged participants again revealed areas of reduced neural activity in the MI group. Multiple regions of differential activation were found in the PFC, localized within the right mPFC, frontal pole, paracingulate gyrus, right middle and superior frontal gyri, and left superior frontal gyrus. Regions in the parietal lobe also displayed reductions in activity for the MI group, with a large swath of activity in medial parietal regions including bilateral precuneus and right posterior cingulate cortex, and another area found in the right superior parietal lobule (SPL), extending into the parieto-occipital junction (Figure 4.4 C-E). Further pairwise comparisons indicated the

observed interaction was also due to the MC group displaying more activity than the YC group in the frontal cortex and left lateral and parietal lobes.

The comparison of correct rejections > baseline did not yield any differential activity related to TBI status among the groups; this indicates that the differences due to TBI group status in the hits > baseline comparison seem to be due to successful memory recognition and not group differences in perception or attention, which is possible due to the baseline comparison. Finally, in all of the above comparisons, there were no brain regions where the MI group had greater activity than the MC group.

Given the differing levels of accuracy between the two groups, it is conceivable that the fMRI differences in activation are due to the performance differences; we believe this is unlikely for two reasons. First, while the difference in the hit rate was significant, the average number of additional trials analyzed in the fMRI data for the MC group was 4.3 out of a possible 36; this modest disparity in trial count reduces the chance that the activation differences are due to performance. Additionally, percent signal change for each participant was extracted from distinct anatomical areas of peak activation for the contrasts of hits > CR and hits > baseline, and then correlated with performance. Correlations were carried out separately for each group, as to avoid circular analyses. Regions of peak activation for hits > CR included: left superior frontal gyrus, right superior frontal gyrus, right middle frontal gyrus, and right medial PFC, while regions for hits > baseline were: right precuneus, right superior parietal lobule, right paracingulate cortex, right middle frontal gyrus, and right frontal pole. Of the 18 correlations, only two were significant at $p < .05$, the right middle frontal gyrus for hits > CR in the MI group, and the right superior parietal lobule in hits > baseline for the MC group. Therefore, the differences in the BOLD response between the two middle-aged groups seem to reflect reduced neural activity

and/or differential neural processing in the MI group rather than a simple lack of power or reflection of performance differences in the MI group.

Comparison of neural activity across groups for Hits > Correct Rejections

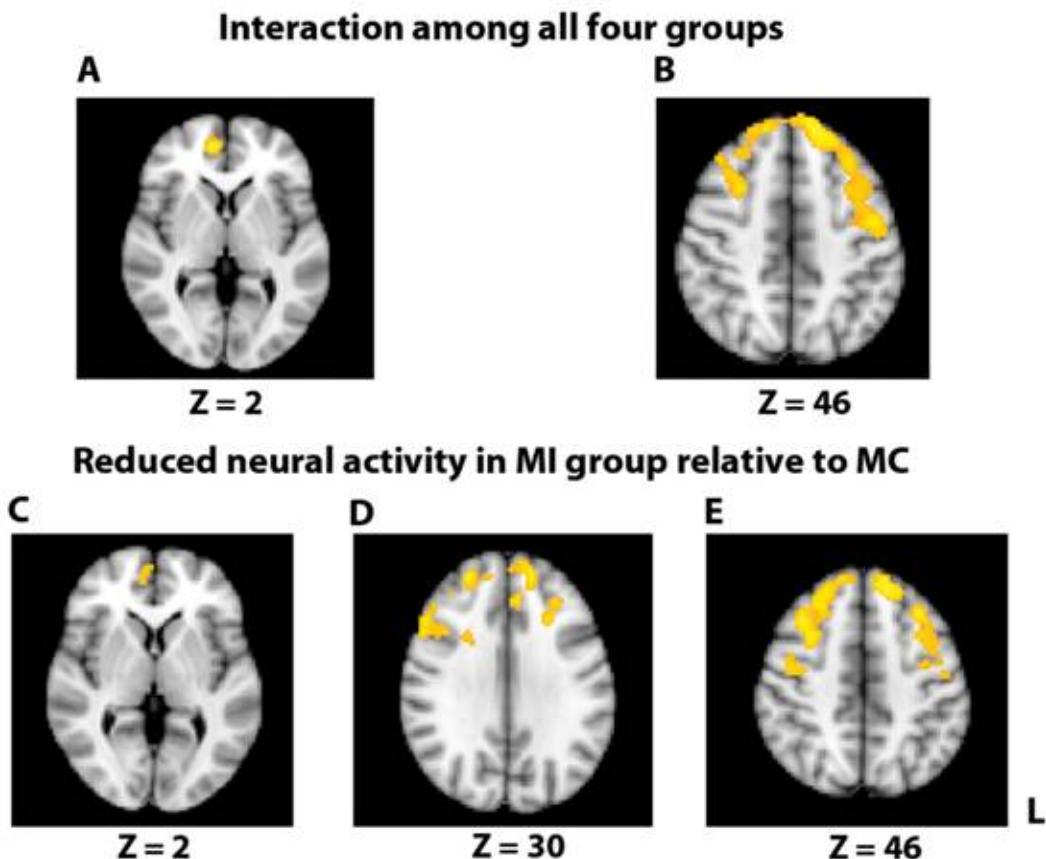


Figure 4.3 Images displayed depict differential group activity for the contrast of hits > correct rejections. (A-B) Brain regions significant for the interaction between age and TBI history, as measured by the contrast (YI + MC > YC + MI). Areas with significant activity include the right medial PFC, left precentral gyrus and bilateral superior frontal gyri. (C-E) Reductions in neural activity for the MI group relative to the MC group in multiple areas of the PFC. Coordinates are in MNI space; images are in radiological orientation (L=R).

Comparison of neural activity across groups for Hits > Baseline

Interaction among all four groups

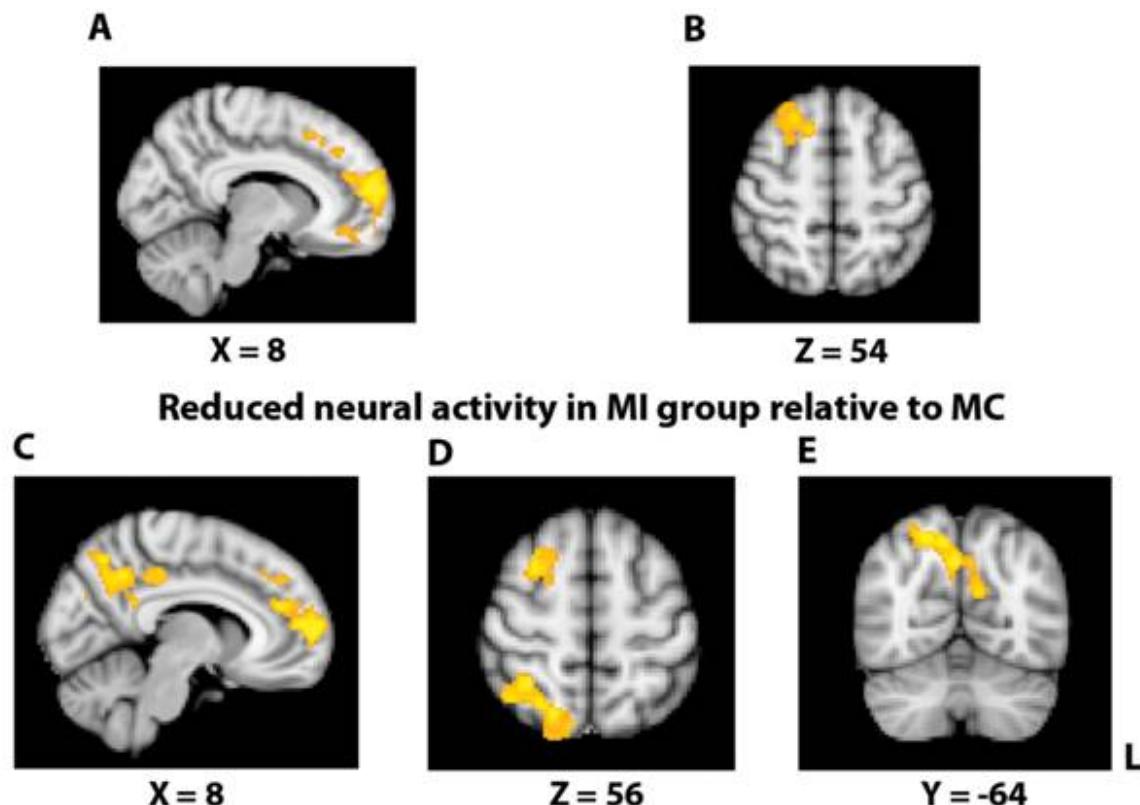


Figure 4.4 Illustration of significant differential group activity for hits > baseline. (A-B) Significant activity for the interaction of age and TBI history, as measured by the contrast (YI + MC > YC + MI). Areas of significant activation included right medial prefrontal cortex and right superior frontal gyrus. (C-E) Reductions in neural activity for the MI group relative to the MC group

Discussion

Compared to age- and education-matched controls with no history of head trauma (MC group), those with an mTBI decades ago (MI group) were less accurate on a face-scene relational memory task, and had less neural activity for successful memory recognition in posterior parietal

cortex and PFC. Moreover, the MI group had smaller hippocampi bilaterally than the MC group. There was no impairment evident in memory or differences apparent in neuroimaging in individuals with recent mTBI (YI group) relative to the neurologically intact comparison group, implicating the combination of aging and a history of mTBI as the source of the deficit observed in the MI group, rather than mTBI alone. Importantly, many of the individuals in our MI sample went on to attain a high level of education and achieved and maintained gainful employment despite their early mTBI. Thus, it does not appear to be the case that acute symptoms from their mTBI simply never resolved. Rather, it is more likely that the biological effects of aging that accrue over time and that are deleterious to brain health in all individuals serve to magnify the effects of early mTBI, eventually altering the cognitive phenotype and manifesting as impairment later in the course of aging.

