Investigating age-related differences in functional brain activity and connectivity underlying source memory: An adult lifespan approach

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List of abbreviations

ANOVA/ANCOVA:	Analysis of (co)variance
BA:	Brodmann area
BDI:	Beck Depression Inventory
BOLD:	Blood-oxygen-level-dependent signal
B-PLS:	Behavior partial least squares analysis
BSR:	Bootstrap ratio
CG:	Cingulate gyrus
CVLT:	California Verbal Learning Test
DLPFC:	Dorsolateral prefrontal cortex
EDU:	Formal education level
EPI:	Echo-planar imaging
FFG:	Fusiform gyrus
fMRI:	Functional magnetic resonance imaging
FWHM:	Full width at half maximum
HC:	Hippocampus
IFG:	Inferior frontal gyrus
IPL:	Inferior parietal lobule
ITI:	Inter-trial interval
LG:	Lingual gyrus
LPC:	Lateral parietal cortex
LV:	Latent variable
MFG:	Middle frontal gyrus
MINI:	Mini-International Neuropsychiatric Interview
MMSE:	Folstein Mini-Mental State Examination
MNI:	Montreal Neurological Institute coordinate system
MTL:	Medial temporal lobe
NART:	American National Adult Reading Test
PFC:	Prefrontal cortex

PHG:	Parahippocampal gyrus
PLS:	Partial least squares analysis
ROI:	Region of interest
RT:	Reaction time
SD:	Standard deviation
SE:	Easy spatial memory task
SFG:	Superior frontal gyrus
SH:	Hard spatial memory task
SPL:	Superior parietal lobule
SPM:	Statistical Parametric Mapping software
STG:	Superior temporal gyrus
SVD:	Singular value decomposition
TE:	Easy temporal memory task
TH:	Hard temporal memory task
VLPFC:	Ventrolateral prefrontal cortex

Abstract

Episodic memory encompasses an extraordinary range of diverse cognitive functions that are integral to daily functioning. Healthy aging is associated with declines in episodic memory, which may impair older adults' ability to remember the rich contextual details of previously experienced events. By the age of sixty, older individuals may have a reduced ability to remember spatial or temporal contextual features of past events (e.g., where or when you last took a prescription medication). Previous studies have focused on understanding the anatomical and functional neural correlates of episodic memory decline in young and older adulthood, but how these underlying mechanisms contribute to episodic memory to across the adult lifespan remains to be explored. In this series of studies, we aim to advance our understanding of the differences in episodic memory that develop across the adult lifespan and the neural basis of this age-related decline, as measured by functional magnetic resonance imaging (fMRI). Using a lifespan sample of young, middle-aged, and older adults, we employ a source memory paradigm to assess individuals' memory for the spatial and temporal contextual details of photographs of faces. In addition, we analyze fMRI data collected during both initial encoding and subsequent retrieval of contextual information in order to examine differential effects of age on encoding- and retrieval-specific processes.

In Study 1, we demonstrate that declines in source memory may be discernible by midlife, extend into older adulthood, and are associated with reduced modulation of phase-specific activity in anterior prefrontal (PFC) and posterior ventral visual areas. We also show that older adulthood may be associated with increased phase-specific modulation, particularly in areas of lateral PFC and medial temporal lobes (MTL) at retrieval. In Study 2, we extend these

findings to show how lifespan differences in phase-specific activity directly contribute to source memory performance. In particular, we find that older individuals engage dorsolateral PFC (DLPFC) to a greater extent at encoding and hippocampus (HC) to a greater extent at retrieval, during the phase when it does not seem to help performance across individuals. In Study 3, we address whether these age-related increases in encoding- or retrieval-specific activation might be related to differences in whole-brain connectivity. We examine whether age-related increases in DLPFC (Study 2 encoding) and posterior HC (Study 2 retrieval) differentially correlate with activity across the rest of the brain and with performance. In young adults, we demonstrate that connectivity between lateral PFC, parietal, and ventral visual cortical regions and our DLPFC seed relates to better performance. In older adults, these same regions show greater connectivity with posterior HC and relate to worse performance. Converging findings across studies suggests that activity and connectivity among fronto-parietal regions support the recollection of visual information and source memory performance in young adults, whereas aging may be associated with altered modulation of fronto-parietal activity and connectivity with posterior HC, which does not support source memory performance.

Résumé

La mémoire épisodique comprend une gamme extraordinaire de diverses fonctions cognitives qui sont essentielles au fonctionnement quotidien. Le vieillissement sain est associé avec des déclins de la mémoire épisodique qui peuvent affaiblir la capacité des adultes plus âgés de se rappeler toutes les facettes contextuelles des évènements vécus antérieurement. À

l'âge de soixante ans, les individus peuvent avoir une capacité réduite de se souvenir des particularités spatiales et temporelles des évènements passés (par ex. où ou quand on a pris sa dernière dose de médicament sur ordonnance). Des études précédentes ont visé la compréhension des corrélats neuronaux anatomiques et fonctionnels du déclin de la mémoire épisodique chez les jeunes adultes (18-35 ans) et les adultes plus âgés (60-80 ans), mais il reste à explorer comment ces mécanismes fondamentaux contribuent à la mémoire épisodique pendant la durée entière de la vie adulte (incluant la période de 35-60 ans). Dans cette série d'études, nous aspirons à avancer notre compréhension des différences qui se développent dans la mémoire épisodique pendant la durée de la vie adulte aussi bien qu'à approfondir notre connaissance de la base neurale de ce déclin lié à l'âge (tel que mesuré par l'imagerie par résonance magnétique fonctionnelle, ou IRMf). Utilisant un échantillon de jeunes adultes, d'adultes d'âge moyen et d'adultes âgés, nous employons un paradigme de mémoire source pour évaluer la mémoire des détails contextuels spatiaux et temporels des photographies de visages. De plus, nous analysons des données d'IRMf récoltées pendant l'encodage initial aussi bien que pendant la récupération ultérieure des informations contextuelles pour examiner les effets différentiels de l'âge sur les processus d'encodage et de récupération de mémoire.

Dans l'Étude 1, nous démontrons que le déclin de la mémoire source peut être discernable pendant l'âge moyen, s'étend dans l'âge adulte plus avancé et est associé avec une modulation réduite de l'activité qui est spécifique ou à l'encodage ou à la récupération de mémoire dans les régions préfrontale antérieure (CPF) et visuelle ventrale postérieure. Nous démontrons aussi que l'âge avancé peut être associé avec une augmentation de modulation lors de la récupération, particulièrement dans la région CPF latérale et les lobes temporaux

médians (LTM). Dans l'Étude 2, nous approfondissons ces résultats pour démontrer comment les différences d'âge durant l'encodage et la récupération contribuent directement à la performance de la mémoire source. En particulier, nous trouvons que les individus plus âgés engagent le CPF dorsolatéral (CPFDL) plus pendant l'encodage et l'hippocampe (HC) plus pendant la récupération, durant la phase où l'activité dans ces régions ne semble pas aider la performance à travers les individus en général. Dans l'Étude 3, nous considérons si cette augmentation de l'activité spécifique à l'encodage et à la récupération, qui est liée à l'âge, pourrait être reliée aux différences dans la connectivité du cerveau. Nous examinons si les hausses de l'activité du CPFDL (Étude 2 encodage) et du HC postérieur (Étude 2 récupération) sont associées avec des changements dans la connectivité de ces régions avec le reste du cerveau et avec la performance dans la tâche de mémoire. Nous démontrons que la connectivité entre le CPF latéral, les régions corticales visuelles ventrales et pariétales et notre région du CPFDL est liée à une meilleure performance chez les jeunes adultes. Chez les adultes plus âgés, ces mêmes régions ont une connectivité plus élevée avec notre région du HC postérieur et sont liées à une performance inférieure. À travers nos études, les résultats suggèrent que l'activité et la connectivité parmi les régions fronto-pariétales soutiennent la récupération de l'information visuelle et une meilleure performance de la tâche de mémoire source chez les jeunes adultes, alors que le vieillissement peut être associé avec une modulation altérée de l'activité et la connectivité fronto-pariétale avec le HC postérieur, ce qui ne soutient pas la performance de la mémoire source.

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Preface and Contribution of Authors

The elements of this thesis listed below constitute distinct and original contributions of knowledge in the domain of the cognitive neuroscience of aging and episodic memory.

Ankudowich, E., Pasvanis, S., & Rajah, M. N. (2016). Changes in the modulation of brain activity during context encoding vs. context retrieval across the adult lifespan. *NeuroImage, 139,* 103–113.

Dr. Natasha Rajah designed and funded this initial lifespan study. Although the study was already underway when I joined the lab in 2013, I aided Stamatoula Pasvanis in the collection of data. Stamatoula Pasvanis and I shared responsibility of preprocessing and management of neuroimaging data. I had the idea for the analytical approach used in the study and carried out data analysis, under Dr. Rajah's oversight. I had primary responsibility of writing the initial manuscript, and Dr. Rajah and I both contributed to subsequent revisions.

Ankudowich, E., Pasvanis, S., & Rajah, M. N. (2017). Changes in the correlation between spatial and temporal source memory performance and BOLD activity across the adult lifespan. Cortex, 91, 234–249.

This study was a follow-up to our initial lifespan study published in 2016 in the journal *NeuroImage*. Additional data collection was performed by Stamatoula Pasvanis. Stamatoula Pasvanis and I shared responsibility of re-preprocessing the neuroimaging data used in this follow-up paper. I spearheaded data analysis and writing of the initial manuscript, under Dr. Rajah's mentorship. Dr. Rajah and I both contributed to manuscript revisions.

Ankudowich, E., Pasvanis, S., & Rajah, M. N. (submitted). Differential prefrontal-hippocampal connectivity in young vs. older adults impacts spatial memory performance.

This study was a follow-up to our previous lifespan study published in 2017 in a special issue of the journal *Cortex* on source memory. Additional data collection was performed by Stamatoula Pasvanis, and I performed the additional preprocessing of the neuroimaging data. I spearheaded data analysis and writing of the manuscript. Dr. Rajah supported the manuscript in an editorial capacity.

Chapter 1. Introduction

Memory encompasses an extraordinary range of diverse cognitive functions. It can involve remembering previously experienced events and learned concepts, acquiring and performing specific skills, or developing emotional associations with the people, places, or things we encounter. Endeavoring to understand the complex and multifaceted nature of memory, researchers over the past century have attempted to delineate more well-defined concepts of memory that could be operationalized for systematic study. As a result, progress has been made in characterizing observable distinctions between different types of mnemonic phenomena. In 1972, Tulving proposed that memory should be divided into two qualitatively different types: memories that feel autobiographical (e.g., the first time I saw the Mona Lisa) and memories that do not (e.g., knowing that DaVinci painted the Mona Lisa). He called these two types of memory episodic and sematic memory, respectively. In devising the term episodic memory, Tulving said:

> It seems to fit well for our purposes. The term "episode" is a somewhat loose synonym of "occurrence," and one of its dictionary definitions is that of "an event that is distinctive and separate although part of a larger series." Episodic memory is about occurrence of such events (Tulving, 1972, p. 385).

In describing two separable "episodic" and "semantic" information processing systems, Tulving aimed to distinguish the ability to remember past occurrences (episodic memory) from the ability to remember facts, knowledge, language, and logical/problem-solving rules (semantic memory).

Although episodic and semantic memory systems may overlap to some extent (see Squire, 1987, for a discussion), one potential distinction between episodic and semantic

memory is that, while aspects of semantic memory remain relatively stable across the adult lifespan, episodic memory is especially susceptible to age-related decline (Craik, 2000). More specifically, as individuals age, it becomes disproportionately harder to recollect the contextual details or features of previously experienced events (i.e., source memory) compared to the events themselves (i.e., item recognition or item memory; Johnson, Hashtroudi, & Lindsay, 1993; Old & Naveh-Benjamin, 2008; Spencer & Raz, 1995). For example, by the age of sixty, older adults may show reduced ability to remember the relative temporal order (e.g., which medication you took first) and spatial location (e.g., where you placed your keys) of events compared to young adults (e.g., Rajah, Languay, & Valiquette, 2010).

Accurate source memory relies on the ability to relate contextual details together during an initial event (encoding phase) and to correctly recollect those details when remembering that event (retrieval phase). Cognitive-behavioral evidence has shown that, relative to young adults, older adults may have deficits in relating relevant contextual features of events together to form initial representations during encoding (e.g., Chalfonte & Johnson, 1996), as well as a reduced ability to selectively recollect specific contextual features of events during retrieval (e.g., Henkel, Johnson, & De Leonardis, 1998). Both source encoding and retrieval are complex operations, which are contingent on the successful interplay of numerous fundamental cognitive processes (i.e., component processes). To illustrate, for a typical source memory paradigm, the processes required during encoding and/or retrieval to make a successful memory judgement might entail: strategically maintaining current task goals/agendas, directing attention to task-relevant information while ignoring distraction, evaluating and organizing

relevant information, relating important associative information in a single "bound" representation, and/or selecting a response consistent with task objectives.

Over the past few decades, the use of functional magnetic resonance imaging (fMRI) has afforded unique insight into the brain regions that support the component processes of source memory, due the ability of this technique to capture event-related, task-specific blood-oxygen level-dependent (BOLD) activation in the brain with a fair degree of spatial specificity. Although there is still much to be learned in the domain of neurocognitive aging and source memory, much work has already been done to elucidate the brain regions associated with successful encoding and retrieval of source information, as measured by fMRI.

1.1. Functional contributions of brain regions to source memory

Broadly-speaking, both encoding and retrieval of source information are fundamentally dependent on 1) the ability to perceive (e.g., take-in, identify) information from the external environment and 2) the ability to reflectively process (e.g., revive, evaluate, organize) internal representations of information in the absence of external stimuli. These operations are guided by strategic processes that serve to direct attention to important information in order to fulfill current tasks or objectives in a flexible manner (i.e., control processes). More specifically, lateral prefrontal (PFC) cortex is thought to be involved in supporting the adoption and application of task-relevant cognitive strategies that direct attention to perceptual events (e.g., at encoding) and mnemonic/reflective events (e.g., at retrieval). For this reason, these frontally-mediated processes have been collectively referred to as top-down cognitive control processes (e.g., Uncapher, Hutchinson, & Wagner, 2011; Zanto, Rubens, Thangavel, & Gazzaley, 2011).

However, there is evidence that subregions of PFC may mediate specific types of strategies and attention involved in source memory (see Chun & Johnson, 2011, Mitchell & Johnson, 2009, Rajah & D'Esposito, 2005, for reviews).

PFC-mediated control operations serve to maintain current goal-relevant agendas, to refresh and rehearse highly relevant information, to direct our attention, and to inhibit distraction. Together, these processes collectively facilitate the ability to foreground important task-relevant information necessary for the creation and recollection of internal mental representations. PFC control regions are thought to work in conjunction with posterior cortical sensory regions to support source memory. Specifically, successful source memory depends on the type of perceptual features that are encoded and how well those features are bound into initial representations. Thus, successful source memory relies, in part, on perceptual processing in category-specific areas of posterior sensory cortices. The ability of individuals to associate and "bind" this perceptual information into a single, rich contextualized event is generally thought to rely on hippocampal-dependent long-term memory formation (M. K. Johnson, Raye, Mitchell, & Ankudowich, 2012). Medial temporal lobe (MTL) structures, especially the hippocampus (HC), are important for binding features of events together into long-term memories, as evidenced, in part, by the profound anterograde amnesia that results from bilateral hippocampal damage (e.g., as in the case of Henry Molaison; Scoville & Milner, 1957). Evidence suggests that frontal control mechanisms may contribute to successful long-term remembering through PFC-MTL connections (Goldman-Rakic, Selemon, & Schwartz, 1984; Simons & Spiers, 2003). More specifically, areas of lateral PFC seem to modulate MTL activity and affect what type of information will (and will not) be subsequently remembered (Anderson

& Huddleston, 2012; Ranganath, Cohen, & Brozinsky, 2005; Ranganath & D'Esposito, 2001). When prefrontal neural mechanisms are disrupted, as in the case of schizophrenia, long-term memory deficits may arise (Lepage et al., 2006).

Current models of cognition propose that top-down signals originating in PFC may help to direct attention to task-relevant information in conjunction with lateral parietal cortical (LPC) areas. During perception, PFC-LPC dorsal processing streams may facilitate goal-directed top-down stimulus and response selection, whereas more ventral processing streams facilitate bottom-up processing of behaviorally relevant stimuli (Corbetta & Shulman, 2002). A parallel dorsal/ventral framework has been proposed for memory-related processing (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Ciaramelli, Grady, & Moscovitch, 2008). Fronto-parietal control mechanisms may be involved in reflectively attending to internal mnemonic representations and monitoring information that is active during remembering, in a manner consistent with top-down goals or agendas. However, more inferior areas of LPC may be involved in the bottom-up capture of attention by salient perceptual events. There is evidence that activity in inferior LPC may support recollection by contributing to the phenomenological experience or remembering (Wagner, Shannon, Kahn, & Buckner, 2005). Moreover, recent evidence suggests that some areas of lateral inferior parietal cortex (namely, angular gyrus) may represent recollected information across different modalities (i.e., by instantiating content-specific mnemonic representations) and that activity in this region might track individuals' vividness ratings of recalled visual images (Kuhl & Chun, 2014). Thus, LPC may support source memory by attending to and/or monitoring mnemonic representations, by helping to integrate perceptual details that are active during remembering (e.g., similar to

Baddeley's buffer; Baddeley, 2000), and/or by signaling recollection success (Cabeza et al., 2008; Chun & Johnson, 2011; Wagner et al., 2005). In this way, LPC, along with MTL, may support the episodic quality of remembered information.

In summary, memory-related operations in PFC, MTL, LPC, and posterior perceptual cortices are fundamental to providing seamless continuity between our recollective experiences and our present goals and actions. Source memory is therefore contingent on the ability to maintain and implement cognitive agendas, to selectively process relevant perceptual and reflective information and ignore distractions, and to relate and represent associative information. Disruptions of these processes during either encoding or retrieval may result in diminished memory for source information.

1.2. Age-related functional differences associated with source memory

Previous aging studies assessing source memory have found age-group differences in regions engaged during both encoding (e.g., Dennis et al., 2008; Mitchell, Johnson, Raye, & D'Esposito, 2000) and remembering (e.g., McDonough, Wong, & Gallo, 2013; Mitchell, Ankudowich, Durbin, Greene, & Johnson, 2013) source information. Across studies, age-group differences have been found in subregions of PFC, MTL, LPC and posterior visual cortices involved in source memory.

1.2.1. Age-related differences during source encoding

In their initial fMRI study, Mitchell et al. (2000) tested young and older adults' memory for object-location associations using a short-term memory paradigm and found a larger age-

related deficit in memory for specific object-location pairings compared to memory for objects or locations alone, consistent with previous behavioral evidence of greater age-related decline in source versus item memory (Chalfonte & Johnson, 1996; M. K. Johnson et al., 1993; Old & Naveh-Benjamin, 2008; Spencer & Raz, 1995). Compared to young adults, older adults in the study showed reduced activation in an area of anterior HC during the short-term delay for the object-location condition relative to the item or location condition alone. This attenuated hippocampal activity during the encoding delay and decreased performance for the object-location condition with age provided the initial evidence that a deficit in the ability to bind contextual features at encoding might be partially responsible for age-related declines in source memory.

A more recent fMRI study on age-related deficits in contextual binding investigated differences in activation in young versus older adults during successful encoding of face-scene associations (Dennis, Hayes, et al., 2008). In addition to finding age-related attenuation in hippocampal activity for the face-scene condition versus the face or scene condition, posterior visual areas related to specialized processing of faces and scenes (fusiform and parahippocampal gyri, respectively) also showed decreases in activation in older adults relative to young adults across conditions. These findings are consistent with the idea that age-related differences in perceptual processing may contribute to an episodic encoding deficit in older adulthood. More specifically, Park and colleagues have reported considerable evidence that the distinctiveness of domain-specific activation in the regions that support visual representations may deteriorate with age (i.e., dedifferentiation; Park et al., 2004; Park, Polk, Mikels, Taylor, & Marshuetz, 2001; Payer et al., 2006).

Furthermore, there is evidence that age-related deficits in PFC-mediated control processes may also contribute to poorer encoding of visual information. Older adults exhibit structural and functional changes to lateral PFC regions that may interfere with source memory encoding and relate to decreased memory performance (Glisky, Rubin, & Davidson, 2001; Mitchell & Johnson, 2009; Rajah & D'Esposito, 2005). Older adults may be more susceptible to task-unrelated and/or distracting information across a variety of contexts (Hasher & Zacks, 1988), impeding their ability to effectively encode important perceptual features (Campbell, Grady, Ng, & Hasher, 2012; Gazzaley, Cooney, Rissman, & D'Esposito, 2005). More specifically, older adults show disruptions in the ability to suppress irrelevant visual information when reflectively attending to (i.e., refreshing) just-seen representations, but not necessarily when information is perceptually present (Mitchell, Johnson, Higgins, & Johnson, 2010). Findings from these studies suggest that age-related decreases in top-down, goal-oriented modulation of posterior visual areas may be attributable, at least in part, to an inability to selectively suppress irrelevant information, making it more likely that irrelevant information stays active during encoding (Gazzaley & D'Esposito, 2007; Hasher, Lustig, & Zacks, 2007).

1.2.2. Age-related differences during source retrieval

Accurate recollection of source information depends not only how well specific perceptual features are encoded and bound into initial representations, it also relies on how well features are revived and used during retrieval. The ability to flexibly retrieve, weight, and/or evaluate specific source information (i.e., source monitoring) according to a set of situationally-relevant criteria (e.g., current situational context, agendas, or goals) can affect

what information is sought and/or how it is used during a memory judgement (M. K. Johnson et al., 1993; Mitchell & Johnson, 2009). Moreover, the same encoded information may give rise to suboptimal performance outcomes depending on what strategies or agendas are engaged during a task (Levine et al., 1998; McDuff, Frankel, & Norman, 2009). Thus, accurate source memory also relies on the ability to adopt and employ appropriate top-down agendas/strategies (Shimamura, 2002) and make efficient use of retrieval cues, which may be disrupted in older adulthood (Gazzaley, 2013). More specifically, older adults may be less able to constrain the focus of their attentional search to target information and ignore task-irrelevant information during retrieval (Jacoby, Bishara, Hessels, & Toth, 2005). Furthermore, they may be less likely to selectively evaluate the most appropriate subset of information once it has been activated in memory, in a manner most consistent with task goals and agendas (Raye, Mitchell, Reeder, Greene, & Johnson, 2008). Age-related differences in the ability to reflectively monitor retrieved information may be associated with functional differences in areas of lateral PFC and parietal cortices involved in memory monitoring (Daselaar, Fleck, Dobbins, Madden, & Cabeza, 2006; McDonough et al., 2013; Morcom, Li, & Rugg, 2007). A recent study that looked at whole-brain differences in young and older adults at retrieval using two different source memory tasks reported prefrontal areas as well as posterior temporal and parietal areas that showed differential task-related activity between groups (Mitchell et al., 2013). Interestingly, targeted correlational analyses between prefrontal and posterior regions revealed more reciprocal activity between representational areas for the two source tasks and greater connectivity between prefrontal and parietal areas in young versus older adults. That is, young adults showed more differential modulation of interregional connections associated with

retrieval of specific source information as a function of the type of task at test. Findings across studies suggest that older adults may not effectively monitor/evaluate information that is activated during retrieval due to deficits in the ability to selectively engage reflective attention (Gazzaley, 2013; Mitchell et al., 2013) and/or efficient retrieval strategies (Rajah, Languay, et al., 2010).

1.3. Functional significance of age-related differences in activation associated with source memory

Previous studies of episodic memory have provided mixed findings on the role of age-related differences in functional activation. Age-related functional differences associated with source memory are often characterized by reduced activation in older adults relative to young adults (e.g., McDonough et al., 2013). However, age-related reductions in regional activation may often be accompanied by increased activity elsewhere in the brain (e.g., Cabeza, Anderson, Locantore, & McIntosh, 2002). While there is general agreement that under recruitment of areas related to source memory in older versus young adults represents a functional deficit with age, there is considerably more debate about the significance of over recruited areas in older versus young adults (Maillet & Rajah, 2013, 2014; Rajah & D'Esposito, 2005). Functional over recruitment with age is sometimes attributed to dedifferentiation, a loss of neural specificity characterized by patterns of task-related activity that are more diffuse and less selective with age (Li & Lindenberger, 1999; D. C. Park et al., 2001, 2004; Payer et al., 2006). Other times, over recruitment with age may be interpreted as activation that serves to compensate for functional deficits elsewhere in the brain in order to aid cognitive performance

(Cabeza, 2002; Reuter-Lorenz, 2002). Whether or not the recruitment of additional regions with age during source memory tasks is thought to be due more to compensation or dedifferentiation often depends on how activation in these regions relates to memory performance (Grady, 2008, 2012; but see Rajah & D'Esposito, 2005, for a discussion of how dedifferentiation can also be compensatory). More specifically, additional activation that is associated with improved source memory performance in older adults relative to young adults has often been interpreted as compensatory (Cabeza, 2002; Cabeza et al., 2002; Reuter-Lorenz, 2002). Across source memory studies, age-related increases or decreases in activation in subregions of PFC, LPC, MTL, and posterior cortex may depend on the types of memory tasks used and the specific source features tested (Grady, 2008, 2012; Mitchell & Johnson, 2009). However, further study of age-related functional change in source memory networks using tasks that test for different types of contextual features will help elucidate how under and over recruitment of network regions with age contribute to performance.

