

Functional Neuroimaging of Autobiographical Memory

by

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Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor of Philosophy in the Department of
Psychology and Neuroscience in the Graduate School
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2010

ABSTRACT

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Abstract

Autobiographical memory (AM) refers to memory for events from our own personal past. Functional neuroimaging studies of AM are important because they can investigate the neural correlates of processes that are difficult to study using laboratory stimuli, including: complex constructive processes, subjective qualities of memory retrieval, and remote memory. Three functional magnetic resonance imaging (fMRI) studies are presented to examine these important contributions of AM. The first study investigates the neural correlates of temporal-order memory for autobiographical events using a novel photo paradigm. Participants took photographs at many campus locations over a period of several hours, and the following day they were scanned while making temporal-order judgments to pairs of photographs from different locations. It was found that temporal-order decisions associated with recollection recruited left prefrontal (PFC) and left posterior parahippocampal cortex, whereas temporal-order decisions relying on familiarity recruited greater activity in the right PFC.

The second study examines self-projection, the capacity to re-experience the personal past and to mentally infer another person's perspective. A novel camera technology was used to examine self-projection by prospectively generating dynamic visuospatial images taken from a first-person perspective. Participants were literally asked to self-project into the personal past or into the life of another person. Self-

projection of one's own past self recruited greater ventral medial PFC (mPFC), and self-projection of another individual recruited dorsal mPFC. Activity in ventral vs. dorsal mPFC was also sensitive to the ability to relive or understand the perspective taken on each trial. Further, task-related functional connectivity analysis revealed that ventral mPFC contributed to the medial temporal lobe network linked to memory processes, whereas dorsal mPFC contributed to the frontoparietal network linked to controlled processes.

The third study focuses on the neural correlates underlying age-related differences in the recall of episodically rich AMs. Age-related attenuation in the episodic richness of AM was linked to reductions in activity elicited during elaboration. Age effects on AM were more pronounced during elaboration than search, with older adults showing less sustained recruitment of the hippocampus and ventrolateral PFC for less episodically rich AMs. Further, there was an age-related reduction in the top-down modulation of the PFC on the hippocampus by episodic richness, possibly reflecting fewer controlled processes operating on the recovery of information in the hippocampus.

Ultimately, the goal of all memory research is to understand how memory operates in the real-world; the present research highlights the important contribution of functional neuroimaging studies of AM in attaining this goal.

Dedication

To my mom, Bonnie P. St. Jacques.

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List of Abbreviations

AM: Autobiographical Memory

BA: Bradman's Area

BDI: Beck Depression Inventory

Ctx: Cortex

DCM: Dynamic Causal Modeling

DL-PFC: Dorsolateral Prefrontal Cortex

EM: Episodic Memory

FIR: Finite Impulse Response

FOV: Field of View

fMRI: Functional Magnetic Resonance Imaging

GLM: General Linear Model

H: Brain Hemisphere

HRF: Hemodynamic Response Function

LM: Laboratory Memory

MMSE: Mini-Mental State Exam

mPFC: Medial Prefrontal Cortex

MTL: Medial Temporal Lobe

MTT: Multiple Trace Theory

OFC: Orbitofrontal Cortex

PFC: Prefrontal Cortex

ROI: Region of Interest

SCM: Standard Consolidation Model

SM: Semantic Memory

SPM: Statistical Parametric Mapping

SPO: Self-Projection of Other Perspectives

SPS: Self-Projection of One's Own Self

TE: Echo Time

ToM: Theory of Mind

TR: Repetition Time

VIF: Variance Inflation Factor

VL-PFC: Ventrolateral Prefrontal Cortex

VOI: Volume of Interest

WASI: Weschler Abbreviated Scale of Intelligence

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St. Jacques, PL, Rubin, DC, LaBar, K, Cabeza, R. (2008). The short and long of it: Neural correlates of temporal-order memory for autobiographical events. *Journal of Cognitive Neuroscience*, 20(7), 1327-1341.

1. Introduction

Autobiographical memory (AM) is what is usually meant by the term "memory;" the ability to remember past events from one's own life. The number of functional neuroimaging studies investigating AM has rapidly increased in recent years. The results of these studies expand functional neuroimaging studies of laboratory memory (LM) in at least three domains. First, AM studies can inform our understanding of the complex construction of memory retrieval, which is not captured well by the retrieval of simple laboratory stimuli. Second, AM studies can investigate qualities of the subjective experience of memories that are often difficult to study on LM, such as reliving. Finally, AM studies can investigate the retrieval of remote memories, which cannot be created in the laboratory, and is a critical issue for aging. The present dissertation focuses on the importance of functional neuroimaging investigations of AM with respect to these three domains.

The current chapter describes the nature of AM, the methods used to elicit AM in the scanning environment, and the brain regions typically recruited during AM retrieval. Chapters 2, 3, and 4 review previous studies examining issues of complex construction, self-referential processing, and remoteness/aging in AM. Chapter 5 summarizes the main findings of functional neuroimaging studies of AM by presenting a description of the AM retrieval network, and discusses the impetus for the empirical studies that follow. Chapters 6, 7 and 8 present studies in which functional magnetic

resonance imaging (fMRI) was employed to examine the neural correlates of AM. Chapter 6 describes a study using a novel photo paradigm to examine temporal-order memory of autobiographical events, Chapter 7 describes a study using a novel camera technology to examine the neural mechanisms of self-projection for self versus other, and Chapter 8 describes a study using a generic cue word technique to examine age-related differences in the construction and elaboration of AM. The final chapter discusses the general findings across these three fMRI studies by expanding the previous description of the AM retrieval network and proposes directions for future studies.

What is Autobiographical Memory?

AM encompasses the processes that are involved in the conscious recollection of the personal past (Baddeley, 1992; Brewer, 1986; Svoboda & Levine, 2003) and involves the interaction of multiple separate systems (Rubin, 2005, 2007b). One useful way to understand AM is to compare it to what we know about laboratory memory (LM), or memory for stimuli encoded in the controlled environment of the laboratory. Some definitions of AM are similar to distinctions of memory types in LM, whereas, others postulate terms specific to AM. AMs are typically more complex than LM because they are hierarchically structured, temporally rich, and multimodal. In the sections below these issues are discussed in more detail.

There is much controversy regarding the components and nature of AM (Brewer, 1986, 1995; Larsen, 1992). On the one hand, AM can be viewed as a distinct memory system, although there is no consensus regarding which new terms should be used (Brewer, 1995; Conway, 2005; Conway & Pleydell-Pearce, 2000). On the other hand, AM is closely related to both episodic memory (EM), which refers to memory for events with specific spatiotemporal coordinates and their associated contextual details, and semantic memory (SM), which refers to factual information not tied to a specific place or time (Tulving, 1972, 1983). Thus, AM can be conceptualized as part of a continuum between EM and SM (Barsalou, 1988; also see Moscovitch et al., 2005). Like EM, AMs comprise spatiotemporally unique memories that are associated with autonoetic consciousness, or the sense of mental time travel to when the event occurred, but similar to SM, AM also entails generic personal facts and knowledge typically associated with noetic consciousness, or simply knowing that events occurred (Tulving, 1985). Thus, AMs are comprised of episodic AMs, specific to time and place, and semantic AMs, memories not located in time (see **Figure 1**). Semantic AMs can also be divided into two further categories: 1) AM Facts, concerning idiosyncratic and shared cultural knowledge, and 2) Repeated Events, involving event-related generic and schematic knowledge (e.g., Bartlett, 1932). Further complicating these distinctions, a single episodic AM can involve a mixture of episodic AMs, semantic AMs, and general semantic knowledge (e.g., Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002). For example, the episodic AM for

a poster session might include a vivid image of a poster board toppling to the ground (episodic AM) intermixed with details about one's general enjoyment in disseminating research (semantic AM: fact), details about the many poster sessions attended (semantic AM: repeated events) and the standard sequence of events of a poster session (general semantic knowledge). In fact, episodic AMs and semantic AMs interact in several ways during the construction of AMs in both patients (e.g., Snowden, Griffiths, & Neary, 1995) and healthy individuals (e.g., Berntsen & Rubin, 2004; Conway & Pleydell-Pearce, 2000; Westmacott & Moscovitch, 2003). Thus, AM is neither purely episodic nor purely semantic, but is an integration of both memory types (Cabeza & St. Jacques, 2007; Levine, 2004).

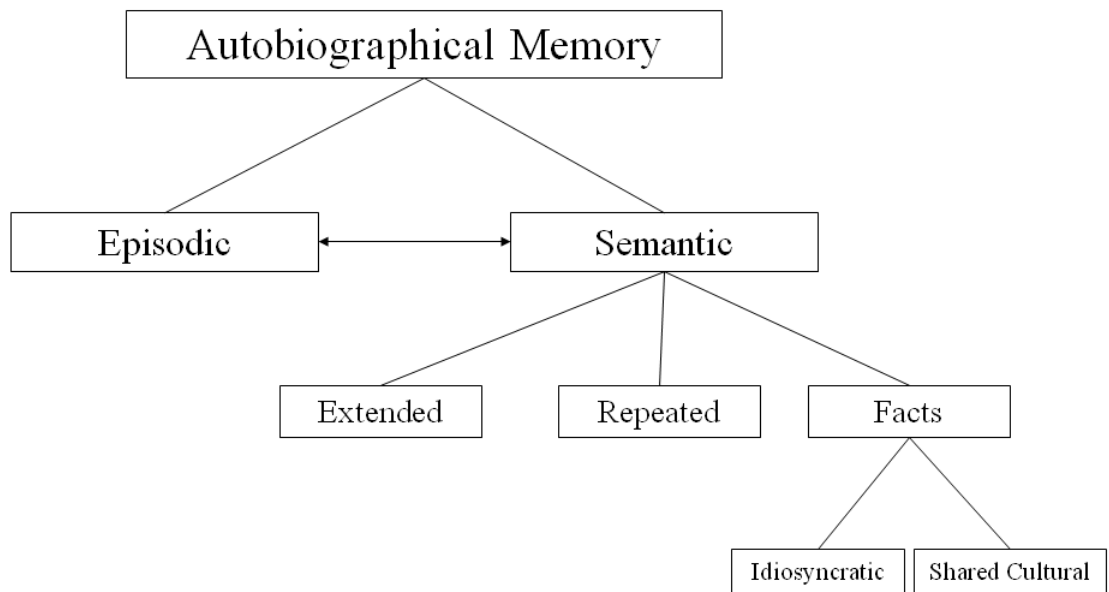


Figure 1: Different Types of Autobiographical Memory

Functional Neuroimaging Methods for Investigation of Autobiographical Memory

The primary challenge of AM research is balancing the ability to exert control over the phenomenological properties of memory retrieval while also maintaining ecological validity (Cabeza & St. Jacques, 2007; Maguire, 2001a; Svoboda, McKinnon, & Levine, 2006). Although there are several methodological challenges in functional neuroimaging studies of AM (for reviews see Maguire, 2001a; Svoboda, et al., 2006), the modification of existing techniques and the advance of new methodologies has resulted in an explosion in the number of functional neuroimaging studies of AM in recent years. Four main methods have been used to investigate AM using functional neuroimaging (see **Table 1**). First, in the generic cues method AMs are generated from novel retrieval cues (e.g., table; Crovitz & Schiffman, 1974). Although the memories elicited by generic cues are not necessarily emotional or significant, they tend to be "fresh," unrehearsed memories. Furthermore, online ratings of reliving, the sense of re-experiencing, and other phenomenological properties associated with memory retrieval during scanning are more accurate. Also, because retrieval in the scanner is protracted and is not contaminated by recent retrieval attempts, memory search processes can be investigated more easily (e.g., Daselaar et al., 2008).