The decreased accuracy in relational memory observed here for the MI group is consistent with previous studies investigating the effects of mTBI on memory in persons who sustained their mTBI several decades ago, including deficits in visuospatial or figural memory tasks, such as the Rey-Osterrieth Complex Figure (De Beaumont et al., 2009; Tremblay et al., 2013). This study expands the domain of memory related deficits to a non-visuospatial/figural memory task, here involving the remembering of arbitrary pairings of faces with scenes. Both the Rey-Osterrieth Complex Figure and memory for face-scene relations are known to be dependent on the hippocampus (Bohbot et al., 1998; Hannula et al., 2006; 2007; Hirni et al., 2013), suggesting the sensitivity of hippocampal-dependent memory processes to the effects of mTBI in interaction with aging.

The finding here of smaller hippocampal volumes bilaterally in the MI group compared to the MC group may be the major driving force of the observed memory differences. It is

becoming increasingly clear that TBI is detrimental to hippocampal structure. Relationships between moderate-to-severe TBI and reduced hippocampal volume have been found when measured within two years of the initial injury (Ariza et al., 2006; Bigler et al., 2002; Hopkins et al., 2005). One study of childhood TBI found hippocampal volumes to be reduced in a sample of mTBI patients at a ten-year-follow-up (Beauchamp et al., 2011). To our knowledge, though, this is the first study reporting smaller hippocampal volumes due to a combination of distal mTBI and aging in middle-aged-to-older adults. Animal models of mTBI indicate the hippocampus is particularly vulnerable to apoptotic changes following mTBI (Tashlykov et al., 2007). Moreover, mTBI leads to states of increased oxidative stress and neuroinflammation in the hippocampus, as well as disruption of calcium ion homeostasis resulting in an influx of Ca^{2+} (Gatson et al., 2013; Giza and Hovda, 2001; Wu et al., 2007) all of which are deleterious to hippocampal health (Ekdahl et al., 2003; Foster, 2007; Serrano and Klann, 2004). Given that processes like neuroinflammation impair neurogenesis, coupled with the recent finding of only modest declines in neurogenesis with aging in adult humans, it is possible that different neurogenesis rates in the two middle-aged groups contribute to the volumetric findings (Ekdahl et al., 2003; Spalding et al., 2013). Finally, tau pathology co-occurs with TBI (McKee et al., 2013), and given the predilection of tau for MTL regions with aging, it is possible this may play a role in the observed volume differences. Since these hypothesized mechanisms are secondary molecular processes of mTBI rather than a direct result of physical trauma due to the initial impact, it is perhaps not surprising that the hippocampus, known to be sensitive to these mechanisms, is the structure that is smaller in the MI group (for review of molecular mechanisms following TBI, see Walker and Tesco, 2013). In considering the current findings, there are a number of potential pathogenic processes of the initial mTBI may mildly injure the hippocampus, leaving it more vulnerable to

the plethora of pathogenic processes that co-occur with aging and constitute a “second hit” to this structure; longitudinal data will be crucial in identifying within-person atrophy in this population.

If aging does cause a second hit to hippocampal volume, the absence of any differences observed here in hippocampal volumes between the MC and YC groups might be somewhat surprising. However, recent research indicates a period of relative stability in hippocampal volume from the third to fifth decades of life, with marked declines in hippocampal volume not beginning until around age 50 (Fjell et al., 2013). Since the mean age of our MC group was 52.5, a significant portion of the current MC sample may not yet be experiencing age-related hippocampal volume loss. Even in those who are experiencing age-related hippocampal volume loss, its effects may be mitigated by the high level of education in the middle-aged groups, as education has been shown to mediate the effects of age-related volume loss in the hippocampus (Noble et al., 2012). By contrast, the large effect of age on putamen volume observed here is consistent with a recent report indicating a linear decline in putamen volume across the lifespan (Fjell et al., 2013).

The current fMRI findings, showing less activity for the MI group in PFC and posterior parietal lobe, implicate potential cortical dysfunction, or cortical involvement in the observed memory impairment. The MTL and PFC share many direct and indirect connections, and it is hypothesized that the ventral and dorsal lateral PFC may serve both to specify the parameters of MTL-dependent memory search, as well as to monitor the products of MTL memory retrieval for their relevance to task goals (Dobbins et al., 2002; Simons & Spiers, 2003). Activity in the posterior parietal lobe during successful memory recognition is consistently observed across many paradigms (Cabeza et al., 2008; Wagner et al., 2005) and posterior parietal regions are also

connected directly or indirectly to regions in the MTL (Kobayashi & Amaral, 2003; Rockland & Van Hoesen, 1999). Current accounts of this posterior parietal activation occurring with successful memory recognition indicate that these regions may be exerting their influence via modulating attention related to memory, or informing memory decisions by integrating or temporarily storing information (Cabeza et al., 2008; Wagner et al., 2005). Therefore, it is possible the memory deficit observed in the MI group also stems from an inadequacy of these PFC and posterior parietal regions to coordinate memory recognition with an already disadvantaged hippocampus.

It should be noted that the cortical areas where differences between the MC and MI groups emerged overlap largely with regions of the default mode network (DMN). Like the hippocampus, DMN regions are also disproportionately susceptible to the aging process, and display reduced activity and connectivity with aging (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008). Interestingly, even when only considering cognitively normal older adults, these DMN areas are known to be the locations of the greatest A β aggregation, and this A β accumulation in these regions is detrimental to hippocampal-based memory (Kennedy et al., 2012; Rentz et al., 2011; Sperling et al., 2009). Animal and human research has established a firm link between A β and TBI (for review, see Johnson et al., 2010; Walker & Tesco, 2013), with even post-mortem samples of individuals suffering mTBI showing expression of the amyloid precursor protein (Blumbergs et al., 1995). Though speculative, it may prove fruitful to examine whether a history of mTBI may help to explain the variability in cognitively normal middle-aged-to-older adults who harbor A β in the cortex (Kennedy et al., 2012).

There are some caveats to acknowledge. This was a cross-sectional study, and although the mTBI and control groups were matched on various factors, it is possible that they had

additional differences other than their head injury; longitudinal studies will prove crucial to fully determining the nature of within subject change emerging from the combinatorial effects of mTBI and aging. Additionally, given the relatively small sample size and the relatively wide age range comprising the middle-aged group, some caution may be warranted in interpreting these results; but it is noteworthy that a similar study with a comparable sample size of middle-aged adults has reported complimentary findings (Tremblay et al., 2013).

Summarizing the findings of the current work, this report corroborates the memory deficit noted in previous studies on mTBI and aging, and includes the critical control of having both younger and older adults with and without a history of mTBI in order to document the interaction of prior mTBI and aging. Furthermore, it provides the first demonstration of reduced hippocampal size in individuals examined several decades following mTBI. Finally, the fMRI findings, revealing reductions in activity in posterior parietal cortex and PFC while performing a hippocampal-based memory task, provide evidence of global brain changes of mTBI in combination with the effects of aging. These data taken altogether make the case that a history of mTBI early in life may be an influencing factor on cognitive and brain health in older adulthood.

Chapter 5: Physical activity and cardiorespiratory fitness are associated with larger left thalamus and better memory function in older adults

Abstract

Relational (declarative) memory decline is a prevalent symptom of cognitive aging, and is likely due at least in part to the atrophy of critical cortical and subcortical structures, such as the hippocampus and thalamus. Another hallmark of cognitive aging however, is inter-individual variability, with some older adults only showing minimal memory decline, and others developing dementia. One set of factors thought to modulate this inter-individual variability is the participation in higher levels of physical activity and/or maintaining high levels of cardiorespiratory fitness. In the current study we sought to further understand these relationships by evaluating how physical activity and cardiorespiratory fitness modulate brain and cognitive health in aging. We selected a relational memory task known to be critically dependent on the hippocampal-memory system, given the extensive research on hippocampal learning and exercise in rodents, but a relative dearth of hippocampal-based tasks in humans. One-hundred thirty older adult participants had physical activity measured by wearing accelerometers for seven days; cardiorespiratory fitness was assessed with a graded maximal exercise test. The relational memory task was conducted during functional magnetic resonance imaging data acquisition; additionally, the volume of subcortical structures vital to learning and memory was quantified. Results indicate that the average amount of activity done during the day was positively related with left thalamus volume; a similar relationship was observed with left thalamus volume and cardiorespiratory fitness. Further, left thalamus volume significantly attenuated the false alarm rate on the relational memory task; mediation analyses indicated both physical activity and cardiorespiratory fitness to have indirect effects on the false alarm rate via their modulation of left thalamus volume. Finally, those with larger left thalamus volumes had a

larger BOLD response in the medial prefrontal cortex when obtaining a correct rejection. Together, these data indicate the salutary contributions made by physical activity and fitness levels to the maintenance of memory networks in aging.