1.4. Age-related functional differences in connectivity associated with source memory

In addition to investigating regional under and over recruitment in older versus young adults related to source memory, recent focus of aging neuroimaging studies has been on understanding age differences in the network connectivity underlying source memory (i.e., correlations in inter-regional coactivation during a task). Specifically, studies have aimed to identify age-related changes in the functional connections between regions supporting source memory at both encoding (Dennis, Hayes, et al., 2008; Maillet & Rajah, 2011) and retrieval (Mitchell et al., 2013) and have found differential correlations of functional activity between

frontal and posterior regions, including areas of parietal and temporal cortices, related to source memory in older compared to young adults. For example, Dennis and colleagues (2008) investigated age-group differences in functional connectivity of cortical regions with the HC during encoding and found greater hippocampal connections with posterior regions in young adults, and greater hippocampal connections with prefrontal regions in older adults. This pattern of increased PFC-HC connectivity was present in older adulthood, despite age-related decreases in regional activation of HC and PFC regions observed in older versus young adults. Connectivity findings from this study, in addition to those discussed briefly in earlier sections (i.e., Mitchell et al., 2013) illustrate that both regional activity and network connectivity must be considered to understand age-related source memory decline.

1.5. Overview and Rationale

Age-related episodic memory decline with age is a prevailing concern among more senior members in our society. In order to devise strategies aimed at maintaining healthy episodic memory function in advancing age, we must understand the brain changes associated with episodic memory decline and determine when these changes emerge. Identifying the earliest stages of brain change that underlie source memory decline would ideally require a longitudinal neuroimaging study of source memory across the adult lifespan from young to older adulthood. However, such a study would be beset by challenges due to limitations in long-term resources and subject attrition. A more pragmatic alternative is to conduct an fMRI study of source memory across the adult lifespan in cross sections of young, middle-aged, and older adults. Such a lifespan approach could elucidate differential patterns of brain function

that are detrimental to memory performance versus those that serve to maintain successful memory with age. Hence, the overarching objective of this series of studies is to investigate what age-related differences in whole-brain function contribute to source memory across the adult lifespan and whether some age-related differences in brain function might serve a compensatory role in the aging brain.

Study 1. Previous fMRI studies have primarily included cross sections of young, middle-aged and older adults to assess age-group differences related to source memory. However, splitting a continuous variable, such as age, into categorical groups inevitably results in a loss of information and may be more susceptible to errors of omission (Streiner, 2002). Examining how activation in the brain regions that underlie source memory change linearly with age may provide a more sensitive assessment of age-related differences across the adult lifespan. The primary aim of Study 1 was to identify whole-brain functional activation, as measured by fMRI, that correlated with age across the adult lifespan. In addition, many previous aging fMRI studies of source memory have assessed encoding and retrieval effects separately. While useful, there is little research to show how age-related differences in functional activation at encoding impact differences during retrieval. A secondary aim of Study 1 was to identify interactions of age with source memory encoding and retrieval functional activation across the adult lifespan (i.e., age × phase interactions). One potential caveat of aging fMRI studies is that age-related differences in functional activation may be potentially attributable to non-cognitive factors, such as overall changes in cerebral blood volume, cerebral blood flow, and/or baseline metabolic state, which can affect the BOLD response (D'Esposito, Deouell, & Gazzaley, 2003). As we did not account for these non-cognitive factors in our acquisition and analysis of these

lifespan data, we limited our interpretations to interactions of age with task-related activity (e.g., differential effects of age at encoding *relative* to retrieval). We did this in order to avoid interpretations of general effects of age on fMRI activity, which could be influenced by altered cerebrovascular dynamics across the lifespan.

Study 2. In aging studies it is often assumed that age-group differences in activation related to a task reflect changes with age, and subsequent brain-behavior correlations may be conducted in order to understand how these age-group differences in activation relate to task performance. However, this two-step approach does not directly assess age-related functional differences that support performance. Rather, identifying patterns of activation that positively or negatively correlate with age across the adult lifespan may offer more direct evidence of how functional differences with age help or hinder performance. The primary aim of Study 2 was to identify differences in whole-brain functional activation during encoding and retrieval that directly contributed to source memory accuracy across the adult lifespan.

Study 3. Previous strategies used in human neuroimaging to investigate the neural correlates of source memory have concentrated on identifying reliable areas of task-dependent activity associated with specialized memory operations. However, we do not yet understand how functional interactions between these regions support successful source memory and differ across the lifespan from young adulthood to midlife and older age. Recent developments in analytical approaches assessing interactive network-level communication between brain regions suggest that distributed functional interactions underlie a diverse range of cognitive operations that affect source memory (Mišić & Sporns, 2016). By examining how network-level functional connectivity contributes to source memory across the adult lifespan, we can

elucidate patterns of connectivity that are directly detrimental to memory performance versus those that support source memory with age. Thus, the primary aim of Study 3 was to identify how patterns of task-related functional connectivity directly relate to source memory accuracy across the adult lifespan.

Chapter 2. Study 1: Changes in the modulation of brain activity during context encoding vs. context retrieval across the adult lifespan

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2.1. Abstract

Age-related deficits in source memory may arise from neural changes underlying both encoding and retrieval of contextual information. Although age-related functional changes in the brain regions supporting source memory begin at midlife, little is known about the functional changes with age that support source memory encoding and retrieval across the adult lifespan. We investigated how age-related functional changes support source memory across the adult lifespan by assessing linear changes with age during successful source encoding and retrieval. Using fMRI, we compared young, middle-aged, and older adults during both encoding and retrieval of spatial and temporal details of faces. Multivariate behavioral partial least squares (B-PLS) analysis of fMRI data identified a pattern of whole-brain activity that correlated with a linear age term and a pattern of whole-brain activity that was associated with an age × memory phase (encoding versus retrieval) interaction. Further investigation of this

latter effect identified three main findings: 1) reduced phase-related modulation in bilateral fusiform gyrus (FFG), left superior/anterior frontal gyrus and right inferior frontal gyrus (IFG) that started at midlife and continued to older age, 2) reduced phase-related modulation in bilateral inferior parietal lobule (IPL) that occurred only in older age, and 3) changes in phase-related modulation in older but not young adults in left middle frontal gyrus (MFG) and bilateral parahippocampal gyrus (PHG) indicative of age-related over-recruitment. We conclude that age-related reductions in source memory arise in midlife and are related to changes in perceptual recollection and changes in fronto-parietal retrieval monitoring.

2.2. Introduction

Healthy, age-related change in episodic memory is characterized by larger deficits in memory for the contextual features of items or events (source memory) relative to memory for the items or events themselves (item memory; Spencer & Raz, 1995). Correct retrieval of specific source information relies on processes that relate contextual features together at encoding and retrieval (Mitchell & Johnson, 2009). Cognitive-behavioral evidence has shown that, relative to young adults (generally 18–35 yrs), older adults (generally 60+ yrs) have deficits in binding together contextual features of events at encoding and/or in recollecting specific contextual features of events at retrieval (Chalfonte & Johnson, 1996; M. K. Johnson et al., 1993; Mitchell, Johnson, Raye, Mather, & D'Esposito, 2000; Old & Naveh-Benjamin, 2008; Spencer & Raz, 1995). Thus, age-related declines in source memory may be associated with neural changes underlying both encoding (e.g., Dennis et al., 2008; Mitchell, Johnson, Raye, &

D'Esposito, 2000) and retrieval (e.g., McDonough et al., 2013; Mitchell et al., 2013) of source information.

Functional neuroimaging studies of episodic memory in young adults have identified a core network of brain regions important for successful episodic memory encoding and retrieval (Cabeza & Nyberg, 2000; Lepage, Ghaffar, Nyberg, & Tulving, 2000; Mitchell & Johnson, 2009; Nyberg, Cabeza, & Tulving, 1996; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). Studies comparing source memory tasks (i.e., left/right spatial source decisions and recency/temporal source decisions) to item memory tasks (i.e., old-new recognition) have found that young adults generally perform worse on source versus item memory tasks (e.g., Ekstrom & Bookheimer, 2007). Subsequent memory analysis of fMRI data indicates that there is increased activity in brain regions related to stimulus perception (i.e., ventral occipito-temporal cortices for visual stimuli), left ventrolateral prefrontal cortex (VLPFC), HC, and other MTL regions during successful source encoding, compared to item encoding (Awipi & Davachi, 2008; Cansino, Maquet, Dolan, & Rugg, 2002; Fan, Snodgrass, & Bilder, 2003; Maillet & Rajah, 2014; Rugg et al., 2012; Uncapher, Otten, & Rugg, 2006). On the other hand, successful retrieval of contextual details has been related to increased activity in the core recollection network, compared to item recognition, which includes the HC, PHG, secondary sensory processing regions (i.e., middle/superior temporal cortex for visual stimuli), inferior and superior parietal cortices, precuneus and medial prefrontal cortex (Dulas & Duarte, 2012; J. D. Johnson, McDuff, Rugg, & Norman, 2009; Leshikar, Dulas, & Duarte, 2015; Newsome, Dulas, & Duarte, 2012; Rajah, Languay, et al., 2010; Rugg et al., 2012). In addition, several studies have reported increased bilateral dorsolateral prefrontal cortex (DLPFC) activity during source versus item retrieval,

which is thought to reflect greater involvement of post-retrieval strategic processing (Morcom & Rugg, 2012; Rajah, Ames, & D'Esposito, 2008; Rajah, Languay, et al., 2010; Spaniol et al., 2009). Thus, in young adults, successful source memory places greater demands than item memory tasks on brain regions related to recollection-based episodic memory and cognitive control.

Functional neuroimaging studies comparing the neural correlates of source memory in young versus older adults have reported age-group differences in source encoding activity (e.g., Dennis, Hayes, et al., 2008; Dulas & Duarte, 2011) and source retrieval activity (e.g., Dulas & Duarte, 2012; McDonough, Cervantes, Gray, & Gallo, 2014; McDonough et al., 2013; Mitchell et al., 2013) in medial and lateral PFC, MTL, LPC, and posterior occipito-temporal cortices. More recently, studies have shown that source memory decline arises as early as midlife (Cansino, 2009; Kwon et al., 2016). For example, in a previous study, we used event-related fMRI to investigate similarities and differences in the neural correlates of source encoding and retrieval in young and middle-aged adults. We observed marked differences in both ventral occipito-temporal and PFC activity, primarily at retrieval, in middle-aged adults relative to young adults. This finding suggests that episodic memory decline, as measured by source memory, arises at midlife and continues into older age. However, to better our understanding of the functional brain changes underlying age-related episodic memory decline, it is necessary to examine the trajectory of functional brain changes during episodic memory task performance across the adult lifespan. A longitudinal study would be the best way to examine this issue. However, due to cost and feasibility, studies to date have used cross-sectional designs to examine the neural correlates of episodic memory in young, middle-aged, and older adults (Cansino, Estrada-

Manilla, et al., 2015; Cansino, Trejo-Morales, et al., 2015; Filippini et al., 2011; Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Kennedy et al., 2012; H. Park, Kennedy, Rodrigue, Hebrank, & Park, 2013). Several of these studies have used item memory paradigms to examine age-related changes in brain function and episodic memory (Grady et al., 2006; Kennedy et al., 2012; H. Park et al., 2013), despite evidence that item memory remains relatively intact until later life. As such, these studies may not have been sensitive at detecting functional changes associated with episodic memory decline in adulthood (Cansino, 2009; Rajah, Languay, et al., 2010; Rajah & McIntosh, 2008). Recently, Cansino and colleagues conducted electroencephalography (EEG) and fMRI studies of source memory across the lifespan to examine changes at encoding (Cansino, Estrada-Manilla, et al., 2015; Cansino, Trejo-Morales, & Hernández-Ramos, 2010) and at retrieval (Cansino, Hernández-Ramos, & Trejo-Morales, 2012; Cansino, Trejo-Morales, et al., 2015). In their more recent fMRI studies, they reported greater activation in PFC in young versus older adults during encoding, and greater right occipital cortex activity in older versus young adults during retrieval (Cansino, Estrada-Manilla, et al., 2015; Cansino, Trejo-Morales, et al., 2015). This is interesting, given that others have reported decreased occipital cortex activation with age and increased PFC activity with age during successful item encoding and retrieval (Grady et al., 2006; Kennedy et al., 2012; H. Park et al., 2013). These between-study differences may be due to the use of different memory tasks and/or different analysis methods. For example, Cansino and colleagues identified group differences in brain activity during successful versus unsuccessful source encoding/retrieval by conducting within-group young, middle-aged, and older adult analyses followed by subsequent between-group comparisons in regions identified per group. In contrast, other studies have

used subjects' age as a continuous variable to examine linear increases and decreases in brain activity across the lifespan during successful memory encoding (Kennedy et al., 2012; Liu et al., 2013; H. Park et al., 2013), or during encoding plus retrieval (Grady et al., 2006). To help clarify among the alternative possibilities, it would be important to conduct a study examining source encoding and retrieval across the adult lifespan by examining both continuous linear changes in brain function with age and post-hoc comparisons of age groups. This is one goal of the current study. An additional goal of the current study is to examine brain activity related to successful source encoding and retrieval, in the same fMRI session, across the adult lifespan. To our knowledge, no study to date has done this.

Therefore, in the current study, young, middle-aged, and older adults will undergo fMRI scanning while encoding and retrieving spatial and temporal contextual features from episodic memory. Multivariate partial least squares (PLS) will be used to investigate similarities and differences in whole-brain patterns of activity during successful source encoding and retrieval across the adult lifespan. This analysis will help identify linear age-related changes in brain function related to source memory decline with age. In addition, we will conduct post-hoc comparisons of encoding- and/or retrieval-related activity in peak activation foci identified by the PLS analysis to determine if there are any non-linear effects in brain activity, and if activity in middle-aged adults differed from young adults and/or older adults. Using this cross-sectional lifespan approach, we aim to identify linear and non-linear patterns of functional brain change with age at encoding and retrieval and to determine how age-related changes in brain activity at encoding relate to changes observed at retrieval.

2.3. Methods

2.3.1. Participants

One hundred and twelve right-handed adults between the ages of 19-76 yrs (mean age = 46.61 yrs; 75 females; mean years of formal education [EDU] = 15.75 yrs) with no history of neurological or psychological illness or family history of Alzheimer's disease were recruited for the study. Having no family history of Alzheimer's disease was defined as the absence of any blood relatives with probable Alzheimer's disease type dementia (Hayden et al., 2009). Of the 112 participants tested, 41 were young adults (age range 19-35 yrs, mean age = 26.20 yrs, 26 females, mean EDU = 16.10 yrs), 32 were middle-aged adults (age range 40-58 yrs, mean age = 48.50 yrs, 24 females, mean EDU = 15.47 yrs), and 39 were older adults (age range 60–76 yrs, mean age = 66.51 yrs, 25 females, mean EDU = 15.62 yrs). Handedness was confirmed using the Edinburgh Inventory for Handedness, and age groups did not differ in level of education.

Participation involved two separate test sessions, conducted on different days. During the first session, participants completed a neuropsychological assessment (i.e., the Mini-International Neuropsychiatric Interview [MINI], inclusion cutoff ≤ 2; the Folstein Mini-Mental State Examination [MMSE], exclusion cutoff < 27; the Beck Depression Inventory [BDI], exclusion cutoff < 15; the California Verbal Learning Test [CVLT], exclusion cutoff based on recommendations by Norman at al. (2000), correct delayed free recall, cued recall and recognition > 12/16 for young, 11/16 for middle-aged, and 9/16 for older adults; the American National Adult Reading Test [NART], inclusion cut-off ≤ 2.5 SD), and completed a practice session of the source memory tasks in a mock MRI scanner. One-way ANOVAs with post-hoc comparisons of young, middle-aged, and older age groups were conducted on MMSE, BDI,

CVLT, and EDU to ascertain if there were any significant differences between age groups on these measures. Additional medical exclusion criteria included having a history of diabetes, having untreated cataracts and glaucoma, smoking > 40 cigarettes a day, and having a current diagnosis of high cholesterol levels and/or high blood pressure left untreated in the prior six months. All participants were paid. Informed consent was obtained from all participants, and protocol was approved by ethics board at the Faculty of Medicine, McGill University.

2.3.2. Behavioral methods

Only participants who met our neuropsychological inclusion/exclusion criteria and who were able to perform above chance on the practice versions of the source memory tasks in the mock scanner were invited to participate in the second, fMRI scanning session. Details about the methods and stimuli are presented in Kwon et al. (2016). In brief, a mixed rapid event-related fMRI design was employed. Participants were scanned during 12 experimental runs, during both encoding and retrieval phases. During each run, participants were scanned as they encoded and retrieved either the spatial (whether a face had appeared on the left or the right at encoding) or temporal (whether a face had appeared least or most recently at encoding) details of faces. Participants performed both easy (six faces viewed at encoding) and hard (twelve faces viewed at encoding) versions of each task in order to dissociate age-related effects from performance effects. Within each run, participants performed the following memory tasks: easy spatial memory task (SE), easy temporal memory task (TE) and either a hard spatial memory task (SH) or a hard temporal memory task (TH), depending on the run.

Across all 12 runs, each participant performed 6 SH tasks, 6 TH tasks, 12 SE tasks, and 12 TE tasks. The order of the 12 experimental runs was counterbalanced across participants.
The task stimulus set was used previously by Rajah et al. (2008) and Rajah et al. (2010) and consisted of black-and-white photographs of faces of different ages, cropped at the neck and rated for pleasantness by two independent raters. Across experimental conditions, faces were not repeated, and stimuli were balanced for age and sex. Each face presented at encoding was subsequently tested at retrieval (see also **Figure 3.1** in Chapter 3 of this thesis for a task depiction).

2.3.3. Encoding phase

At the start of each encoding phase, participants were cued (9s) to memorize either the spatial location or the temporal order of the faces. Six (easy) or 12 (hard) faces were then presented serially either to the left or the right of a centrally presented fixation cross. Each stimulus was presented for 2s followed by a variable inter-trial interval (ITI) of 2.2–8.8s. During encoding, participants were required to rate each face as either pleasant or neutral. In total, there were 72 encoding events presented per task type. Between encoding and retrieval phases, subjects performed a word alphabetization distractor task (60s) to inhibit rehearsal of encoded information.

2.3.4. Retrieval phase

After the distractor task, participants were cued to what the upcoming retrieval task would be: spatial or temporal. During spatial memory tasks, participants were presented with

two previously encoded faces and were asked to indicate which of the faces was originally presented on the left/right of the monitor at encoding. During temporal memory tasks, participants were presented with two previously encoded faces and were asked to indicate which of the faces was originally seen most/least recently. During easy tasks, there were three retrieval pairs presented serially, and during hard tasks, there were six pairs. Each retrieval pair was presented for 6s followed by a variable ITI (2.2–8.8s). In total there were 36 retrieval events per task type.

2.3.5. Behavioral data analysis

Age group (3: young, middle-aged, older adults) × task (2: temporal, spatial) × difficulty (2: easy, hard) repeated-measures ANOVAs were conducted using SPSS (version 17.0) to determine if there were significant group, task, and difficulty main effects and interactions in retrieval accuracy (% correct) or reaction time (ms; significance threshold $p < 0.05$). Tukey's b post-hoc tests were conducted on the independent variable of age group, and post-hoc t-tests were conducted on other independent variables as needed to clarify significant effects and interactions.

2.3.6. MRI methods

Structural and functional magnetic resonance images were acquired using a 3T Siemens Trio scanner, located at the Douglas Brain Imaging Centre. Participants lied supine in the scanner wearing a standard head coil. T1-weighted structural images were acquired at the beginning of the fMRI session using a 3D gradient echo MPRAGE sequence (acquisition time:

5min 3s, TR = 2300ms, TE = 2.98ms, flip angle = 9°, 176 1mm sagittal slices, 1×1×1mm voxels, FOV= 256). BOLD images were acquired using a single-shot T2*-weighted gradient echo-planar imaging (EPI) pulse sequence (TR = 2000ms, TE = 30ms, FOV = 256, matrix size = 64×64, in-plane resolution 4×4mm, 32 oblique 4mm slices with no slice gap) while participants performed the memory tasks. A mixed rapid event-related design was used with variable ITI (as stated above) to add jitter to the event-related acquisitions.

Visual task stimuli were generated on a computer using E-Prime (described above) and were back-projected onto a screen in the scanner bore. The screen was visible to participants lying in the scanner via a mirror mounted within the standard head coil. Participants requiring correction for visual acuity wore plastic corrective glasses. A fiber-optic 4-button response box was used by subjects to make task-related responses.

2.3.7. Preprocessing

Images were reconstructed from raw (k-space), converted to ANALYZE format, and preprocessed using Statistical Parametric Mapping (SPM) version 8 software (http://www.fil.ion.ucl.ac.uk/spm) run with MATLAB (www.mathworks.com) on a Linux platform. Images acquired during the first 10s of scanning were removed from analysis to ensure all tissue had reached steady state magnetization. The origin of all functional images was reoriented to the anterior commissure of the T1-weighted structural image. All functional images were realigned to the first image and corrected for movement artifacts using a 6-parameter rigid body spatial transform and a least squares approach. If a subject had > 4mm movement, they were discarded from analysis. Functional images were then spatially

normalized to the MNI EPI template (available in SPM) at 4 × 4 × 4mm voxel resolution and smoothed using an 8 mm full-width half-maximum (FWHM) isotropic Gaussian kernel. ArtRepair toolbox for SPM8 was used to correct for bad slices prior to realignment and for bad volumes after normalization and smoothing (http://cibsr.stanford.edu/tools/human-brain-project/artrepair- software.html).

2.3.8. Multivariate partial least squares analysis

Multivariate B-PLS was used to analyze the fMRI data to identify whole-brain patterns of task-related activity at encoding and retrieval that correlate with age (McIntosh, Chau, & Protzner, 2004). This multivariate approach was chosen due to its ability to detect spatially and temporally distributed patterns of activated voxels that differ across experimental conditions and/or relate to a specific behavioral measure. For this reason, it is particularly well suited to assess task-general and task-specific patterns of whole-brain activation associated with source memory across the lifespan. fMRI data at encoding and retrieval for correct trials were included in the analysis and stored in a data matrix that coded events for each condition at encoding and retrieval. This data matrix was then cross-correlated with the behavioral vector of age. Singular value decomposition (SVD) of the resulting brain-behavior correlation matrix was conducted to yield a set of latent variables (LVs). Each LV is composed of task saliences, which show similarities/differences in brain-behavior correlations across tasks for the LV, and voxel saliences, which show the corresponding spatiotemporal activation pattern of the LV. Finally, each LV also contains a singular value, which corresponds to the amount of variance in the

correlation matrix that is accounted for by an LV. Significance of LVs was assessed through permutation tests on the singular values ($p < 0.005$; 1000 permutations).

Bootstrapping was used to assess the reliability of voxel saliences for significant LVs with a bootstrap ratio (BSR) of ±3.28 ($p < 0.001$, 500 iterations; minimum cluster size of 10 contiguous voxels). Thus, this analysis identified LVs that maximally relate whole-brain task-related activity with the continuous variable of age.

The B-PLS identifies stable patterns of whole-brain task-related activity that directly correlate with age (i.e., brain-behavior correlations). However, B-PLS does not elucidate how activation in identified brain regions differs across tasks (i.e., task-specific differences in activation). We were interested in examining functional changes with age in source encoding and retrieval networks. Hence, for LVs from the B-PLS that indicated an age × phase interaction, we extracted the mean percent signal change for the peak of each region and calculated the mean activation for lags 2–5 in each participant. In order to examine differential phase-related activity within these regions for each age group, we conducted phase (2: encoding, retrieval) × group (3: young, middle-aged, older) repeated-measure ANOVAs and identified regions of interest (ROIs) that were sensitive to phase and interacted with group. Due to the fact that between-group differences in phase-specific activation could be influenced by reductions in regional cardiovascular reactivity in older age groups (Handwerker, Gazzaley, Inglis, & D'Esposito, 2007; Liu et al., 2013), within-group pairwise comparisons (e.g., encoding versus retrieval within each age group) were conducted in order to clarify age-group interactions.

2.4. Results

2.4.1. Neuropsychological tests

Table 2.1 displays group means for years of education and each of the administered neuropsychological tests in all three groups. One-way between-group ANOVAs indicated there were no significant group differences in neuropsychological measures.

2.4.2. Behavior

Table 2.2 presents the mean retrieval accuracy (% correct) and reaction time (ms) with standard errors for each age group.

Accuracy results. The group × task × difficulty repeated-measures ANOVA for retrieval accuracy identified significant main effects of task ($F[1,109] = 569.40$, $p < 0.001$), difficulty ($F[1,109] = 97.74$, $p < 0.001$) and age group ($F[2,109] = 10.07$, $p < 0.001$). In addition, there were significant age group × difficulty ($F[2,109] = 3.50$, $p < 0.05$), and task × difficulty ($F[1,109] = 20.03$, $p < 0.001$) interactions. No other effects were significant.

Table 2.1. Mean neuropsychological measures.

		Young	Middle Age	Older
Education (yrs)	mean	16.10	15.47	15.62
	se	0.29	0.37	0.34
MMSE	mean	29.54	29.34	29.13
	se	0.13	0.15	0.17
BDI	mean	3.27	3.97	3.90
	se	0.56	0.72	0.56
CVLT-Delayed Free Recall	mean	13.80	12.69	12.97
	se	0.27	0.42	0.38
CVLT – Delayed Cued Recall	mean	13.93	13.22	13.23
	se	0.27	0.36	0.33
CVLT- Delayed Recognition	mean	15.49	15.31	15.21
	se	0.11	0.13	0.13

Note: Mean values reported with standard error (se). MMSE = Mini-Mental State Examination; BDI = Beck Depression Inventory; CVLT = California Verbal Learning Test.