Table 1: Main Methods of Eliciting Autobiographical Memory in Functional Neuroimaging Studies

Method	Advantages	Disadvantages
Generic Cues	Retrieval during scanning is not contaminated by recent retrieval episodes Memory search processes can be investigated Typically unpracticed "fresh" memories	Less control over the age and content of the memory Memory search requires longer retrieval times Difficult to access memory accuracy
Pre-Scan Interview	More control over the age and content of the memory Shorter trials can be used	Retrieval during scanning is contaminated by the pre-scan session Memory search processes cannot be investigated Difficult to access memory accuracy
Independent Sources	Retrieval during scanning is not contaminated by recent retrieval episodes More control over the age and content of the memory	Variability in ability to remember the events selected Difficult to access memory accuracy
Prospective Method	Retrieval during scanning is not contaminated by recent retrieval episodes Greater control over the age and content of the memory Retrieval accuracy can be accessed	Impractical to investigate remote memories Some methods interfere with the natural encoding of events

Second, in the pre-scan interview method AMs are elicited by cues that refer to specific events (e.g., visiting the London Eye) collected prior to the scanning session (e.g., Maguire, Henson, Mummery, & Frith, 2001). The memories retrieved in the scanner can be controlled using pre-scan ratings (e.g., age of the memory, emotion, vividness, etc.), and trials are often shorter because retrieval cues identify particular memories. The main disadvantage with this method is that the additional retrieval practice may alter the original phenomenological properties of the memories, but this problem might be attenuated by interposing a substantial time interval between pre-scan and scanning sessions (e.g., Maguire & Mummery, 1999).

Third, in the independent sources method cues to elicit AMs are generated by relatives or friends (e.g., Gilboa, Winocur, Grady, Hevenor, & Moscovitch, 2004). This method combines the advantages of the foregoing two methods, in that it tends to elicit unrehearsed memories and additional information provided by the sources can constrain the types of memories recalled during scanning. One disadvantage is that participants might have trouble remembering the event provided by the sources; however, this can also be seen as an advantage by providing greater variability in the amount of memory details and the phenomenological properties under investigation (e.g., vividness, reliving, etc.).

Finally, in the prospective method participants are asked to keep a record of events in their lives to be used as retrieval cues in the scanner (e.g., Cabeza, Prince, et al., 2004). The main advantage of the prospective method is that it allows accuracy assessment which is important given that brain activity in medial temporal and other regions tends to vary as a function of retrieval accuracy. The prospective method does not easily allow the study of remote memories (i.e., decades old), and in some cases, it might interfere with the natural encoding of AMs.

In sum, each of these four methods has advantages and disadvantages that can impact the construction, self-projection and remoteness of AM retrieval. These advantages and disadvantages are discussed in more detail as they relate to each of the chapters that follow.

Common and Unique Neural Activations in Autobiographical Memory

Consistent with the idea that AM has both shared properties with EM and SM and unique properties, functional neuroimaging studies have revealed both common and distinct activations when comparing AM retrieval to EM and to SM (e.g., Burianova & Grady, 2007; Maguire & Mummery, 1999; for meta-analysis see Svoboda, et al., 2006). Both AM and EM studies often report activations in prefrontal cortex (PFC), lateral parietal, posterior midline (posterior cingulate, precuneus), and medial temporal lobe (MTL) regions, whereas both AM and SM often report activations in lateral temporal cortices (for a meta-analysis of EM and SM imaging studies see Cabeza, Anderson, Houle, Mangels, & Nyberg, 2000). However, differences in the frequencies of AM and EM or SM activations across studies are difficult to interpret and is not particularly useful unless the several factors that tend to differ between these tasks are taken into account (for some of these factors see **Table 2**). A recent meta-analysis (Gilboa, 2004), which controlled several critical factors (e.g., test type), concluded that AM and EM recruited similar pre-retrieval regions involved in search processes, but led to distinct activations in subregions of the PFC during post-retrieval monitoring and verification. While AM tasks typically activate the ventromedial PFC, involved in the quick intuitive 'felt rightness' (e.g., Moscovitch & Winocur, 2002), EM recruited activity in the dorsolateral PFC (DL-PFC), involved in more elaborative monitoring. Thus, recollection process in AM might differ in important ways from EM.

Table 2: Factors that tend to differ between typical AM and EM conditions

Factors	AM studies	EM studies	SM studies	Regions that might be affected
1. Test type	usually recall	usually recognition	usually recall	left vs. right PFC
2. Emotional content	more	less	less	amygdala, medial PFC, ctx
3. Visual/spatial imagery	more	less	less	visual ctx, parahipp. ctx., precuneus
4. Age of memories	recent to remote	recent	n/a	hippocampus
5. Retrieval success	unknown	measured	measured	MTL, PFC, parietal ctx., etc.
6. Semantic memory content	more	less	more	left PFC, left temporal ctx.
7. Episodic memory content	more	more	less	hippocampus
8. Internal structure	complex, connected events	simple, disconnected events	n/a	PFC, parietal ctx.
9. Self-referential processing	more	less	none	medial PFC
10. Context (time,space)	more	less	less	MTL, parietal ctx.
11. Rehearsal	more	less	more	hippocampus

Very few studies have directly contrasted AM and EM within the same study and most of them did not control for many of the confounding factors between AM and EM. For example, in most of these studies AMs were likely older than the EMs (e.g., Conway et al., 1999; Fink et al., 1996; Greenberg et al., 2005; Maguire, et al., 2001). One way of exerting greater control over the factors that differ between AM and EM is to use the prospective method to elicit memories. For example, in a study using the photo paradigm (Cabeza, Prince, et al., 2004), participants took photographs in different campus locations and were fMRI-scanned while recognizing the photographs they took (AM condition) and similar photographs viewed previously in the laboratory (EM condition). This method controlled for differences in type of test (recognition in both), emotional content (minimal in both), memories' age (recent in both), retrieval success (measured and similar in both), SM (similar in both), and internal structure (simple,

disconnected events in both). With these six factors controlled, AM and EM yielded very similar activations in several brain regions, including right DL-PFC. It is possible that when accuracy is assessed, retrieving AMs involves the same kind of 'elaborate monitoring' (Gilboa, 2004) usually engaged by EM. The two factors that were not controlled, visuospatial imagery and self-referential processing, can account for greater activity for AM than for EM in visual cortex and medial PFC, respectively. AM also elicited greater activity in the hippocampus, possibly reflecting richer recollection than in the EM condition. In this study, greater recollection for AM than for EM probably reflected the fact that AMs were encoded in the rich multisensory environment of the real world with the participant controlling the picture-taking event, whereas EMs were encoded in the impoverished environment of a computer screen with little self-involvement. Thus, these results do not necessarily mean that recollection is always greater for AM than for EM, and it is not difficult to imagine situations in which the opposite could be the case.

Even fewer functional neuroimaging studies have directly compared AM and SM (e.g., Denkova, Botzung, Scheiber, & Manning, 2006b; Graham, Lee, Brett, & Patterson, 2003; Ryan et al., 2001). One consistent difference is that AM retrieval is associated with greater medial PFC activity than SM retrieval. For example, in two parallel studies, Denkova et al. (2006b) found that AMs triggered by non-verbal and verbal cues elicited greater activity in medial PFC, when compared to control conditions

involving a semantic relatedness task or identification of famous people, respectively. The medial PFC is frequently associated with self-referential processing (e.g., Craik et al., 1999; Kelley et al., 2002; Macrae, Moran, Heatherton, Banfield, & Kelley, 2004), including self-related judgments versus semantic decisions (e.g., Johnson et al., 2002), inference of mental states to self versus other (for a review see Gallagher & Frith, 2003), and AM retrieval (for a meta-analysis see Svoboda, et al., 2006). The greater involvement of medial PFC in AM compared to SM is consistent with the importance of the self as a defining feature of AM (Conway & Pleydell-Pearce, 2000), and as a critical component in the development of AM (e.g., Howe, 2003). Alternative theories of medial PFC suggest that this region is involved in internal representation of thoughts and feelings (e.g., Simons, Owen, Fletcher, & Burgess, 2005), which is likely to be recruited more during AM compared to SM retrieval.

2. Complex Construction of Autobiographical Memories

Construction of AM involves the interaction of semantic AM, both at the macro (hierarchically, nested structure) and micro levels (e.g. scripts & schematic information), which guide and support particular episodic components to create a coherent story-like event full of visuospatial imagery. Construction may be modified according to the current goals of the task such that a particular AM can have social functions (Bluck, 2003) and be used to entertain and inform (Marsh & Tversky, 2004). Thus, it is not surprising that compared to the retrieval of LM, retrieval of AM typically requires a protracted retrieval length.

It is generally agreed that AMs are organized within a nested, hierarchical structure (Barsalou, 1988; Conway & Bekerian, 1987; Conway & Pleydell-Pearce, 2000; Linton, 1986; Schooler & Herrmann, 1992). The lowest level of the hierarchy might be an episodic event (e.g., *visit to the London Eye*), nested in a more intermediate level that could involve repeated (e.g., *attending conferences*) or extended events (e.g., *two week vacation*), which are part of a higher-level hierarchy involving a longer period of time (e.g., *when I was in graduate school*; see **Figure 2**).

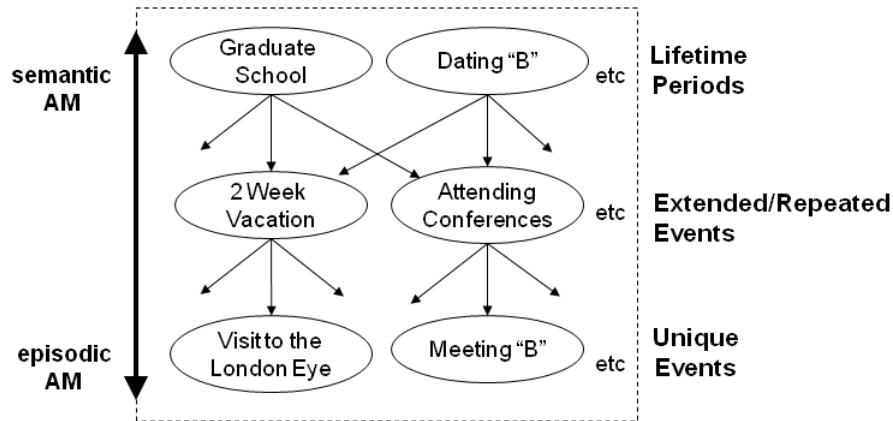


Figure 2: The Hierarchical Nested Structure of Autobiographical Memory

Thus, episodic AMs are at the lowest level of this hierarchy, with extended and repeated semantic AMs at higher levels. Within this framework, higher levels provide access to lower levels in a top-down fashion, such that providing participants with cues from higher levels facilitates retrieval of episodic AMs (e.g., Conway & Bekerian, 1987) and providing temporal structure (e.g., morning versus afternoon) may lead to more accurate temporal ordering of episodic AMs. A single episodic AM, which represents the lowest or most specific level of the hierarchy, is typically what we think of as AM, however, there is substantial evidence suggesting that semantic AMs are the preferred level of recall (Barsalou, 1988; Burt, Kemp, & Conway, 2003; Conway & Pleydell-Pearce, 2000). Generic knowledge is the basic level or entry point to AMs and episodic AMs are only accessed via additional generative or direct retrieval processes (Conway, 2005; Conway & Pleydell-Pearce, 2000). Generative retrieval is effortful and requires longer retrieval times, whereas, direct retrieval is effortless and requires shorter retrieval times.

In contrast to voluntary retrieval, episodic AMs can also be retrieved involuntarily, where there is no conscious attempt at retrieval (for a review see Berntsen, 2007). Functional neuroimaging studies have generally focused on voluntary, generative retrieval. The sections below review evidence from functional neuroimaging studies on the construction of AMs, and the influence of retrieval length and phase.