Introduction

Accumulating evidence suggests that higher levels of cardiorespiratory fitness (CRF) and engaging in aerobic exercise have widespread beneficial effects on brain and cognition in older adult humans see (Hayes, Hayes, Cadden, & Verfaellie, 2013; Hillman, Erickson, & Kramer, 2008 for review). For instance, several cross-sectional studies indicate older adults higher in CRF have larger tissue volumes in the prefrontal cortex (PFC), as well as lateral parietal and temporal cortex (Colcombe et al., 2003; Gordon et al., 2008; Johnson, Kim, Clasey, Bailey, & Gold, 2012; Weinstein et al., 2012). The strongest evidence for the effects of aerobic exercise on neocortical structures may come from the result of a six-month randomized controlled trial comparing regular aerobic exercise to stretching in toning. Those in the aerobic exercise group had gains in tissue volume in the anterior cingulate cortex, supplemental motor area, right inferior frontal gyrus, left superior temporal lobe, and anterior white matter (Colcombe et al., 2006). Moreover, higher fitness or aerobic exercise participation is associated with better cognitive performance on tasks that tap into the brain regions and networks listed above, such as executive control and working memory (Colcombe et al., 2004; Kramer et al., 1999; Voss, Erickson, et al., 2010; Weinstein et al., 2012).

The study of movement and brain health in aging is not limited to exercise and improving CRF, but also investigates how all types of physical activity (PA), even light PA that may only slightly raise one's heart rate (if at all), influences cognitive aging. An objective method for

assessing the amount of daily PA by an individual is through accelerometry, where a participant wears an accelerometer for several days to quantify the amount and intensity of PA. Though studies aimed at understanding brain health in aging have measured PA subjectively with questionnaires, few have objectively measured this construct with accelerometry. In the studies that have implemented accelerometry, the data indicate protective effects of increased PA in cognitive aging. For instance, total PA has been linked with better overall cognitive function in older adults, as well as reduced rates of cognitive decline and Alzheimer's disease (Barnes et al., 2008; Buchman et al., 2012; Wilbur et al., 2012). Further, one longitudinal study indicated the total number of steps taken during the day to be inversely related to PFC shrinkage in males (Yuki et al., 2012).

An intriguing brain region to consider when investigating aging, fitness, and physical activity is the medial temporal lobe (MTL), in particular the hippocampus. In addition to certain cortical areas, the hippocampus and MTL cortex are disproportionately affected by the aging process (Small et al., 2011). Additionally, animal research in exercise has historically focused on the hippocampus, finding very strong effects of plasticity in this region; these changes include higher rates of neurogenesis in young and old rats in the dentate gyrus, increased dendritic complexity, and vascular growth (Clark, Brzezinska, Puchalski, Krone, & Rhodes, 2009; Eadie, Redila, & Christie, 2005; Pereira et al., 2007; van Praag, Kempermann, & Gage, 1999; van Praag, Shubert, Zhao, & Gage, 2005).

Several cross-sectional studies have indeed found a positive relationship between tissue volume and fitness or exercise in older adults, with Erickson and colleagues (Erickson et al., 2009) reporting larger bilateral hippocampal volumes in more fit older adults, and several other reports finding associations with the MTL and fitness (Bugg & Head, 2011; Gordon et al., 2008;

Honea et al., 2009). The study by Honea and others reported this relationship in those with early Alzheimer's disease (AD), indicating even in those with AD, maintaining fitness may be beneficial; however, it should be noted this study failed to find such a relationship in the healthy control group. Two additional studies help to solidify the relationship between hippocampal volume and exercise. In a nine-year follow-up that tracked individuals who participated in a physical activity intervention, those who self-reported they continued to walk had larger hippocampal volumes compared to those who walked less (Erickson et al., 2010). Finally, a recent exercise intervention with older adults containing an aerobic exercise group and a stretching and toning control group furthered the causal link between hippocampal volume and exercise, as results from this experiment indicated that those in the aerobic group experienced an increase in anterior hippocampal volume over the course of 12 months, whereas those in the other condition experienced the typical decrease in hippocampal volume, given their age (Erickson et al., 2011).

The studies described above indicate that aerobic fitness, exercise, and PA have clear benefits to maintaining, and even increasing, tissue volume in multiple areas of the brain, and also may yield better performance in certain realms of cognition, yet several critical questions remain in the study of cognitive aging and movement. For instance, previous work indicates higher levels of CRF are associated with larger hippocampi or caudate nuclei in aging (Erickson et al., 2009; Verstynen et al., 2012); however, to our knowledge no reports have investigated how objectively measured levels of PA relate to the size of subcortical structures critical for learning and memory that suffer age-related degeneration. Such an investigation would shed light on whether only the types of movement that would potentially raise one's CRF level (e.g.

moderate-to-vigorous) lead to a larger hippocampus, or if the totality of movement throughout the day affords some benefit.

Additionally, despite the fact that the majority of tasks used in animal models of exercise are hippocampal learning tasks (e.g. Morris Water Maze; van Praag, 2009), very few studies in humans have used memory tasks critically dependent on the hippocampal network. Erickson and colleagues (Erickson et al., 2009, 2011) have found relationships between spatial working memory and the hippocampus as a function of fitness, but this task may only be marginally related to the types of computations and processes performed by the hippocampus (see chapter three). To our knowledge no groups have looked at relational memory and CRF or PA. Finally, the investigation of CRF, PA and/or exercise effects on brain function, as measured by functional magnetic resonance imaging (fMRI), in older adult humans is in its nascent stages. The majority of studies have used resting state paradigms or tasks emphasizing fronto-executive networks, with the results being largely in line with the structural imaging data, indicating benefits to fitness or exercise (see Hayes et al., 2013 for review). In the only experiment using a task intended to reliably activate the hippocampus, Holzschneider and colleagues (2012) found that hippocampal activity (and many other regions) correlated with VO₂ peak fitness scores for a spatial encoding task in participants who completed either a cycling or stretching intervention, coupled with a spatial learning training intervention (Holzschneider, Wolbers, Röder, & Hötting, 2012). Only one study measured PA with accelerometry and related it to fMRI measures of aging, with the results indicating those who engaged in moderate PA for longer durations had more PFC activity during a task-switching paradigm (Kimura, Yasunaga, & Wang, 2013).

Here we seek to fill some of these gaps by objectively measuring CRF and PA in older adults and relating these measures to behavioral performance and BOLD activity during a

relational memory task; additionally, CRF and PA measures were used to investigate their relationship with the size of the hippocampus, as well as the caudate and thalamus, given that both of these regions are implicated in learning and memory and interact with the hippocampus (Aggleton, 2012; Scimeca & Badre, 2012). Since relational memory is dependent not just on the hippocampus, but an entire network of structures (Eichenbaum & Cohen, 2001), the implementation of such a task allows for the evaluation of how CRF or PA may influence brain activity across a network of regions. Further, the simultaneous evaluation of PA and CRF will allow for the teasing apart of which aspects of cognitive aging differentially benefit from the totality of PA, and which may require more intense movement/exercise to maintain higher levels of CRF. To this end, we quantified both daily PA using accelerometry, and obtained CRF measures via VO₂peak during a graded maximal exercise test. We expect CRF and PA to have beneficial effects on subcortical structures important for learning and memory, namely the hippocampus, either manifested through volume or BOLD response, which in turn would improve relational memory function.

Materials and Methods

Participants

One-hundred forty-eight older adults participated in this study as part of their baseline evaluation prior to entering a randomized controlled trial investigating the effects of exercise and nutrition on health in late adulthood. Of this original sample, 134 were retained for data analysis, as 12 participants displayed chance performance on the relational memory task, and four exceeded our motion criterion (movement > 4 mm); two subjects violated both of these criteria. Finally, four participants were removed from the sample due to having subcortical volume

measures less than three standard deviations below the mean ($N = 2$) or daily PA counts above ($N = 1$) or below ($N = 1$) three standard deviations from the sample mean. Thus, the final sample contained 130 individuals (females = 88) ranging in age from 60 to 77 ($M = 65.12$, $SD = 4.3$). All individuals were screened for the presence of dementia using the Mini Mental Status Exam (Folstein, Folstein, & McHugh, 1975) and were excluded if they scored below 24 out of 30 on the test. Participants were also excluded if they had a history of stroke or other neurological condition, contraindication to MRI, or were left-handed. Finally, all participants obtained clearance from a physician to engage in the maximal graded exercise test, and signed an informed consent document approved by the University of Illinois Institutional Review Board.