Table 2.2. Mean retrieval reaction time (RT) and accuracy in fMRI tasks.

Group		Spatial Easy	Spatial Hard	Temporal Easy	Temporal Hard
Young Adults	Mean RT (ms)	2236.87 (81.44)	2341.67 (77.49)	2584.93 (88.00)	2744.46 (100.54)
	Mean Accuracy	0.87 (0.01)	0.86 (0.02)	0.75 (0.02)	0.66 (0.02)
Middle-aged Adults	Mean RT (ms)	2572.72 (85.73)	2677.08 (72.41)	2965.58 (86.80)	3102.18 (96.11)
	Mean Accuracy	0.85 (0.02)	0.79 (0.02)	0.68 (0.02)	0.58 (0.02)
Older Adults	Mean RT (ms)	2763.29 (73.04)	2840.84 (74.53)	3154.31 (88.50)	3221.28 (98.86)
	Mean Accuracy	0.83 (0.01)	0.78 (0.02)	0.66 (0.02)	0.54 (0.01)

Note: Accuracy values are shown as proportion correct per task type with standard error. Reaction time values are shown in milliseconds (ms) per task type with standard error. RT = Reaction time.

The Tukey's b post-hoc test indicated that the significant main effect of age group was due to there being a significant mean difference in retrieval accuracy between young adults and the other two age groups ($p < 0.05$), and no significant mean difference in retrieval accuracy between middle-aged and older adults ($p > 0.05$). Post-hoc paired t-tests comparing the mean retrieval accuracy on spatial versus temporal source memory tasks, averaged across levels of difficulty, indicated the main effect of task was due to significantly lower retrieval on temporal versus spatial source memory tasks ($p < 0.05$). Post-hoc paired t-tests comparing the mean accuracy on easy versus hard source memory tasks, averaged across task types, indicated the main effect of difficulty was due to significantly lower retrieval accuracy on hard versus easy source memory tasks ($p < 0.05$), demonstrating that increasing encoding load significantly impacted task difficulty.

To clarify the significant age group × difficulty interaction, we conducted within-group paired t-tests comparing easy and hard versions of the spatial and temporal memory tasks, respectively. The interaction was due to there being no significant differences in retrieval

accuracy during easy versus hard spatial memory tasks in young adults ($t < 1$), and there being a significant difference in easy versus hard versions of spatial memory tasks in middle-aged and older adults ($p < 0.05$). All three age groups exhibited significantly lower retrieval accuracy on hard versus easy temporal memory tasks ($p < 0.05$).

To clarify the significant task × difficulty interaction, we conducted paired t-tests comparing easy and hard versions of spatial and temporal memory tasks, respectively, across groups. Post-hoc paired t-tests indicated that the significant task × difficulty interaction was due to the difficulty manipulation having a significantly greater impact in reducing retrieval accuracy on the temporal memory tasks ($t[1,111] = 9.33$, $p < 0.001$) versus the spatial memory tasks ($t[1,111] = 4.29$, $p < 0.001$).

Reaction time results. The between-group repeated-measures ANOVA for retrieval reaction time (RT; ms) identified significant main effects of task ($F[1,109] = 132.95$, $p < 0.001$), difficulty ($F[1,109] = 25.34$, $p < 0.001$) and age group ($F[2,109] = 12.45$, $p < 0.001$). There were no other significant effects.

The Tukey's b post-hoc test indicated that the significant main effect of age group was due to there being a significant mean difference in retrieval RT between young adults and both middle-aged and older adults ($p < 0.05$). There was no significant difference in retrieval RT between middle-aged and older adults ($p > 0.05$). Post-hoc paired t-tests comparing the mean retrieval RT on spatial versus temporal memory tasks, averaged across levels of difficulty, indicated the main effect of task was due to significantly slower RT on temporal versus spatial source memory tasks ($p < 0.05$). Post-hoc paired t-tests comparing the mean accuracy on easy versus hard memory tasks, averaged across task types, indicated the main effect of difficulty

was due to significantly slower retrieval RT on hard versus easy source memory tasks ($p < 0.05$), which demonstrated that increasing encoding load significantly impacted task difficulty.

2.4.3. fMRI results

Figure 2.1 shows two significant LVs identified by the B-PLS analysis. The singular image for the first LV (LV1), which accounted for 34.88% of the total cross-block covariance, is presented in **Figure 2.1A**, and the local maxima for this LV are listed in **Table 2.3**. The brain-behavior correlation profile for LV1 (**Figure 2.1B**) indicated that activity in brain regions with positive voxel saliences negatively correlated with age at encoding and retrieval. Regions showing this pattern of decreased activity with age included: bilateral FFG (BA 19, 37), bilateral cingulate gyrus (CG; BA 23, 24), and right lingual gyrus (LG; BA 18). Brain regions with negative voxel saliences in LV1 showed the inverse effect, where activity was positively correlated with age at encoding and retrieval. Regions showing this pattern of activity included: bilateral IPL (BA 40), bilateral PHG (BA 34), left middle and superior temporal/occipital gyri (BA 37, 22, 19), left dorsal MFG (BA 6), right medial frontal gyrus (BA 6) and right IFG (BA 47).

LV1 reflected a main effect of age and identified a whole-brain pattern of general linear changes with age across encoding and retrieval phases, consistent with evidence from previous cross-sectional studies that functional changes in distributed episodic memory network regions occur across the adult lifespan (Grady et al., 2006) into older adulthood (Spreng, Wojtowicz, & Grady, 2010). Although the general changes in brain function observed in LV1 may reflect age-related changes in cognition, they may also be attributable, at least in part, to non-cognitive factors, such as changes in cerebrovasculature with age (D'Esposito et al., 2003; Liu et al., 2013;

Maillet & Rajah, 2014). Taking into consideration this caveat, along with our principle interest in understanding how flexible engagement of encoding- and retrieval-specific processing changes across the adult lifespan, the general linear effects with age from LV1 will not be discussed further. Remaining focus will be on patterns of whole-brain activation where age-related changes in activation differed by phase.

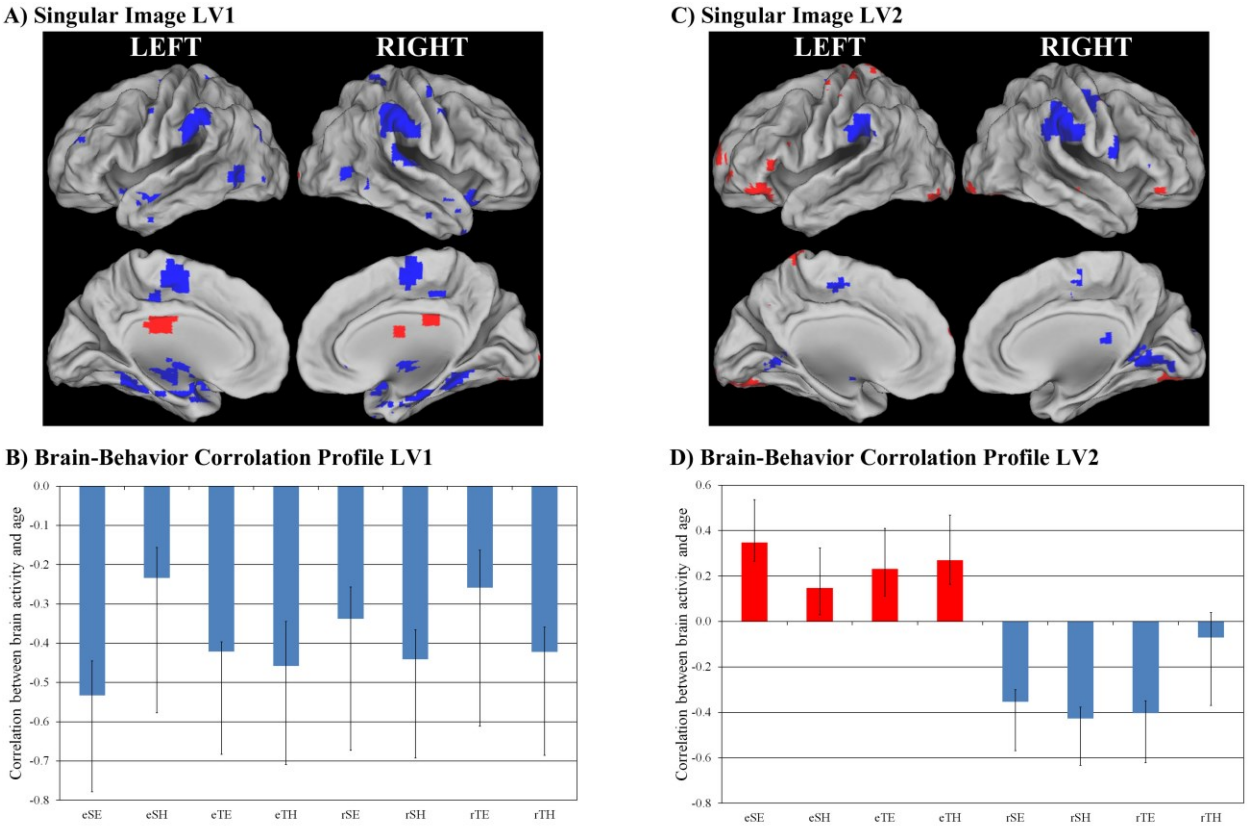

Figure 2.1. Singular images and corresponding brain-behavior correlation profiles for LVs 1 and 2. (A) The singular image for B-PLS LV1, threshold bootstrap ratio of ±3.28, $p < 0.001$. Red brain regions reflect positive brain saliences and blue regions reflect negative brain saliences. (B) The brain-behavior correlation profile for each event type for LV1. The correlation profile indicates that positive brain saliences negatively correlated with age at encoding and retrieval. In contrast, negative voxel saliences positively correlated with age at encoding and retrieval. (C) The singular image for B-PLS LV2, threshold bootstrap ratio of ±3.28, $p < 0.001$. Red brain regions reflect positive brain saliences and blue regions reflect negative brain saliences. (D) The brain-behavior correlation profile for each event type for LV2. The correlation profile indicates that i) positive brain saliences correlated positively with age at encoding and ii) correlated negatively with age at retrieval. In contrast, negative voxel saliences i) correlated positively with age at retrieval and ii) correlated negatively with age at encoding. Activations are presented on template images of the lateral and medial surfaces of the left and right hemispheres of the brain using Caret software (http://brainvis.wustl.edu/wiki/index.php/Caret:Download).

Table 2.3. Local maxima for LV1: Regions where activation correlated with age at encoding and retrieval.

			Talairach coordinates					
Temporal Lag	Bootstrap ratio	Spatial extent	x	y	z	HEM	Gyral location	BA
Decreased activation with age								
2	5.88	99	-27	-75	-14	Left	Fusiform gyrus	19
3,4	5.34	55	-1	-26	23	Left	Posterior cingulate	23
2,3	5.08	70	25	-72	-9	Right	Lingual gyrus	18
5	3.98	17	10	-4	26	Right	Cingulate gyrus	24
2	3.73	12	32	-45	-17	Right	Fusiform gyrus	37
Increased activation with age								
2,3,4	-5.76	84	-61	-43	39	Left	Inferior parietal lobule	40
4	-5.40	36	-31	-79	25	Left	Superior occipital gyrus	19
2,3,4	-5.12	28	-53	-61	-6	Left	Middle temporal/occipital gyrus	37/19
2,4,5	-4.56	34	-45	0	-7	Left	Superior temporal gyrus	22
4	-4.34	42	-27	4	-17	Left	Parahippocampal gyrus	34
4	-4.03	10	-28	23	56	Left	Middle frontal gyrus	6
2,3,4	-7.07	240	58	-39	41	Right	Inferior parietal lobule	40
2,3	-5.55	145	6	-15	61	Right	Medial frontal gyrus	6
3,4	-5.20	378	10	-18	-26	Right	Parahippocampal/fusiform gyrus	
4,5	-5.04	76	25	26	-7	Right	Inferior frontal gyrus	47
5	-4.53	87	10	-12	-7	Right	Hippocampus/amygdala	
2	-4.19	25	36	-12	-4	Right	Claustrum	
3	-4.08	12	47	-2	45	Right	Precentral gyrus	4
4	-3.79	24	58	-29	46	Right	Postcentral gyrus	2
3	-3.78	13	20	-49	61	Right	Superior parietal lobule	7
2	-3.77	20	25	3	-6	Right	Lentiform nucleus	

Note: Temporal lag represents the time after event onset, when a cluster of voxels exhibited an effect of interest. Bootstrap ratio threshold was set to ±3.28 and identified dominant and stable activation clusters. Spatial extent refers to the total number of voxels included in the voxel cluster (threshold = 10). Stereotaxic coordinates are measured in millimeters, and gyral location and Brodmann areas (BAs) were determined by referring to Talairach and Tournoux (1988). HEM = Cerebral hemisphere in which activation occurred.

The second LV (LV2) accounted for 21.77% of the cross-block covariance and reflected an age × phase interaction. That is, LV2 identified linear changes with age that were specific to encoding and retrieval phases. **Figure 2.1C** shows the singular image for LV2, and local maxima are listed in **Table 2.4**. The correlation profile for this LV (**Figure 2.1D**) indicated that activation in positive salience brain regions was positively correlated with age at encoding and negatively correlated with age at retrieval, with the exception of the TH retrieval condition. Positive salience brain regions included: bilateral FFG (BA 19), bilateral IFG (BA 47), left MFG and superior frontal gyri (SFG; BA 9/44, 10), right superior parietal lobule (SPL; BA 7), and right superior temporal gyrus (STG; BA 22). Regions with negative voxel saliences showed the inverse effect, where, with the exception of the TH retrieval condition, activation positively correlated with age at retrieval and negatively correlated with age at encoding. Negative salience brain regions included: bilateral IPL (BA 40), bilateral PHG (BA 30), left CG (BA 24, 31), right dorsal IFG (BA 44, 6), and right middle occipital gyrus (BA 18).

Overall, LV2 reflected an age × phase interaction and identified whole-brain patterns of linear change with age specific to encoding versus retrieval. In order to determine if age-related change in LV2 brain regions was due to increases or decreases in activity in specific age groups (versus the linear measure of age) during encoding versus retrieval, we conducted post-hoc 2 (phase: encoding, retrieval) × 3 (group: young, middle, older) repeated-measures ANOVAs on the mean activity of ROIs identified in LV2. **Figure 2.2** shows the mean activation plots for LV2 regions that showed a significant group × phase interaction. Within-group follow-up pairwise comparisons of activation in these regions revealed differential phase-specific activation in

Table 2.4. Local maxima for LV2: Regions where activation differentially correlated with age at encoding vs. retrieval.

			Talairach coordinates					
Lag	BSR	Spatial extent	x	y	z	HEM	Gyral location	BA
Increased activation with age at encoding, decreased at retrieval								
3,4	5.30	47	-27	-75	-14	Left	Fusiform gyrus	19*
5	4.98	39	-38	30	-8	Left	Inferior frontal gyrus	47
5	4.58	11	-57	19	27	Left	Middle/inferior frontal gyrus	9/44*
3,4	4.53	16	-23	57	24	Left	Superior/middle frontal gyrus	10*
5	4.51	28	-35	-34	65	Left	Postcentral gyrus	1/2*
2	4.45	59	-39	-30	58	Left	Postcentral gyrus	3*
5	4.15	11	-13	-49	64	Left	Postcentral gyrus	7
5	4.13	29	-19	10	-2	Left	Lentiform nucleus	
3	4.09	15	-46	13	44	Left	Middle frontal gyrus	8*
5	3.74	10	-61	8	26	Left	Inferior frontal gyrus	44
5	4.72	10	44	33	-6	Right	Inferior frontal gyrus	47
5	4.71	80	50	-11	55	Right	Postcentral gyrus	3/4
5	4.45	21	21	14	-5	Right	Lentiform nucleus	
3,4	4.42	25	29	-75	-13	Right	Fusiform gyrus	19*
5	4.36	11	16	-68	63	Right	Superior parietal lobule	7
5	3.70	10	47	-19	-11	Right	Superior temporal gyrus	22
Increased activation with age at retrieval, decreased at encoding								
3	-5.67	80	-57	-37	25	Left	Inferior parietal lobule	40*
3	-5.04	16	-16	33	0	Left	Cingulate gyrus	24*
2	-4.59	53	-23	7	-3	Left	Lentiform nucleus	
3	-4.31	64	-24	-44	18	Left	Caudate	*
5	-4.22	33	-27	-47	7	Left	Parahippocampal gyrus	30*
3	-4.12	42	-2	-13	46	Left	Cingulate gyrus	24/31
2,3,4	-6.68	526	50	-35	31	Right	Inferior parietal lobule	40*
2	-4.74	70	21	10	2	Right	Lentiform nucleus	
4	-4.71	102	21	-41	19	Right	Caudate	*
2,3	-4.53	22	54	4	20	Right	Inferior frontal/precentral gyrus	44/6*
5	-4.43	61	25	-44	8	Right	Hippocampus/parahippocampal gyrus	*
3	-4.30	62	39	-14	47	Right	Precentral gyrus	4*
3	-3.91	23	10	-93	17	Right	Middle occipital gyrus	18*

Note: Lag represents the time after event onset when a cluster of voxels exhibited an effect of interest. Bootstrap ratio (BSR) threshold was set to **±**3.28 and identified dominant and stable activation clusters. Spatial extent refers to the total number of voxels included in the voxel cluster (threshold = 10). Stereotaxic coordinates are measured in millimeters, and gyral location and Brodmann areas (BAs) were determined by referring to Talairach and Tournoux (1988). HEM = Cerebral hemisphere in which activation occurred. Regions marked with * were ROIs for which post hoc analysis revealed a significant group × phase interaction (see also **Table 2.5** for region-specific interactions).

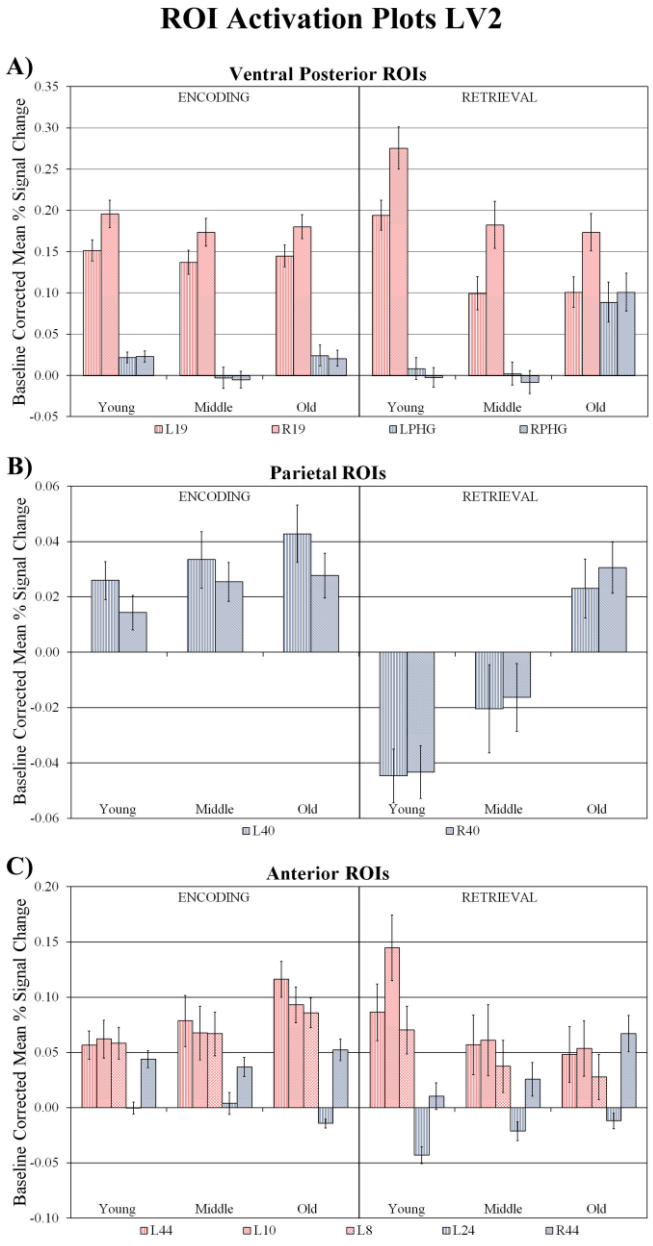

Figure 2.2. Bar graphs with standard error bars representing mean encoding and retrieval activation. Activation for each group in ventral posterior (A), parietal (B), and anterior (C) regions of interest (ROIs) from the LV2 B-PLS that demonstrated a group × phase interaction.

young, middle-aged, and older adults for these regions (**Table 2.4**; see also **Table 2.5** for region-specific interactions).

Ventral posterior ROIs. **Figure 2.2A** depicts ventral posterior regions that showed significant group × phase interactions in brain activity, and included an area of left FFG (BA19; $F[(2,109] = 7.25$, $p < 0.001$). Follow-up within-group pairwise comparisons of activity during encoding versus retrieval revealed that young adults showed more activity in this region during retrieval > encoding, but older adults showed more activity for encoding > retrieval (both $p < 0.05$), and middle-aged adults showed no difference in activity by phase in this region. The right homologue of this area (BA 19) also showed a significant group × phase interaction ($F[2,109] = 5.99$, $p < 0.01$). Post-hoc comparisons indicated that young adults showed more activity in this region at retrieval > encoding ($p < 0.001$), but both middle-aged and older adults showed no differences in activity by phase.

Figure 2.2A also shows bilateral PHG (BA 30) activity in each age group at encoding and retrieval. The group × phase interaction was significant in both the left ($F[2,109] = 7.57$, $p < 0.001$), and right ($F[2,109] = 13.55$, $p < 0.001$) regions, with young and middle-aged adults showing no differences in activation by phase, but with older adults showing more activity at retrieval > encoding (both $p < 0.001$).

Parietal areas. **Figure 2.2B** shows the activation profiles for bilateral IPL ROIs (BA 40). A significant group × phase interaction in brain activity was found for both left ($F[2,109] = 4.92$, $p < 0.01$) and right ($F[2,109] = 9.53$, $p < 0.001$) homologues. In both regions, young and middle-aged adults showed greater activity during encoding > retrieval (all $p < 0.001$), and older adults showed no difference between phases.

Table 2.5. Regions extracted from LV2 where activation showed a significant group × phase interaction.

Lag	BSR	Spatial extent	Talairach coordinates x	y	z	HEM	Gyral location	BA	Phase effects within age
							Y=M=O		
5	4.58	11	-57	19	27	Left	Middle/inferior frontal gyrus	9/44	Y: e=r; M: e=r; O: e>r
3,4	4.53	16	-23	57	24	Left	Superior/middle frontal gyrus	10	Y: e<r; M: e=r; O: e=r
3	4.09	15	-46	13	44	Left	Middle frontal gyrus	8	Y: e=r; M: e=r; O: e>r
3	-5.04	16	-16	33	0	Left	Cingulate gyrus	24	Y: e>r; M: e>r; O: e=r
3	-3.91	23	10	-93	17	Right	Middle occipital gyrus	18	Y: e>r; M: e>r; O: e>r
							Y=M≠O		
3	-5.67	80	-57	-37	25	Left	Inferior parietal lobule	40	Y: e>r; M: e>r; O: e=r
5	-4.22	33	-27	-47	7	Left	Parahippocampal gyrus	30	Y: e=r; M: e=r; O: e<r
2,3,4	-6.68	526	50	-35	31	Right	Inferior parietal lobule	40	Y: e>r; M: e>r; O: e=r
5	-4.43	61	25	-44	8	Right	Hippocampus/ parahippocampal gyrus		Y: e=r; M: e=r; O: e<r
							Y≠M=O		
3,4	5.30	47	-27	-75	-14	Left	Fusiform gyrus	19	Y: e<r; M: e=r; O: e>r
3,4	4.42	25	29	-75	-13	Right	Fusiform gyrus	19	Y: e<r; M: e=r; O: e=r
							Y≠O, M=Y,O		
2,3	-4.53	22	54	4	20	Right	Inferior frontal/precentral gyrus	44/6	Y: e>r; M: e=r; O: e=r

Note: Regions were ROIs from LV2 for which: i) mean activity was extracted and ii) region-specific post hoc analysis revealed a significant group × phase interaction. Lag represents the time after event onset when a cluster of voxels exhibited an effect of interest. Bootstrap ratio (BSR) threshold was set ±3.28 and identified dominant and stable activation clusters. Spatial extent refers to the total number of voxels included in the voxel cluster (threshold = 10). Stereotaxic coordinates are measured in millimeters, and gyral location and Brodmann areas (BAs) were determined by referring to Talairach and Tournoux (1988). HEM = Cerebral hemisphere in which the activation occurred.