Constructing Autobiographical Memories

Functional neuroimaging studies have associated the construction of AMs with different PFC regions. In particular, memory search and controlled retrieval processes involving left lateral PFC and monitoring processes with ventromedial PFC. The link between memory search and controlled retrieval processes in AM and lateral PFC regions was detected by an early positron emission tomography study (Conway, et al., 1999) that found activation here when comparing AM (generic cues method) to LM retrieval. Although activation differences between these tasks may reflect many different factors (Cabeza, Prince, et al., 2004), the link between AM and activations in lateral PFC and other brain regions was supported by subsequent meta-analyses (Maguire, 2001a; Svoboda, et al., 2006). Lateral PFC regions are assumed to be hierarchically organized, with ventrolateral PFC (VL-PFC) involved in cue specification and controlled retrieval of information from posterior regions, and DL-PFC manipulating the products of retrieval in working memory (Petrides, 2005). For example, Steinvorth, Corkin and Halgren (2006) found activity in both dorsolateral and

ventrolateral PFC during an initial search period for remote events when comparing AM to LM retrieval, while only DL-PFC activity remained online during reminiscence. These results are also consistent with the idea that AM construction is an iterative process (Conway & Pleydell-Pearce, 2000). Lateral PFC activity involved in memory search and controlled retrieval is predominantly left-lateralized (Maguire, 2001a; Svoboda, et al., 2006), which is thought to reflect the contribution of semantic information to AM, consistent with a left-lateralized pattern of activation in PFC irrespective of the nature of the eliciting cue (Denkova, et al., 2006b).

Monitoring processes during AM have been associated with activations in ventromedial PFC (Gilboa, 2004), a region that encompasses the ventral medial PFC and portions of the orbitofrontal cortex (OFC). For example, Graham, Lee, Brett and Patterson (2003) found greater activity in ventromedial PFC associated with the recall of AM compared to SM. It has been suggested that AM involves a type of monitoring different than the one typically required by LM, which have been linked to right DL-PFC (Henson, Rugg, Shallice, & Dolan, 2000). According to Moscovitch and collaborators (Moscovitch & Winocur, 2002), LM tasks typically require elaborate, conscious monitoring, whereas AMs normally involve a quick, intuitive, and pre-conscious form of monitoring called feeling-of-rightness (FOR). Consistent with the FOR hypothesis, a meta-analysis found that ventromedial PFC regions tend to be more frequent in AM than in LM studies (Gilboa, 2004). Although ventromedial PFC activations are not

typical in LM studies, they can be found during illusory recognition (Cabeza, Rao, Wagner, Mayer, & Schacter, 2001). Moreover, ventromedial PFC damage has been associated with confabulation (Gilboa et al., 2006).

Variability in the Length of Autobiographical Memory Retrieval

Functional neuroimaging studies of AM have used retrieval lengths that have varied from a few seconds to minutes long (Svoboda, et al., 2006), but only a few have directly examined activation differences related to differences in the length of retrieval (Addis, McIntosh, Moscovitch, Crawley, & McAndrews, 2004; Graham, et al., 2003). For example, using PET imaging, Graham et al. (2003) varied the length of time allotted to AM retrieval during PET scanning from 15 seconds (study 2) to 30 seconds (studies 1 & 3), and found a greater proportion of specific AMs retrieved in the longer retrieval time. Furthermore, they found that activity in the middle temporal cortices, a region involved in semantic knowledge, was initially engaged in the left hemisphere for shorter retrieval lengths and was more right lateralized for longer retrieval lengths. Similarly, a recent meta-analysis (Svoboda, et al., 2006) found that AM studies using shorter retrieval lengths (< 10 s) often found activity in left middle temporal cortices, whereas, studies using longer retrieval lengths (> 20 s) tended to find activity in the right temporal cortex. Thus, allocating more time for AM retrieval should increase the amount and specificity of the semantic information retrieved via the increasing involvement of middle temporal cortices, which subsequently supports the retrieval of episodic AMs. In an fMRI study,

Addis, McIntosh et al. (2004) directly examined differences in the time course of activity between generic (repeated AMs) and unique (episodic AMs) events collected in a pre-scan interview. They found that there were differences in the peak of the time lags, with regions associated with generic AMs peaking much earlier (2 to 4 s) following the cue to elicit a memory, whereas regions involved in unique AMs peaked later (6 to 8 s). Thus, generic AMs were accessed more quickly than unique AMs. The results of these studies are consistent with theories of AM which suggest that semantic AM is the preferred level of access during retrieval (Conway & Pleydell-Pearce, 2000), and that with increasing effort and subsequently longer retrieval times, the retrieval of more specific information leading to an episodic AM and richer recollection is more likely. However, there are two important caveats to the assumption that longer retrieval lengths elicit episodic AMs: 1) retrieval of episodic AMs can fail (Barsalou, 1988; Conway, 2005), in which case longer retrieval lengths would not reliably elicit episodic AMs, and 2) retrieval of episodic AMs can occur directly, in which case a shorter retrieval length would be sufficient.

Whether generative or direct retrieval occurs likely depends on the method used to elicit AMs (see **Table 1**). The generic cue method, which typically requires long trials, likely involves more generative retrieval, whereas other methods, such as the prospective method, which involves more recent memories, or the pre-scan interview, where memories are initially retrieved prior to scanning, might involve more direct

retrieval. For example, in a recent meta-analysis, Svoboda et al. (2006) found that fMRI studies using the prospective method (e.g., Cabeza, Prince, et al., 2004; Levine et al., 2004) failed to find activity in lateral temporal cortices involved in SM, which they interpreted as evidence for greater direct retrieval processes. In order to precisely examine brain regions that are recruited during successful generative versus direct retrieval it might be necessary to acquire reaction time data.

Phases of Autobiographical Memory Retrieval

Several functional neuroimaging studies have sought to segregate the brain regions involved during different phases of AM retrieval by using a self-paced design, in which participants indicate when a memory is retrieved and then maintain or further elaborate upon the memory. The self-paced design has been used primarily to examine generative retrieval. For example, using slow cortical potentials Conway, Pleydell-Pearce, and Whitecross (2001) found that left PFC regions came online early as participants searched for a cue, whereas posterior temporal and occipital regions came online later during the formation and maintenance of the retrieved memory (also see Conway, Pleydell-Pearce, Whitecross, & Sharpe, 2003). Similarly, in an fMRI study Botzung, Denkova, Ciuciu, Scheiber and Manning (2008) showed that left PFC peaked earlier than did left MTL regions. Thus, during the initial generative search for a memory, left PFC regions supporting strategic retrieval are involved, whereas when a

specific memory is formed and held in mind, posterior regions come online to support the retrieval of specific contextual details.

Although several studies have used the self-paced design (Botzung, et al., 2008; Conway, et al., 2001; Daselaar, et al., 2008; Steinvorth, et al., 2006), none have examined the effects of response times to elicit an AM. According to models proposed by Conway and colleagues (Conway & Pleydell-Pearce, 2000), direct retrieval should be associated with shorter retrieval times compared to generative retrieval. Although the generic cue method tends to engage generative retrieval processes, there is considerable variance in the response times necessary to elicit an AM. Indeed, participants frequently note that sometimes the memory seemed to appear effortlessly, whereas other times retrieval was more effortful. In order to examine these issues more closely it is important to examine the influence of reaction time to construct an AM.

Given the iterative nature of AM, one interesting line of research is to examine the common and unique activations involved during the initial access of an AM and the sustained elaboration of that memory. For example, Steinvorth et al. (2006) examined fMRI activity related to search and reminiscence periods, and found a common pattern of activity. However, they did not directly compare the activity between these two phases. In contrast, Daselaar et al. (2008) compared activity related to accessing an AM to activity related to maintaining and elaborating the memory. They found that the initial access period engaged frontal regions involved in search (VL-PFC) and self-

referential processes (medial PFC), and posterior regions involved in accessing the memory trace (e.g., hippocampus, retrosplenial cortex), whereas the later period recruited regions involved in the retrieval of contextual details (e.g., visual cortices, precuneus).

Summary

AM typically involves a protracted retrieval length, especially when the generic cue method is employed, which is an advantage in fMRI studies because it allows the segregation of the time courses of brain regions involved during search, formation, and elaboration. Search has been linked to brain regions involved in strategic retrieval that is guided by semantic information (e.g., VL-PFC and temporal cortices), formation to accessing the memory trace (e.g., hippocampus), and elaboration to posterior brain regions involved in the recovery of contextual details (e.g., precuneus and visual cortices). However, consistent with the iterative nature of AM retrieval, there is also overlap in the brain regions involved in search and elaboration phases. Furthermore, brain regions supporting the retrieval of episodic AMs peak much later than those regions supporting retrieval of semantic AMs, with longer retrieval times tending to elicit episodic AMs and shorter retrieval times eliciting semantic AMs. However, some AMs are formed more quickly via direct retrieval, and might reflect access of the memory trace. In sum, during generative retrieval longer search periods tend to elicit greater recollection in AM studies because episodic AMs can be accessed; however,

future research is needed to examine how the time-course of activity might differ in direct retrieval.

3. Qualities of Autobiographical Memory

AMs are ideal to investigate the contribution of emotion, vividness and reliving to the neural correlates of event memory because they often involve rich emotional content, vivid sensory details and a rich sense of re-experience (Rubin, 2007a), which are qualities typically absent in LMs. The sections below describe the qualities of emotion, vividness and reliving in AM, and link these ideas to functional neuroimaging studies.

Emotion

Emotion, which varies along the two dimensions of valence, from positive to negative, and arousal, from calm to excited (Bradley & Lang, 2000), is an important component of AM that imparts meaning to the experiences in our lives and can lead to memorable- or even indelible- memories. In LM, arousal enhances memory via the modulation of memory encoding and consolidation processes in the hippocampus by the amygdala (for reviews see LaBar & Cabeza, 2006; Phelps, 2004), and there is growing evidence that emotional arousal can also influence memory during retrieval (for a review see Buchanan, 2007). For example, Dolcos, LaBar, and Cabeza (2005) found that activity in the amygdala and hippocampus was greater for emotionally arousing stimuli associated with recollection versus familiarity. They suggest that the amygdala and hippocampus involve a “synergistic mechanism in which emotion enhances recollection

and recollection enhances emotion” (p. 2631). Thus, it might be difficult to tease apart the effects of emotional arousal on the process of retrieval versus the emotional response elicited by the products of retrieval (Buchanan, 2007). Emotional valence can also influence memory by increasing attention and controlled processes during encoding mediated by frontal cortices (Kensinger & Corkin, 2004), but there is less evidence about the effects of valence during retrieval in LM studies, perhaps because of difficulty in equating the arousal associated with positive and negative memories. Consistent with the influence of emotion on LM, AMs that are more arousing (Reisberg, Heuer, McLean, & O’Shaughnessy, 1988; Talarico, LaBar, & Rubin, 2004) or positively valenced (D’Argembeau, Comblain, & Van der Linden, 2003; Destun & Kuiper, 1999; Schaefer & Philippot, 2005) are also more richly recollected. However, very few studies have directly investigated how the effects of emotion on richly recollecting AMs are instantiated in the brain (for meta-analysis see Svoboda, et al., 2006).

AM retrieval is influenced by emotional intensity. For example, Addis et al. (2004) found that the emotional intensity associated with AM retrieval modulated activity in the hippocampus, although amygdala activity was not directly observed. Similarly, in an fMRI study Greenberg et al. (2005) found greater amygdala-hippocampal interactions during AM compared to SM. Activity in the amygdala was also correlated with activity in right VL-PFC, which might suggest a possible interaction between the emotional response and memory construction. Consistent with this idea,

Daselaar et al. (2008) found that emotional intensity influenced amygdala activity during the initial search for a memory, but there was less of an effect here during elaboration or after a memory was retrieved. They suggested that activity in emotional brain regions should occur relatively early during the retrieval process, if emotions signal appropriate actions (e.g., Leventhal & Scherer, 1987) to guide construction. Emotional AMs are often associated with a right lateralized or more bilateral pattern of activation compared to the typical left-lateralized pattern (Denkova, Botzung, Scheiber, & Manning, 2006a; Fink, et al., 1996; Markowitsch et al., 2000; Vandekerckhove, Markowitsch, Mertens, & Woermann, 2005), and patients with damage to the right hemisphere recall less emotional AMs (Cimino, Verfaellie, Bowers, & Heilman, 1991). Furthermore, evidence from patients with damage to the amygdala also suggests that this region is necessary for the recall of emotionally arousing AMs (Buchanan, Tranel, & Adolphs, 2005, 2006).