Cardiorespiratory Fitness Assessment

Each participant partook in a maximal graded exercise test with a modified Balke protocol in order to obtain an estimate of cardiorespiratory fitness (CRF), defined as their peak oxygen consumption measured in ml/kg/min, which represents one's ability to consume and utilize oxygen during physical exertion. Oxygen consumption (VO_2) was calculated from expired air samples measured every 30 seconds until the participant's maximum VO_2 was reached, or the test was terminated due to volitional exhaustion and/or symptom limitation. CRF was defined as the highest recorded VO_2 value ($VO_{2\text{peak}}$) after two of three criteria were met: (1) a plateau in VO_2 after increase in workload, (2) a respiratory exchange ratio >1.10 , and/or (3) a maximal heart rate within 10bpm of their age-predicted maximum. The test took place on a motor driven treadmill in the presence of a cardiologist and nurse, and respiration, heart rate, and blood pressure were monitored at all times.

Physical Activity Measurement

To objectively quantify the amount of total physical activity characteristic of an individual's daily routine, participants were asked to wear TG3X ActiGraph accelerometers (ActiGraph: Pensacola, Florida) for seven consecutive days during all waking hours, excluding bathing or swimming. Accelerometers were attached via an elastic belt and placed on the left hip. Data were processed with ActiLife v5.6.0 software, with a minimum of ten hours of data collection in a day necessary for that day to be deemed "valid" and thus included in the data analysis. On average, participants had 6.9 valid days, with a standard deviation of 1.0; only participants who had a minimum of three valid days were included for analysis. Average daily physical activity (average PA) was calculated by summing the total number of activity counts for a participant across the data collection period, and then divided by the number of valid days.

Relational Memory Task and Behavioral Analysis

The relational memory task used here is identical to the version in chapters three and four (Figure 3.1). For the purposes of data analysis a correct response to an intact pair was classified as a "hit," with an incorrect response categorized as a "miss;" a correct response to a re-pair trial was a "correct rejection," whereas an incorrect response was a "false alarm." A hit rate was derived for each participant by calculating the proportion of hits on trials with intact pairs, and a false alarm (FA) rate was obtained for each participant by finding the proportion of FAs on re-pair trials. Finally a d' value was calculated for each participant by subtracting the normalized FA rate from that of the normalized hit rate. The accuracy variable of main interest from the task in this experiment was the FA rate. This was due both to its strong relationship with age (see Results) as well as the tendency for older adults to respond to foil stimuli that are perceptually

similar to previously seen stimuli as “old” (thereby making the ability to correctly reject similar foils a potential marker of more youthful memory functioning; Yassa, Mattfeld, Stark, & Stark, 2011). Response times (RTs) for hits and correct rejections were also analyzed for all participants. Hierarchical linear regression was used to determine the relationship between fitness, physical activity, and behavioral measures, after accounting for age and education level, as these were significantly related to fitness and PA (see Results). Education was recorded as an ordinal variable of 1-8, where 1 = “did not finish junior high,” 2 = “graduated junior high,” 3 = “some high school,” 4 = “high school graduate,” 5 = “1-3 years of college/two-year college graduate/vocational or trade school,” 6 = “college graduate,” 7 = “master’s degree,” 8 = “PhD or equivalent.” Gender was not considered in these or subsequent analyses, as it is accounted for in the CRF measure, and the two genders did not differ in the PA measure.

MRI Acquisition

All images were collected on a Siemens Trio 3-Tesla full body magnet, using a 12-channel birdcage headcoil. Functional BOLD images were acquired parallel to the anterior commissure - posterior commissure (AC-PC) line with a T2*-weighted echo-planar imaging sequence of 35 contiguous axial slices collected in ascending fashion [repetition time (TR) = 2000 ms; echo time (TE) = 25 ms; BOLD volumes = 299; flip angle = 80°; field of view (FOV) = 220*220 mm; voxel size = $3.4 \times 3.4 \times 4$ mm]. Structural images were acquired with a T1-weighted 3D magnetization prepared rapid gradient echo imaging (MPRAGE) protocol of 192 contiguous sagittal slices collected in an ascending manner parallel to the AC-PC line [TR = 1900 ms; TE = 2.26 ms; flip angle = 9°; FOV = 256*256 mm; voxel size = $1 \times 1 \times 1$ mm].

Subcortical volume analysis

Automated segmentation of subcortical regions was conducted using Freesurfer (v 5.3); details of the subcortical segmentation process utilized by Freesurfer are available in Fischl et al., (2002). The algorithm employed by Freesurfer for subcortical segmentation has been shown to have a very high correlation with manual tracing, particularly for the hippocampus, and has proven to be sensitive to volume differences between groups (Morey et al., 2009). An automated measure of intracranial volume (ICV), which is comparable to manual tracing, was obtained for each participant via Freesurfer using the methods described in Buckner et al., (2004). This measure of estimated ICV was used to correct subcortical volume for head size by regressing each ROI volume onto ICV in order to obtain a slope (b) for the relationship between an ROI and ICV. The resulting slope was then used to normalize each ROI for head size via the following formula: normalized volume = raw volume – b (ICV - mean ICV); this correction has been used in multiple studies reporting subcortical volume measures (Erickson et al., 2009; Head et al., 2008; Raz et al., 2005).

Functional imaging analysis

Preprocessing of the fMRI data was done using FSL 5.02 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The first three volumes of each run were removed prior to analysis. For each run of functional data, a 100-second temporal high pass filter was applied, and data were smoothed with a Gaussian kernel of full width at half-maximum at 6 mm³. Also, motion correction was applied using MCFLIRT. Non-brain structures from the structural scan were removed and the image was co-registered to the subject's mean functional scans using boundary based registration (Greve & Fischl, 2009) and included the use of a gradient field map. The co-

registered images were normalized into Montreal Neurological Institute (MNI) template space using linear registration (12 degrees of freedom) in FLIRT followed by a non-linear registration with an eight mm warp resolution in FNIRT.

Each participant's three runs of the memory task were analyzed individually using FSL's FEAT (version 6.00) function. The hemodynamic response was convolved with a double-gamma HRF function. The statistical model for the task contained three regressors from the encoding phase, corresponding to whether a face-scene pair was later correctly remembered, forgotten, or went on to be a re-pair trial, and then five regressors in the recognition phase, with four coding the outcome of a trial (hit, miss, false alarm, correct rejection) and a nuisance variable tracking trials that were not responded to. All eight regressors corresponded to the onset of the scene and had a duration of four seconds. This model was then regressed against the observed fMRI data from each run. Analysis of each run consisted of creating contrasts from the events described above compared to baseline, and then each contrast was averaged across an individual's three runs via a fixed effects analysis.

One focus of the fMRI analysis was to ascertain to what degree fitness and PA influence brain function during memory retrieval. To accomplish this, fitness and average PA were entered (separately) into mixed effects models using FSL's FLAME function with outlier de-weighting selected in order to identify voxels where the BOLD activity is significantly correlated with these measures (Beckmann, Jenkinson, & Smith, 2003). The fMRI measure of interest for this analysis compared hits versus correct rejections. In choosing these two trial types to compare against each other, one is equating for other cognitive abilities such as visual perception and attention. However, correctly rejecting familiar pairings likely requires more cognitive control than

recognition, and for reasons discussed below, may be more sensitive to memory function in older adults; thus an emphasis has been placed on the contrast of correct rejections > hits.

Additionally, since fitness and/or PA may influence the volume of subcortical structures important for memory retrieval, volume estimates of these structures were included in fMRI models when there was a significant relationship (see Results), as structural differences can influence functional activation. Age, education, and performance were entered as covariates into the fMRI model when these variables correlated with fitness or PA. All continuous variables were mean-centered, and all models included a constant.

Statistical Analyses

The relationship between PA/CRF, on brain structure and/or behavioral measures of the relational memory task was investigated first in a correlational fashion, with significant correlations followed up in regression models accounting for covariates. Multiple comparison correction for these analyses was achieved by implementing a Bonferroni correction at the level of a family of tests when investigating how CRF or PA influenced behavioral performance or subcortical volume. To investigate the indirect effect of PA/CRF on FA rate through its modulation of subcortical structure (see Results), mediation analyses were conducted with the SPSS macro PROCESS (<http://afhayes.com/spss-sas-and-mplus-macros-and-code.html>) by using bootstrap sampling to create a confidence interval for the indirect effect of X on Y through the mediating variable. Finally, analyses for fMRI data used an activation threshold of $Z > 2.3$, and a family wise error cluster correction of $p < .05$.

Results

Behavioral performance

The overall sample had a mean d' score of 1.13 ($SD = .57$), with the mean hit rate equaling .79 ($SD = .13$), and the false alarm (FA) rate at .42 ($SD = .15$). Mean RT data were as follows, hits, ($M = 1403$ ms, $SD = 262$), correct rejections, ($M = 1612$ ms, $SD = 283$). Task performance was first analyzed as a function of gender, age, and education. There were no differences between gender and any measure of task performance. Age was positively correlated with RTs for hits, $r(128) = .34, p < .001$, and correct rejections, $r(128) = .35, p < .001$. There was no effect of education on RTs (all r 's $< .05$, all p 's $> .6$). Both age, $r(128) = -.22, p = .01$, and education, $r(128) = .20, p = .02$ correlated with d' . A closer examination of the data indicated that it was the FA rate driving the relationship between d' and age, as the FA rate and age were negatively correlated, $r(128) = .27, p = .002$, whereas age and hit rate had no significant relationship, $r(128) = -.06, p = .49$. There was no differential effect of education on the hit rate versus the FA rate. Additionally, a measure of criterion, c was calculated to evaluate response bias. The mean value for c was -.33, which was significantly below zero, $t(129) = 10.3, p < .001$. Therefore, given that the only age-related accuracy impairment was in the FA rate, coupled with a strong tendency for participants to respond “yes,” which clouds the interpretation of hits, subsequent analyses regarding fitness and PA focused on their relationship with the FA rate and the BOLD response for correct rejections relative to hits. Given the age related effects on RTs for both hits and false alarms, these were both investigated for possible effects of modulation due to CRF or PA.