Anterior areas. **Figure 2.2C** shows encoding and retrieval activation in frontal regions that exhibited significant group × phase interactions in brain activity: left MFG/IFG (BA 9/44; $F[2,109] = 4.05$, $p < 0.05$); right IFG (BA 44/6; $F[2,109] = 3.68$, $p < 0.05$); left MFG (BA 8; $F[2,109] = 3.30$, $p < 0.05$); and left SFG (BA 10; $F[2,109] = 5.78$, $p < 0.01$). In both the left BA 9/44 and left

BA 8, young and middle-aged adults did not differ in encoding and retrieval activity, but older adults showed more activity for encoding > retrieval (both $p < 0.01$). Thus older adults exhibited more left MFG activity during encoding > retrieval. Conversely, in the right IFG, young adults showed more activity for encoding > retrieval ($p < 0.01$), but middle-aged and older adults' activity did not differ between encoding and retrieval. In left SFG, an encoding < retrieval effect was observed in young adults only ($p < 0.01$), whereas middle-aged and older adults showed similar activity across phases.

Figure 2.2C also shows the activation profile for the CG (BA 24) ROI that demonstrated a significant group × phase interaction in brain activity ($F[2,109] = 6.25$, $p < 0.003$) due to young and middle-aged adults exhibiting greater activity (i.e., less deactivation) during encoding > retrieval (both $p < 0.05$), and older adults exhibiting similar activity across phases.

2.5. Discussion

The current study used event-related fMRI to identify age-related changes in source memory for spatial and temporal information across the adult lifespan. Behaviorally, we found the usual pattern of age-related deficit in accuracy and response latency on source memory tasks (Cansino, 2009; M. K. Johnson et al., 1993). We found that young adults outperformed both middle-aged and older adults across tasks. Our results converge with prior studies of spatial and/or temporal source memory that show age-related deficits occurring both at midlife (e.g., Cansino, Estrada-Manilla, et al., 2015; Cansino, Trejo-Morales, et al., 2015; Kwon et al., 2016) and in older adulthood (e.g., Parkin, Walter, & Hunkin, 1995; Perlmutter, Metzger, Nezworski, & Miller, 1981; Rajah et al., 2010). In addition, we saw that there was a significantly

greater decline in retrieval accuracy on more difficult versus easy versions across tasks in middle-aged and older adults compared to young adults, supporting the idea that stimulus load at encoding significantly impacts source memory performance as early as midlife (Cappell, Gmeindl, & Reuter-Lorenz, 2010; Kwon et al., 2016).

With respect to the fMRI data, our analyses revealed two significant LVs. LV1 revealed general increases and decreases with age in network activation across encoding and retrieval phases. We observed linear age-related increases in left secondary visual-semantic processing areas (middle-superior temporal cortices), bilateral IPL, and right IFG activity. In contrast, linear age-related decreases in more primary visual processing areas (LG and FFG) and CG activity were observed. LV1 results are consistent with previous cross-sectional fMRI studies of episodic memory across the adult lifespan that have also reported linear age-related decreases in primary visual cortex activity and linear age-related increases in temporal, parietal and PFC activity across the adult lifespan (Grady et al., 2006; Kennedy et al., 2012; H. Park et al., 2013).

Although some of the effects identified in LV1 may be due to changes in cognition with age, it is highly likely that these linear changes in brain activity may be due to non-cognitive factors. Prior work suggests that some age-related increases and/or decreases in brain activation may be due to overall changes in cerebral blood flow, cerebral blood volume, vascular reactivity, and/or metabolism with age, which impact neuro-vascular coupling and in turn the BOLD signal (D'Esposito et al., 2003; Grady & Garrett, 2014; Handwerker et al., 2007; Kannurpatti, Motes, Rypma, & Biswal, 2010, 2011; Liu et al., 2013). As such, it has been recommended that researchers focus on age-group interactions instead of main effects of age to account for these confounding factors (D'Esposito et al., 2003; Rajah & D'Esposito, 2005).

Due to the fact we did not control for changes with age in these factors in the current study, we decided to focus on areas found in LV2 that exhibited an age × phase interaction.

LV2 identified linear changes with age during encoding versus retrieval phases. Overall, activation in LV2 regions with positive saliences correlated positively with age at encoding and correlated negatively with age at retrieval. Conversely, in regions with negative voxel saliences from LV2, activation correlated positively with age at retrieval and correlated negatively with age at encoding. Based on LV2 results, we identified the following three patterns of age-related changes in source encoding versus retrieval activity: 1) We found negative salience areas (bi-lateral IPL, BA 40) where young, but not older, adults showed significant phase-related activation, indicative of a pattern of reduced phase-specific modulation (i.e., flexibility) with age; 2) We found positive salience and negative salience areas (FFG, BA 19; left SFG, BA 10; right IFG, BA 44/6) where middle-aged and older adults showed reduced phase-specific activation relative to young adults; and 3) We found positive (left MFG/IFG, BA 9/44 and BA 8) and negative (bilateral PHG, BA 30) salience areas where older adults showed a phase-specific increase in brain activity compared to young adults.

2.5.1. Late life reductions in phase-related modulation of activation

We observed age-group differences in phase-related activity in bilateral IPL (BA 40). This was due to a lack of phase-specific activation in older adults and greater activation during encoding > retrieval in young and middle-aged adults. This pattern of activation in older adults may reflect reduced flexibility, or generalization, of bilateral IPL function in late life. Recent evidence has shown that decreases in flexibility and/or variance of fronto-parietal network

regions with age may account, in part, for age-related changes in performance across a variety of cognitive tasks (Grady & Garrett, 2014).

More specifically, fMRI studies of episodic memory have emphasized the role of LPC in post-retrieval monitoring (Nelson et al., 2010) and/or reflectively attending to internal representations (Chun & Johnson, 2011) during successful retrieval. In a previous fMRI study comparing source encoding and retrieval in young and older adults, Mitchell and colleagues (2013) reported increased activation of LPC in older versus young adults during retrieval of source information relative to item recognition. This increase in older versus young adults was attributed to differences in the ability of older adults to monitor and/or reflectively attend to active representations during retrieval in order to make a correct memory judgment (Mitchell et al., 2013). It is also possible that parietal increases observed in older versus young adults in the current study reflect age-related reductions in the ability to suppress task-irrelevant information at retrieval (Gazzaley et al., 2005). Interestingly, in the study by Mitchell et al. (2013), both young and older adults similarly engaged bilateral IPL during source encoding. However, the fMRI analyses were conducted within memory phase, and not across memory phases, as was done in the current study. Nonetheless, in considering our data within encoding and retrieval phases, we observe similar patterns to Mitchell et al. (2013): No group differences in activity at encoding, and greater activity in older adults at retrieval. Thus, our finding of reduced phase-specific modulation of inferior parietal regions during late life lends support to the idea that older adults may have decreased ability to attend to the most relevant source information activated during retrieval and/or to ignore unrelated perceptual information present during retrieval (Healey, Campbell, & Hasher, 2008).

2.5.2. Midlife changes in phase-related modulation of activation

We found a pattern of reduced phase-related modulation that occurred at midlife and was also present in older age in the following regions identified in LV2: left SFG (BA 10), right IFG (BA 44/6), and right FFG (BA 19). In the two positive salience regions (left SFG, right FFG), decreases in phase-specific modulation observed with age were due to the fact that young adults exhibited increased activation during retrieval relative to encoding, but middle-aged and older adults showed similar activation at encoding and retrieval. Similar areas of left SFG have been found to be associated with retrieval monitoring in young adults (McDonough et al., 2013), and age-related changes in SFG function during source memory paradigms have been reported in previous studies (Mitchell et al., 2013; Rajah, Languay, et al., 2010).

Both IPL and anterior prefrontal (i.e., SFG) regions are involved in monitoring retrieved information (Ciaramelli et al., 2008; Mitchell et al., 2013; Mitchell & Johnson, 2009; Nelson et al., 2010; Rajah & D'Esposito, 2005). As discussed earlier, older adults showed reduced phase-specific activation in both these regions. The observation that middle-aged adults showed a similar reduced phase-specific modulation pattern to older adults in left SFG relative to young adults, but not in bilateral IPL suggests that phase-specific functional changes in fronto-parietal network activity may begin to occur at midlife, within the PFC (Kwon et al., 2016).

A common view of age-related functional changes in episodic memory networks is that there is a shift in network dynamics away from engagement of more posterior regions (i.e., visual areas) towards more anterior prefrontal regions with advanced age (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008; Maillet & Rajah, 2014). Support for this idea comes from

evidence that older, relative to young adults show attenuated activation in posterior visual areas during passive viewing and during memory tasks (Chee et al., 2006; D. C. Park et al., 2004; J. Park et al., 2012). In the current study, young adults engaged bilateral FFG (BA 19) to a greater extent during retrieval relative to encoding. In both regions, we observed reduced phase-specific modulation in middle-aged adults relative to young adults, suggestive of age-related changes in ventral visual processing during retrieval at midlife. Interestingly, this pattern was only significant in right FFG (BA 19) in older adults. However, in general, both middle-aged and older adults exhibited similar patterns of bilateral fusiform activity, compared to young adults. In the current study, at retrieval there were two 'old' face stimuli presented, whereas at encoding, only one face stimulus was presented. Thus, increased bilateral fusiform activity at retrieval in young adults versus middle-aged and older adults may reflect greater recollection of contextual details of both 'old' faces in young adults compared to the other two groups, which may have aided young adults' source memory performance. This interpretation is consistent with results from previous studies that suggest greater reactivation of visual cortex supports episodic recollection (St-Laurent, Abdi, Bondad, & Buchsbaum, 2014), and with the idea that with increasing age, adults may inherently use less perceptual-based strategies at encoding and/ or subsequent retrieval to support more vivid recollection (M. K. Johnson, Kuhl, Mitchell, Ankudowich, & Durbin, 2015). Finally, these results are consistent with prior adult lifespan studies of episodic memory function that also indicated that changes in ventral visual function arise at midlife and may contribute to episodic memory decline (Grady et al., 2006; H. Park et al., 2013).

We also observed phase-specific modulation in right IFG in young adults, which was not present in middle-aged and older adults. Right IFG activity is observed during face processing (Andreasen et al., 1996; Grady et al., 1996; Kim et al., 1999). In a previous functional neuroimaging study comparing face matching, face encoding, and face recognition in young adults, network analysis of brain activation data indicated that right IFG activity was positively associated with right occipito-temporal activity at encoding but negatively associated with right occipito-temporal activity at retrieval (Rajah, McIntosh, & Grady, 1999). In the current study, all age groups similarly activated right IFG and bilateral FFG during encoding; however, at retrieval, young adults exhibited decreased activity in IFG and increased activity in bilateral FFG at retrieval compared to encoding. Middle-aged and older adults did not exhibit phase-specific modulations in either region. One possibility is that phase-specific modulation in right IFG reflected focused face-selective processing at retrieval in young adults, which may in turn have supported the recollection-related reactivation of bilateral FFG during retrieval in this age group. In contrast, the reduced modulation of bilateral FFG and right IFG in middle-aged and older adults may reflect failures in selection and reduced perceptual recollection at retrieval. Overall, this pattern of activation in middle-aged and older adults may reflect dedifferentiation of function in right IFG and FFG (Goh, Suzuki, & Park, 2010).

2.5.3. Late life increases in phase-related modulation of activation

We observed late life changes in dorsal posterior left MFG activity. Older adults exhibited greater activity in left BA 9/44 and left BA 8 during encoding > retrieval. Young and middle-aged adults did not exhibit phase-associated modulation in either region. Previous

studies have reported concurrent age-related increases in left MFG activity and age-related decreases in posterior occipito-temporal activity (Davis et al., 2008). It has been proposed that in such cases, age-related increases in MFG activity may reflect attempted compensation for posterior cortical dysfunction. In the current study, we did not observe decreased activity in posterior cortical regions during encoding in older adults versus young and middle-aged adults. Thus, it is unlikely that the increased dorsal posterior left MFG activity observed in older versus young adults at encoding reflected compensation. Instead, it is possible that increased left MFG activity at encoding may reflect either reduced neural efficiency (Morcom et al., 2007) or greater reliance on alternate left MFG-related strategies at encoding; i.e., relational processing of face stimuli (Blumenfeld, Parks, Yonelinas, & Ranganath, 2011). Given that increased left MFG activity in older > young adults was not observed during both encoding and retrieval, it is unlikely that over recruitment of this region at encoding by older adults reflected reduced neural efficiency. It is also notable that left MFG regions association with relational processing at encoding have been localized to more anterior MFG, in BA 9/46; and in the current study one left MFG peak did include BA 9 (BA 9/44), but the other peak, which exhibited a similar activation profile, was more dorsal and posterior and nearer to premotor and supplementary motor areas (BA 8). Thus, it is debatable that both left MFG regions in the current study served similar functional roles despite having similar activation profiles. It may be that left BA 9/44 activity reflected greater utilization of relational encoding strategies in older adults, and that left BA 8 activity was related to increased motor effort, as indicated by longer RT in this age group compared to the young adult group.

In addition to observing age-related over recruitment of left MFG at encoding in older versus young and middle-aged adults, we also found age-related over recruitment of bilateral PHG during retrieval in older versus young and middle-aged adults. Older adults exhibited phase-specific modulation in bilateral PHG, with greater activity in these regions at retrieval > encoding. In contrast, young and middle-aged adults did not exhibit phase-related modulation of PHG activity across encoding and retrieval. Some previous studies have reported over recruitment of MTL areas in older adults during retrieval (Duverne, Habibi, & Rugg, 2008), particularly in areas of right MTL for retrieval of self-relevant or autobiographical information (Maguire & Frith, 2003). Over activation of MTL areas in older adults at retrieval has sometimes been interpreted as compensatory, where, due to declines in neural inefficiencies in posterior representational and/or binding areas at encoding (Mitchell, Johnson, Raye, & D'Esposito, 2000; D. C. Park et al., 2004), older adults show increased hippocampal activation in order to achieve similar levels of recollection performance (Duverne et al., 2008). However, in the current study, we did not observe any encoding-specific deficits in older compared to young adults. Evidence from previous neuroimaging aging studies suggests that older adults may rely on internal, self-referential information to a greater extent than young adults (Leshikar et al., 2015; Maillet & Rajah, 2014), even when directed to attend to external contextual details (Dulas & Duarte, 2014). It is therefore possible that the PHG increases observed in older, relative to young, adults at retrieval may have been due to older adults retrieving more internal, self-relevant, or autobiographical information during retrieval (Maguire & Frith, 2003). Our encoding task required participants to rate the pleasantness of age-variant faces. Thus it could be that at retrieval, older adults revived more internally generated and/or self-relevant

information related to encoded faces. Although speculative, this interpretation would be consistent with the idea that older adults were less constrained in the type of information evaluated during retrieval and with the pattern of increased parietal and decreased prefrontal and ventral visual activity observed in older relative to young adults during retrieval. Together these findings suggest that older adults may have revived greater amounts (Vilberg, Moosavi, & Rugg, 2006) of less source-specific (Mitchell et al., 2013) information during retrieval.

2.6. Conclusion

We observed age-related deficits in source memory beginning at midlife. The PLS analysis indicated that overall, young, middle-age, and older adults exhibited similar encoding activity in occipital, parietal and right inferior frontal cortices, and that the majority of age group × phase interactions was driven by group differences in retrieval activity. At retrieval, we found evidence consistent with an age-related functional deficit in an area of anterior PFC (BA 10) previously been shown to play a role in retrieval monitoring (McDonough et al., 2013), and the selection/maintenance of retrieval goals or agendas (Mitchell & Johnson, 2009). Young adults activated this region to a greater extent than middle-aged and older adults at retrieval versus encoding. In addition, we found reduced phase-related modulation in bilateral FFG and right IFG that arose at midlife, which may be indicative of dedifferentiation of function and reduced perceptual recollection.

We also found increased phase-specific modulation of bilateral PHG and left MFG in older adults. Older adults over recruited left MFG during encoding and bilateral PHG at retrieval, compared to other age groups. One may argue that this over activation in left MFG

and bilateral PHG in older adults may be in response to underlying grey matter loss in these regions, since age-related volume loss in MFG and MTL regions have been reported in previous studies examining age-related changes in brain structure (Head, Rodrigue, Kennedy, & Raz, 2008; Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010). However, the fact that over activation of left MFG and bilateral PHG was phase-specific argues against this possibility, since over activation in response to volume loss is hypothesized to be ubiquitous across tasks and phases (Maillet & Rajah, 2013). Therefore, we conclude that these differences indicate that older adults processed qualitatively different amounts, and/or types, of information at encoding and retrieval, compared to young adults. These differences, in combination with altered perceptual recollection and changes in fronto-parietal function with age, likely contributed to the source memory deficits observed in middle-aged and older adults in the current study.

It is notable that we did not identify any age-related differences in neuropsychological measures; i.e., the CVLT free recall. Previous studies have reported reduced CVLT free recall scores in older versus young adults (Cabeza, McIntosh, Tulving, Nyberg, & Grady, 1997; Rajah, Languay, et al., 2010). This raises the possibility that the older adult sample in the current study was more high-functioning compared to samples tested in prior studies. We employed stringent inclusion/exclusion criteria, which included excluding adults with: a family history of Alzheimer's disease, diabetes, heavy smoking and uncontrolled high blood pressure and cholesterol. Despite these stringent criteria, we still observed age-related differences in memory-related brain function. This suggests that these brain changes are apparent even in high-functioning older adults with low cardiovascular risk.

Finally, we did not observe task-related differences in brain activation at encoding and retrieval, nor did we observe age × task, or age × difficulty interactions using B-PLS with age as the behavioral vector. This implies that age has its strongest impact on phase-related differences in brain activity, and that this generalizes across tasks and levels of difficulty. However, this does not mean that there are no task, difficulty, age × task, and age × difficulty differences in brain activation across spatial and temporal source memory tasks in the current study. Such distinctions are better investigated using task-based PLS and/or univariate analyses, which are beyond the scope of the current manuscript but may be addressed in later publications of this cohort.

Chapter 3. Study 2: Changes in the correlation between spatial and temporal source memory performance and BOLD activity across the adult lifespan

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Preface

As mentioned in the general introduction, in order to understand the functional significance of age-related differences in functional activation during episodic memory tasks, previous aging fMRI studies have often tried to associate age-related functional differences with performance. Recent studies have suggested that many of the age effects observed in episodic memory tasks are due, at least in part, to differences in performance with age (Rugg, 2016). That is, because aging is related to decreased memory performance, prior studies have shown that when controlling for individual differences in performance, effects of age on brain activation largely disappear during both encoding and retrieval (de Chastelaine, Mattson, Wang, Donley, & Rugg, 2016b, 2016a). The approach taken in these studies has been two-step: Researchers conduct a typical mass univariate analysis to uncover effects of age on task-related activation and then perform subsequent analyses on extracted activity in regions of interest using ANCOVAs that control for task performance as a covariate. However, Study 2 assessed

how lifespan differences in activation during encoding and retrieval relate to source memory performance using a different approach. Using B-PLS, we assessed patterns of whole-brain activation that were directly correlated with age and/or retrieval accuracy, which were both included as continuous variables. Prior to the B-PLS analysis, we orthogonalized the continuous age and accuracy terms used in order to test for independent effects of age and performance. In this way, we could assess independent effects of age and accuracy on task-specific fMRI activation by treating age and accuracy as continuous individual difference measures (thereby reserving power; Streiner, 2002), and we could assess these effects during both encoding and retrieval simultaneously in the same analysis.

3.1. Abstract

Studies investigating age-related functional differences associated with source memory have recently focused on the importance of clarifying the relationship between effects of age and performance on memory-related brain activations. One methodological challenge has been in discriminating between effects of age on memory-related brain activations that are independent from age-related differences in performance. In the current study, event-related fMRI was used to identify brain activity during spatial and temporal source encoding and retrieval across the adult lifespan. We used multivariate B-PLS to identify patterns of brain activity during source encoding and source retrieval that were associated with age and/or retrieval accuracy. The PLS analysis identified three significant effects. The first effect indicated that encoding and retrieval activity in fusiform, middle occipito-temporal, and inferior parietal cortices increased with age and decreased with performance. The second effect showed that dorsolateral prefrontal cortex and limbic activity increased with age at encoding and increased with performance at retrieval. The third effect indicated that activity in right VLPFC and bilateral HC increased with age during retrieval and was differentially related to performance during encoding versus retrieval. We conclude that although some age-related differences in brain activity observed during source encoding and retrieval are associated with individual differences in performance, age-related differences in prefrontal and hippocampal areas exhibit more complex patterns of interactions between age, performance, and phase-related activity.

3.2. Introduction

Healthy aging is associated with reduced memory for the contextual features of items or events (source memory; see Old and Naveh-Benjamin (2008), Spencer and Raz (1995) for reviews). Age-related source memory impairment may result from a reduced ability in older adults to bind contextual features of events together at encoding (Chalfonte & Johnson, 1996; Naveh-Benjamin, 2000) and/or to selectively recollect specific features at retrieval (Gallo, 2013; M. K. Johnson et al., 1993). Considerable work has been done using neuroimaging in order to investigate how age-related differences in source memory relate to differences in the neural correlates of source encoding and retrieval in older versus young adults.

In young adults, successful encoding and retrieval of source information has been associated with activity in primary and secondary sensory cortices (e.g., ventral occipito-temporal cortices in the case of visual information), HC, MTL, LPC, and PFC (Awipi & Davachi, 2008; Hayama, Vilberg, & Rugg, 2012; King, de Chastelaine, Elward, Wang, & Rugg, 2015; Mitchell & Johnson, 2009; Spaniol et al., 2009; Uncapher et al., 2006). Functional neuroimaging studies that have compared source memory in young and older adults have found age-related differences in activity in the majority of these regions (Grady, 2008; Mitchell & Johnson, 2009; Rajah & D'Esposito, 2005; Spreng et al., 2010). For example, at encoding, studies have reported age-related decreases in MTL activity, which is thought to be reflective of a deficit in associative binding of object-source information in older relative to young adults (Dennis, Hayes, et al., 2008; Mitchell, Johnson, Raye, & D'Esposito, 2000). Age-related reductions in encoding activity have also been shown in lateral PFC regions thought to play a role in strategic relational encoding of task-relevant information (Dennis, Hayes, et al., 2008; Dulas & Duarte, 2011, 2014).

In addition, age-related decreases in posterior perceptual cortical activation have been reported during encoding and suggest that older adults may exhibit reduced specificity of sensory/perceptual areas during initial perception and subsequent recollection (Chee et al., 2006; J. Park et al., 2012; St-Laurent et al., 2014). Collectively, these findings suggest that aging is associated with a reduced ability to successfully integrate contextual features together to form detailed perceptual representations during encoding.

In addition to age-related changes in brain activity during episodic encoding, several studies have also reported age-related differences in retrieval activity within posterior perceptual, parietal, and PFC regions. For instance, in a recent study, St-Laurent and colleagues (2014) found reduced specificity of patterns of activation in primary sensory/perceptual areas in older versus young adults during retrieval of complex video stimuli. In addition, age-related reductions in retrieval activity have also been found in lateral and anterior PFC regions (Dulas & Duarte, 2012; McDonough et al., 2013; Mitchell et al., 2013; Rajah, Languay, et al., 2010). This has been interpreted as reflecting an age-related decrease in the ability to selectively retrieve and/or evaluate appropriate goal-relevant information active during remembering.

Age-related reductions in PFC, MTL, and posterior perceptual areas may be accompanied by increased activation in older versus young adults in lateral prefrontal areas during encoding (Maillet & Rajah, 2014) and/or in lateral parietal regions at retrieval (Davis et al., 2008). For example, older adults in one recent study showed increased activation relative to young adults in an area of LPC during retrieval of source information, independent of the type information that was remembered (Mitchell et al., 2013). Age-related increases in activation in parietal, as well as PFC regions, have often been attributed to dedifferentiation related to

reduced neural efficiency with age (Morcom et al., 2007). However, to the extent that these age-related increases are positively related to older adults' memory performance, they may be considered compensatory (Cabeza, 2002; Reuter-Lorenz, 2002).

We recently conducted an fMRI study of spatial and temporal source memory across the adult lifespan and identified age-related increases and decreases in task-related activation during encoding versus retrieval (Ankudowich, Pasvanis, & Rajah, 2016). Behaviorally, we found that source memory decline started in early midlife and continued into older age. Our fMRI results identified a set of brain regions that exhibited an age $\times$ memory phase (encoding/retrieval) interaction. For example, we identified no significant age-related difference in bilateral FFG and left anterior PFC activity at encoding but identified significant group differences in activity in these regions at retrieval. This was due to young adults exhibiting more activity in these regions at retrieval compared to encoding, whereas middle-aged and older adults did not exhibit this effect. In addition, we found that older adults exhibited more activity in left lateral PFC during encoding and in bilateral hippocampal/parahippocampal and LPC during retrieval, compared to young and middle-aged adults. We concluded that source memory decline at midlife was associated with changes in ventral visual and left anterior PFC function, whereas additional changes in left lateral PFC, bilateral parietal and hippocampal/parahippocampal cortices were evident by late life. However, it remained unclear how these age-related changes in brain activity contributed to source memory performance, since we did not directly examine the association between brain activity, age and source retrieval accuracy. Age-related differences in brain activity during source memory tasks may reflect fundamental differences in brain function with age (i.e., age

effects) or they may reflect age-differences in memory performance (i.e., performance effects; de Chastelaine et al., 2016a, 2016b). Since increased age is significantly related to decreases in memory performance, one methodological challenge has been in identifying age-group differences in activation related to memory tasks that are independent from group differences in performance. So, it is possible that findings from previous neuroimaging studies of age-related differences in source memory that neglected to account for age differences in memory performance may have, to some degree, confounded dissociable effects of age and performance on task-related activity. As such, it is possible that some of the age $\times$ phase interactions we observed in our previous study (Ankudowich et al., 2016) were due to group differences in performance, and not due to age.