The pattern of activity during AM retrieval is also influenced by emotional valence, with positive and negative AMs leading to differential activity in subregions of the OFC. For example, in a PET study Markowitsch, Vandekerckhove, Lanfermann, and Russ (2003) asked participants to retrieve happy or sad AMs associated with high emotional intensity. Sad AMs led to greater bilateral activity in OFC, whereas happy AMs resulted in greater medial OFC activity. Furthermore, greater left hippocampal activity was found in happy compared to sad AMs, consistent with behavioral results of greater intensity felt for the happy AMs, perhaps relying on greater recollection of these

memories. Similarly, in a blocked design fMRI study, Piefke, Weiss, Zilles, Markowitsch, and Fink (2003) found that positive memories led to greater activity in medial OFC (also see Keedwell, Andrew, Williams, Brammer, & Phillips, 2005). Thus, these results point to the importance of the subregions in OFC and medial PFC that are differentially involved in the retrieval of positive AMs, via medial OFC and ventromedial regions, and negative AMs, mediated by lateral OFC (e.g., Kuchinke et al., 2006). These results are consistent with the involvement of different OFC subregions in emotional evaluation of valence (for a review see Kringelbach & Rolls, 2004), with medial areas involved in reward processing and lateral areas in evaluation of punishers.

Vividness

AMs are typically richer in sensorial details or vividness than LMs because they are composed of multisensory information (Rubin, 2007b) associated with a complex, 3D environment. Subjective reports of vividness are one of the best predictors of subjective reports of recollection (Rubin, Burt, & Fifield, 2003; Rubin & Siegler, 2004), and for distinguishing real versus imagined events (Johnson, Foley, Suengas, & Raye, 1988). Visuospatial imagery, involving both descriptive imagery and spatial imagery, is particularly important in AM (Brewer, 1986; Rubin & Kozin, 1984) and might be a necessary component of AM retrieval (for a review see Greenberg & Rubin, 2003). For example, patients with visual memory-deficit amnesia, a deficit in visual descriptive memory following damage to the visual cortex, are severely impaired in retrieval of AM

(Rubin & Greenberg, 1998). Not only are these patients impaired on retrieval of AMs via visual cues, but they also show deficits in the recall of memories cued via other modalities. Greenberg and Rubin (2003) interpreted these findings by proposing that impairment of visual memory disrupts the entire retrieval process because AM retrieval depends upon the interconnection and activation of many separate systems (also see Rubin, 2007b). Consistent with these findings, Rubin, Burt, and Fifield (2003) showed that degrading visual input in healthy individuals during the encoding of staged laboratory events, by asking participants to wear blindfolds, impaired some phenomenological aspects of later memory recall.

Turning to spatial imagery, the ability to construct a spatial scene is an essential component of AM (Hassabis, Kumaran, Vann, & Maguire, 2007), just as the ability to link a memory to a specific spatial location is an integral feature of EM (Tulving, 1983). Allocentric spatial representations stored in memory have been linked to the MTL, such that patients with damage to the hippocampus were shown to be impaired on spatial memory tasks, whereas egocentric spatial representations that allow for imageable representations are supported by posterior parietal and precuneus cortices, such that patients with lesions to parietal cortices are impaired on viewpoint dependent spatial imagery tasks (for reviews see Burgess, Becker, King, & O'Keefe, 2001; Moscovitch, et al., 2005). The link between these impairments on spatial tasks and AM are readily apparent in patients with damage to the MTL who have amnesia. For example, patient

K.C., who has damage to the hippocampus and other MTL regions, has severe loss of both AMs and the detailed spatial representations of familiar neighborhoods (for a review see Moscovitch, et al., 2005). However, there is less evidence regarding the effects of parietal lesions on AM, suggesting that the egocentric aspects of spatial imagery in AM might be more subtle (e.g., Berryhill, Phuong, Picasso, Cabeza, & Olson, 2007).

Functional neuroimaging studies of AM have linked visuospatial imagery with activity in visual cortex (cuneus), posterior midline regions (precuneus and parietal cortices), and MTL regions. For example, the retrieval of images from AM (test driving a Honda Civic) versus specific images (imagining a Honda Civic) yielded greater activity in left precuneus, parahippocampal gyrus, and bilateral posterior cingulate cortices (Gardini, Cornoldi, De Beni, & Venneri, 2006). Similarly, AM elicited greater activity in cuneus and parahippocampal cortices compared to LM, as would be expected given the richer sensory details associated with these memories (Cabeza, Prince, et al., 2004). Furthermore, vividness of details is modulated by activity in the hippocampus (Addis, Moscovitch et al., 2004), consistent with the strong association between vividness and recollection.

Reliving

The ability to relive or re-experience the personal past is a critical and defining characteristic of AM (Brewer, 1986). The ability to re-experience AMs is linked to the

rich recovery of contextual details (Cabeza & St. Jacques, 2007) particularly those that evoke visual imagery (Rubin, Schrauf, & Greenberg, 2003). For example, in one study Daselaar et al. (2008) found that activity in the visual cortex was positively correlated with subjective ratings of reliving following the formation of an AM, when participants were maintaining and elaborating further details about the memory (also see Conway et al., 2001). In combination with other brain regions (e.g., MTL, frontal), visual cortex activity could initiate the vivid sense of reliving associated with remembering the personal past (Rubin & Kozin, 1984), just as the reactivation of posterior cortices in EM tasks results in vivid remembering (Wheeler, Petersen, & Buckner, 2000).

Very few functional neuroimaging studies have directly examined the neural mechanisms associated with reliving, however, some have compared episodic AM and semantic AM, including AM facts and repeated events (Addis, Moscovitch, et al., 2004; Levine, et al., 2004; Maguire & Mummery, 1999), which may differ in the sense of re-experience. The results of these studies suggest that there is substantial overlap in the regions recruited by episodic AM and semantic AM (for a meta-analysis see Svoboda, et al., 2006), but potential differences in the involvement of typical recollection regions including subregions of the MTL (for review see Diana, Yonelinas, & Ranganath, 2007), posterior cingulate/retrosplenial and posterior parietal cortices (for reviews see Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Wagner, Shannon, Kahn, & Buckner, 2005) and frontal cortices (for review see Rugg & Yonelinas, 2003). Further, they emphasize that

retrieval of AMs involves more or less recollection. Indeed, the recall of an AM can contain several contextual details that might be recollected (e.g., sensorial, thoughts/feelings, temporal/spatial, etc.), and thus, there might be a considerable amount of variability in the amount of recollection.

Some studies have found that episodic AMs recruited greater activity in the hippocampus compared to semantic AM (facts) and SM (Maguire & Mummery, 1999), and greater activity in the parahippocampal cortex (Levine, et al., 2004) compared to semantic AMs (repeated events) and SM. These results are consistent with evidence from patients with retrograde amnesia which suggest that the hippocampus is necessary for retrieving episodic AMs but less important for semantic AMs (although see Bayley, Gold, Hopkins, & Squire, 2005; for reviews see Nadel & Moscovitch, 1997). On the other hand, it might not be the type of memory per se that is critical in the engagement of MTL (Ryan, Cox, Hayes, & Nadel, 2008), but rather the vividness associated with retrieval (although see Bayley, Hopkins, & Squire, 2003; e.g., Steinvorth, Levine, & Corkin, 2005). Indeed, it seems possible to vividly recollect both a unique, episodic AM of last year's Christmas Eve, as well as a more general semantic AM of repeated Christmas Eves spent at home. Consistent with this idea, Addis et al. (2004) found that the level of detail, but not the type of memory retrieved (i.e., episodic AM or semantic AM), modulated activity in the hippocampus. However, retrieving many contextual details for a semantic AM might not be equivalent to reliving a unique episodic AM.

Future research is needed to directly examine the contribution of recollection in episodic AMs and semantic AMs that are comprised of both repeated and AM facts, as well as to understand the contribution of episodic and semantic components in these memories.

Episodic AMs were also found to recruit greater activity in the posterior cingulate/retrosplenial cortex, which has direct anatomical connections to the hippocampus (Kobayashi & Amaral, 2003) and is an area where lesions can result in amnesia (e.g., Valenstein et al., 1987). For example, Addis et al. (2004) found that episodic AMs recruited greater activity in left posterior cingulate, albeit at a slightly lower threshold, and were also given higher subjective ratings on the amount of detail, compared to semantic AMs (repeated events). Similarly, Levine et al. (2004) found that episodic AMs, compared to repeated events and SM, relied more on posterior cingulate/retrosplenial cortices and tended to have higher subjective ratings of vividness. Furthermore, activity in posterior cingulate cortices has also been found to be sensitive to the amount of reliving associated with AM retrieval (Daselaar, et al., 2008). Thus, greater activity here for episodic AMs likely contributes to greater recollection compared to semantic AMs.

Another region that has been found to show greater activity for episodic than semantic AM is the angular gyrus, roughly Brodmann Area (BA) 39. Although this region is activated in most AM conditions (for a meta-analysis see Svoboda, et al., 2006), there is evidence that the right angular gyrus is more activated for episodic AM than

semantic AM (Levine, et al., 2004). Together with the supramarginal gyrus (roughly BA 40), the angular gyrus is part of the ventral parietal cortex (VPC), whereas intraparietal sulcus (IPS) and the superior parietal lobule (roughly BA 7) constitute dorsal parietal cortex (DPC). Although parietal lesions are not associated with severe AM deficits, recent studies have found that VPC regions can produce significant AM deficits (Berryhill, et al., 2007; Davidson et al., 2008). For example, Berryhill et al. (2007) examined verbal recall of AMs in patients with bilateral damage to ventral parietal cortices using the autobiographical interview (Levine, et al., 2002), which distinguishes episodic and semantic components in AM while varying retrieval support. Compared to controls, they found that the parietal patients were unable to spontaneously recover details, although they could retrieve this information when provided with specific retrieval prompts. These results are consistent with the Attention to Memory (AtoM) model (Cabeza, 2008; Cabeza, et al., 2008; Ciaramelli, Grady, & Moscovitch, 2008), which postulates that during episodic retrieval, VPC mediates bottom-up attentional processes captured by the retrieval output, whereas DPC mediates top-down attentional processes that control the retrieval search. Thus, the greater involvement of parietal cortices in episodic AMs could reflect increased attention to details recovered during retrieval and lead to the enhanced specificity and richness associated with these events.

Finally, there is some evidence suggesting that episodic AMs might recruit greater activity in medial PFC, a region associated with self-referential processes and

mental time travel (Buckner & Carroll, 2007a; Schacter, Addis, & Buckner, 2007; Wheeler, Stuss, & Tulving, 1997). For example, Levine et al. (2004) found that both episodic AMs and semantic AMs (repeated events) were associated with activity in the medial PFC, but episodic AMs recruited greater activity in this region (Maguire & Mummery, 1999). Levine et al. (2004) interpreted this finding by suggesting that episodic AMs might involve a greater sense of the self in subjective time or auto-noetic awareness. These results fit well with current definitions of EM that focus on the importance of auto-noetic consciousness and the role of the frontal lobes in fulfilling this capacity (Wheeler, et al., 1997). Indeed, patients with degenerative damage to the frontal lobes resulting from frontotemporal dementia were shown to be impaired on auto-noetic consciousness (Piolino et al., 2003) and focal lesion studies have suggested that the sense of remembering (i.e., subjective reporting of recollection) is supported by frontopolar regions that overlap with medial PFC (Duarte, Ranganath, & Knight, 2005; Wheeler & Stuss, 2003).

Summary

AMs are ideal for investigating the contribution of properties that modulate the neural correlates of recollection because they often involve rich emotional content and vivid sensory details. Emotional AMs are associated with activity in the amygdala and subregions of the OFC, whereas vividness is associated with visual cortex activity. Although functional neuroimaging evidence is missing, AMs that involve strong

auditory, tactile, or taste sensations should also involve activity in the corresponding sensory regions. Emotion and vividness have also been associated with increased activity in the hippocampus, which together with medial PFC, posterior cingulate cortex, retrosplenial cortex, and posterior parietal cortices, contributes to the rich sense of reliving in AM retrieval.