Age was significantly correlated with CRF, $r(128) = -.29$, $p = .001$, and PA, $r(128) = -.30$, $p = .001$. The same was true with education and these measures: CRF, $r(128) = .29$, $p = .001$, PA, $r(128) = .23$, $p = .01$. Therefore, both age and education were entered as covariates in regression models predicting FA rate and RTs. Correlations between PA and CRF were first carried out with the FA rate, using a Bonferroni corrected significance value for two comparisons of $p < .025$. Higher levels of CRF were associated with a lower FA rate, $r(128) = -.20$, $p = .02$; there was no significant relationship with PA, $r(128) = -.09$, $p = .29$. However, as summarized in Table 5.1, despite the overall model significantly predicting FA rate, CRF did not independently contribute to the FA rate after including age and education as covariates. RTs for hits and correct rejections were tested for correlation with CRF and average PA, with the corrected significance level set at $p < .0125$. Average PA was marginally, negatively associated with RT for correct rejections, $r(128) = -.21$, $p = .02$; all other correlations were not significant, (all r 's $> -.13$, all p 's $> .15$).

Table 5.1
Results from hierarchical linear regression analyses of CRF predicting FA rate

Step	Variable(s)	ΔR^2	$\Delta F\text{-value}$	p-value
One	Age & Education	7.3	4.98 (2,127)	.008
Two	CRF	1.5	2.12 (1,126)	.15

CRF, PA, and subcortical volume

Correlations between left and right caudate, thalamus, and hippocampus with CRF and PA, were first carried out to establish if any of these variables had a relationship with the size of these subcortical structures; significant relationships were followed up with regression analyses controlling for age and education. The p -value for this series of correlational analyses was set at $< .004$, correcting for the 12 comparisons. With regard to CRF, both left thalamus, $r(128) = .31$,

$p < .001$, and right thalamus, $r(128) = .27, p = .002$, volume were positively associated with fitness. The right hippocampus displayed a marginal relationship with CRF, $r(128) = .18, p = .04$; all other regions were not significant (all r 's $< .13$, all p 's $> .14$). As with CRF, PA was related to bilateral thalamus volume: left thalamus: $r(128) = .32, p < .001$, right thalamus: $r(128) = .26, p = .003$. PA also had modest relationships with right caudate, $r(128) = .21, p = .02$, and right hippocampus, $r(128) = .17, p = .05$; all other brain regions were not significant (all r 's $< .16$, all p 's $> .06$).

Given the highly significant relationships between bilateral thalamus and CRF/PA, these variables were followed up with hierarchical linear regression analyses to ascertain if they predict thalamus volume after accounting for age and education. The Bonferroni corrected p-value for the beta weights of age, education, and the PA/CRF variables was set at $< .0125$ due to the four regression models. For each model, age and education were entered in step one, with the PA/CRF variable of interest entered in step two to isolate the percent of explained variance from these variables. When using an uncorrected p-value ($p < .05$) it was the case in each model that age was negatively associated with thalamus volume, and each PA/CRF measure was positively associated with thalamus volume; there was no relationship with education and thalamus volume. After applying the multiple comparison correction though the only significant relationships were for the left thalamus with CRF, $t(126) = 2.74, p = .007$, and average PA, $t(126) = 2.9, p = .004$. Table 5.2 summarizes the results from the two models predicting left thalamus volume.

Table 5.2
Results from hierarchical linear regression analyses predicting left thalamus volume

Model 1: CRF

Step	Variable(s)	ΔR^2	$\Delta F\text{-value}$	p-value
One	Age & Education	8.3	5.74 (2,127)	.004
Two	CRF	5.1	7.48 (1,126)	.007
	Variable	standardized beta		p-value
	Age	-.21		.02
	Education	-.04		.97
	CRF	.25		.007

Model 2: PA

Step	Variable(s)	ΔR^2	$\Delta F\text{-value}$	p-value
One	Age & Education	8.3	5.74 (2,127)	.004
Two	PA	5.7	8.41 (1,126)	.004
	Variable	standardized beta		p-value
	Age	-.20		.02
	Education	.01		.89
	PA	.26		.004

In order to understand if there were unique contributions of CRF and PA to left thalamus volume, we carried out a regression with both variables in the model. In particular, we wished to ascertain if, after accounting for CRF, daily PA still affords benefits to brain health. This hierarchical regression analysis included age and education in step one, CRF in step two, and PA in step three. After accounting for CRF, daily PA explained 2.4% of the variance in left thalamus volume, a marginally significant amount, $\Delta F(1, 125) = 3.5, p = .06$, despite PA and CRF being highly correlated, $r(128) = .52, p < .001$. The full results of this analysis can be found in Table 5.3.

Table 5.3*Inclusion of average PA and CRF in same model predicting left thalamus*

Step	Variable(s)	ΔR^2	$\Delta F\text{-value}$	p-value
One	Age & Education	8.3	5.74 (2,127)	.004
Two	CRF	5.1	7.48 (1,126)	.007
Three	PA	2.4	3.5 (1,125)	.06
Variable		standardized beta	p-value	
Age		-.18	.04	
Education		-.02	.86	
CRF		.16	.11	
PA		.18	.06	

Mediation analysis: CRF/PA, left thalamus, FA rate

Although there was no direct relationship between CRF or PA and task performance, there were significant relationships for these variables and left thalamus volume. Therefore, we wished to understand if CRF/PA had an indirect effect on the FA rate through its modulation of left thalamus volume, particularly given this brain regions role in memory processing. We first confirmed that greater left thalamus volume was associated with a reduced FA rate by carrying out a hierarchical linear regression analysis predicting the FA rate from left thalamus, after accounting for age and education. As seen in Table 5.4, greater left thalamus volume was significantly associated with a lower FA rate, $t(127) = -2.18$, $p = .03$.

Table 5.4
Hierarchical regression analysis predicting FA rate from left thalamus volume

Model 1: CRF

Step	Variable(s)	ΔR^2	F-value	p-value
One	Age & Education	7.0	9.7 (2,127)	.002
Two	Left thalamus	5.1	3.4 (1,126)	.03
Variable		standardized beta	p-value	
Age		.21	.02	
Left thalamus		-.19	.03	

Next we conducted two mediation analyses to test for an indirect effect of CRF or PA on the FA rate, using left thalamus volume as the mediating variable and including age and education as covariates. The indirect effect was tested using bias-corrected bootstrap samples ($N = 10000$) to determine if the 95% confidence interval (CI) included zero for either CRF or PA. Both the standardized effects of average PA, (95 % CI: -.14, -.01) and CRF (95% CI: -.11, -.01), were significant, indicating an indirect effect of PA/CRF in reducing the FA rate through left thalamus volume.

CRF, PA, and brain activity

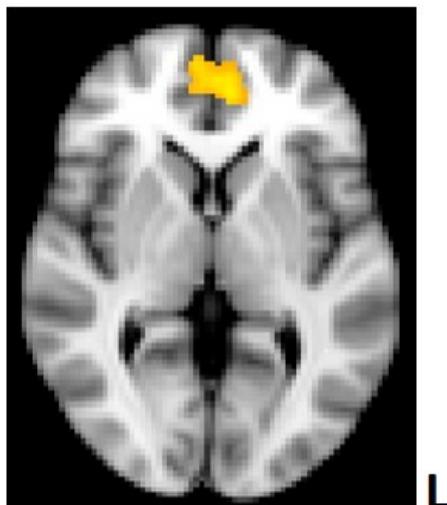
In order to understand the relationship between CRF, PA, and brain activity during memory retrieval, one model for each fitness/PA variable of interest was created by entering these variables as continuous measures into the model. Also, each model included age, education, and the FA rate as continuous variables given their relationship with the fitness and PA variables of interest. The fMRI contrast of interest was correct rejections > hits, given the age-associated impairment in correctly rejecting new face-scene pairs. For both models, there

were no significant relationships, positively or negatively (i.e. hits > correct rejections), for the CRF/PA variables and whole-brain BOLD signal.

Left thalamus volume, brain activity, and correct rejections

To understand if left thalamus volume influenced whole-brain activity when correctly rejecting a new face-scene pair, an fMRI model was constructed entering left thalamus volume as a continuous variable, along with age and FA rate as covariates for the contrast of correct rejections > hits. As seen in Figure 5.1, greater left thalamus volume was associated with a greater BOLD signal in bilateral medial prefrontal cortex.