The primary aim of the present study is to expand upon our prior findings (Ankudowich et al., 2016) and investigate how age *and performance* affect brain activity during source encoding and retrieval. To this aim, we tested additional participants (n=16) using the Ankudowich et al. (2016) paradigm and conducted a novel multivariate analysis on this increased sample (n=128). In order to derive independent age versus performance effects, we orthogonalized the continuous variables of age and retrieval accuracy. We then submitted these orthogonalized age and accuracy terms to a multivariate B-PLS analysis to identify whole-brain patterns of encoding and retrieval activity that maximally related to age and accuracy on spatial and temporal source memory tasks across the adult lifespan. Thus, the methodological approach used in the current study is novel and allowed us to differentiate patterns of encoding and retrieval activity that reflect age effects and performance effects in a data-driven way. Furthermore, by using two separate source memory tasks that test for different types of

information, our data-driven B-PLS should identify whether differential effects of age and performance during encoding or retrieval were primarily driven by task-specific or task-general patterns of activity.

Based on our previous findings in Ankudowich et al. (2016) and those of others, we expected to find differential effects of age on encoding and retrieval activity in posterior visual areas and fronto-parietal attentional network areas important for recollection-based episodic memory and cognitive control (Grady, 2008; Mitchell & Johnson, 2009; Rajah & D'Esposito, 2005). Specifically, we hypothesize that age-related differences in posterior visual and parietal activity would be evident in the current study, and would be associated with task performance (Chee et al., 2006; J. Park et al., 2012; St-Laurent et al., 2014). In contrast, we hypothesize that task-related activity in PFC and HC would display more complex effects reflective of both age- and performance-specific effects, since gray matter volume reductions and functional changes in PFC and the HC have consistently been associated with age-related memory decline (Head et al., 2008; Maillet & Rajah, 2011, 2013; Raz, Gunning-Dixon, Head, Dupuis, & Acker, 1998; Spencer & Raz, 1995; West, 2000).

3.3. Methods

3.3.1. Participants

One hundred and twenty-eight healthy adults between the ages of 19-76 yrs (mean age = 46.96 yrs; 85 females; mean years of formal EDU = 15.68 yrs) were recruited for participation in the study. Participants reported having no history of serious cardiovascular disease, neurological or psychological illness, or a family history of Alzheimer's disease, defined as the

absence of any blood relatives with probable Alzheimer's disease type dementia (Hayden et al., 2009). Of the 128 participants tested, 45 were young (age range 19-35 yrs, mean age = 26.13 yrs, 29 females, mean EDU = 16.09 yrs), 39 were middle-aged (age range 40-58 yrs, mean age = 48.87 yrs, 28 females, mean EDU = 15.33 yrs), and 44 were older adults (age range 60-76 yrs, mean age = 66.57 yrs, 28 females, mean EDU = 15.57 yrs). All participants were right-handed, confirmed using the Edinburgh Inventory for Handedness.

The study involved two sessions, conducted on separate days. The first session consisted of a neuropsychological eligibility assessment (i.e., the MINI, inclusion cutoff ≤ 2; the MMSE, exclusion cutoff < 27; the BDI, exclusion cutoff < 15) and a practice session of the source memory tasks in a mock MRI scanner. Additionally, the CVLT was also administered during the first session as an assessment of item memory recall. One-way ANOVAs were conducted on CVLT and level of EDU (yrs) to assess any significant differences on these measures between groups. All individuals gave informed consent to participate and were paid, and the ethics board of the Faculty of Medicine at McGill University approved the study protocol.

3.3.2. Behavioral methods

Only participants who met the neuropsychological cutoff criteria and had above-chance performance on the mock-scanner practice versions of the source memory tasks participated in the current fMRI study, and fMRI scanning took place during a second, separate session. Details about the methods and stimuli used in the present study have been previously specified in Kwon et al. (2016). In brief, participants were scanned across 12 experimental runs, using a mixed rapid event-related fMRI design. Each run included easy versions of spatial source

memory and temporal source memory tasks (i.e., SE, TE), and a hard version of either a spatial or temporal (i.e., SH, TH) source memory task (see **Figure 3.1** for details). In each run, participants were scanned during both encoding and retrieval phases. The order of runs was counterbalanced across participants. Thus, across all 12 runs, each participant performed SH and TH tasks 6 times, and SE and TE tasks 12 times. The tasks are described below.

Stimuli were used in prior studies by Rajah, Ames, and D'Esposito (2008) and Rajah et al. (2010), and consisted of black-and-white photographs of faces, cropped at the neck. Face stimuli were varied in age and had previously been independently rated for pleasantness. Across experimental conditions, stimuli were balanced for age and sex, and faces were not repeated. All faces shown at encoding were subsequently tested at retrieval. The temporal distance between faces at encoding that were then paired together at retrieval was pseudorandomized across trials. The average number of intervening faces for tested pairs was 2.17 in easy conditions and 4.03 in hard conditions.

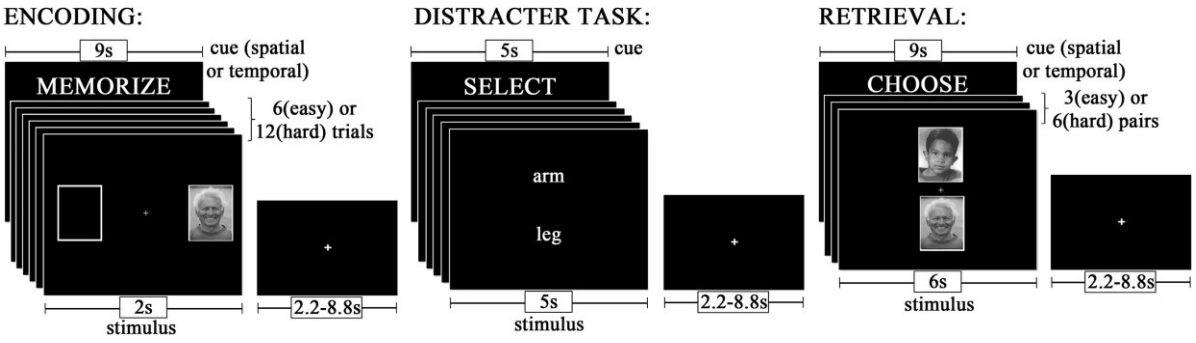

Figure 3.1. Task fMRI procedure and event timeline.

3.3.3. Task description

Encoding was intentional, and participants were cued (9s) at the start of each encoding phase to memorize either the spatial location or the temporal order of the faces. Six (easy) or 12 (hard) faces were then serially presented either to the left or the right of a central fixation cross. Each stimulus appeared for 2s and was followed by a variable ITI (2.2-8.8s). Participants were also instructed to rate each face at encoding as either pleasant or neutral. Responses were collected via an MRI-compatible fiber optic response box held with two hands; participants pressed a button with their right thumb for *pleasant* and a button with their left thumb for *neutral*. In total there were 72 encoding events presented for each event type (i.e., 288 total encoding events). Between encoding and retrieval phases, participants performed an alphabetization distracter task (60s) to deter rehearsal of encoded information. During the alphabetization task, participants were presented with two words on the screen and were instructed to select the word that comes first in the alphabet.

After the distracter task, at the start of each retrieval phase, a cue (9s) indicated to participants what the upcoming retrieval task would be: spatial or temporal. For the spatial task, participants were cued to choose the face that they saw previously on the *LEFT* (or *RIGHT*). For the temporal task, participants were cued to choose the face that they saw *LEAST* (or *MOST*) recently. For each retrieval event following the cue, participants viewed two previously encoded faces presented above and below a central fixation cross. Participants pressed the button under their right thumb to choose the face at the top of the screen, and they pressed the button under their left thumb to choose the face at the bottom of the screen. For easy tasks, three face pairs were presented serially during retrieval, and for hard tasks, six face pairs

were presented serially during retrieval. Each retrieval pair appeared for 6s followed by a variable ITI (2.2-8.8s). In total, 36 retrieval events were presented per event type (i.e., 144 total retrieval events).

3.3.4. Behavioral data analysis

Repeated-measures ANOVAs were conducted on retrieval accuracy (% correct) and RT (ms) with age group (3: young, middle-aged, older adults) as a between-subjects factor, and task (2: temporal, spatial) and difficulty (2: easy, hard) as within-subject factors, to determine significant group, task, and difficulty main effects and interactions (significance threshold $p < 0.05$). Post-hoc pairwise comparisons were conducted as needed to clarify significant effects and interactions. In addition, we performed polynomial contrasts to test for linear trends in task performance across age groups.

3.3.5. MRI methods

Structural and functional magnetic resonance images were acquired at the Douglas Institute Brain Imaging Centre while participants lied supine in a 3T Siemens Trio scanner. T1-weighted anatomical images were acquired at the start of the fMRI session using a 3D gradient echo MPRAGE sequence (TR=2300ms, TE=2.98ms, flip angle=9°, 176 1mm sagittal slices, $1 \times 1 \times$ 1mm voxels, FOV=256). BOLD images were acquired using a single-shot T2*-weighted gradient EPI pulse sequence (TR=2000ms, TE=30ms, FOV=256). Brain volumes with 32 oblique slices of 4mm thickness (no slice gap) and an in-plane resolution of 4×4mm were obtained while participants performed the source memory tasks. A mixed rapid event-related design with a

variable ITI (as stated above) was used to add jitter to event-related acquisitions. Visual task stimuli were back-projected onto a screen in the scanner bore using E-Prime software (described above). The screen was visible to participants lying in the scanner via a mirror mounted on a standard head coil. Participants requiring correction for visual acuity wore corrective plastic lenses.

Preprocessing. Reconstructed images were converted to ANALYZE format and preprocessed in SPM8 software. Images from the first 10s of scanning prior to task onset were discarded to ensure all tissue had reached steady state magnetization. For each participant, the origin of each functional image was reoriented to the anterior commissure of the acquired T1-weighted anatomical image. Functional images were then realigned to the first acquired image and corrected for motion artifacts using a 6-parameter rigid-body spatial transform. Participants with more than 4mm of within-run movement were discarded from analysis. Functional images were then spatially normalized to the MNI EPI template available in SPM ($4 \times 4 \times 4$mm voxel resolution) and spatially smoothed (8mm FWHM isotropic Gaussian kernel). ArtRepair toolbox for SPM8 was used to detect and correct (<5% interpolated data) slice artifacts prior to realignment and volume artifacts after normalization and smoothing (http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html). Interpolated data for one run in one participant exceeded 5%, and so this run was dropped from analysis. Due to time constraints, some participants were unable to complete all 12 runs of the source memory tasks, and retrieval accuracy for these individuals was adjusted accordingly. Across all participants, the minimum number of observations included in the fMRI analysis per event type was 11 (min SE = 17, min SH = 13, min TE = 11, min TH = 11).

Multivariate partial least squares analysis. We used multivariate spatiotemporal B-PLS to analyze the fMRI data in order to identify whole-brain patterns of task-related encoding and retrieval activity that correlated with age and/or retrieval accuracy. This approach was chosen due to its capacity to detect spatially and temporally distributed patterns of activated voxels that differ across experimental conditions and/or relate to a specific behavioral measure. (McIntosh et al., 2004). Details on this method have been published elsewhere (Krishnan, Williams, McIntosh, & Abdi, 2011; McIntosh & Lobaugh, 2004). First, fMRI encoding and retrieval data for correctly remembered events were stored in a data matrix by event type and stacked across participants. This stacked matrix contained fMRI data for each event onset (time lag = 0) as well as the subsequent seven TRs/time lags (TR = 2s $\times$ 7 = 14s) following event onset. In a step that was separate from the B-PLS, we conducted a regression analysis in which task-specific retrieval accuracy (X) was used to predict age (Y) to obtain the age-residual (error) vector that would be uncorrelated to retrieval accuracy (% correct). The age-residual vector and the retrieval accuracy (% correct) vector were then stacked in the same manner as the fMRI data matrix. The stacked fMRI data matrix was then cross-correlated with the similarly stacked behavioral vectors. The resulting cross-correlation matrix was submitted to SVD, which yielded an orthogonal set of LVs. Each LV consists of: i) a singular value that reflects the amount of covariance accounted for by the LV, ii) a correlation profile that depicts how the age-residual and retrieval accuracy vectors correlate with a pattern of whole-brain activity identified in the singular image (described next), and iii) a singular image representing a pattern of brain saliences. These brain saliences are numerical weights assigned to each voxel at each TR/time lag included in the data matrix, and they identify a pattern of whole-brain activity that is

symmetrically related to the correlation profiles for age residual and retrieval accuracy. Brain saliences can be negative or positive. Brain regions with positive voxel saliences are positively related to the correlation profile, whereas those with negative voxel saliences are negatively related to the correlation profile. Thus, each LV reflects a symmetrical pairing of correlation profiles with a pattern of whole-brain activity. Positive values in the correlation profiles indicate a *positive* association (i.e., correlations with 95% confidence intervals) with positive salience brain regions in the singular image, but they also indicate a *negative* association with negative salience brain regions in the singular image. The inverse can be said of negative values in the correlation profiles; they indicate a *negative* association with positive salience brain regions in the singular image and a *positive* association with negative salience brain regions.

Significance testing of LVs identified from the B-PLS analysis was conducted using permutation tests ($p < 0.05$, 1000 permutations) on the singular values. In addition, the stability of each voxel's contribution to an LV was assessed with bootstrapping (BSR = ±3.28, $p < 0.001$, 500 iterations; minimum cluster size = 15). Significant peaks identified with bootstrapping reflect regions that are maximally stable and significant across subjects and are presented in the singular image as positive or negative brain saliences. The BSR of a significant voxel salience reflects the stability of its activation. To determine at which time lags the correlation profiles of LVs were maximally represented, we computed temporal brain scores for each event type in each significant LV. Temporal brain scores represent the degree to which each subject expresses the pattern of brain activity identified by the singular image (in relation to its paired correlation profile) at each time lag. The temporal brain score can be used to indicate the time lags in which the correlation profile is maximally differentiated within the temporal window

sampled (McIntosh et al., 2004). We used this temporal score to identify the subset of time lags that maximally represented the effects of interest, and only report activations from those time lags (Crane, Maillet, Floden, Valiquette, & Rajah, 2011; Vallesi, McIntosh, Alexander, & Stuss, 2009). In the current analyses the peak time lags were lags 2-5 (4-10s post event onset). Peak coordinates are only reported from these time lags at which task differences were maximal. These peak coordinates were converted from MNI to Talairach space using the icbm2tal transform (Lancaster et al., 2007), as implemented in GingerAle 2.3 (Eickhoff et al., 2009). Since our acquisition incompletely acquired the cerebellum, peak coordinates from this region are not reported. The Talairach and Tournoux atlas (Talairach, Rayport, & Tournoux, 1988) was used to identify the Brodmann area (BA) localizations of significant activations.

In sum, the B-PLS analysis identified LVs that maximally related whole-brain task-related encoding and retrieval activity with the continuous, orthogonal variables of age (residualized) and retrieval accuracy. It is important to note that the B-PLS analysis used in the current study was data-driven, and the resultant LVs therefore do not reflect any a priori manipulations of task-related activations that would be associated with an imposed contrast. Moreover, because the age term that was entered into the B-PLS analysis was residualized with retrieval accuracy, age effects reported in the current study are independent of individual differences in task performance. The same cannot be said of the performance effects reported in the current study, which may reflect some degree of age-related variance. That is, the retrieval accuracy term included in the B-PLS was a non-residualized variable and therefore included the shared variance of both age and performance.

3.4. Results

3.4.1. Behavior

Table 3.1 displays group means for the CVLT, EDU, retrieval accuracy scores (% correct) and RTs (ms) for each source memory event type. One-way ANOVAs indicated there was a significant group difference on the CVLT delayed free recall ($F(2,125) = 3.53$, $p < 0.05$) due to the fact that young adults outperformed both middle-aged and older adults (both $ps < 0.05$).

Accuracy results. The task (2) × difficulty (2) × group (3) repeated-measures ANOVA on retrieval accuracy identified significant main effects of task ($F(1,125) = 611.53$, $p < 0.001$), difficulty ($F(1,125) = 106.34$, $p < 0.001$), and age group ($F(2,125) = 15.34$, $p < 0.001$). In addition, there was a significant task × difficulty interaction ($F(1, 125) = 29.54$, $p < 0.001$). The main effect of age was due to young adults outperforming both middle-aged and older adults and middle-aged adults outperforming older adults across conditions (all $ps < 0.05$). Between-group contrasts assessing polynomial trends further qualified that this effect of age was linear ($p < 0.001$). Although across groups, participants performed better on spatial versus temporal tasks and on easy versus hard tasks, the significant task × difficulty interaction indicated that the difficulty manipulation had a larger impact in reducing retrieval accuracy on the temporal task (*M difference* = 0.11; $F(1,125) = 105.02$, $p < 0.001$) compared to the spatial task (*M difference* = 0.04; $F(1,125) = 20.88$, $p < 0.001$). Furthermore, within-subject contrasts testing polynomial trends in retrieval accuracy qualified that the task × difficulty interaction was linear (SE > SH > TE > TH) across groups ($p < 0.001$). Thus, increasing encoding load significantly impacted task difficulty in young, middle-aged, and older adults. No other main effects or interactions were significant.

Table 3.1. Demographics and behavioral data.

	Young adults	Middle-aged adults	Older adults
Sample size (n)	45	39	44
Age (mean ± se)	26.13 ± 0.55	48.87 ± 0.92	66.57 ± 0.56
Gender (n, [%] females)	29 [64.4%]	28 [71.8%]	28 [63.6%]
Education (Years, mean ± se)	16.09 ± 0.30	15.33 ± 0.33	15.57 ± 0.35
DFR_CVLT (mean ± se)*	13.82 ± 0.25	12.69 ± 0.36	12.86 ± 0.36
DCR_CVLT (mean ± se)	13.93 ± 0.26	13.15 ± 0.32	13.11 ± 0.31
DRG_CVLT (mean ± se)	15.49 ± 0.10	15.26 ± 0.14	15.11 ± 0.14
Spatial Easy retrieval accuracy (% correct, mean ± se)	0.88 ± 0.01	0.85 ± 0.02	0.81 ± 0.02
Spatial Hard retrieval accuracy (% correct, mean ± se)	0.87 ± 0.02	0.79 ± 0.02	0.77 ± 0.02
Temporal Easy retrieval accuracy (% correct, mean ± se)	0.76 ± 0.02	0.70 ± 0.02	0.65 ± 0.02
Temporal Hard retrieval accuracy (% correct, mean ± se)	0.67 ± 0.02	0.58 ± 0.02	0.54 ± 0.01
Spatial Easy retrieval RT (ms, mean ± se)	2221.73 ± 76.13	2455.75 ± 85.20	2808.11 ± 73.20
Spatial Hard retrieval RT (ms, mean ± se)	2320.69 ± 72.72	2570.72 ± 73.14	2883.36 ± 76.97
Temporal Easy retrieval RT (ms, mean ± se)	2577.28 ± 80.40	2871.04 ± 85.75	3145.06 ± 89.94
Temporal Hard retrieval RT (ms, mean ± se)	2767.14 ± 94.19	2988.54 ± 93.00	3201.69 ± 93.37

Note: This table presents the group means and standard errors (se) for demographic, neuropsychological and fMRI behavioral measures. DFR= Delay Free Recall; DCR= Delay Cued Recall; DRG= Delay Recognition; CVLT = California Verbal Learning Test; RT= Reaction time. *Denotes a significant effect of age group, where young > middle-aged = older ($p < 0.05$).

Reaction time results. The task (2) × difficulty (2) × group (3) repeated-measures ANOVA on retrieval RT (ms) identified significant main effects of task ($F(1,125) = 135.85$, $p < 0.001$), difficulty ($F(1,125) = 31.47$, $p < 0.001$), and age group ($F(2,125) = 13.42$, $p < 0.001$). Young adults performed faster than both middle-aged and older adults, and middle-aged adults performed faster than older adults across conditions (all p*s* < 0.05). Between-group contrasts assessing

polynomial trends confirmed that the main effect of age was linear ($p < 0.001$). Across groups, individuals were slower on temporal versus spatial tasks and on hard versus easy versions of the tasks (both ps < 0.001). No other effects or interactions were significant.

3.4.2. fMRI results

The data-driven B-PLS analysis identified four significant LVs ($p < 0.05$). The first LV (LV1) accounted for 23.46% of the total cross-block covariance ($p < 0.001$) and is presented in **Figure 3.2A**. Only negative salience brain regions from this LV survived our spatial threshold cutoff of 15 contiguous voxels ($p < 0.001$), and local maxima are listed in **Table 3.2**. The PLS correlation profile in **Figure 3.2B** indicates that, at encoding, activity in negative salience regions (colored in blue, **Figure 3.2A**) increased with age across all event types and with subsequent SH accuracy.

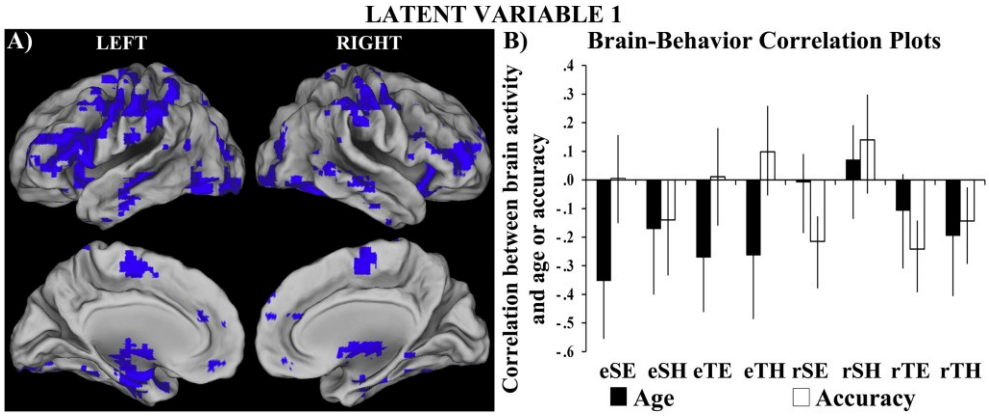

Figure 3.2. Singular image and corresponding correlation profile for B-PLS LV1. (A) Singular image for LV1. Red brain regions reflect positive brain saliences and blue regions reflect negative brain saliences, threshold bootstrap ratio of ±3.28, $p < .001$. (B) Brain-behavior correlation profile for each event type for LV1. The correlation profile indicates that negative voxel saliences positively correlate with age at encoding and with accuracy at retrieval. Error bars represent 95% confidence. Activations are presented on template surface images of the left and right hemispheres of the brain using Caret software (http://brainvis.wustl.edu/wiki/index.php/Caret:Download). SE = spatial easy; SH = spatial hard; TE = temporal easy; TH = temporal hard; e = encoding; r = retrieval.

Table 3.2. LV1 brain regions in which task-related activity was related to age at encoding and to accuracy at retrieval.

Lag	BSR	Spatial extent	Talairach coordinates x	y	z	HEM	Gyral location	BA
Negative Saliences: Regions where activity was positively correlated with age at encoding and with accuracy at retrieval								
2,3,5	-5.85	285	50	-29	49	Right	Inferior parietal lobule/postcentral gyrus	40
2	-5.36	144	-2	-14	53	Left	Medial frontal gyrus	6
2,3,5	-5.16	147	-50	-40	47	Left	Inferior parietal lobule/supramarginal gyrus	40
2,3	-5.01	85	-31	-15	60	Left	Precentral gyrus	6
3,5	-5.47	180	47	-23	-8	Right	Superior/middle temporal gyrus*	22/21
3	-3.99	19	-19	-14	-26	Left	Parahippocampal gyrus	35
5	-6.20	251	-27	-86	-19	Left	Fusiform gyrus	18
4,5	-4.75	153	40	42	20	Right	Middle frontal gyrus	10
4,5	-4.71	119	32	-82	12	Right	Middle occipital gyrus	19
4	-4.62	109	-38	19	23	Left	Inferior frontal gyrus	44/46
4	-4.04	24	-31	-75	22	Left	Middle occipital gyrus	19
5	-5.87	185	25	18	-8	Right	Inferior frontal gyrus	47
5	-4.66	70	40	-68	-12	Right	Fusiform gyrus	19
5	-4.58	20	-4	44	-2	Left	Ventromedial frontal gyrus/anterior cingulate	32
5	-4.41	65	-1	43	52	Left	Superior frontal gyrus	8
5	-3.91	16	39	11	28	Right	Inferior/middle frontal gyrus	44/9
5	-3.90	16	-53	-22	23	Left	Postcentral gyrus	2/40
5	-3.84	23	39	36	37	Right	Middle frontal gyrus	8/9
5	-3.78	15	14	48	31	Right	Superior frontal gyrus	9

Note: Lag represents the time after event onset when a cluster of voxels exhibited an effect of interest. Bootstrap ratio (BSR) threshold was set to ±3.28 and identified dominant and stable activation clusters. Spatial extent refers to the total number of voxels included in the voxel cluster (threshold = 15). Stereotaxic coordinates are measured in millimeters, and gyral location and Brodmann areas (BAs) were determined by referring to Talairach and Tournoux (1988). HEM = Cerebral hemisphere in which the activation occurred. *Extends medially into right amygdala.

At retrieval, activity in negative salience regions increased with higher retrieval accuracy for all event types, except for SH, and with age for TH. These regions included: bilateral FFG, bilateral

IPL, bilateral middle occipital gyrus, bilateral IFG and SFG, left PHG, ventromedial PFC/anterior cingulate, right superior/middle temporal gyrus extending into amygdala, and right MFG. Therefore, LV1 primarily identified brain regions in which event-related activity was positively correlated with age at encoding and with accuracy at retrieval.