4. Aging and Remote Autobiographical Memory

One of the main strengths of functional neuroimaging of AM is that it allows the study of the neural correlates of remote memories, which cannot be created in the laboratory, and recent memories, which is a critical issue for current models of memory consolidation. Compared to LM, there is a considerable temporal range in AMs from recent (e.g., days) to remote (e.g., decades), and the remoteness of the event might affect how the memory will be recollected. Indeed, the accumulation of episodes in time is one possible mechanism by which episodic AMs become more semanticized, or semantic-like, and eventually make the transition from episodic AM to semantic AM (Barsalou, 1988; Linton, 1982; Neisser, 1986). The properties of recent and remote episodic AMs typically differ. Thus, recent AMs might be more easily accessible (Linton, 1986), frequent (Rubin & Wenzel, 1996), mundane (Barclay & DeCooke, 1988), and might be initially vivid but are more likely to be forgotten unless they are linked to AM knowledge (Conway, 2001). In the literature, recent episodic AMs have ranged from days old to years old, whereas, remote episodic AMs might be decades old or only a couple years old.

The study of very remote AM demands the consideration of aging. AM studies of aging are consistent with findings from LM studies of cognitive aging, such that aging is associated with an increase in semantic AMs, accompanied by a decrease in the episodic components and a greater reliance on semantic components in episodic AMs

that are retrieved (Levine, et al., 2002; Piolino, Desgranges, Benali, & Eustache, 2002; Piolino et al., 2006; St. Jacques & Levine, 2007). There are inconsistent findings regarding age-related differences in recent versus remote AMs, however, possibly due to methodological differences in eliciting AMs across studies these studies. Thus, when retrieval is more open fewer age-related differences between recent and remote time periods are found (e.g., Dijkstra & Kaup, 2005), because older adults might self-select from a pool of well-rehearsed events. The sections below review evidence from functional neuroimaging studies on the retrieval of remote memories and the influence of age.

Remote Autobiographical Memories

The neural substrates of recent versus remote AMs have been the focus of many neuroimaging studies especially with respect to the permanent involvement of the hippocampus. According to the standard consolidation model (SCM), the hippocampus has a time-limited role in the storage and retrieval of AMs, whereby memories become independent from the hippocampus and dependent upon neocortical areas following consolidation (Alvarez & Squire, 1994). This idea is consistent with evidence from patients with focal lesions in the MTL who demonstrate AM loss that is temporally graded in the favor of remote AMs (for a review see Squire & Bayley, 2007). For example, Bayley, Hopkins and Squire (2003) asked patients with MTL damage and healthy controls to recall remote AMs (i.e., decades old) and coded these memories with

respect to the number of details. They found that patients were able to retrieve detailed remote AMs that were on par with the controls. In contrast, the multiple trace theory (MTT) posits a permanent role for the hippocampus in the retrieval of memories that are detailed and vivid (Nadel & Moscovitch, 1997). Consistent with MTT, emerging evidence from patients with hippocampal damage suggests that the impairment in the ability to re-experience AMs from across the lifespan is greater than was previously found (Moscovitch, et al., 2005). For example, Steinvorth, Levine and Corkin (2005) asked patients with bilateral MTL to recall AMs and they used a more sensitive coding scheme which included specific prompts to examine the full potential of retrieval. Consistent with MTT, they found no temporal gradient in the AM impairment, although both patients performed normally on SM.

The issue of remoteness continues to be strongly debated (Moscovitch, et al., 2005) and functional neuroimaging studies of AM provide the opportunity to examine them in healthy individuals. SCM predicts greater hippocampal activity for recent than remote AMs (i.e., a remoteness effect), whereas MTT predicts that if both types of AMs are equally detailed and vivid, they should elicit similar hippocampal activity (i.e., no remoteness effect). Although a few functional neuroimaging studies found the remoteness effect predicted by SCM (Niki & Luo, 2002; Piefke, et al., 2003) most of the studies comparing remote and recent AMs did not, supporting MTT (Addis, Moscovitch, et al., 2004; Conway, et al., 1999; Gilboa, et al., 2004; Maguire & Frith, 2003b;

Maguire, et al., 2001; Piolino et al., 2004; Rekkas & Constable, 2005; Ryan, et al., 2001; Viard et al., 2007) and consistent with emerging evidence in the patient literature, which suggests that MTL damage can impact remote AMs greater than was previously found (Steinvorth, et al., 2005). However, neuroimaging evidence cannot irrefutably determine the necessity of the hippocampus in the retrieval of remote AMs. Furthermore, the interpretation of functional neuroimaging evidence supporting MTT is also complicated by a number of factors that modulate hippocampal activity during AM, including the following seven.

1. Re-Encoding of AMs. Hippocampal activity can reflect re-encoding processes that occur during retrieval (Stark & Okado, 2003). Yet, consistent with MTT, a study using self vs. other photographs as retrieval cues, found greater left hippocampal activity during AM retrieval for both recent and remote events when compared to viewing novel 'other' photographs (Gilboa, et al., 2004). Further research is needed to determine whether these results persist when controlling for encoding success on novel items.

2. Vividness and Detail of AM. MTT predicts similar hippocampal activity for remote and recent AMs only if these two kinds of AMs are matched in vividness and detail. Supporting the importance of this condition, in a study that found a remoteness effect in the hippocampus, the effect disappeared when potential confounding factors,

including detail, were entered as covariates in fMRI analyses (Addis, Moscovitch, et al., 2004).

3. Method Used to Elicit AM. In the pre-scan interview method, participants may recall the interview rather than the original event, dramatically reducing the age of memories retrieved in the scanner. This could explain why some studies using this method failed to find a remoteness effect (Conway, et al., 1999; Maguire, et al., 2001). Yet, consistent with MTT, a remoteness effect has also been missing in studies using other methods (Gilboa, et al., 2004; Piolino, et al., 2004; Rekkas & Constable, 2005; Steinvorth, et al., 2006).

4 Amount of Time Allowed for AM Retrieval. It has been suggested (Gilboa, et al., 2004; Ryan, et al., 2001) that shorter retrieval times allow the retrieval of details for recent but not for remote memories, leading to a remoteness effect (Maguire & Frith, 2003b), whereas longer retrieval times allow the retrieval of details for both kinds of memories, reducing or eliminating the remoteness effect (Ryan, et al., 2001).

5. How Remote Are "Remote Memories." Memories labeled as "remote" in functional neuroimaging studies have been as recent as 2 years (Rekkas & Constable, 2005) and as old as 30 years (Ryan, et al., 2001). This variability reflects a general lack of specificity in theories of memory consolidation. In fact, functional neuroimaging studies of LM have looked for consolidation-related changes in hippocampal activity during

intervals that would be normally classified as "recent" in AM studies, such as one week (Stark & Squire, 2000).

6. Lifetime Period of Remote Memories. There is considerable behavioral evidence that AMs from adolescence and early adulthood are remembered better than AMs from other time periods, a phenomenon known as the reminiscence bump (Rubin, 2002). Thus, the quality of remote AMs and their associated hippocampal activity may vary depending on when they are sampled.

7. Age of the Participants. Investigating the neural correlates of truly remote AMs requires scanning older participants, but aging by itself can lead to a reduction in hippocampal activity (Daselaar, Fleck, Dobbins, Madden, & Cabeza, 2006). Also, there is evidence of hemispheric asymmetries in the remoteness effect (Maguire & Frith, 2003b; Viard, et al., 2007), and aging is known to reduce hemispheric asymmetries in brain activity (Cabeza, 2002). In fact, fMRI studies have found activity in the left hippocampus in young adults, whereas, bilateral activity has been found in older adults for some remote periods (Maguire & Frith, 2003a; Viard, et al., 2007), but the effects of remoteness and age have not been disentangled.

Although the hippocampus has been the focus of most functional neuroimaging studies, other brain regions are also sensitive to memories' age. The most consistent finding is greater activation in the retrosplenial cortex for recent compared to remote AMs (Gilboa, et al., 2004; Piefke, et al., 2003; Rekkas & Constable, 2005; Steinvorth, et al.,

2006). Several accounts have been suggested for the role of the retrosplenial cortex in recent AMs including the construction of generic visual representations, retrieval of personally familiar information, emotional processing, and vivid recollection. PFC regions were also found to be sensitive to the age of AMs, but results have been more variable, with some studies showing greater PFC activity for recent AMs (Maguire, et al., 2001; Piolino, et al., 2004), and other studies, for remote AMs (Steinvorth, et al., 2006). Moreover, there is evidence that different PFC regions are activated depending on the age of the AMs (Niki & Luo, 2002; Rekkas & Constable, 2005).

Age-Related Differences in Autobiographical Memory

To date, only a handful of studies have examined the impact of age on the neural mechanisms of AM (Maguire & Frith, 2003a; Viard, et al., 2007). Previous functional neuroimaging studies examining age-related differences in AM have been primarily focused on the role of the hippocampus- especially as it relates to the remoteness and vividness during retrieval. For example, in an fMRI study, Maguire and Frith (Maguire & Frith, 2003a) compared activity in young and older adults when retrieving episodically rich AMs, semantic AM facts, public events, and general knowledge. AMs were elicited via a pre-scan interview. During scanning, participants listened to statements reflecting each of the conditions and were asked to verify the truthfulness of the statements. The main finding from this study was that while young adults recruited left hippocampus during recall of episodic AMs, older adult recruited bilateral

hippocampus. More recently, Viard et al. (2007) examined AM in older adults across 5 life-time periods. They found that retrieval of vivid AMs was associated with recruitment of the left hippocampus across the lifespan, and that the right hippocampus was recruited to a greater extent for those life-time periods associated with richer recollection.

Summary

Functional neuroimaging studies of AM enable the investigation of the neural correlates of memory for remote versus recent events, which cannot easily be investigated in the laboratory and is a crucial issue for current models of memory consolidation. These studies have generally shown that the hippocampus is important for the retrieval of vivid or richly re-experienced AMs, irrespective of the remoteness. Although many functional neuroimaging studies of AM have considered the influence of the age of the memory, very few studies have considered the impact of the age of the participant.

5. The AM Retrieval Network

Recalling memories from our personal past involves a distributed set of primarily left-lateralized brain regions (Cabeza & St. Jacques, 2007; Svoboda, et al., 2006), which has been referred to as the AM retrieval network (see **Figure 3**).