Activity positively related to left thalamus volume Correct Rejections > Hits



Z = -2



X = -6

Figure 5.1: Greater BOLD activity in the medial prefrontal cortex a function of left thalamus volume after correcting for age and FA rate for correct rejections relative to hits. The activity threshold is set at $Z > 2.3$, with a cluster correction threshold of $p < .05$

Discussion

To our knowledge, this is the first study reporting a relationship between thalamic integrity in aging with PA/CRF and memory performance. Prior to using a conservative correction for multiple comparisons, CRF and average PA predicted bilateral thalamus volume even when accounting for age; after Bonferroni correction, average PA and CRF still predicted left thalamus volume. The magnitude of this effect is particularly striking. Both average PA and CRF predicted left thalamus volume as well as age (Table 5.2), indicating all else being equal,

one may be able to offset the effects of chronological age on left thalamus volume through PA and exercise.

In speculating the reason for the relationship between thalamus volume and PA/CRF, two potential candidate mechanisms emerge. First, the ventral lateral nucleus of the thalamus is critical to motor function, as it receives input from cerebellar neurons and projects to motor cortex (Shinoda, Futami, & Kano, 1985). To the extent that movement stimulates this pathway (or the lack thereof causes degeneration), higher levels of daily PA may preserve thalamic integrity, attenuating age-related shrinkage. The idea that movement stimulates and protects the thalamus from atrophy may also explain the stronger relationship for the left thalamus, albeit speculatively. In this study, all participants were right-handed; thus, they may favor the right side of their body more often when moving, and these signals would be routed through the left thalamus. One issue that may need reconciliation with this interpretation is that the ventral lateral nucleus of the thalamus serves in motor processing, whereas the anterior and/or mediodorsal nuclei are generally implicated in memory processes (Aggleton, 2012; Shinoda et al., 1985). Thus, the effects of increased stimulation of the ventral lateral nucleus would presumably have to extend over to other thalamic nuclei, should this be one of the mechanisms by which greater PA leads to a larger thalamus later in life. This speaks to the larger issue of the heterogeneity within the thalamus, and future work may wish to subdivide this large structure by its constituent nuclei to further parse the effects of PA and CRF. A non-exclusive second potential mechanism relates to the thalamus's sensitivity to lacunar infarcts, with these ischemic injuries often causing mediodorsal and/or anterior thalamic damage and cognitive deficits (Carlesimo et al., 2011). If it is the case that poorer cerebrovascular health in general has more subtle effects on thalamic integrity, even in the absence of a major infarct, it is conceivable that higher levels of CRF

and/or PA would lead to healthier neurovasculature, which in turn may protect the thalamus from age-related degeneration.

The relationship between PA/CRF and a larger left thalamus also seemed to benefit memory, as mediation analyses confirmed an indirect effect of PA/CRF on the false alarm rate, via the effect of PA/CRF on left thalamus volume. It may appear surprising that it was the left thalamus, and not the hippocampus, that mediated performance on the relational memory paradigm; however, the thalamus is richly interconnected with the hippocampus and is implicated in memory processes (Aggleton et al., 2010). Damage to the thalamus, most commonly caused by Korsakoff's syndrome or vascular etiologies, is associated with profound amnesia, similar to medial temporal lobe (MTL) amnesic patients, coupled with dysexecutive symptoms mirroring those with PFC lesions (Carlesimo et al., 2011; Kopelman, 1991). The inclusion of deficits in executive function adds an important modifier to the manifestation of amnesia in those with thalamus damage compared to MTL lesions. In those with amnesia due to Korsakoff's syndrome, there is an inability to suppress irrelevant mnemonic information, whereas this does not occur in those with MTL damage, presumably because the mnemonic information does not accumulate in the first place (Schacter, Verfaellie, Anes, & Racine, 1998). This inability to select the proper mnemonic information for completing a task is likely related to the frontal dysfunction of Korsakoff's patients, since monitoring the output of memory retrieval from the MTL is generally ascribed to the PFC (Simons & Spiers, 2003).

In the current experiment, left thalamus volume selectively mitigated the FA rate, and did not enhance the hit rate. In this task, in order for a participant to avoid a false alarm, he or she must evaluate the displayed face-scene pair and determine that one or both of the images was paired with a different image during the study phase. This process likely involves a large amount

of cognitive control and PFC-hippocampal interaction. Given that a major output of the hippocampus runs through the anterior nucleus of the thalamus and then to the medial PFC (Aggleton, 2012), the integrity of this pathway may be critical to the types of memory processes required to record a correct rejection on a trial. This idea is bolstered by the finding of those with larger left thalamus volume having more medial PFC activity for correct rejections. Thus, higher levels of CRF and/or PA were associated with a larger left thalamus, which aided in memory through its interactions with medial PFC, and presumably the hippocampus.

PA and CRF were highly correlated in our sample, but it is important to note that these are different measures and they have different implications for public health. In our analysis, it was somewhat ambiguous as to whether CRF or PA was the prime mover in determining thalamic volume, as both were highly significant in individual regression models, but each became individually non-significant when included in the same model, likely reflecting their shared variance. But, after including CRF, average PA nearly explained a significant amount of left thalamus volume variance, with the contribution of CRF appearing to remain relatively independent, given its near marginal effect. While one must not make too much of these marginal effects, its implication warrants a brief discussion. To date, many studies have focused on CRF and its effect on brain health and aging. Using CRF is certainly informative, but one's VO₂peak is modified by certain uncontrollable factors such as genetics (Peter et al., in press), and has a rate-limiting factor of how well the cardiorespiratory system can transmit oxygen to the muscles (which of course can be improved with exercise; Bassett & Howley, 2000). Theoretically, there is no limiting factor to how much one can move throughout the day. Practically, daily PA may be limited by physical abilities (especially in the elderly) or one's occupation; however, increasing daily PA is simpler than raising one's CRF. Thus, if the totality

of all movement during the day benefits the brain, even after accounting for one's fitness level, research and public health agencies may wish to focus on all forms of movement, rather than just exercise and raising CRF. To be sure, the best strategy is likely a combination of various types of PA, such as meeting the daily recommendations for moderate-to-vigorous PA which may raise one's CRF level, but also continuing to move throughout the day, even at a light pace.

Though there were large effects of CRF and PA on thalamus volume, both the hippocampus and caudate were not influenced by these measures. The null result of CRF modulating hippocampal and caudate volume is surprising, given previous studies have found higher fitness levels corresponding to larger volumes of these structures (Erickson et al., 2009; Verstynen et al., 2012). One possibility for this discrepancy is the difference in methodology to quantify tissue volumes, as Freesurfer was used here, whereas the previous reports used FIRST in FSL.

Despite the inconsistencies between previous work on CRF and subcortical structure, the data here clearly indicate the size of the left thalamus to be larger in those who are more active and fit. This effect was just as large as the negative effect of age on left thalamus volume. The cross-sectional nature of this investigation makes it unclear as to whether PA and CRF actually buffer against age-related atrophy; thus longitudinal studies are warranted. Regardless, having a larger left thalamus was additionally associated with better memory performance and more activity in the medial PFC. Together, these data underscore the importance of physical activity and cardiorespiratory fitness to brain health in cognitive aging.

Chapter 6: General discussion and future directions

This series of experiments endeavored to contribute to the understanding of successful cognitive aging, with an emphasis in distinguishing aging from very mild AD, and the identification of lifestyle choices and environmental factors that enhance or diminish one's cognitive phenotype in late life. There are several main conclusions that can be made from the empirical chapters: 1) the memory impairments in the earliest stages of clinical AD seem to be due to at least two factors, one stemming from aging and one from the disorder itself, with the latter manifesting as a sensitivity to interference, 2) tasks with a demand for relational processing, regardless of timescale, stimulus modality, or response type relate strongly to hippocampus and cluster with canonical neuropsychological tests of hippocampal function; these tasks can also be used as indicators of function of the hippocampal memory system in the assessment of cognitive aging, aiding in identifying that, 3) the combination of mTBI plus aging results in worse memory performance, smaller hippocampal volumes, and less cortical BOLD signal due to successful memory, and 4) higher levels of daily physical activity (PA) and cardiorespiratory fitness (CRF) are associated with larger left thalamus volume, which in turn was associated with a better false alarm rate, potentially through medial PFC (mPFC) modulation. The broader implications of these results, their inter-relatedness, and how the underlying ideas may affect future directions in the field are discussed in this final section.

From the perspective of healthcare, socioeconomic, and emotional burdens, the primary endpoint of successful aging is arguably staving off the development of a neurodegenerative disease like AD. A disorder such as AD is difficult to identify in the very early stages for numerous reasons including: 1) certain cognitive symptoms of AD may masquerade as so-called "normal" age-related cognitive decline, 2) many procedures which aid in diagnosis are costly or

invasive (e.g., PET or lumbar puncture), and 3) it is unclear when the disease process actually starts, as the identification of "preclinical AD" suggests a process years-to-decades prior to detectable clinical symptoms emerge (Sperling et al., 2011). Thus, the development of cognitive tasks that find dissociations between healthy aging and very early AD participants, and that can be employed cheaply and during a screening phase, are of paramount importance. The data reported from the task in chapter two provide a step towards this goal. In this dataset, all older adults showed reduced overall accuracy compared to young adults. In addition to this, there was evidence for those with very mild AD to be more sensitive to interfering stimuli when searching for a target that matched with an internal mnemonic representation, indicating evidence for memory impairments in AD being due to at least two different factors, with one of them specifically unique to AD.