LV2 identified a pattern of event-related brain activity during both encoding and retrieval, which was differentially correlated with age versus retrieval accuracy. This LV accounted for 15.31% of the cross-block covariance ($p < 0.001$). The singular image and correlation profile for this LV are presented in **Figures 3.3A and 3.3B**, respectively, and the local maxima are presented in **Table 3.3**. The correlation profile indicates that activity in positive salience regions (colored in red in **Figure 3.3A**) was positively correlated with age and negatively correlated with retrieval accuracy across all event types during both encoding and

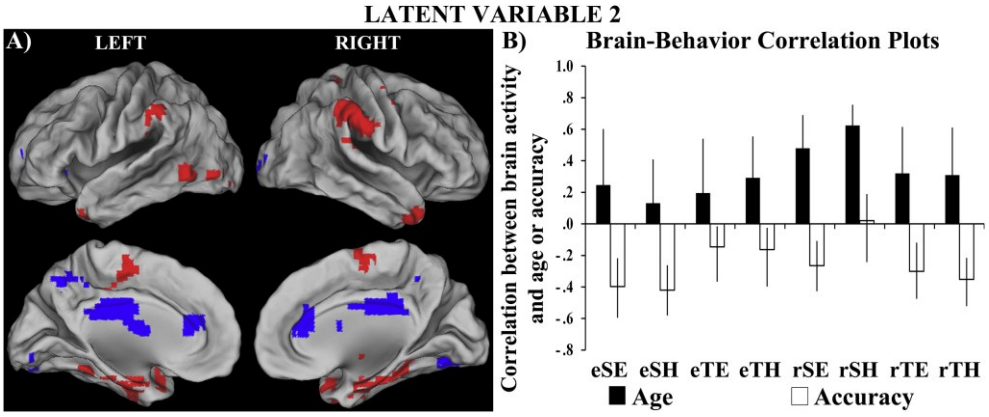

Figure 3.3. Singular image and corresponding correlation profile for B-PLS LV2. (A) Singular image for LV2. Red brain regions reflect positive brain saliences and blue regions reflect negative brain saliences, threshold bootstrap ratio of ±3.28, $p < 0.001$. (B) Brain-behavior correlation profile for each event type for LV2. The correlation profile indicates that positive brain saliences i) correlate positively with age at encoding and retrieval ii) correlate negatively with accuracy at encoding and retrieval. In contrast, negative voxel saliences i) correlate positively with accuracy at encoding and retrieval and ii) correlate negatively with age at encoding and retrieval. Error bars represent 95% confidence. Activations are presented on template images of the lateral and medial surfaces of the left and right hemispheres of the brain using Caret software (http://brainvis.wustl.edu/wiki/index.php/Caret:Download). SE = spatial easy; SH = spatial hard; TE = temporal easy; TH = temporal hard; e = encoding; r = retrieval.

Table 3.3. LV2 brain regions in which task-related activity was differentially related to age vs. accuracy across encoding and retrieval.

			Talairach coordinates					
Lag	BSR	Spatial extent	x	y	z	HEM	Gyral location	BA
Positive Saliences: Regions where activity was positively correlated with age and negatively correlated with retrieval accuracy								
2,3	6.26	70	-57	-61	-6	Left	Inferior temporal gyrus	37
2,3	6.25	159	54	-39	41	Right	Inferior parietal lobule	40
2,3	4.90	19	40	16	-26	Right	Superior temporal gyrus	38
2,3	4.07	16	6	-15	61	Right	Medial frontal gyrus	6
2	3.75	17	25	2	5	Right	Putamen	
3	4.92	33	-61	-43	39	Left	Inferior parietal lobule	40
4	6.57	159	-34	-10	-30	Left	Uncus	20
4	5.59	237	21	-18	-22	Right	Parahippocampal gyrus	28
4	4.82	41	-46	-75	-11	Left	Ventral occipital gyrus	18
4	4.59	39	-30	9	-24	Left	Superior temporal gyrus	38
Negative Saliences: Regions where activity was negatively correlated with age and positively correlated with retrieval accuracy								
2,3,5	-5.17	53	25	-69	-5	Right	Fusiform gyrus	19
2	-4.66	34	-23	-75	-14	Left	Fusiform gyrus	19
2	-4.38	76	-5	26	25	Left	Anterior cingulate	24
3	-4.69	78	3	31	18	Right	Anterior cingulate	24
3	-4.34	16	-27	57	16	Left	Superior frontal gyrus	10
3,4	-4.19	21	-13	-64	30	Left	Precuneus	7
4	-6.58	754	-1	-30	23	Left	Posterior cingulate	23
5	-4.92	323	-16	-7	21	Left	Caudate	

Note: Lag represents the time after event onset when a cluster of voxels exhibited an effect of interest. Bootstrap ratio (BSR) threshold was set to ±3.28 and identified dominant and stable activation clusters. Spatial extent refers to the total number of voxels included in the voxel cluster (threshold = 15). The stereotaxic coordinates are measured in millimeters, and gyral location and Brodmann areas (BAs) were determined by referring to Talairach and Tournoux (1988). HEM = Cerebral hemisphere in which the activation occurred.

retrieval phases (with the exception of SH accuracy at retrieval). These regions included: left ventral occipital gyrus, left inferior temporal gyrus and bilateral STG, bilateral IPL, and PHG. Negative salience regions from this LV reflected the inverse pattern of correlations with age and

retrieval accuracy. That is, activity in negative salience regions (colored in blue in **Figure 3.3A**) positively correlated with accuracy across event types (except for SH) at encoding and retrieval, and it negatively correlated with age across event types at encoding and retrieval. These regions included: bilateral FFG, bilateral anterior cingulate, left SFG, left precuneus, and posterior cingulate.

LV3 accounted for 11.92% of the total cross-block covariance ($p < 0.01$) and is presented in **Figures 3.4A and 3.4B**. The local maxima for this LV are listed in **Table 3.4**. LV3 identified a pattern of event-related brain activity that was differentially correlated with age versus retrieval accuracy at retrieval and was correlated with spatial task accuracy at encoding. Specifically, the correlation profile for this LV indicates that, at encoding, activity in positive salience regions was positively correlated with subsequent retrieval accuracy on spatial tasks. In

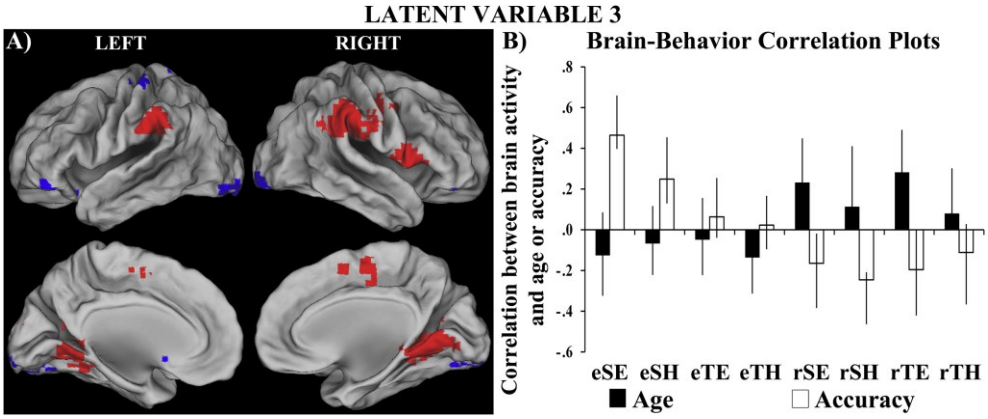

Figure 3.4. Singular image and corresponding correlation profile for B-PLS LV3. (A) Singular image for LV3. Red brain regions reflect positive brain saliences and blue regions reflect negative brain saliences, threshold bootstrap ratio of ±3.28, $p < 0.001$. Activations are presented on template surface images of the left and right hemispheres of the brain using Caret software (http://brainvis.wustl.edu/wiki/index.php/Caret:Download). (B) Brain-behavior correlation profile for each event type for LV3. The correlation profile indicates that positive brain saliences i) correlate positively with accuracy at encoding for spatial tasks and with age at retrieval for all event types ii) correlate negatively with accuracy at retrieval. In contrast, negative voxel saliences i) correlate positively with accuracy at retrieval and ii) correlate negatively with accuracy at encoding for spatial tasks and with age at retrieval for all event types. SE = spatial easy; SH = spatial hard; TE = temporal easy; TH = temporal hard; e = encoding; r = retrieval.

Table 3.4. LV3 brain regions in which task-related activity showed age effects at retrieval and was differentially related to performance.

			Talairach coordinates					
Lag	BSR	Spatial extent	x	y	z	HEM	Gyral location	BA
Positive Saliences: Regions where activity at retrieval positively correlated with age and negatively correlated with retrieval accuracy, and where activity at encoding positively correlated with spatial accuracy								
2,3,4	4.81	64	51	8	13	Right	Inferior frontal/precentral gyrus	44
2	3.97	20	-23	1	11	Left	Putamen	
3	6.09	219	50	-35	31	Right	Inferior parietal lobule	40
3	5.10	76	-50	-42	28	Left	Inferior parietal lobule	40
3,5	4.28	67	29	-39	1	Right	Hippocampus	
3	4.16	31	43	-2	44	Right	Middle frontal/precentral gyrus	6
3	4.03	26	6	-18	53	Right	Medial frontal gyrus	6
4	3.99	16	20	-22	57	Right	Precentral gyrus	4
4	3.65	19	13	-20	35	Right	Cingulate gyrus	31
5	4.41	44	-27	-39	4	Left	Hippocampus	
Negative Saliences: Regions where activity at retrieval negatively correlated with age and positively correlated with retrieval accuracy, and where activity at encoding negatively correlated with spatial accuracy								
2	-4.31	19	-39	-33	58	Left	Postcentral gyrus	2
3,4	-4.31	27	-27	-79	-14	Left	Fusiform/lingual gyrus	18/17
4	-4.50	37	25	-87	-14	Right	Fusiform gyrus	18

Note: Lag represents the time after event onset when a cluster of voxels exhibited an effect of interest. Bootstrap ratio (BSR) threshold was set to ±3.28 and identified dominant and stable activation clusters. Spatial extent refers to the total number of voxels included in the voxel cluster (threshold = 15). Stereotaxic coordinates are measured in millimeters, and gyral location and Brodmann areas (BAs) were determined by referring to Talairach and Tournoux (1988). HEM = Cerebral hemisphere in which the activation occurred.

contrast, at retrieval, activity in these same regions across event types was negatively correlated with accuracy, but positively correlated with age. Positive salience regions included: bilateral HC, bilateral IPL, and right IFG. Negative brain salience regions exhibited the opposite pattern of correlations. In other words, activity in negative salience regions at encoding was negatively correlated with subsequent retrieval accuracy on spatial tasks, but activity in these regions at retrieval was positively correlated with accuracy and negatively correlated with age.

These regions included: left LG and bilateral FFG. Thus, the overall pattern of this LV indicates an interaction of age and accuracy × phase.

LV4 accounted for only 7.60% of the cross-block covariance ($p < 0.05$). It identified brain regions in which task-related activity was similarly correlated with accuracy during encoding and retrieval and with age during spatial context retrieval. However, only one negative brain salience peak was identified at the thresholds employed in left postcentral gyrus (BA 5; x = -2, y = -42, z = 65 mm; BSR = -4.05; spatial extent = 33). Activity in this region was negatively related to accuracy across encoding and retrieval conditions and negatively related to age during spatial retrieval.

3.4.3. Summary

Overall, LV2 identified a whole-brain pattern of activation that reflected a trade-off between age and performance across event types and memory phases, whereas LVs 1 and 3 reflected differential associations between age, performance, and phase-related activity. LV1 identified brain areas where activity positively related to age at encoding and where activity was negatively related to source memory accuracy at retrieval. LV3 primarily identified areas in which activity was positively related with age during retrieval and negatively related to source memory accuracy. Consistent with our previous study (Ankudowich et al., 2016), the patterns resulting from the data-driven B-PLS analysis did not largely differentiate task-specific effects. Rather, we found that the LVs in the current study largely represented effects that generalized across tasks and levels of difficulty, suggesting that effects of age and performance on phase-related activity accounted for the largest amount of variance in the dataset. Finally, LV4

represented an effect of accuracy that generalized across encoding and retrieval conditions and that related to age only for spatial retrieval conditions. Due to the fact that LV4 accounted for less than 10% of the overall variance of this lifespan data set and to the fact that it showed minimal age effects, it was not of primary relevance to our hypotheses. For this reason, LV4 will not be discussed further. Our principle aim was to identify dissociable effects of age on patterns of encoding and retrieval activity that differentially related to source memory performance across the adult lifespan. Thus LV1, LV2, and LV3 showed effects that were of primary relevance to our interests and will be the focus of our discussion.

3.5. Discussion

In the current study, we aimed to differentiate effects of age and performance on brain activity during source encoding and retrieval. The behavioral results show that, across all source memory tasks, young adults had significantly higher source retrieval accuracy compared to middle-aged and older adults, and that middle-aged adults had significantly higher source retrieval accuracy than older adults. These findings are consistent with previous studies that have shown source memory reductions begin at early midlife (Cansino, 2009) and continue into older adulthood (Spencer & Raz, 1995). Across participants, accuracy changed linearly as a function of task and difficulty, where accuracy was highest on spatial easy tasks and lowest on temporal hard tasks. Importantly, we found no evidence that age group interacted with retrieval accuracy on different tasks or levels of difficulty, indicating that performance in older age groups was not disproportionately affected by increases in task difficulty. Our behavioral

results therefore suggest that young, middle-aged, and older adults in the current study showed a similar linear pattern of performance across event types.

Our B-PLS analysis of the fMRI data identified three significant effects. The first effect (LV2) identified a pattern of brain activity that reflected a generalized age/performance trade-off. In other words, this effect identified bilateral ventral visual and parietal regions in which age-related differences in brain activity were indeed associated with individual differences in retrieval accuracy (de Chastelaine, Mattson, Wang, Donley, & Rugg, 2015; de Chastelaine et al., 2016a, 2016b), consistent with our first hypothesis. In contrast, the second (LV1) and third (LV3) effects identified brain regions in which encoding and/or retrieval activity was distinctly associated with age or performance. However, we observed substantial overlap in the brain regions identified in LV2 and those identified in LV1 and LV3, which suggests that some of the brain regions exhibiting an age/performance effect in LV2 were also more strongly associated with either age or performance during encoding or retrieval. Importantly, there were regions identified in LV1 and LV3 that were distinct from regions identified in LV2 (i.e., bilateral lateral PFC and limbic regions in LV1; and right VLPFC and bilateral HC in LV3), which exhibited strong associations with age at either encoding or retrieval consistent with our hypotheses. Age-related differences in brain activity within these areas were not due to performance, but more directly reflective of an age effect. In the following sections we discuss each LV effect in greater detail.

3.5.1. Age/performance effects in ventral visual and parietal regions (LV2)

LV2 identified a pattern of brain activity that was differentially related to age and source memory performance across all event types during both encoding and retrieval. The peaks from this LV were largely localized in posterior regions of the core recollection network, including lateral and medial areas of ventral visual and parietal cortex. Age-related differences in activity in these regions were directly related to individual differences in performance. This pattern of findings appears to be consistent with prior studies that have suggested that age-related differences in brain activity during encoding and retrieval of source information may largely be attributed to age differences in performance effects (de Chastelaine et al., 2015, 2016a, 2016b). For example, a recent study found that, when controlling for group differences in performance, effects in anterior and posterior regions of the core recollection network in middle-aged and older adults were similar in size to those that would be expected in young adults with equivalent performance (de Chastelaine et al., 2016a).

In the current study, within regions of occipito-temporal cortex, there was a distinction between posterior medial fusiform cortex (BA 19; a negative salience region in LV2), where activity decreased with age but increased with retrieval accuracy, and lateral occipito-temporal regions (BAs 20/37/38; positive salience regions in LV2), where activity increased with age but decreased with retrieval accuracy. Areas of fusiform cortex are important for initial processing of perceptual details of faces (Kuhl, Rissman, & Wagner, 2012; Puce, Allison, Asgari, Gore, & McCarthy, 1996; Weiner & Grill-Spector, 2010). The pattern of activity in these regions suggests that face-related processing across event types elicited activity in earlier visual areas in young adulthood and elicited activity in later visual areas in older adulthood. Moreover, increased

activity in young adulthood in earlier visual areas was positively related to performance across encoding and retrieval. Young individuals may therefore have activated face-sensitive regions of bilateral FFG during both encoding and retrieval in order to correctly recollect a greater amount of relevant perceptual details related to the faces (McDonough et al., 2014).

In contrast, older individuals engaged more anterior temporal regions associated with secondary processing of the faces during both encoding and retrieval. There is evidence to suggest that more anterior temporal activation during memory tasks is associated with less specific perceptual processing of target items, which may support general item recognition, but not recollection of specific features (Garoff, Slotnick, & Schacter, 2005; Slotnick & Schacter, 2004). For instance, anterior portions of temporal cortex are associated with semantic representation and categorical labeling (e.g., identification) of individual faces (Kriegeskorte, Formisano, Sorger, & Goebel, 2007; Leveroni et al., 2000). Moreover, evidence from false memory literature shows that, in older adults, activation in secondary sematic visual processing areas elicited during remembering may not distinguish true from false perceptual recollection (Dennis, Bowman, & Peterson, 2014). In the current study, increased activation of secondary visual processing streams in older adulthood was related to decreases in performance across event types at encoding and retrieval. Thus, older individuals may have engaged in more semantic and/or categorical processing of the faces in a task-general way, which may have negatively impacted their memory for specific task-related source information. This pattern of findings is consistent with the idea that better recollection of perceptual features is supported by activation in ventral extrastriate cortex and that reduced specificity of these regions may contribute to poorer source memory performance with age (J. Park et al., 2012; St-Laurent et

al., 2014). Further support for this idea comes from the *performance* effects observed in LVs 1 and 3, where increased bilateral activity in early ventral visual areas (BAs 17/18/19) was associated with higher retrieval accuracy across individuals during encoding and retrieval, respectively. Interestingly, similar effects of *age* on activity in secondary ventral visual processing regions were also evident in LV1, suggesting that increased age-related activity in these regions was more evident at encoding. Therefore, one of the overall findings from the current study suggests that young and older adults may have attended to different kinds of perceptual features and/or processes (e.g., processing perceptual versus semantic features) at encoding, which had subsequent impacts on retrieval-related activations and performance.

LV2 also showed age-related increases in bilateral parietal activity during encoding and retrieval. These regions of LV2 were similar in location and extent to the bilateral ventral parietal regions identified in LV3. This overlap suggests that age-related increases in ventral parietal activation were more prevalent during retrieval than encoding. This pattern of findings is consistent with findings from our previous study (Ankudowich et al., 2016), where older adults exhibited greater activity in bilateral ventral parietal cortex during retrieval > encoding compared to young and middle-aged adults. In the current study, increased activation of ventral parietal regions was directly related to decreased memory performance, suggesting that the age effects observed during retrieval in Ankudowich et al. (2016) may reflect an age/accuracy trade-off.

In young adults, activation in lateral parietal cortex during episodic memory tasks has been associated with retrieval of task-relevant information (Kuhl, Johnson, & Chun, 2013) and recollection success (Kuhl & Chun, 2014). It has been hypothesized that ventral areas of parietal

cortex are important for integrating and/or attending to bottom-up activation of source features at retrieval (Cabeza, Ciaramelli, & Moscovitch, 2012). fMRI studies that have compared memory-related activation in young versus older adults have reported reduced modulation of ventral parietal activity in older adults that is characterized by increased activation in older versus young adults on source memory tasks (Ankudowich et al., 2016; Mitchell et al., 2013). Previous studies have also found that, compared to young adults, older adults show reduced suppression of task-irrelevant information during reflective attention (Gazzaley et al., 2005; Mitchell et al., 2010) and decreased task-specific modulation of posterior representational areas during retrieval (Healey et al., 2008; Mitchell et al., 2013). Assuming that activation of ventral parietal cortex reflects bottom-up attention to retrieved/integrated source features, age-related increases in ventral parietal cortex activity in the current study may be related to older adults remembering greater amounts of task irrelevant features related to the faces, and/or an inability of older adults to constrain their attention to the most relevant information at retrieval (Mitchell et al., 2013). However, these interpretations are speculative and future studies should aim to test them directly. Collectively, findings in the current study suggest that a pattern of reduced specificity in ventral visual areas (primarily at encoding) and ventral parietal areas (primarily at retrieval) may directly contribute to declines in source memory performance in older adulthood.

3.5.2. Phase differences in age vs. performance effects in DLPFC and limbic areas (LV1)

LV1 identified a positive relationship between bilateral DLPFC activity and age at encoding, and between bilateral DLPFC activity and source memory performance at retrieval.

This effect was unique to LV1, as these DLPFC regions were not identified in either LV2 or LV3. The fact that we observed age-specific effects in bilateral DLPFC regions at encoding and performance-specific effects at retrieval suggests that activation in these regions in older adulthood does not reflect an age/accuracy trade-off. In our previous study (Ankudowich et al. 2016), we reported age-related increases in an area of left lateral PFC that was specific to encoding and that generalized across event types. This region overlapped with the left DLPFC activation in LV1of the current study, suggesting that these age-related increases in encoding-related activity may be due to effects of age, independent of performance. In general, our findings are consistent with prior studies that have reported age-related increases in activation in DLPFC at *encoding* (see Maillet & Rajah, 2014; Rajah & D'Esposito, 2005 for reviews).

In young adults, DLPFC activity at encoding has been interpreted as reflecting its role in the instantiation of relational and/or organizing strategies (e.g., ordering, comparing; Blumenfeld et al., 2011; Blumenfeld & Ranganath, 2007). In the current study, at encoding, participants were required to simultaneously encode a face-context association while also making a pleasantness judgment for each face seen. Therefore, the age-related increase in bilateral DLPFC activation at encoding may reflect unconstrained relational encoding of both the pleasantness information along with the face-context information at encoding. Consistent with this interpretation of our findings, there is behavioral evidence to suggest that older and young adults preferentially weight the importance of different types of source features (M. K. Johnson et al., 1993). Whereas young adults might give preferential importance to sensory details, older adults give preferential weight to more subjective thoughts/feelings (e.g., Hashtroudi, Johnson, & Chrosniak, 1990). In a recent meta-analysis of aging studies that used

the subsequent memory paradigm, older adults exhibited greater activation relative to young adults in bilateral areas of middle and superior frontal gyri during successful > unsuccessful encoding (Maillet & Rajah, 2014). The fact that these regions supported successful memory in older but not young adults led the authors to conclude that activation of these regions across studies reflected age-related differences in the types of cognitive operations (e.g., evaluative thoughts, feelings elicited by stimuli) performed during encoding events. We observed age-related increases in encoding activity in limbic regions in LV1 concurrent with bilateral DLPFC. Specifically, LV1 showed age-related increases in ventromedial PFC/anterior cingulate (BA 32), amygdala and parahippocampal gyrus activity at encoding. This is consistent with the interpretation that the encoding task in the current study may have elicited greater attention to personally-relevant and/or socio-affective aspects of the faces (Macrae, Moran, Heatherton, Banfield, & Kelley, 2004; Northoff et al., 2006; Svoboda, McKinnon, & Levine, 2006) with increased age.

Alternatively, DLPFC activity during memory tasks has also been linked to this region's role in domain-general monitoring of information that is active during encoding (Champod & Petrides, 2007; Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999) and task-switching processes (e.g., Clapp, Rubens, Sabharwal, & Gazzaley, 2011). Therefore, given the dual-task nature of the current study's encoding task, it is also possible that maintenance/management of conflicting task goals becomes more challenging during intentional encoding with age and thus relies more on DLPFC-mediated control processes (Clapp et al., 2011; Paxton, Barch, Racine, & Braver, 2008; Verhaeghen, Steitz, Sliwinski, & Cerella, 2003). It is not possible to distinguish between these interpretations in the current study. However, the observation of

concurrent age-related increases in DLPFC and limbic activity at encoding (mentioned above) in combination with prior studies showing a preference for subjective memory processing with age (Mitchell & Johnson, 2009), leads us to favor our first interpretation of our findings.

Interestingly, activation of these same areas during *retrieval* was positively associated with source memory performance (LV1). These performance effects (LV1) are consistent with previous studies showing that DLPFC activity is related to successful source retrieval (Gallo, 2013; McDonough et al., 2013; Mitchell et al., 2013; Rajah, Languay, et al., 2010), and that activity in midline limbic regions supports memory for items previously encoded in a personally and/or emotionally relevant context (Erk, Martin, & Walter, 2005; Markowitsch et al., 2000). At retrieval, engagement of DLPFC is thought to be involved in reflective monitoring (e.g., selective retrieval, evaluation) of previously encoded information, in line with current, relevant agendas (e.g., task goals; Mitchell & Johnson, 2009). Our findings suggest that individual differences in the ability to engage these PFC-mediated processes at retrieval directly relate to task performance.