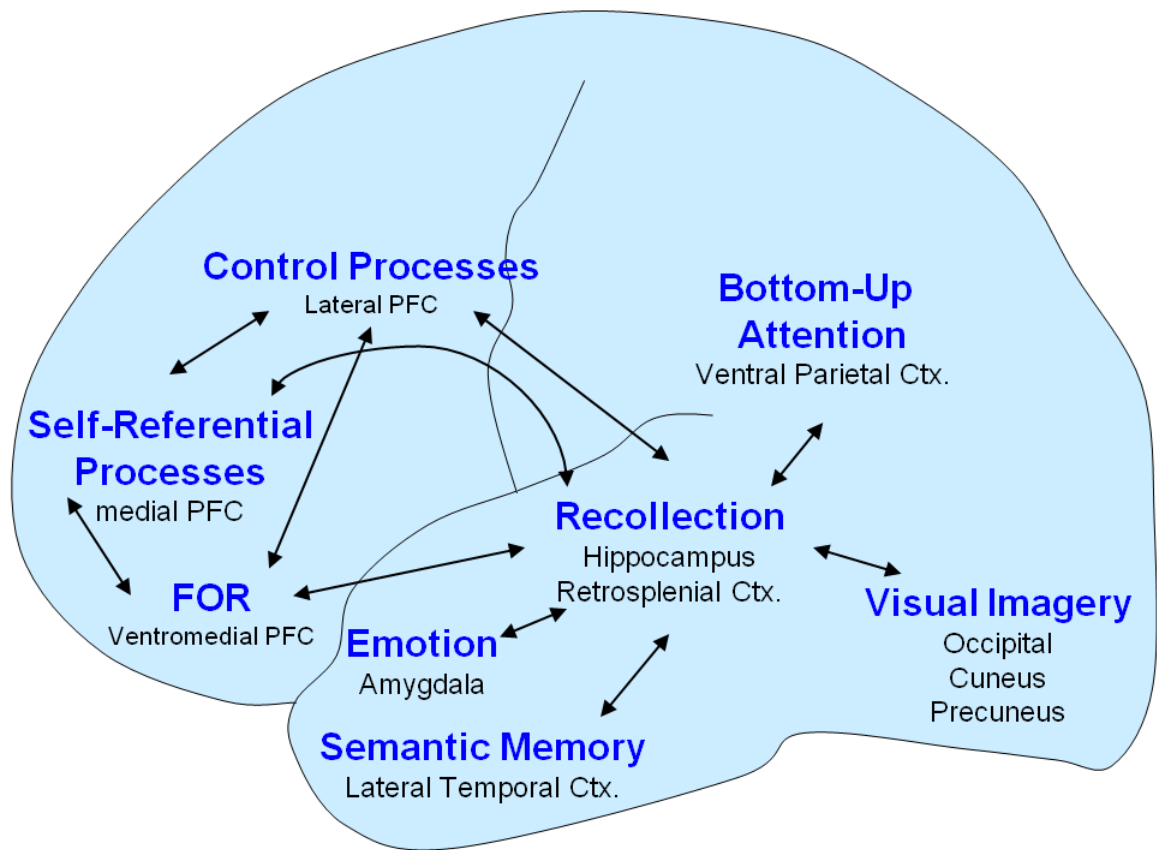


Figure 3: Autobiographical Memory Retrieval Network

AM retrieval depends upon *control processes* mediated by left lateral PFC that guide the search and construction of unique episodic AMs via recall of semantic AMs. These semantic AMs represent the basic level for AM, with retrieval of episodic AMs requiring greater effort. As the semantic components within an AM increase, greater activity in

lateral temporal regions might be observed, consistent with semantic processing mediated by this region. Because the final target of AM construction is a personal memory, it is critically dependent on self-referential processing involving the recruitment of the medial PFC. The ability to retrieve a rich episodic AM also depends upon *recollection*, mediated by the hippocampus and retrosplenial cortex, and is enhanced by early *emotion* responses in the amygdala and *visual imagery* in occipital and cuneus/precuneus regions. The rich sense of reliving is modulated by activity occurring later during AM retrieval, when a recovered memory is elaborated upon through the additional recruitment of visual imagery regions. As memory details are retrieved there is greater *bottom-up attention* mediated by the ventral parietal cortex. The recall of these vivid and rich episodic AMs recruits the hippocampus for both recent and remote AMs. Finally, the appropriateness of retrieved events is monitored via *FOR* in ventromedial PFC regions. Of course other brain regions might also be involved, but this simplistic model represents the most important regions relevant to the present discussion.

Understanding the function of the AM retrieval network has provided important insight into the complex nature of retrieval processes, the subjective qualities of retrieval and the impact of the remoteness of events. However, several issues still remain concerning the function of the AM retrieval network. First, regarding the complexity of retrieval, most studies have focused on the recall of a single AM without considering how a particular memory is distinguished among several others. Further, these studies

have primarily examined recollection processes, but have not considered familiarity processes during AM retrieval. Second, while it is clear from behavioral studies that AM retrieval involves a rich sense of re-experience, only one prior directly examined how the neural mechanisms change under varying levels of reliving. Further, little is known whether the capacity of temporal projection differs from the ability to mentally project to understand the mind of another individual. Third, despite the large number of studies investigating the impact of memory remoteness there is a lacuna of evidence regarding potential age effects on the AM retrieval network. Three empirical studies were conducted to address these issues. To preview, Chapter 6 describes Study 1 which uses a novel photo paradigm to examine how AMs are temporally distinguished and the impact of recollection and familiarity processes on the neural correlates underlying this process, Chapter 7 describes Study 2 which uses a novel camera technology to examine the neural mechanisms of self-projection for self versus other, and Chapter 8 describes Study 3 which uses a generic cue word technique to examine age-related differences in the construction and elaboration of AM.

6. Study 1: The Neural Correlates of Temporal-Order Memory for Autobiographical Events

When we remember personally experienced past events, or EM retrieval (Tulving, 1983), we usually retrieve not only what events happened (item memory) but also when they happened (temporal-order memory). Temporal-order memory is an important form of source memory (Johnson, Hashtroudi, & Lindsay, 1993) and an integral and a defining characteristic of EM (Wheeler, et al., 1997). Indeed, in many situations, episodic memories are useful only to the extent that temporal-order information is also available (e.g. remembering today's vs. yesterday's parking spot). Lesion (Milner, Corsi, & Leonard, 1991; Petrides, 1991) and functional neuroimaging (Cabeza et al., 1997; Nyberg, McIntosh, Cabeza, Habib, et al., 1996; Zorrilla, Aguirre, Zarahn, Cannon, & D'Esposito, 1996) studies have shown that the PFC is a critical region for temporal-order memory. There is also evidence of the important role of the MTL (Downes, Mayes, MacDonald, & Hunkin, 2002; Eichenbaum & Fortin, 2003; Konishi et al., 2002). However, the neural correlates of temporal-order memory, especially as they relate to autobiographical events, are not well understood. Addressing this issue was the goal of the present fMRI study.

It has been suggested that temporal-order memory for AMs involves both reconstruction and distance processes (Friedman, 1993, 2004). Reconstruction processes are effortful operations that include retrieving contextual details and using them to infer the order of past events (Curran & Friedman, 2003; Skowronski, Walker, & Betz, 2003).

For example, when trying to determine if, during a one-day tour of Paris, the visit to the Louvre occurred before or after lunch, one might remember the pleasant feeling of resting tired legs in a comfortable restaurant chair and conclude that the visit to the Louvre happened before lunch. Moreover, this inference might be confirmed by the image of walking from the Louvre to a nearby restaurant in the Rue de Rivoli. In contrast, distance processes are less effortful operations that rely on feelings associated with the strength of the memory trace. For example, one does not need to use reconstruction processes to conclude that the clearly remembered trip to Paris occurred more recently than a vaguely remembered trip to London. Although reconstruction and distance processes could be used to discern the temporal order of the same set of events, reconstruction processes are generally more effective for events that are relatively close in time whereas distance processes are usually more effective for events that are sufficiently far away (Burt, Kemp, Grady, & Conway, 2000; for reviews see Friedman, 1993; Friedman, 2004). Closeness in time benefits reconstruction processes because it makes causal links more obvious. In the aforementioned example, reconstructing the Louvre-restaurant order is facilitated by the causal relationship between walking and feeling tired, which might not exist if these events occurred farther away in time. In contrast, closeness in time reduces the effectiveness of distance processes because it attenuates differences in memory strength. It is worth noting that distance processes might be used for ordering events that are close in time when the interval between

encoding and retrieval is very short, as is the typical case in laboratory studies of temporal-order memory (e.g., comparing the order of words presented two minutes ago vs. five minutes ago in the same list). In contrast, the use of sensory-poor, causally unrelated stimuli in these studies hinders the use of reconstruction processes (e.g., it is difficult to reconstruct what happened between the two words).

In sum, temporal-order memory for autobiographical events is likely to involve both reconstruction processes (increase with closeness) and distance processes (decrease with closeness); in contrast, temporal-order memory for laboratory events often taps mainly distance processes. Thus, although several functional neuroimaging studies have investigated temporal-order memory for laboratory events (Cabeza, et al., 1997; Konishi, Asari, Jimura, Chikazoe, & Miyashita, 2006; Konishi, et al., 2002; Nyberg, McIntosh, Cabeza, Habib, et al., 1996; Suzuki et al., 2002; Zorrilla, et al., 1996), it is critical to also investigate the neural correlates of temporal-order memory for more complex real-world events, such as AMs.

The reconstruction-distance distinction (Friedman, 1993, 2004) in retrieving temporal order memory for autobiographical events is similar the recollection-familiarity distinction (Yonelinas, 2002) in memory retrieval (also see Bastin, Van der Linden, Michel, & Friedman, 2004; Curran & Friedman, 2003). Like recollection, reconstruction involves the recovery of contextual details, and, similar to familiarity, distance processes rely on the strength of memory traces. There is growing evidence

that recollection and familiarity involve distinct neural correlates (Diana, et al., 2007; Rugg & Yonelinas, 2003). Recollection is associated with greater activity in regions including the left PFC (Dobbins, Rice, Wagner, & Schacter, 2003; Dobbins, Simons, & Schacter, 2004; Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Henson, Rugg, Shallice, Josephs, & Dolan, 1999), hippocampus and posterior parahippocampal cortices (Eldridge, et al., 2000), posterior cingulate/ precuneus cortices (Wagner, et al., 2005) and visual cortex (Cabeza, Prince, et al., 2004; Kahn, Davachi, & Wagner, 2004; Wheeler, et al., 2000). In contrast, familiarity processes have been associated with greater activity in regions such as the right PFC (Dobbins, et al., 2003; Dobbins, Simons, et al., 2004; Henson, et al., 1999), and perirhinal cortices (for a review see Diana, et al., 2007). In sum, recollection and familiarity processes differ with respect to activation in MTL and posterior brain regions and hemispheric asymmetry in the PFC. Previous fMRI studies have also associated differences in PFC lateralization with retrieval success (hits > misses) and retrieval effort (misses > hits). Left PFC is associated with retrieval success (Prince, Daselaar, & Cabeza, 2005) and right PFC with retrieval effort (Fleck, Daselaar, Dobbins, & Cabeza, 2006; Henson, et al., 2000). Others have found that hemispheric asymmetries in PFC activity reflect qualitative rather than quantitative differences (Dobbins, Foley, Schacter, & Wagner, 2002; Dobbins, et al., 2003; Ranganath, Johnson, & D'Esposito, 2000). For example, in an event-related fMRI study Dobbins et al. (2003) found that source memory judgments activated left more than right PFC,

whereas recency judgments activated right more than left PFC, but importantly lateralization differences were independent of retrieval success. Thus, accuracy might also be an important factor in distinguishing the neural correlates of the reconstruction-distance distinction.

Although some fMRI evidence is available regarding the contribution of these regions in temporal-order memory for laboratory stimuli (Konishi, et al., 2006; Konishi, et al., 2002; Suzuki, et al., 2002), their contribution to temporal-order memory for autobiographical stimuli is unknown. The goal of the present study was to investigate the neural correlates underlying temporal-order memory for autobiographical events. To address this goal while maintaining control over critical memory factors, such as accuracy, a novel photo paradigm previously applied to recognition memory of autobiographical versus laboratory events (Cabeza, Prince, et al., 2004) was adapted to investigate memory for temporal order. Cabeza, Prince et al. (2004) found that memories elicited via the photo paradigm contained greater self-referential processing, visual/spatial imagery and recollection compared to laboratory memories, therefore validating the use of this paradigm to study the retrieval of complex real-life events or controlled AMs (for a review see Cabeza & St. Jacques, 2007).

Given that reconstruction processes are more effective for discriminating events close in time whereas distance processes are more effective for discriminating events farther away in time, we assumed that brain regions involved in reconstruction

processes would show greater activity for shorter than longer lags, whereas regions involved in distance processes would show greater activity for longer than shorter lags (e.g., Suzuki, et al., 2002). Our fMRI predictions were based on the similarity between the reconstruction-distance distinction (Friedman, 1993, 2004) and the recollection-familiarity distinction (Yonelinas, 2002). We predicted that reconstruction processes during shorter lags would involve regions previously associated with recollection, such as left PFC, hippocampus and posterior parahippocampal cortices, posterior cingulate/precuneus cortices and visual cortex. In contrast, distance processes during longer lags would involve regions previously associated with familiarity, such as right PFC and perirhinal cortices. In sum, we predicted that temporal-order decisions for shorter lags (reconstruction processes/recollection) would differentially engage left PFC and temporal-order decisions for longer lags (distance processes/familiarity) would differentially engage right PFC. On the basis of Dobbins et al.'s (2003) findings we predicted that this hemispheric asymmetry would not vary with retrieval success (hits vs. misses). Additionally, we predicted that shorter lags would elicit greater activity in other regions associated with recollection, such as the hippocampus and posterior parahippocampal cortices, posterior cingulate/precuneus cortices, and visual cortex.