This dissociation based on a sensitivity to interference is but one of many such dissociations among patterns of cognitive data from diverse domains that differentiate healthy older adults from those with very mild AD. For instance, similar dissociations have been found when comparing recollection vs. familiarity, types of prospective memory, attentional control with regard to multiple facets of memory, Stroop task performance, intraindividual variability, and even retrieval of proper names (Budson, Daffner, Desikan, & Schacter, 2000; Duchek et al., 2009; McDaniel, Shelton, Breneiser, Moynan, & Balota, 2011; Semenza, Mondini, Borgo, Pasini, & Sgaramella, 2003; Wolk, Mancuso, Kliot, Arnold, & Dickerson, 2013). This non-exhaustive list is provided to underscore the complexity of AD and the lack of unanimity with regard to the cognitive manifestations of very early AD; it also provides evidence clearly suggesting that early stage AD is marked by more than simply episodic memory loss. Importantly though, the above list of dissociations, along with the one in chapter two, provides

an opportunity for synthesizing the commonalities amongst these dissociations in order to develop better cognitive diagnostic tools at earlier stages of the disease process.

It is clear that by the time a patient has the clinical syndrome of AD, amyloid-beta (A β) has been accumulating in the brain for a much longer period of time (Sperling et al., 2011). It is also the case that this A β , when studied in "cognitively normal" older adults (i.e. adults free of dementia and not showing impairments on standard neuropsychological tasks), has been shown to negatively impact multiple areas of cognition when using sensitive tasks (Rentz et al., 2011; Rodrigue et al., 2012). If it is indeed the case that the amyloid build-up in these cognitively normal adults is preclinical AD (Price et al., 2009), then it may be possible to identify AD at the preclinical stage through the use of cognitive tasks devised from the dissociations found in individuals who are further along in the disease process; using cognitive tasks to achieve this goal has the added advantage of being cheaper, more available, and less invasive than another method such as PET scanning. It is the promise of detection of AD in the preclinical phase that is the ultimate utility of the task in chapter two. The work in chapter two represents a necessary first step by showing usefulness in differentiating those in the very mild stage of clinical AD; however, in terms of the first goal outlined within the working definition of "successful aging" in this undertaking, the prevention of clinical AD, it is less valuable given that the individuals in the CDR 0.5 group were already diagnosed with AD. Future work must focus in on the refinement of this task and others so that they can efficiently hone in on the cognitive manifestations of the underlying pathology thought to be the first sign of the disease so that it can be identified even earlier, which will likely lead to a better prognosis.

The adage, "an ounce of prevention is worth a pound of cure" may ring especially true in the case of AD. An obvious reason for this is that there is currently no cure or even disease

modifying treatment for AD. However, even if there was a drug that could immediately halt the disease progress and remove any underlying pathology, a cure for AD in the clinical phase would not mean the same thing as a cure for some others disorders does, in the sense that one would likely not return to premorbid levels of functioning. This is due to the fact that substantial neuron death has occurred by the stage of clinical AD and even MCI, and despite the brain's extraordinary capacity for plasticity, those neurons are not likely to return. Even though neurogenesis occurs within the hippocampus, an area greatly affected by AD, it is limited to the dentate gyrus; the most damage within the MTL due to AD seems to occur in the CA1 region, subiculum, and entorhinal cortex (Small et al., 2011). Therefore, even though arresting AD in the very mild clinical stage would unquestionably be beneficial, it may potentially also leave the individual with an impoverished quality of life, in that he or she may not be able to drive or work anymore. However, it is thought that very little neuron loss and minimal synaptic damage occurs in preclinical AD, especially during the early portion of this phase; thus, preventative screening measures that could detect signs of the disease earlier would leave an individual with a higher quality of life, should a cure ever be developed. Even in the absence of a pharmaceutical intervention that could completely counteract the disease process, identification of preclinical AD would potentially give other interventions such as exercise or nutrition a greater probability of being effective, since less damage will have occurred. Thus, there is a strong need for effective cognitive screening tools.

One outstanding question with the task used in chapter two which could be informative in creating a battery for the screening of preclinical AD would be to understand how it relates to the tasks which loaded onto the relational memory component in chapter three. There are reasons to believe that this task would cluster with the other tasks that composed the relational memory

component, but other indications suggesting the relationship may be less straightforward. On the one hand, the stimuli used in this task are designed to drive relational processing, due to the novel designs and three distinct sections of each stimulus which must be processed together; moreover, a version of this task with the same stimuli proved useful in differentiating hippocampal-amnesic patients from neurologically-intact controls, especially when more lure items were viewed prior to identifying the target (Warren et al., 2011). However, an association with hippocampal structure does not necessarily equal a demand for the relational processing that the tasks in the relational memory component in chapter three have. This can be derived from the observation that the processing speed component was strongly related to hippocampal volume, and that the spatial working memory task has previously been linked to hippocampal size (chapter three; Erickson et al., 2009; 2011). Thus, the answer to the question is more at the cognitive level, and hinges on whether a task such as the one in chapter two, where the paradigm has stimuli that have a relational demand but also systematic interference from lure stimuli, would cluster with other tasks relying on relational processing, or if the systematic interference feature would shift it to another cognitive construct.

Some information in answering this question can be gleaned from examining the individual tasks which comprised the relational memory component in chapter three. For instance, in the face-scene task, participants saw 24 face-scene pairs during encoding, and it could be argued that the natural overlap between faces and scenes (i.e. two faces share many common features) cause a degree of perceptual interference which builds as both the encoding phase and recognition phase continue. Also, the data from the verbal tasks came from the delayed recall portions, where participants were completing other tasks between encoding and retrieval. Therefore, there seems to be a common role for interference in these tasks. On the other

hand, aside from perhaps the similarities of the individual stimuli on each trial causing some interference, the SR task had only a four second delay between study and test, yet also clustered with the three above mentioned tasks. One may envisage that if the task from chapter two had been included in chapter three, perhaps it would have formed a component with the face-scene task based on relational load plus interference, as both had many intermittent stimuli with similar perceptual features, though the interference in the face-scene task was less systematic. Other possibilities are that it may have joined the other tasks with a relational load, as that factor seems robust to a variety of task manipulations, as evidenced by the diverse tasks forming the component; finally, it could have linked with the executive function tasks, given the role of PFC and certain types of interference. Future research will hopefully be able to discern if there is a separate role for relational load plus interference, how the hippocampus and neocortical areas (e.g., PFC) modulate successful performance on these tasks, and how this may play into the screening of preclinical AD.

With respect to screening the function of the hippocampal memory system, which is important not only in identifying AD but the broader field of cognitive aging, the results from chapter three, especially from the SR task, are intriguing and may have practical utility in science and healthcare. The traditional neuropsychological technique for assessing hippocampal function relies on testing memory at long delays; typically ranging from 25-45 minutes when assessed in the same testing session. The data from chapter three and previous work with this task suggest that these delays may not be necessary in evaluating hippocampal function (Watson et al., 2013). The delay on the SR task used here was four seconds, with the entire task taking approximately 15-20 minutes. The total length of time may not seem like a very large savings over the current long-term memory tasks in place, but given that the delay is only four seconds, it seems that with

task refinement it could be possible to make the task shorter, thereby providing an assessment of hippocampal function in less than five minutes. From the scientific perspective, this would free up time in cognitive batteries for the investigation of other domains. The implications for the healthcare field have a tremendous upside, in that one can assess hippocampal function quickly and in a relatively automated fashion, which can have value in neurology, geriatric, and even general practitioner settings. This is not to suggest that the SR task will be the only tool needed for diagnosing a medical condition or even completely characterizing one's hippocampal function. Rather, it underscores the notion that the contribution of the hippocampus is not limited to long-term memory, and consequently, one need not test its function only using word-lists with long delays. With this notion in mind, researchers are afforded a wider toolbox to study the hippocampal memory system, particularly for understanding how lifestyle/environmental factors influence its aging trajectory.

It is becoming clear that the choices made and events that occurred in one's life shape an individual's cognitive aging trajectory. The results from chapter four detailing a history of mTBI directly speak to this. It would be inappropriate and inaccurate to suggest that the pattern of data from the middle-aged participants with a history of mTBI in this study indicates these individuals have AD. The participants comprising this group were relatively young ($M = 52.9$), and all were still gainfully employed. However, it will be interesting to conduct longitudinal or epidemiological studies investigating whether a history of mTBI carries with it a higher risk for developing AD late in life, similar to what has been observed in moderate-to-severe TBI (Plassman et al., 2000). An interesting modifier to the risk of mTBI and aging may be *APOE e4* allele status, as (Plassman et al., 2000) observed a trend towards those with one or both e4 alleles plus an mTBI having a higher risk of dementia. Irrespective of whether a history of mTBI raises

the probability of developing AD, the results from this study do help explain one novel source contributing to the wide range of cognitive variability among middle-aged-to-older adults in that, compared to age, education, and gender matched peers, those with a history of mTBI who are now in mid-life perform worse in relational memory and have smaller bilateral hippocampal volumes (Monti et al., 2013).