3.5.3. Phase differences in age vs. performance effects in right VLPFC and HC (LV3)

In contrast to the pattern of effects in DLPFC and limbic regions of LV1 (age effects at encoding, performance effects at retrieval), LV3 identified right VLPFC and bilateral hippocampal regions. In these LV3 regions, activity during spatial memory encoding predicted better subsequent retrieval (performance effects), whereas activity during retrieval increased with age and predicted poorer retrieval accuracy (age/performance trade-off). The performance effects observed at encoding are consistent with several studies that have shown

that VLPFC and hippocampal activity is generally greater at encoding than retrieval (Spaniol et al., 2009) and is associated with subsequent retrieval success (Maillet & Rajah, 2014). During encoding, it has been proposed that activation in VLPFC reflects control processes associated with selective focus of item-specific features, particularly for visuo-perceptual information (Blumenfeld et al., 2011; Blumenfeld & Ranganath, 2007). Hippocampal activity during source encoding is thought to reflect the associative binding of item-context information (Davachi, 2006). It is somewhat surprising that we did not see an associative age deficit during encoding in the present study, given the evidence from prior studies of age-related reductions in hippocampally-mediated associative binding (Dennis, Hayes, et al., 2008; Mitchell, Johnson, Raye, & D'Esposito, 2000). However, a recent aging study of associative memory encoding that controlled for individual differences in performance found that effects in the HC were age-invariant and predictive of subsequent memory (de Chastelaine et al., 2016b). Effects in LV3 are consistent with this recent evidence that encoding activity in the HC is more directly related to subsequent memory performance.

We observed increased VLPFC with age at retrieval, which was linked to poorer retrieval accuracy. During retrieval, VLPFC activity has been associated with greater attention to specific perceptual characteristics of active item representations (Dobbins & Wagner, 2005; Mitchell et al., 2008). In the current study, activation of this region at encoding was directly related to subsequent performance on spatial tasks, suggesting that recruitment of this area across individuals was important for successfully encoding the visuo-spatial characteristics of the faces. During retrieval, however, we observed age-related increased activation in VLPFC coupled with decreased activation in face-selective ventral visual processing regions (discussed

above). This pattern of findings suggests that older individuals may have engaged this region at retrieval in an effort to evaluate poorly encoded perceptual information. This interpretation is consistent with previous findings that, when perceptual source information is poor, individuals may be more inclined to recruit visuo-perceptual attentional processes mediated by right VLPFC (Mitchell et al., 2008). Thus, older individuals may have engaged VLPFC to a greater extent to support retrieval, but this was directly associated with worse source memory performance.

LV3 also identified an age-related increase in bilateral hippocampal activity at retrieval. These regions were unique to LV3 in the current study and were similar to bilateral hippocampal/parahippocampal regions reported in Ankudowich et al. (2016), where activation was greater during retrieval > encoding in older but not young or middle-aged adults. Our results from LV3 extend our previous findings by showing that age-related increases in bilateral hippocampal cortex were detrimental to source memory performance. Interestingly, in young adults, greater hippocampal activation during associative versus non-associative retrieval has been reported in several studies and was interpreted as reflecting this region's general role in relational binding of retrieved information (Bunge, Burrows, & Wagner, 2004; Diana, Yonelinas, & Ranganath, 2007; Giovanello, Schnyer, & Verfaellie, 2004; Kirwan & Stark, 2004; Meltzer & Constable, 2005; Yonelinas, Hopfinger, Buonocore, Kroll, & Baynes, 2001). This view supports the hypothesis that hippocampal activity should be greater during successful encoding and retrieval of source memories. However, in the current study we observed a negative association between hippocampal activity at retrieval and memory performance, and a positive association between hippocampal activity and age. Moreover, increased activation with age in bilateral HC was concurrent with *decreased* activation in posterior visual areas that related to better source

memory across individuals. This pattern is consistent with the idea that successful recollection in older adulthood is characterized by reduced retrieval of specific source features that are perceptual in nature (Boywitt, Kuhlmann, & Meiser, 2012; Spaniol et al., 2009). Thus, our pattern of findings in LV3 suggests that older adults' worse performance did not result from a lack of retrieved associative information per se. Rather, older adults in the current study may have recollected less task-specific perceptual source information (e.g., noncriterial information; Parks, 2007) that was suboptimal for making memory judgments. This, in turn, may have resulted in more hippocampal retrieval activity, but poorer memory. Our interpretation is consistent with the view that hippocampal activity reflects how much relational processing is engaged, but not necessarily successful retrieval of relevant associative information (Diana, Yonelinas, & Ranganath, 2007). These effects may be due to differential processing (e.g., poorer binding) of task-relevant features in older versus young adults during initial encoding of the faces (e.g., reflected by age-related increases in limbic regions). Alternatively, these effects may be due to a reduced ability to modulate bottom-up attention to salient features during retrieval (e.g., reflected by age-related increases in ventral fronto-parietal attentional network areas). Additional studies are needed to explore more fully how differential effects of age on operations engaged during encoding versus retrieval directly relate to declines in source memory performance.

3.6. Conclusion

In the present study, our principal aim was to discern effects of age on encoding and retrieval of spatial and temporal source information that were dissociable from effects of

performance. We identified a set of brain regions (LV2) that showed effects consistent with the hypothesis that some age-related differences in brain activity observed during source encoding and retrieval are associated with individual differences in performance. However, we also identified two patterns of brain activity that reflected higher-order interactions between age, performance and phase-related activity, indicating that age-related changes in brain activity during source memory tasks may not necessarily exhibit a direct age-performance tradeoff. In one pattern (LV1), increased activity in DLPFC and non-hippocampal limbic areas was associated with age during encoding and with performance during retrieval. The other pattern (LV3) showed performance effects in VLPFC and HC regions at encoding, and an age/performance trade-off at retrieval. Whether these effects of age at retrieval are primarily the result of differential processing of task-relevant features of the faces during initial encoding or a reduced ability to reflectively attend to task-relevant features during remembering is unclear from the present data. However, our findings suggest that these two alternatives might not be mutually exclusive. When age effects found at encoding (LV1) and retrieval (LV3) are considered together, the pattern of results suggests that 1) differential processing of the faces (e.g., greater semantic or socio-affective processing) may have detracted from older adults' effectiveness to encode task-relevant visual information. 2) At retrieval, posterior representations of the faces in older individuals were less perceptual in nature. 3) Across individuals, recollecting less perceptual information at retrieval related to worse source memory performance.

Findings in the present study have implications regarding the methodological approaches used to dissociate age from performance effects related to source memory. We used a multivariate approach in order to identify age effects that were independent from accuracy. Prior to

analysis, we residualized the age term used in the current study with retrieval accuracy. With this approach, we were able to dissociate effects of age on task-related encoding and retrieval activity that were not attributable to individual differences in task performance, suggesting that age-related differences in functional activation associated with source memory cannot wholly be accounted for by age differences in performance effects. Collectively, the patterns of age-related activity identified in the current study underscore the importance of considering how age effects on cognitive operations engaged during encoding or subsequent retrieval (or operations engaged across encoding and retrieval) might differentially contribute to declines in source memory performance across the adult lifespan.

Chapter 4. Study 3: Differential prefrontal-hippocampal connectivity in young vs. older adults impacts spatial memory performance

Article submitted

Preface

After Study 2, we were still left with some perplexing questions about the functional significance of age-related increases in dorsolateral PFC during encoding and the HC increases at retrieval that we observed. Our pattern of findings in Study 2 suggested that older adults did not engage these regions when it would have been most beneficial for performance across individuals. In fact, they seemed to be showing greater engagement of these regions during the phase when it did not help them. One possibility is that, for episodic memory network hubs like the HC, functional role is not determined by the *amount* of activity in a given region, but by the way in which is communicates, its interactions with other network regions (McIntosh, Rajah, & Lobaugh, 2003). The functional contribution of the specialized regions important for source memory, such as lateral PFC and HC, may be shaped by their pattern of interregional connections (Mišić & Sporns, 2016; Mitchell & Johnson, 2009). However, it is unclear how the patterns of brain connectivity with these specialized regions differ across the lifespan and contribute to behavioral deficits in source memory. To assess this in Study 3, we performed a seed-based PLS to examine how connectivity of dorsolateral PFC and HC with the rest of the brain during encoding and retrieval directly related to source memory accuracy. We hypothesized that increased lateral PFC and HC activity may not help performance in older adults if these regions are interacting with other cortical areas (e.g., prefrontal and/or posterior

representational areas) that are suboptimal for making successful memory judgements. Thus, we were particularly interested in whether the age-related increases that we observed in dorsolateral PFC and HC in were related to differential connectivity with visual areas that were critical for the task in Study 2. We were also interested to know how these differences in connectivity directly related to task performance.

4.1. Abstract

Age-related episodic memory decline may arise from altered functional connectivity between DLPFC, posterior HC and other brain regions with advanced age. In the current fMRI study of spatial source memory, we used seed connectivity analysis to test this hypothesis in an adult lifespan sample. In young adults, we found that functional connectivity between right DLPFC and other PFC regions, parietal cortex, precuneus, and ventral visual cortices during encoding was positively related to performance. Positive functional connectivity amongst these regions, and negative connectivity with posterior HC at retrieval was also positively correlated with retrieval accuracy in young adults. In older adults, activity in right DLPFC was positively correlated with activity in this same set of brain regions, *and with posterior HC* during encoding and retrieval. Interestingly, this pattern of functional connectivity in older adults was negatively correlated with retrieval accuracy. Thus, age-related declines in source memory may be related to altered frontal-parietal and visual cortical interactions with posterior HC.

4.2. Introduction

Reductions in episodic memory for contextual details (source memory) emerge by midlife and continue into older adulthood. fMRI studies have shown that age-related declines in source memory are often associated with task-related increases in PFC activity with age (Cabeza & Dennis, 2013; Davis et al., 2008). Task-related increases in brain activity in older adults, compared to young adults, are often thought to be beneficial for memory performance (Dennis & Peterson, 2012), but this may not always be the case. For example, in an fMRI study of source memory across the adult lifespan, we observed age-related increases in DLPFC activity at

encoding. However, these increases were not strongly correlated with subsequent memory. In addition, at *retrieval,* age-related increase in HC activity was related to worse memory performance. These results are somewhat surprising given that, in young adults, recruitment of lateral PFC and HC regions are thought to support successful source memory (Mitchell & Johnson, 2009). One possibility is that age-related differences in functional connectivity involving PFC and/or HC during source encoding and/or retrieval may help explain why age-related increases in activation of these brain regions are detrimental to memory.

There is growing consensus that cognitive abilities, such as source memory, are mediated by dynamic, functionally-connected brain networks (Friston, 1994; McIntosh, 2000; Mesulam, 1990; Sporns & Betzel, 2016; Strother, Kanno, & Rottenberg, 1995). Moreover, the functional contributions of specialized regions important for source memory, such as the HC and PFC, may be shaped by their pattern of interregional connections (e.g., McIntosh, Rajah, & Lobaugh, 2003). From this theoretical perspective, increased DLPFC and HC activity may not help performance in older individuals if these regions differentially interact with other cortical areas implicated in successful source memory encoding and retrieval (Davis et al., 2008). One theory to have emerged in recent years is that frontal-parietal activity and connectivity are important for mediating cognitive control processes that facilitate the flexible engagement of other specialized networks in order to meet task demands (Cole et al., 2013). As such, age-related source memory decline may arise from attenuated connectivity between frontal-parietal control regions and other brain regions critical for successful recollection of source features; i.e, the HC and posterior sensory cortices.

Some previous aging studies have assessed differences in connectivity associated with episodic memory encoding or retrieval (Campbell et al., 2012; Dennis, Hayes, et al., 2008; Dennis & Peterson, 2012; Dew, Buchler, Dobbins, & Cabeza, 2012; Foster, Picklesimer, Mulligan, & Giovanello, 2016; Grady, 2016; King, de Chastelaine, & Rugg, 2018; Mitchell et al., 2013). Many of these studies used targeted correlations to assess connections among frontal and posterior regions, including MTL. For example, Dennis et al. (2008) investigated age-group differences in functional connectivity of cortical regions with the HC at encoding. Their findings revealed greater hippocampal connections with posterior regions in young adults and greater hippocampal connections with prefrontal regions in older adults. They interpreted this pattern of connectivity as evidence of a shift away from using perceptually-driven processes to support performance in older adulthood. However, further work is needed in order to understand how differential connectivity during source memory tasks in older adulthood might directly impact performance.

In the current study, we present a novel seed-based connectivity analysis of an fMRI study of spatial source memory previously conducted in our lab (Ankudowich et al., 2016; Ankudowich, Pasvanis, & Rajah, 2017). Here we used multivariate seed-based partial least squares analysis (seed-PLS; McIntosh et al., 2004) to test the hypothesis that age-related differences in functional connectivity between DLPFC, HC and the rest of the brain contribute to age-related declines in spatial source memory. Specifically, we hypothesized differential connectivity between fronto-parietal, hippocampal, and sensory regions with age would negatively impact the retrieval of spatial contextual details.

4.3. Methods

4.3.1. Participants

fMRI data were collected from 45 young adults (age range 19-35 yrs, mean age = 26.13 yrs, 29 females, mean years of EDU = 16.09 yrs), 39 middle-aged adults (age range 40-58 yrs, mean age = 48.87 yrs, 28 females, mean EDU = 15.33 yrs) and 44 older adults (age range 60-76 yrs, mean age = 66.57 yrs, 28 females, mean EDU = 15.57 yrs) while they performed easy and hard versions of a left/right face-location source memory task (see Ankudowich et al., 2017, for task details). Demographic information and episodic memory assessment for this lifespan sample have been previously reported (Ankudowich et al., 2017). Participants were healthy, right-handed, met inclusion criteria published in detail (Kwon et al., 2016), which included MMSE score > 27, and reported having no history of serious cardiovascular disease, neurological or psychological illness, or a family history of Alzheimer's disease. All individuals gave their informed consent and were paid for their participation. The ethics board of the Faculty of Medicine at McGill University approved the study protocol.

4.3.2. Stimuli and Procedure

Participants who met the above neuropsychological criteria and performed greater than chance on a mock-scanner practice task participated in a second, subsequent fMRI session. Stimuli consisted of black-and-white photographs of faces (Rajah et al., 2008) that were balanced for age and sex, and were not repeated across experimental conditions. Each face shown at encoding was subsequently tested at retrieval.

In brief, using a mixed rapid event-related fMRI design, participants were scanned across 12 experimental runs during both encoding and retrieval of the spatial location of faces. The order of runs was counterbalanced across individuals. At the start of each encoding phase, participants were cued (9s) to memorize the spatial location of the faces. Six (easy) or 12 (hard) faces were then serially presented on either the left or the right side of the screen. Participants saw each face for 2s at encoding and rated each face as either pleasant or neutral by pressing a button under their right thumb for pleasant or a button under their left thumb for neutral. In total, there were 72 encoding events presented for each event type (i.e., easy, hard). Between encoding and retrieval phases, participants performed an alphabetization task (60s) to deter rehearsal of encoded stimuli. At the start of each spatial retrieval phase, a cue (9s) instructed participants to choose the face that they saw previously on the LEFT (or RIGHT). On each retrieval event, participants saw two previously encoded faces presented above and below a central fixation cross, and they pressed the button with their right thumb to choose the face at the top of the screen or the button with their left thumb to choose the face at the bottom of the screen. For the easy retrieval task, three face pairs were presented serially, and for the hard retrieval task, six face pairs were presented serially. Each retrieval pair appeared for 6s. In total, 36 retrieval events were presented per event type (i.e., easy, hard). Although participants also performed a temporal memory task (Ankudowich et al., 2016, 2017) during the fMRI session, only data from the spatial memory portion of the study was included in the present analysis.

4.3.3. Imaging

BOLD fMRI was acquired on a 3T Siemens Magnetom Trio scanner using single-shot gradient echo-planar imaging and standard 12-channel head coil (TR = 2000 ms, TE= 30 ms, FOV = 256 mm^2, matrix size = 64 × 64, in-plane resolution = 4 × 4 mm; 32 oblique slices/whole-brain volume). Task stimuli were back-projected onto a screen in the scanner bore using E-Prime software, and behavioral responses were made using an optical response box. A variable ITI (2.2-8.8s) added jitter to event-related acquisitions. Images from the first 10s of scanning prior to task onset were discarded to allow steady state magnetization.

4.3.4. Analyses

Details about the fMRI preprocessing can be found in Ankudowich et al. (2017). Briefly, SPM8 software was used for realignment, normalization and smoothing (using an 8 mm FWHM isotropic Gaussian kernel). Subjects with head motion exceeding 4 mm were discarded from analysis. Multivariate between-group seed-PLS (McIntosh et al., 2004) was used to assess age-related differences in right lateral PFC (Seed 1; Talairach coordinates: x = 40, y = 42, z = 20 mm) and left HC (Seed 2; Talairach coordinates: x = -27, y = -39, z = 4 mm) connectivity with whole-brain activation during spatial source encoding and retrieval, and how this related to source memory performance (% retrieval accuracy). These two seeds were chosen due to their putative involvement in successful source memory (Mitchell & Johnson, 2009) and because they exhibited age-related increases in activity related to performance in our previous study (Ankudowich et al., 2017). Specifically, the selected PFC seed region was the strongest cluster (based on BSR) that showed a pattern of age-related increase at encoding and peaked in the

right DLPFC. The selected HC seed region showed the strongest pattern of age-related increase at retrieval and peaked in left posterior HC[1]. The 4 mm^3 peak voxel for each region constituted the seeds used in the current analysis. Our prior fMRI analyses indicated age- and performance-related differences in brain activity during encoding versus retrieval that were largely generalized across tasks and levels of difficulty accounted for the largest amount of variance in this dataset (Ankudowich et al., 2016, 2017). Therefore, in the present study, we focus on understanding effects of age-group (young, middle-aged, and older adults) on phase-specific connectivity and its relation to retrieval accuracy using a set of 6 pre-specified orthogonal contrasts listed in **Table 4.1**. Contrasts 1-3 assessed group similarities in connectivity associated with each seed during encoding and/or retrieval, whereas contrasts 4-6 assessed group differences in connectivity associated with each seed during encoding and/or retrieval. In this way, our contrasts allowed us to dissociate differential connectivity between groups that was related to either our PFC or our HC seed, at encoding or retrieval. We were especially interested

Table 4.1. Prespecified contrasts included in the seed-PLS.

Contrast number	Contrast	Conditions
Group similarities		
1	Encoding > retrieval ME	All conditions
2	Accuracy > right PFC > left HC	Encoding
3	Accuracy > right PFC > left HC	Retrieval
Group differences		
4	Encoding > retrieval ME; Y > M > O	All conditions
5	Accuracy > right PFC > left HC; Y > M > O	Encoding
6	Accuracy > right PFC > left HC; Y > M > O	Retrieval

Note: ME = Main Effect; PFC = Prefrontal Cortex; HC = Hippocampus; Y = Young; M = Middle-aged; O = Older.

[1] The right PFC seed was taken from LV1 age effects at encoding (spatial extent of k = 119, BSR = -4.75), whereas the left HC seed was taken from LV3 age effects at retrieval (spatial extent of k = 44, BSR = 4.41) as reported in Ankudowich et al. (2017).

in age-group interactions in seed connectivity that were related to task performance during encoding and retrieval. To this aim, we focus on results from the highest-order contrast effects 5 and 6, respectively.

Event-related fMRI data for successfully encoded and retrieved events were stored in a data matrix organized by event-type across participants. Columns of the matrix contained data for each voxel in the brain, at each of 7 time lags after event onset, where each lag represented 1 TR. Hence, this matrix contained fMRI data spanning 14s after event onset for each event-type. The fMRI data matrix was then cross-correlated with a similarly organized matrix containing retrieval accuracy scores, average right lateral PFC and average left HC seed activation per event-type and coded orthogonally according to the contrast of interest. The number of LVs equals the number of contrasts tested, which in this case was 6. Each LV consists of: i) a singular value reflecting the amount of covariance accounted for by the LV, ii) a correlation profile depicting retrieval accuracy, right PFC activity and left HC activity correlated with a pattern of whole-brain activity identified in the singular image and iii) a singular image containing positive and negative brain saliences that reflect a pattern of whole-brain activity symmetrically related to the correlation profile. Voxels with positive saliences positively relate to the correlation profile, whereas those with negative saliences negatively relate to the correlation profile. Thus, each LV reflects a symmetrical pairing of a pattern of whole-brain activity with a correlation profile. Significance testing of LVs was conducted with permutation testing ($p < 0 .01$, 1000 permutations) of singular values. Stability of voxel contributions to LVs was assessed using bootstrapping (BSR = ±3.28, $p < 0.001$, 500 iterations; minimum cluster size

of 10 for cortical regions). Peak coordinates were converted to Talairach space using the icbm2tal transform in GingerAle 2.3 (www.brainmap.org). We identified two outliers in the PLS analyses (one young adult, one middle-aged adult). Results presented excluded these two participants.

4.4. Results

Behaviorally, there was a significant age-related decline in retrieval accuracy [$F(2,123) = 11.13$, $p < 0.001$]. On the easy task, young adults ($M = 0.89$, $SD = 0.09$) outperformed older adults ($M = 0.81$, $SD = 0.10$, $p < 0.001$). In contrast, there was no significant difference in easy retrieval accuracy between middle-aged ($M = 0.85$, $SD = 0.10$) and young adults, and between middle-aged and older adults. On the hard task, young adults ($M = 0.88$, $SD = 0.10$) outperformed both middle-aged ($M = 0.79$, $SD = 0.13$, $p < 0.001$) and older adults ($M = 0.77$, $SD = 0.11$, $p < 0.001$), but there was no significant difference in hard retrieval accuracy between middle-aged and older adults.

The seed-PLS analysis identified four significant LVs ($p < 0.01$). Only two LVs are presented here, which reflected interactions of age and performance of experimental interest: LVs 5 (encoding effects) and LV 6 (retrieval effects). **Figure 4.1** shows singular images and corresponding correlation profiles for these two LVs that revealed differential age-group effects on phase-related patterns of connectivity related to performance. That is, these LVs showed a flip in HC connectivity across age groups that was related to worse performance at encoding and retrieval. Local maxima for these LVs are listed in **Table 4.2**.

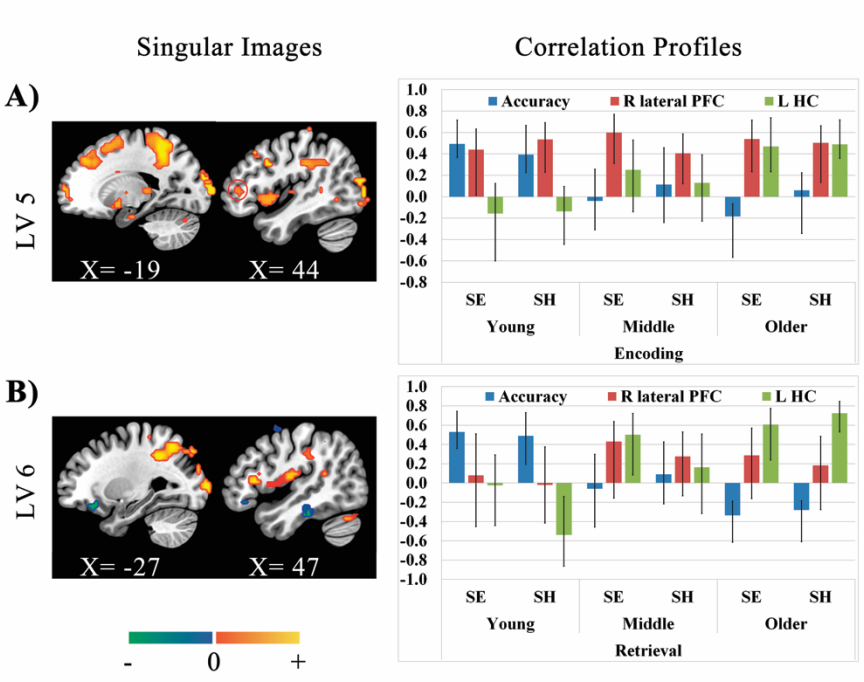

Figure 4.1. Singular images and corresponding correlation profiles for the seed-PLS. Red brain regions reflect positive voxel saliences and blue regions reflect negative voxel saliences at a bootstrap ratio threshold of ±3.28, $p < 0.001$. Activations are projected onto a template brain using Mango software (http://ric.uthscsa.edu/mango/). (A) Singular image and correlation profile for LV5 at encoding. The red circle on the singular image indicates activation in proximity of the PFC seed. The correlation profile indicates positive voxel saliences were positively correlated with retrieval accuracy and PFC seed activation in young adults (YA). In older adults (OA), positive voxel saliences were positively correlated with both PFC and HC seed activation and were negatively correlated with SE accuracy. (B) Singular image and correlation profile for LV6 at retrieval. The correlation profile indicates positive voxel saliences that were positively related to accuracy (and negatively correlated with HC seed activity on SH) in YA were positively correlated with HC seed activity in OA (and negatively correlated with OA performance). Conversely, negative salience voxels that positively related to performance (and negatively related to HC seed activity) in OA were positively related to HC seed activity on SH in YA (and negatively related to YA performance). Error bars reflect 95% confidence. SE = spatial easy; SH = spatial hard.

LV5 (11.86% crossblock covariance) identified a similar pattern of right PFC seed connectivity across all age groups at encoding. Only significant positive salience brain regions were identified, and included: bilateral VLPFC, DLPFC and anterior PFC, inferior parietal cortices, ventral occipital cortex, precuneus and left superior parietal cortex (see **Table 4.2**). The pattern of connectivity related to right PFC activity at encoding was also positively correlated with subsequent memory in young adults. In contrast, in older adults, this pattern of right PFC

Table 4.2. Local maxima for LVs showing significant contrast effects.