Methods

Participants

Seventeen young adults (9 males; Mean Age = 21.6, S.D. = 2.7) participated in the study. Participants were healthy, right-handed, native English speakers, with no history of neurological or psychiatric episodes. They were mostly undergraduate students at Duke University and in all cases were very familiar with the Duke campus. Participants gave written informed consent for a protocol approved by the Duke University Institutional Review Board.

Materials and Procedure

Photo-taking session. The study took place on two consecutive days. On Day 1, participants took 480 photographs at 80 campus locations (6 pictures per location). The locations were well-known places within the Duke West Campus (e.g., the Duke Chapel), both indoors and outdoors. The order of the locations was selected to reduce the correlation between temporal distance and spatial distance, $r = .13$, $p = .07$, such that participants visited new locations in the same building/spatial region at different time points during the day and followed a circular route in that they started and ended at the same building (for examples see **Figure 4A**). Participants were provided with a digital camera (Kodak Easy Share CX6200), a booklet with 80 locations (one per page), and training on how to use the camera and take photos. Participants were provided with instructions during the encoding task. They were told that the study was interested in

how people take photographs and they were asked to consider each photo as a distinct event by paying attention to the particular physical (e.g., viewpoint, body position, etc.) and psychological (e.g., preference, mood, etc.) phenomena associated with each picture to ensure that they were not simply clicking the camera without viewing the scene they were photographing. The photo-taking session was a classic incidental encoding task with instructions designed to draw attention from intentional memory encoding and with no mention of a subsequent memory test. Participants were instructed to complete the photo-taking task without stopping for breaks so that picture taking was continuous (mean time = 5.00 hours, S.D. = 0.40 hours). The camera's LCD screen was blocked to prevent participants from reviewing the photos. At each location participants took six pictures from different positions and/or angles. Participants were instructed to tear off one page of the booklet after each location so that at the end of the photo session the whole booklet would be completed. The cameras were returned to the lab immediately after the last picture was taken and the photographs were digitally enhanced using a finite impulse response filter.

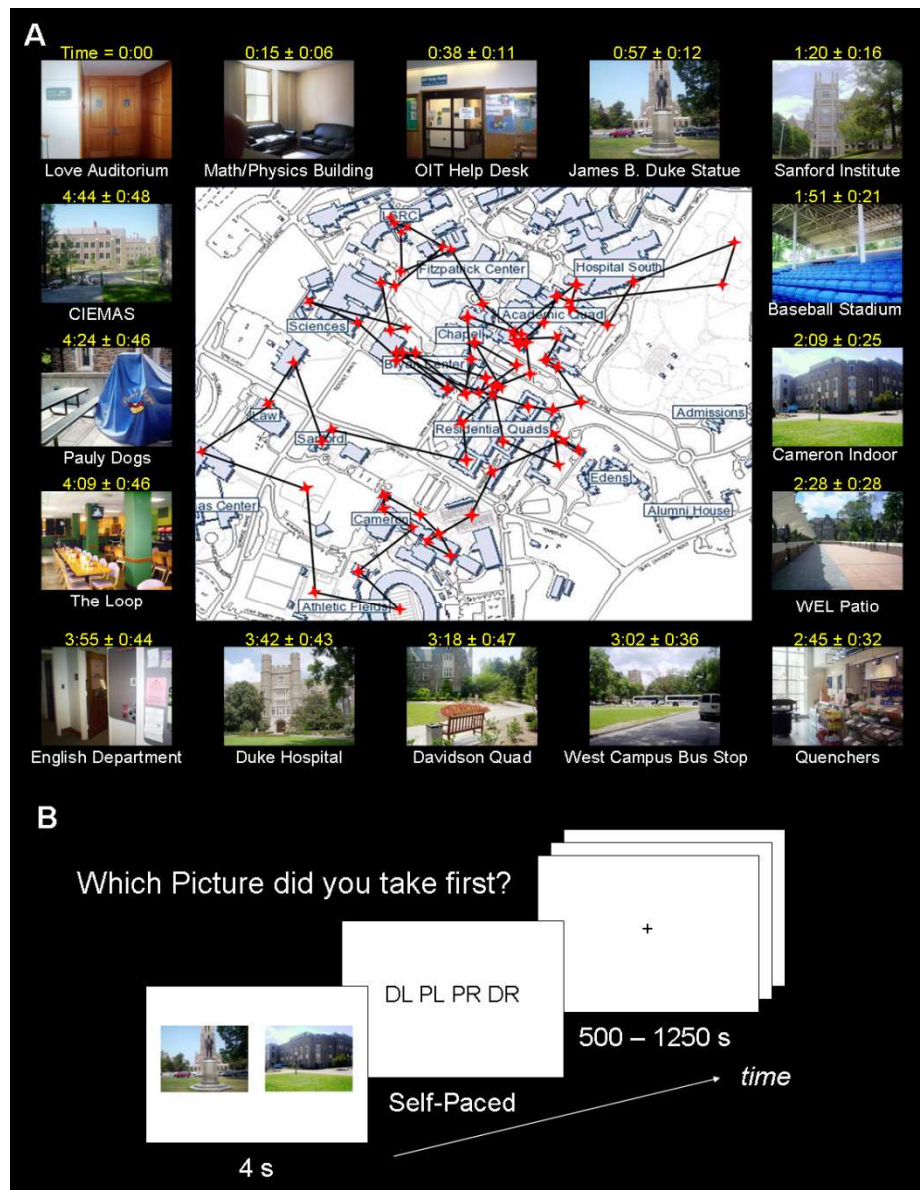


Figure 4: Novel Photo Paradigm Design

(A) The Duke Campus map shows the locations and route of the locations where the photographs were taken prior to scanning. Examples of photographs taken by participants with the average time (in hours and minutes) and the SD to visit the locations are depicted. (B) During scanning participants saw pairs of photographs taken on the previous day and were asked to make temporal-order judgments and whether the decision was made with low or high confidence. DL = Definitely Left, PL = Probably Left, PR = Probably Right, DR = Definitely Right

Scanned task. On day two, participants were scanned using an event-related fMRI design while making temporal-order judgments on their photographs from the previous day. Across 5 scans of 30 trials each, they were shown 180 photograph pairs from different locations (2 photos side by side) and asked to indicate which picture they took first and whether the decision was made with low or high confidence, i.e., Definitely Left (DL), Probably Left (PL), Probably Right (PR), and Definitely Right (DR). We manipulated the lag between pairs of photos from short (1 to 9 locations apart), medium (10 to 39 locations apart), and long (40 to 80 locations apart) so that lags were equally spaced on a logarithmic scale. Photo pairs were selected so that the campus locations were equally represented across time lag. Each photo was presented for 4 sec, followed by a self-paced response screen (up to 6 sec), and then by a fixation cross for a varying interval between 500 ms to 2500 ms plus any additional time from the response screen (total trial length = 10.50 to 12.50 s; see **Figure 4B**). Reaction times were not informative because participants were required to wait until the response screen appeared before making a response. The rationale for this procedure was to allow for equal viewing time in each condition. Post-scanning, participants were asked rate their familiarity with each of the 80 campus locations (1 = low to 4 = high). Debriefing suggested that participants were unaware of the nature of the scanning task during the photo-taking session.

fMRI Methods

Scanning. Scanning was conducted using a 4T GE magnet. Stimuli were presented using liquid crystal display goggles (Resonance Technology, Northridge, CA) and behavioral responses were recorded using a four-button fiber optic response box (Resonance Technology). Head motion was minimized using foam pads and a headband. Anatomical scanning started with a T1-weighted sagittal localizer series. The anterior and posterior commissures were identified in the midsagittal slice, and 34 contiguous oblique slices were prescribed parallel to the AC-PC plane. High resolution T1-weighted structural images were acquired with a 12 ms repetition time (TR), a 5 ms echo time (TE), 24 cm field of view (FOV), 68 slices, 1.9 mm slice thickness, and a 256^2 matrix. Functional scanning employed an inverse spiral sequence with a 1500 ms TR, 36 ms TE, 24 cm FOV, a 64^2 image matrix, and a 60° flip angle. Thirty-four contiguous slices were acquired with the same slice prescription as the anatomical images. Slice thickness was 3.75 mm, resulting in cubic 3.75 mm^3 isotropic voxels.

fMRI analyses. Image processing and analyses were performed using Statistical Parameter Mapping software implemented in Matlab (SPM2; Wellcome Department of Cognitive Neurology, London, UK). Functional images were corrected for slice acquisition order, realigned to correct for motion artifacts, and then spatially normalized to a standard stereotactic space, using the template implemented in SPM2. Subsequently, the functional images were spatially smoothed using an 8 mm isotropic

Gaussian kernel. For each subject, evoked hemodynamic responses to event types were modeled with a delta (stick) function corresponding to two seconds after stimulus presentation (the middle of the photograph presentation time), convolved with a canonical hemodynamic response function (HRF) within the context of the general linear model (GLM). This onset was selected because behavioral pilot data suggested that it took participants a couple of seconds to identify the locations, and we were primarily interested in the decision process.

Short vs. Long contrast. To isolate activity in the brain that was exclusively involved in the short and long time lag conditions we employed the GLM to generate contrasts for the temporal-order memory for correct trials with each of the time lag conditions, as well as, the short versus long contrast. Subsequently, random-effects analysis was performed on the parameter estimates of the conditions ($P = .05$, uncorrected, with a cluster size > 15 voxels). We used a cluster-size threshold ($R = 15$) to establish a Type 1 error level of $p < .005$ for false discovery of voxels within each cluster (Forman et al., 1995). In order to isolate activity exclusive to short versus long conditions, we inclusively masked this contrast with the effect of the time lag condition of interest (short or long) greater than baseline fixations at $P = .001$. Thus, the resulting activity isolating activity related to short or long conditions also had to be confirmed by real differences observed in each time lag condition in comparison with the implicit baseline (short $>$ baseline, long $>$ baseline).

Parametric contrasts. To examine changes in the neural correlates modulated by temporal distance we employed a parametric approach, which allowed us to examine how activity was modulated as a function of discrete changes in time lag as opposed to examining only the overall activity level averaged within the short and long time lag bins. To identify regions of interest showing temporal-order memory-related activity increases as a function of increasing lag, we created a GLM in which correct trial onsets were modulated by the lag between pairs of photographs (e.g., from lags of 1 to 80) using the first-order parametric modulation option integrated in SPM2 and its reverse (i.e., increasing activity associated with decreasing time lag). The pairs of photographs also differed with respect to spatial distance and we also entered this factor as a covariate in the model. Thus, we examined the unique contribution of temporal lag orthogonalized with respect to spatial distance in the design matrix. We did not further examine spatial distance because it was not the main focus of the study (i.e. participants were only asked to make a temporal-order decision). Confidence responses were combined because they did not produce any additional information. Subsequently, random-effects analysis was performed on the parameter estimates of the parametric regressor for temporal lag ($P = .05$, uncorrected, with a cluster size > 15 voxels). We used a cluster-size threshold ($R = 15$) to establish a Type 1 error level of $p < .005$ for false discovery of voxels within each cluster (Forman, et al., 1995). In order to examine

positive activations in the condition of interest we inclusively masked with a contrast of the main effect of temporal order trials greater than baseline fixations at $P = .001$.