As alluded to in the introduction of chapter four, an individual's cognitive and brain health in their seventh or eighth decade is not simply the reflection of one or two factors, but a unique interplay between the passage of time, genetics, and life events/choices (Mesulam, 2000). Thus, even though the effect of reduced hippocampal volume was strong in the mTBI study, it probably is not the case that one is doomed to a smaller hippocampus and worse memory later in life if he or she has had an mTBI. Instead, it may be a risk factor for poorer cognitive aging, but one that can be ameliorated by other lifestyle factors, such as increasing physical activity and exercise. Since the experiment in chapter five used the same relational memory task and imaging methodology, a comparison between the two studies can help to address this question indirectly, bearing in mind that the participants in chapter five were older than the middle-aged group in chapter four.

In chapter five it was clear that higher PA and CRF were linked to better brain health in the form of larger left thalamus volume. The larger left thalamus may then interact with the mPFC to aid in performance on the relational memory task. In this sample, better performance came in the form of a reduced false alarm (FA) rate, whereas the hit rate did not benefit from higher PA/CRF, nor was it influenced by brain volume measures. Furthermore, none of the measures of PA or CRF were associated with larger hippocampi. In the middle-aged mTBI participants, their memory deficit was due to a lower hit-rate. Moreover, the mTBI individuals

differed from controls in their hippocampal volume, whereas thalamus and other subcortical structures were equal across the two groups. Thus, even though a history of mTBI produced worse memory overall, and higher PA/CRF led to better memory overall, the mechanisms through which these were accomplished may have differed. Such an interpretation is consistent with animal work where hippocampal lesions cause a primary deficit in the hit rate, whereas mPFC lesions predominantly affect the FA rate (Farovik, Dupont, Arce, & Eichenbaum, 2008; Fortin, Wright, & Eichenbaum, 2004). To be sure, obtaining a hit or a correct rejection entails contributions from both the hippocampus and mPFC, but evidence here and elsewhere indicates the two structures may contribute disproportionately to the two cognitive operations.

Therefore, if one were to stick closely to the data from chapter four and five, an individual with a history of mTBI who increased his/her physical activity levels would probably see some benefit to memory, but in a way that may leave the deficit caused by the original mTBI unaltered, since there was no benefit of PA/CRF to the hippocampus or hit rate. Such an interpretation does ignore previous work indicating higher CRF levels predict larger hippocampal volumes, and participation in a 12-month walking intervention increases the size of the hippocampus in older adults (Erickson et al., 2009, 2011). Further, the totality of evidence from animal models of exercise indicates benefits to the hippocampus from exercise (van Praag, 2009). As such, even though PA/CRF did not influence hippocampal volume in the chapter five sample, engaging in more PA and exercise is still probably advisable for those with a history of mTBI and others at risk for worse cognitive aging, given its benefit to memory as well as the broader positive health outcomes it affords.

The comparison of the results of chapters four and five also highlights the richness afforded to the study of cognitive aging by using a complex cognitive process like relational

memory that can be broken down into constituent processes. For instance, using the same task and MR procedures across two experiments allowed for the elucidation of the effects of separate lifestyle or environmental factors on multiple brain regions/pathways, as well as differing aspects of memory. To be sure, other cognitive domains and tasks provide a similar richness, such as distinguishing recollection versus familiarity, or proactive versus retroactive cognitive control. The broader point is that in the search to explain non-obvious (i.e. not brain damage or dementia) sources of variance within cognitive aging, the field may need to implement tasks that are more complex and assess multiple sub-domains of cognition, rather than using standard neuropsychological tasks such as word-list recall. To illustrate this point, though not reported in chapter five, data from the Wechsler Memory Scale, including word-list recall, Logical Memory, and Paired-Associates Learning, all proved insensitive to CRF/PA and brain measures, either when entered individually or as a latent variable.

The use of such complex tasks may help to partially clarify a major area of promise in the field of cognitive aging, and that is the role of nutrition. In many ways, the scientific literature supports the idea that one's diet can help the brain weather advancing age. Animal models in rodents and canines suggest certain foods rich in polyphenols, antioxidants, or omega-3 fatty acids to protect from AD-like pathology, boost neurogenesis, and/or benefit cognition (Casadesus et al., 2004; Green et al., 2007; Lim et al., 2001; Pop et al., 2010). Furthermore, epidemiological studies in humans indicate protective roles in cognitive aging for dietary vitamin E, fish consumption, polyphenols, and adherence to a Mediterranean diet (Leteunneur, Proust-Lima, Le Gouge, Dartigues, & Barberger-Gateau, 2007; Morris, Evans, Bienias, Tangney, & Wilson, 2002; Morris, Evans, Tangney, Bienias, & Wilson, 2005; Scarmeas, Stern, Mayeux, & Luchsinger, 2006). However, when testing causation in humans through randomized controlled

trials, the results have been largely disappointing (Aisen et al., 2008; Ford et al., 2010; Quinn et al., 2010; Stough et al., 2012; though see Douaud et al., 2013; Durga et al., 2007 for successful trials).

There are myriad of reasons why a clinical trial may fail, but in the case of nutrition and cognitive aging, one major culprit has been the use of insensitive tasks to assess cognitive change (see Macready et al., 2010 for review). Many of the tasks used in these trials are neuropsychological tasks that were developed for the detection of major brain changes, such as AD. As such, they may not be sensitive enough to distinguish what are surely to be less drastic, but still meaningful, changes in cognition arising from nutrition. To this end, a new class of cognitive paradigms, similar to the face-scene and SR task used in this report, may be necessary for the investigation of nutrition (or similar factors) and cognitive aging to succeed. These tasks would likely be more difficult and hone in on specific areas (or even sub areas) of cognition. One consideration to such an endeavor would be to ensure these new tasks have high reliability and they would also benefit from normative data as well, both of which are characteristic of many neuropsychological tests.

Continuing to use nutrition as an example in understanding the variables that influence the study of successful cognitive aging, a final consideration centers on the optimal time to intervene. Most interventions of nutrition and cognitive aging enroll participants who are already aged, with the typical minimum age of entry at 60 or 65; this procedure is similar for many types of aging interventions. However, one of the few successful nutritional interventions in aging selected slightly younger participants. In addition to a long supplement period (three years), Durga and colleagues (2007) enrolled participants between the ages of 50-70. One reason their intervention may have been successful could be that by selecting younger participants, the effects

of nutrition can operate in an environment where less age-related changes have occurred, thereby bolstering the chances of success. This is particularly true if nutrition is to have a role in the prevention of AD, given the protracted period of development of the disorder (Sperling et al., 2011).

This illustration with nutrition speaks to a much larger issue for understanding successful cognitive aging; to truly ascertain the antecedents in one's life that allows him/her to reach the age of 80 free of dementia and largely cognitively intact, we in all likelihood need to longitudinally study middle-aged (40-60) individuals. The development of AD potentially accrues over a period of decades, and it could be argued that the effects on the brain from one's lifestyle likely accumulate during middle-age to produce the aged phenotype. For example, vascular and metabolic risk factors, physical activity, and diet all play a role in the risk of dementia (Middleton & Yaffe, 2009), but many of these factors, such as obesity and hypertension, have stronger relationships when measured in mid-life rather than late-life (Fillit, Nash, Rundek, & Zuckerman, 2008; Fitzpatrick et al., 2009). One possibility for this discrepancy is that in measuring lifestyle choices or vascular risk factors late in life, one is not observing a risk factor for the development of AD, but rather, manifestations of the disease in certain people. An example of this is obesity, where a body mass index (BMI) of greater than 30 (obese) indicates risk for AD in mid-life, yet in late-life the pattern is reversed and those who are underweight ($BMI < 20$) are more likely to have AD (Fitzpatrick et al., 2009). With the end goal of successful aging in mind, it may be more beneficial to conduct longitudinal and intervention studies in individuals who are in their 40s, 50s, and 60s, rather than in their 70s and 80s. This is of course costly and difficult, given that someone who is 50 may have to be followed for 25-30 years to see if he or she develops AD; nonetheless, the best opportunity for exercise or diet to

interfere with the development of AD is likely closer to the age of 50 than 75. Further, cross-sectional evidence indicates most brain regions begin deteriorating in mid-life or before, as do many cognitive functions (Fjell et al., 2013; Park, Polk, Mikels, Taylor, & Marshuetz, 2001). Thus, shorter studies could also be implemented to ascertain whether various interventions can stay these declines in mid-life, which presumably would lead to better outcomes in late-life (Stern, 2009). In general, a shift towards prevention and screening in mid-life, similar to that observed with heart disease and cancer, may be beneficial for brain and cognitive health.

Most people take cognitive decline to be a natural part of aging, and to some extent, this may be true. However, certain individuals show very little memory decline past their eighties, and have quite healthy brains (Harrison, Weintraub, Mesulam, & Rogalski, 2012; Rogalski et al., 2013). Understanding how an individual can attain this successful aging is of paramount importance. The current series of reports hopefully furthers this goal, by isolating characteristics unique to AD, developing sensitive tasks to assess the hippocampal memory system, and identifying lifestyle and environmental factors, such as a history of mTBI or PA/CRF levels that interact with aging. Much work remains however, and with a shift towards the use of new cognitive paradigms that provide rich data and the study of adults across the entire lifespan, we can move closer to mitigating the supposed inevitable and drastic cognitive decline with aging, vastly enhancing quality of life for future generations.

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