Contrast	Temporal lag	BSR	Spatial extent	Talairach coordinates			HEM	Gyral location	BA
				x	*y*	*z*			
LV 5 Local Maxima									
Positive Salience Regions									
Left Hemisphere									
	1	3.61	13	-42	-85	6	Left	Middle occipital gyrus	19
	1	4.30	74	-2	-48	54	Left	Precuneus	7
	1	4.37	67	-20	-103	1	Left	Cuneus	18
	4	3.50	10	-53	4	29	Left	Precentral gyrus	6
	4	4.35	25	-45	6	1	Left	Insula	13
	4	4.52	31	-23	-1	-7	Left	Putamen	
	4	5.32	30	-5	-97	13	Left	Cuneus	18
	5	3.70	13	-45	3	0	Left	Insula	13
	5	3.75	10	-60	5	18	Left	Precentral gyrus	6
	5	3.94	23	-61	-49	31	Left	Supramarginal gyrus	40
	5	4.42	23	-42	47	12	Left	Middle frontal gyrus	10
	5	4.52	58	-5	-97	13	Left	Cuneus	18
	5	5.21	98	-46	-84	3	Left	Middle occipital gyrus	18
	5	5.26	42	-53	25	6	Left	Inferior frontal gyrus	45
	6	3.59	14	-24	-55	49	Left	Precuneus	7
	6	3.65	10	-20	-96	9	Left	Middle occipital gyrus	18
	6	4.06	20	-16	57	17	Left	Superior frontal gyrus	10
	6	4.93	88	-46	-76	-4	Left	Middle occipital gyrus	19
	7	3.66	10	-53	7	29	Left	Inferior frontal gyrus	44
	7	4.22	88	-9	-31	30	Left	Cingulate gyrus	23
	7	4.40	246	-12	-10	7	Left	Thalamus	
	7	4.63	50	-5	-94	24	Left	Cuneus	19
	7	5.49	838	-2	13	49	Left	Superior frontal gyrus	6
	7	5.76	596	-27	-49	32	Left	Superior parietal lobule	7
	7	5.95	186	-57	17	5	Left	Inferior frontal gyrus	45
Right Hemisphere									
	1	4.33	21	24	8	59	Right	Superior frontal gyrus	6
	1	4.41	40	17	-103	-2	Right	Cuneus	18
	4	3.77	14	2	12	56	Right	Superior frontal gyrus	6
	5	3.52	19	43	-31	31	Right	Inferior parietal lobule	40
	5	3.72	26	10	-58	-1	Right	Lingual gyrus	19
	5	3.79	22	55	20	11	Right	Inferior frontal gyrus	45
	6	4.11	25	6	-72	-10	Right	Lingual gyrus	18

	7	3.56	10	47	15	28	Right	Middle frontal gyrus	9
	7	4.42	170	21	-46	36	Right	Precuneus	31
	7	4.50	142	32	10	-1	Right	Claustrum	
	7	3.70	10	40	-43	4	Right	Middle temporal gyrus	21
LV 6 Local Maxima									
Negative Saliences									
Left Hemisphere									
	1	-4.61	26	-5	32	4	Left	Anterior cingulate	24
	2	-4.11	16	-27	26	-8	Left	Inferior frontal gyrus	47
	2	-5.74	126	-4	33	-4	Left	Anterior cingulate	24
	3	-4.11	18	-56	-26	-17	Left	Inferior temporal gyrus	20
	4	-3.59	14	-8	25	-4	Left	Anterior cingulate	24
	5	-3.80	12	-2	23	60	Left	Superior frontal gyrus	6
	5	-4.11	16	-6	-57	67	Left	Postcentral gyrus	7
	6	-3.90	24	-12	40	-3	Left	Anterior cingulate	32
	6	-4.41	13	-56	-26	-14	Left	Middle temporal gyrus	21
Right Hemisphere									
	1	-3.75	11	9	-57	68	Right	Postcentral gyrus	7
	1	-3.77	18	55	-27	-8	Right	Middle temporal gyrus	21
	2	-4.08	38	51	-22	-19	Right	Inferior temporal gyrus	20
	3	-4.78	37	55	-35	-9	Right	Middle temporal gyrus	20
	3	-4.93	149	3	32	7	Right	Anterior cingulate	24
	5	-4.57	17	47	-26	-19	Right	Fusiform gyrus	20
	7	-3.95	10	44	-26	-16	Right	Fusiform gyrus	20
Positive Saliences									
Left Hemisphere									
	2	3.81	10	-38	9	15	Left	Insula	13
	2	4.08	44	-39	-32	44	Left	Inferior parietal lobule	40
	2	4.15	27	-38	10	37	Left	Middle frontal gyrus	9
	2	4.65	16	-1	8	16	Left	Caudate	
	3	4.21	49	-9	-11	25	Left	Cingulate gyrus	23
	6	4.72	50	-9	-60	20	Left	Precuneus	31
	7	3.49	12	-9	-65	38	Left	Precuneus	7
	7	3.53	12	-24	-84	36	Left	Cuneus	19
	7	3.93	48	-16	-60	20	Left	Precuneus	31
	7	3.95	10	-42	18	34	Left	Middle frontal gyrus	9
	7	4.28	50	-27	-99	-2	Left	Cuneus	18
	7	4.36	92	-27	-49	32	Left	Superior parietal lobule	7
	7	4.36	178	-5	-35	33	Left	Cingulate gyrus	31
Right Hemisphere									

2	3.95	46	32	4	16	Right	Insula	13
2	3.95	17	28	-65	31	Right	Precuneus	7
3	4.24	49	32	-80	33	Right	Cuneus	19
3	4.76	28	50	-28	35	Right	Postcentral gyrus	2
7	3.64	10	10	-60	20	Right	Precuneus	31
7	3.66	14	36	-3	12	Right	Claustrum	
7	3.90	63	32	-50	40	Right	Superior parietal lobule	7
7	3.96	10	39	-44	15	Right	Superior temporal gyrus	22
7	3.99	14	2	-88	0	Right	Lingual gyrus	18
7	4.03	17	40	20	14	Right	Inferior frontal gyrus	45
7	4.06	22	3	-6	11	Right	Thalamus	
7	4.06	27	21	-18	14	Right	Thalamus	
7	4.24	28	25	10	38	Right	Middle frontal gyrus	8
7	4.54	35	10	-16	32	Right	Cingulate gyrus	23

Note: Temporal lag represents time after event onset when clusters exhibited the contrasted effect. Bootstrap ratio (BSR) threshold was set to ±3.28 and identified dominant and stable clusters. Spatial extent indicates the total number of voxels included in the cluster (threshold = 10). Stereotaxic coordinates are indicated in millimeters, and gyral location and Brodmann areas (BAs)were verified by Talairach and Tournoux (1988). HEM = cerebral hemisphere in which activation occurred.

connectivity was also correlated with encoding activity in left HC but was negatively correlated with subsequent memory for easy tasks (**Figure 4.1A**). This suggests that PFC-HC connectivity at encoding increased with age, which was detrimental to subsequent memory in the current study.

LV6 (13.11% crossblock covariance) identified a set of brain regions that were differentially connected with left HC activity in young adults versus middle-aged and older adults during source retrieval (**Figure 4.1B**). Positive salience regions included: bilateral DLPFC, superior parietal cortex, precuneus, ventral occipital cortices and left inferior parietal cortex and cingulate cortex. In young adults, activity in these regions was negatively correlated with retrieval activity in HC, but positively correlated with retrieval accuracy. In older adults, activity in these regions was positively correlated with HC activity, but negatively correlated with

retrieval accuracy. Negative salience regions included: bilateral ventromedial PFC/anterior cingulate, lateral temporal and left VLPFC. In young adults, activity in these regions was positively correlated with HC activity at retrieval, and negatively correlated with retrieval accuracy. Older adults displayed the opposite pattern of effects to young adults. To summarize within age-group effects of LV6, increased connectivity between left HC and its associated brain regions was negatively correlated with memory performance in young and older adults.

4.5. Discussion

Our results show that right DLPFC activity at encoding (LV5) and HC activity at retrieval (LV6) were both functionally correlated (connected) with activity in bilateral PFC, inferior and superior parietal cortices, precuneus and bilateral ventral occipital cortex in young and older adults. What differed in each age group was the direction of connectivity with HC during encoding compared to retrieval. In young adults, HC activity at encoding was not significantly correlated with activity in the aforementioned brain regions, and HC activity at retrieval was negatively correlated with activity in these same brain regions. Moreover, in young adults, positive correlations in brain activity among frontal, parietal and ventral visual cortex at encoding (including the right DLPFC seed) and retrieval was also positively correlated with spatial source retrieval accuracy. In contrast, in older adults, HC activity at encoding and at retrieval was positively correlated with activity in this set of regions. This altered pattern of connectivity involving the posterior HC was negatively correlated with spatial source retrieval accuracy.

In young adults, negative connectivity between DPLFC and HC at retrieval may support top-down inhibitory mechanisms (Benoit & Anderson, 2012). For example, previous studies have shown that attempts to suppress unwanted and/or intrusive retrieval is associated with increased activity in DLPFC coupled with reduced activity in posterior HC (Benoit, Hulbert, Huddleston, & Anderson, 2015). In older adults, increased positive connectivity between PFC and HC regions may reflect disruptions to this inhibitory mechanism during reflective processing, such that older adults in the current study were less likely to suppress unwanted or intrusive information. One possibility is that increased HC connectivity in the older adult group during encoding and/or retrieval may have resulted in older individuals forming associations with contextual information related to the faces that was not necessarily the most important or relevant for a source memory judgement (e.g., hyper-binding; Campbell, Hasher, & Thomas, 2010; Campbell, Trelle, & Hasher, 2014; Weeks & Hasher, 2017). In addition, better performance in the older adult group was associated with processing in ventromedial prefrontal and lateral temporal areas. Previous aging studies that have found increased activation of these areas in may relate to better source memory performance in older individuals (Duarte, Henson, & Graham, 2008). They interpreted this pattern of activation as reflecting greater recollection of internally-generated and/or self-relevant thoughts when making objective source memory decisions. Thus, our pattern of results might suggest that older individuals may have recollected more extraneous associations with the faces, but the extent to which they can remember internally-generated, personally-relevant information may bolster performance.

Interestingly, an overall finding in the current study was that, regardless of age, positive connectivity of cortical regions with HC during retrieval was negatively related to performance. It is important to note that the HC seed used in this study was localized in posterior HC. One possible interpretation is that recruitment of posterior HC does not benefit memory on this task. This would make sense if activation of more posterior regions of HC reflects recollection of contextual information that was not specific enough to facilitate successful source memory judgement (Chua, Schacter, Rand-Giovannetti, & Sperling, 2007; Duarte et al., 2008; Poppenk, Evensmoen, Moscovitch, & Nadel, 2013). To a limited extent, we did observe activity in LV5 at encoding in anterior portions of MTL that were positively connected to DLPFC and supported performance in young adults, which suggested a possible anterior versus posterior dissociation of MTL connectivity that was differentially related to performance across age groups. Specifically, we found a small cluster (k=7; Talairach coordinates: x = -16, y = -14, z = -23) in left parahippocampal gyrus (seen in **Figure 4.1A**) that was positively connected to our DLPFC seed as well as other frontal, parietal, and visual areas important for performance. Although speculative, this would be consistent with previous evidence showing that activity in more anterior, relative to posterior, MTL areas relates to successful encoding of associative information (Chua et al., 2007; Rajah, Kromas, Han, & Pruessner, 2010) and supports recollection-based memory judgements (Giovanello et al., 2004). Future investigation is warranted to dissociate potential age-related differences in anterior versus posterior hippocampal network connectivity related to successful encoding and subsequent retrieval of source information.

4.6. Conclusion

In the present study, we provide novel evidence that increased fronto-parietal and ventral visual connectivity with posterior HC in older adulthood may directly contribute to declines spatial memory performance. During both encoding and retrieval, connectivity of these regions with left posterior HC was found to be related to poorer memory performance in older individuals. Our results are consistent with previous cross-sectional study findings that functional connectivity of specialized episodic memory regions (i.e., PFC, HC) may occur at different developmental stages across the lifespan and may impact performance (Foster et al., 2016; King et al., 2018). More specifically, our findings illustrate the importance of identifying age-related changes in how fronto-parietal control regions interact with hippocampally-dependent memory operations to support source memory function across the adult lifespan.

Chapter 5. General Discussion and Future Directions

The overarching objective of this thesis was to investigate patterns of whole-brain activation across the adult lifespan that underlie encoding and retrieval of source information, and to understand how lifespan differences in patterns of brain function contribute to declines in source memory performance with age. As alluded to in the introduction, a useful framework for understanding the functional significance of age-related differences in brain activity is to characterize how decreases or increases in task-related activity with age contribute to performance. Age-related functional differences in the brain regions involved in source memory are often characterized by reduced activity in older adults relative to young adults. However, age-related reductions in regional activation may often be accompanied by additional task-related activation elsewhere in the brain. Perhaps the most important and novel benefit of this thesis is that the multivariate approach that we used across studies allowed us to assess, within the same sample, how lifespan decreases and increases in functional activity (Studies 1 and 2) and connectivity (Study 3) support source memory. In Study 1, we determined that declines in source memory discernable by midlife were associated with decreases in task-specific activity, whereas age-related increases in activity were apparent in older adulthood. In Study 2, we clarified how age-related increase and decreases in activity across the adult lifespan were directly related to source memory decline. Finally, in Study 3, we found converging evidence that lifespan increases in activity (Study 2) were differentially related to patterns of whole-brain connectivity that supported performance in young, middle-aged, and older adults.

In addition, our secondary goal was to understand more fully how interactions of age with phase-specific encoding and retrieval activity contribute to source memory. That is, an

age-related functional deficit during *both* encoding and retrieval probably has a different functional significance than a deficit during *either* encoding or retrieval alone. Many studies that have analyzed encoding and retrieval separately have reported age-related functional deficits specific to each phase. However, an early finding in Study 1, which was the only study to assess the actual magnitude of phase-specific activation, showed that when we looked at decreases in *relative* activation during encoding and retrieval across the lifespan, we only found age-related reductions in activity during retrieval *relative* to encoding in regions of PFC and ventral visual cortex. This initial finding suggested that older individuals *can* activate these regions during encoding, but they may not activate them to the same extent at retrieval. Hence our findings underscored the importance of age-related differences in phase-specific modulation of activity in the regions involved in source memory. These differences in modulation in Study 1 also reflected age-related increases in phase-specific activity, particularly during retrieval, in LPC and MTL regions. The work of subsequent studies (Studies 2 and 3) was therefore to assess how these interactions of age on phase-specific modulation of activity impacted performance. We hope an integrative discussion of our findings across studies will help elucidate how simultaneous patterns of increase and decrease of phase-specific activity and connectivity in the aging brain contribute to differences in episodic memory function across the adult lifespan.

5.1. The functional significance of age-related decreases in activation of posterior sensory cortices

In Study 2, we found evidence that the pattern of age-related reductions in ventral visual activity during retrieval (initially observed in Study 1) was directly related to worse performance. Like in Study 1, this pattern occurred despite the fact that we found increased age-related activity in these perceptual areas during encoding, suggesting that older individuals may initially process perceptual information in ventral visual areas to a greater extent during encoding, but they differentially access and/or use perceptual information when making a memory judgement at retrieval compared to young adults. Across Studies 1 and 2, our results would seem to support the idea that declines in source memory with age may be more associated with difficulties in reflective processing of information in posterior representational areas, rather than perceptual processing per se (Mitchell et al., 2013, 2010).

We also observed age-related increases in activity in areas of lateral frontal and parietal as well as non-hippocampal limbic areas during Study 2 encoding, including areas of ventromedial PFC and amygdala. Though activation of these regions benefitted performance across individuals during retrieval, older individuals showed increased activity in this set of regions during encoding, when it did not seem to benefit them. We interpreted these age effects as activation that was related to differences in the manner in which faces were processed during initial encoding (e.g., differential processing of socio-affective features). Hence, though older adults may have been attending to the faces during initial perception, differential processing of source features may still have occurred to interfere with older adults ability to retrieve task-relevant perceptual features (Campbell et al., 2012; Gazzaley et al., 2005;

Maillet & Rajah, 2014). At subsequent retrieval, older adults exhibited less engagement of regions of ventral visual cortex, regions in which activity across individuals directly related to better performance.

5.2. The functional significance of age-related increases in retrieval-specific activation

Although the implications for performance of age-related reductions in retrieval-related activation in Studies 1 and 2 would appear reasonably straightforward, interpretation of age-related increases in retrieval-specific activation is less clear. A consistent effect that we observed across Studies 1 and 2 was a pattern of age-related increase of retrieval-specific activity in LPC and MTL regions. In addition, in Study 2, these age-related increases were accompanied by increases in VLPFC. Brain-behavior correlations in Study 2 further showed that this pattern of over activation during retrieval in older adulthood related to reduced performance, suggesting that it may not be 'compensatory' per se (in fact, one overall observation from Study 2 is that we found little evidence of age-related increases in activation that actually benefited performance during either encoding or retrieval). An alternate hypothesis briefly discussed in Studies 1 and 2 is that this over recruitment might reflect dedifferentiation. As described by Park et al. (2002), dedifferentiation may occur through several means. One is through unique recruitment by older adults of regional activation that is either contralateral or nonhomologous to regional activation in young adults. Another method is through substitution, whereby older adults may recruit an alternative region than that of young adults to perform a similar task. The pattern of results that we saw in Studies 1 and 2 would be roughly consistent with these criteria: We observed age-related reductions of more

upstream ventral visual processing areas concomitant with more age-related increases in activity of posterior LPC and MTL regions at retrieval. Moreover, in Study 2 we saw across encoding and retrieval that older individuals activated more anterior temporal regions associated with secondary processing of the faces. These patterns of activation reflected age-accuracy trade-off (i.e., age effects that directly related to worse performance). It stands to reason that more diffuse, less punctate patterns of activation in posterior representational areas may result in declines in memory for specific types of visual information in older versus young adults. However, a larger, more complex picture of these findings starts to emerge when we consider connectivity findings from Study 3.

5.3. Age-related increases in activation during encoding and retrieval: Implications for connectivity

In Study 3, we investigated how activity in DLPFC and posterior HC correlated with activity across the rest of the brain and related to performance. These selected seed regions were two areas that showed increases in activity in older individuals in Study 2 during encoding and retrieval, respectively, when it did not seem to benefit performance. It is important to note that Study 3 was the only study to assess within-group effects of age related to performance in young, middle-aged, and older adults. When we looked at within-group patterns of connectivity associated with the areas that exhibited age-related increases in activation in Study 2, we found that in the young adult group, activity in regions of lateral prefrontal, parietal, and visual cortex positively related to activity in our DLPFC seed and supported performance. In the older adult

group, these same regions were more correlated with posterior HC and did not support performance.

In addition, when we looked at patterns of connectivity associated with age-related increases during retrieval, we found that a similar pattern of fronto-parietal and visual cortical activity associated with performance in young individuals was *negatively* correlated with retrieval accuracy in the older adult group. Moreover, unlike in the young adult group, activity among these regions was more correlated with activity in HC. Thus, to summarize Study 3 encoding and retrieval effects, fronto-parietal and visual areas comprised a network that was beneficial for memory performance in young adults, whereas fronto-parietal and posterior HC comprised a network that was detrimental to memory performance in older adults.

Interestingly, at retrieval we found that the older adult group seemed to engage a dissociable network that showed negative connectivity with HC comprised of midline anterior/ventromedial prefrontal and lateral temporal cortical regions. As discussed in Study 2, increased age-related activity in these areas may reflect a greater tendency in older adults to overweight personally-relevant or socio-affective, and/or semantic features relative to sensory features during source memory tasks (Dennis, Kim, & Cabeza, 2008; Hashtroudi et al., 1990; Kensinger & Schacter, 2008; Maillet & Rajah, 2014). Study 3 provides more direct evidence that performance in the older adult group was negatively associated with processing of perceptual information and positively associated with processing of secondary socio-affective and/or semantic processing associated with the faces (Svoboda et al., 2006). It is important to note that only correct trials on the source memory tasks were included in the analyses across studies. Thus, during successful remembering, young and older adults may be basing memory

judgements on different sets of retrieved information to support performance. That is, older adults may use perceptual information to a lesser extent than young adults when making a memory judgement, even when perceptual source features are accurately remembered (Boywitt et al., 2012). When considering the findings of Studies 2 and 3 together, we might conclude that age-related increases in activation may be associated with an altered pattern of fronto-parietal and HC connectivity related to reduced recollection of visual information. As a result, older adults' retrieved representations may be less perceptual in nature and may reflect greater task-unrelated associations with the faces (e.g., personally-relevant, socio-affective, or semantic information). Finally, across Studies 2 and 3, we found evidence that activation of posterior HC at retrieval related to worse performance across individuals and regardless of age group. This overall finding would suggest that increased activity and connectivity with posterior HC may be associated with successful recollection (Poppenk et al., 2013), but may not directly support performance on specific source memory tasks (Duarte et al., 2008).

5.4. Limitations

Several limitations of these studies should be discussed. Firstly, due to the design of our source memory paradigm, it was impossible to disentangle differential effects of age on perceptual versus reflective processing during encoding and retrieval. At encoding, the ability to reflectively attend (i.e., refresh) to a just-seen representation relates to subsequent long term memory performance (Raye, Johnson, Mitchell, Reeder, & Greene, 2002). In addition, the extent to which encoded information is reinstated in representational areas at retrieval may depend on what reflective agenda is enacted during recollection (McDuff et al., 2009). Across

our three studies, participants viewed faces for the duration of both encoding and retrieval events, making it impossible for us to dissociate reflective processing that was independent from perceptual processing. Further work must be done in order to dissociate the role of perceptual and reflective attention related to encoding and retrieval of source information across the adult lifespan (Chun & Johnson, 2011).

Secondly, our three studies only investigated age effects on fMRI activity during successful source memory, and so our findings only represent one piece of a larger puzzle. In addition to reductions in veridical memories, age-related declines in episodic memory are also characterized by greater tendency to falsely remember or misattribute erroneous details of past events (Schacter, Koutstaal, & Norman, 1997), which may be equally disruptive to memory processes in older adulthood (McCabe, Roediger, McDaniel, & Balota, 2009). If older adults do use categorically different types of information to make successful memory judgements, as supported by our findings in Study 3, this might make them more susceptible to specific types of memory errors (e.g., source misattributions related to reliance on self-referential or general semantic information; Mather, Johnson, & De Leonardis, 1999). In order to obtain a more complete picture of age-related declines in episodic memory, an important step forward would be to assess how age-related increases and/or decreases in whole-brain activity and connectivity differentially contribute to successful versus erroneous source memory (i.e., source forgetting and false remembering) across the adult lifespan.

5.5. Future directions

Findings across these studies have naturally incited a number of additional lines of inquiry. For example, the relationship between age-related increases and/or decreases in activity and their roles in overall network function seems to be a complex one. In Studies 2 and 3, we found clear evidence that age-related increases in activity may be directly related to differences in whole-brain connectivity. To what extent might observable lifespan differences in regional function during episodic memory tasks be the product of overall changes in whole-brain task-related network function? One might even speculate whether some age-related increases and/or decreases in regional modulation of activity might be epiphenomenal effects of lifespan differences in whole-brain network dynamics. This may be especially important for elucidating the functional significance of age-related differences in activation of regions that have no discernible implications for performance, where overall changes in network dynamics between regions does have clear implications for performance (as was the case for right DLPFC in Studies 2 versus 3). Further work is already being undertaken in our lab to clarify how overall patterns in task-related whole-brain connectivity (as opposed to the seed-based approach in Study 3) directly relates to source memory performance.

Furthermore, how should regional contributions to large-scale task-related functional networks be determined? Across studies, the large sample sizes that were included in analysis and the multivariate approach that was used necessitated that we analyze the fMRI data at a resolution of $4mm^3$ due to computational limitations. This resolution may be too rough for discerning more subtle network contributions of smaller subregions (especially, e.g., of MTL structures) with a level of reliable precision. Our low resolution is also not ideal for discerning

structure-function relationships within these regions. The potential for understanding the functional role of more refined anatomical (sub)structures in determining functional network dynamics across the lifespan may progress with the combined advancement of imaging resolution and computational capabilities in order to overcome these practical limitations.

5.6. Conclusion and final remarks

"We are endlessly fascinated by memory; we desire to improve it and fear its loss" (Maguire, 2014, p. 471). This statement by Eleanor Maguire aptly captures the prevailing concern held by aging individuals about the cognitive decline experienced with age in the domain of episodic memory. If we are to develop effective interventional strategies to maintain healthy episodic memory function in advancing age, it is imperative that we understand the brain changes associated with episodic memory decline and determine how these changes impact memory performance across adult lifespan. To summarize the contributions of the lifespan studies herein, the pattern of results suggests that (1) fronto-parietal network function supports the recollection of visual information to a greater extent in young adulthood. (2) Across individuals, the recollection of perceptual information at retrieval directly contributes to improved source memory performance. (3) Aging is associated with altered fronto-parietal network modulation and connectivity with posterior HC regions that does not support successful source memory. (4) Older adults may rely on representations that are characterized by fewer task-relevant perceptual features and more additional features associated with the faces (e.g., socio-affective or semantic features of the faces) to support memory judgements. While the work continues, we hope that the findings from this body of research play their

instrumental part in helping to understand the brain-behavior relationships that link lifespan differences in brain activity and connectivity with episodic memory function.

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