Accuracy and Difficulty. Regions identified by the parametric modulation of time lag, which were greater than baseline, were further interrogated to determine if there were effects of accuracy (Hits > Misses). To create these contrasts, we employed the GLM to generate parameter estimates for Hit and Miss responses in a separate design matrix. Statistical Parametric Maps were created for each subject by applying linear contrasts to the parameter estimates for these events of interest, resulting in a t statistic for every voxel. We performed additional random-effects analyses to determine the effects of retrieval accuracy. A liberal threshold was chosen in order to maximize the power to detect the effects of accuracy in regions demonstrating parametric modulation (both at $P = .05$, uncorrected, with cluster size > 5). Because we were only interested in changes in the neural correlates of temporal-order memory, we used the results from the parametric modulation and its reverse as spatial inclusive masks for the contrasts of retrieval accuracy. Thus, we defined masks in which activity had to be above baseline fixation, demonstrate a parametric modulation by temporal lag and show changes as a function of accuracy. Finally, we examined the effects of task difficulty and familiarity by entering each participant's overall accuracy and familiarity scores as a covariate in the parametric analysis on temporal lag.

Results

Behavioral Results

As expected, there was a significant difference in accuracy (proportion correct) as a function of lag, $F(2,16) = 24.05, p < .0001$ (see **Figure 5**, error bars indicate standard error of the mean). Shorter lags ($M = .74, SD = .07$) were less accurate than medium lags ($M = .82, SD = .07$), $t(16) = 4.49, p < .0005$, and longer time lags ($M = .87, SD = .06$), $t(16) = 6.42, p < .0001$, which also differed from one another, $t(16) = 2.85, p < .05$. The overall familiarity scores suggested that participants were generally familiar with the campus ($M = 3.08, SD = 0.51$).

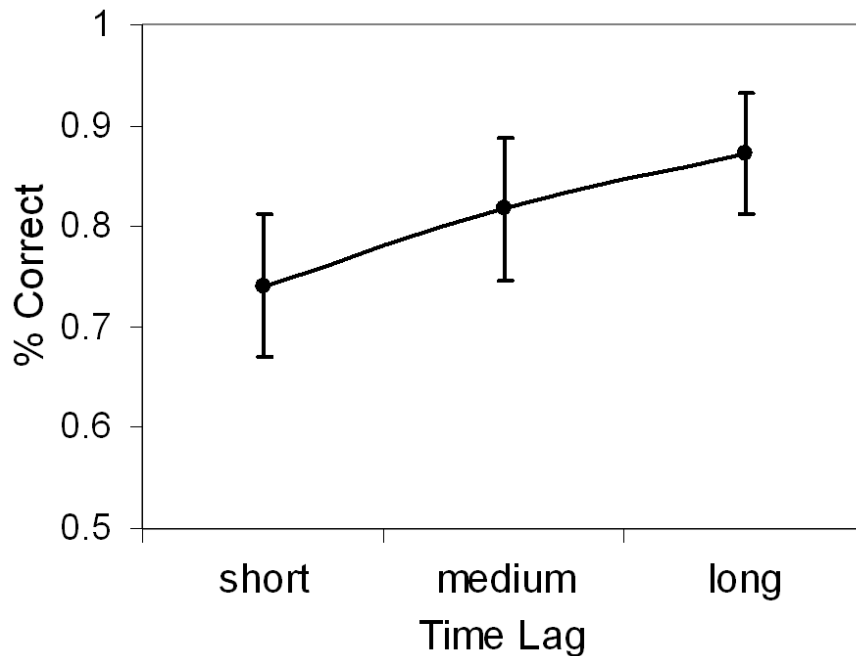


Figure 5: Mean Proportion Correct for Short, Medium and Long Time Lags.

fMRI Results

Table 3 lists regions revealed in the direct contrast of the short versus long time lag conditions. Consistent with our predictions, left DL-PFC showed greater activity for the short lag condition, whereas right DL-PFC showed greater activity for the long time lag condition. Given that left vs. right PFC regions have been respectively associated with recollection and familiarity (Dobbins, et al., 2003; Henson, et al., 1999), this hemispheric asymmetry finding supports our hypothesis that reconstruction processes depend on recollection whereas distance processes depend on familiarity. Also consistent with our hypotheses, the short time lag condition elicited greater activity in other regions associated with recollection, including MTL (right parahippocampal gyrus), posterior midline cortex (retrosplenial, posterior cingulate, precuneus), and visual cortex/cuneus, extrastriate including bilateral activity in the precuneus, posterior cingulate, and cuneus. Although the long time lag condition did not show activity in perirhinal cortex, we also found activity in right fusiform gyrus, angular gyrus, and superior parietal cortex.

Table 3: Brain Regions Showing Activity in Short vs. Long Time Lags

Region	BA	H	Talairach Coordinates			voxels	T Score
			x	y	z		
<i>Long > Short</i>							
Dorsolateral PFC	9	R	48	8	24	30	2.70
Premotor Cortex	6	L	-41	6	49	15	3.05
Superior Parietal	7	R	26	-53	41	27	2.55
Angular Gyrus	39	R	52	-69	14	19	3.43
Fusiform Gyrus	37	R	37	-44	-14	91	3.16
<i>Short > Long</i>							
Dorsolateral PFC	46	L	-41	26	20	49	2.93
Premotor Cortex	6	L	-30	6	56	23	3.36
Central Cingulate Gyrus	32	L	-4	17	45	43	3.99
Parahippocampus		R	19	-37	-5	60	3.46
Posterior Cingulate	31	L	-7	-65	21	224	3.75
		R	11	-57	20	224	3.50
Retrosplenial Cortex	30	L	-7	-51	6	224	2.85
Precunues	7	R	7	-63	52	15	3.24
Visual Cortex/Cuneus	17/18	L	-15	-99	-5	91	4.60
		R	15	-98	-1	75	2.94
	19	L	-37	-78	35	43	4.08

Note. BA, Brodmann's Area; H, Hemisphere. All p's < .005.

Furthermore, we also identified regions where activity monotonically increased or decreased as a function of time lag using parametric modulation analyses on the fMRI activity in which we covaried out the effects of spatial distance (see **Table 4** and **Figure 6**). In these parametric analyses, lag was entered as a continuous variable (lag 1 to 80), but, for display purposes, the line graphs in Figure 6 show fMRI activity averaged across three lag ranges: short (lag 1 to 9), medium (lag 10 to 39), and long (lag 40 to 80). Likewise, to simplify the description of results, activity that parametrically decreased or increased as a function of lag is respectively described as "greater for shorter lags" or "greater for longer lags."

Table 4: Brain Regions Showing Activity Parametrically Modulated by Time Lag

Region	BA	H	Talairach Coordinates			voxels	T Score
			x	y	z		
<i>Longer Time Lags</i>							
Dorsolateral PFC	9	R	48	8	24	16	3.35
Fusiform Gyrus	37	R	48	-52	-13	65	2.84
<i>Shorter Time Lags</i>							
Dorsolateral PFC	46	L	-41	23	20	51	2.66
Central Cingulate Gyrus	32	L	-4	17	45	61	3.95
Parahippocampus		R	19	-37	-5	-	3.42
Posterior Cingulate	31	L	-15	-61	21	123	4.28
	31	R	11	-57	20	-	3.63
Retrosplenial Cortex	30	L	-11	-54	6	-	3.75
	29/30	R	11	-51	10	-	3.81
Precuneus	7	L	-30	-45	41	30	2.62*
Visual Cortex/Cuneus	17/18/19	L	-15	-99	-5	136	4.58
	18	R	19	-98	-1	298	2.75
	19	L	-37	-79	32	59	4.05
		R	41	-75	35	17	3.27

Note. All p's < .005, unless indicated * p < .01.

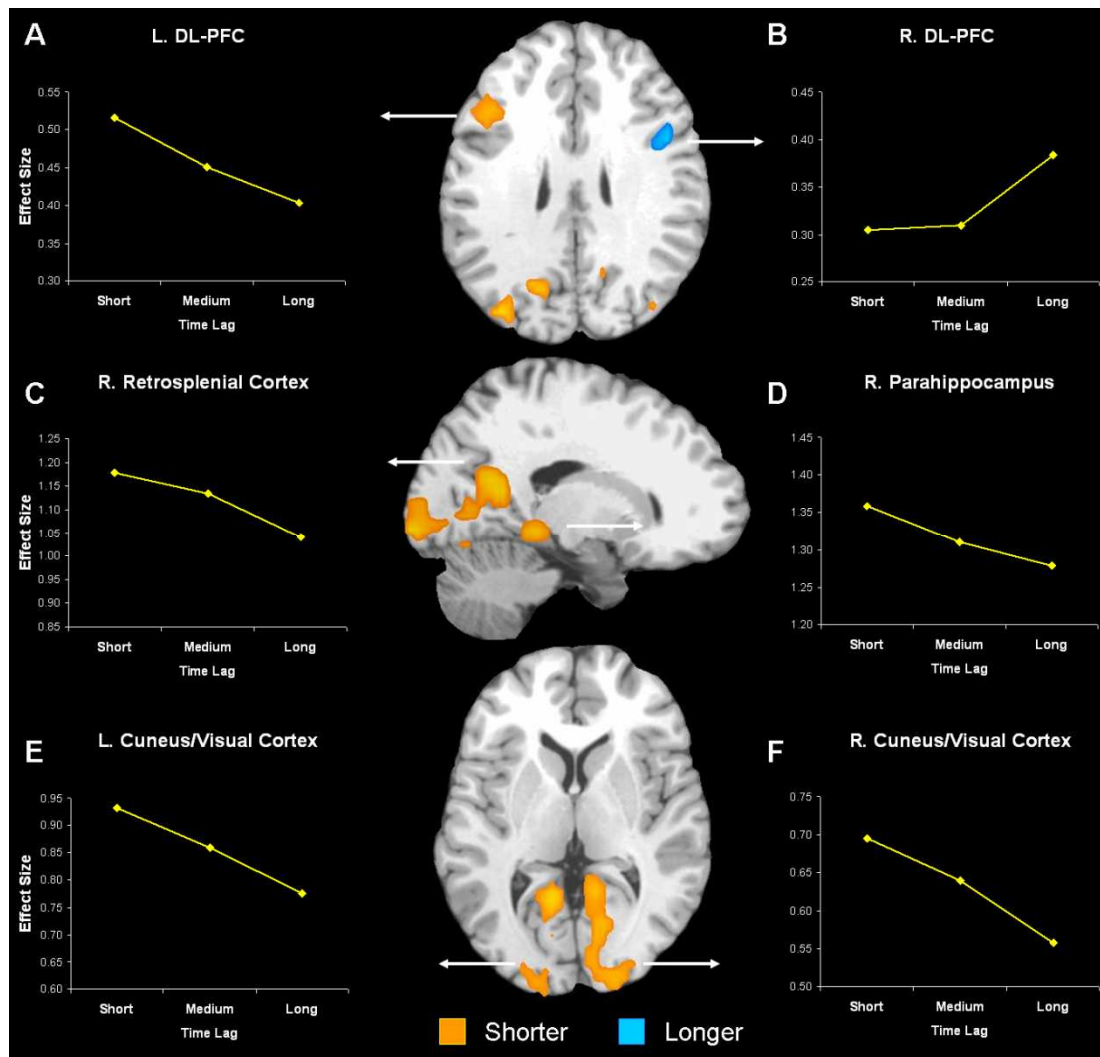


Figure 6: Activity Parametrically Modulated by Increasing Time Lag (Longer) and Decreasing Time Lag (Shorter)

As indicated by Table 4 and Figure 6, a subset of the regions found in the direct contrast also showed activity that monotonically increased or decreased as a function time lag, and are consistent with our predictions. We found hemispheric asymmetry in the PFC, with greater activity in left DL-PFC for shorter lags, whereas right DL-PFC showed greater activity for longer lags. Shorter lags also elicited greater activity in other

regions associated with recollection, including MTL (right parahippocampal gyrus), posterior midline cortex (retrosplenial, posterior cingulate, precuneus), and visual cortex/cuneus, extrastriate including bilateral activity in the precuneus, posterior cingulate, and cuneus. In contrast, longer lags revealed greater activity in the right fusiform gyrus. Because of our *a priori* hypothesis about the hippocampus and perirhinal cortices, we further examined activity in the MTL using a less conservative threshold ($P = .05$, with a cluster size > 5 voxels and inclusively masked with the main effect of temporal order trials greater than baseline fixations at $P = .05$). Shorter lags revealed greater activity in the left hippocampus, whereas, longer lags did not reveal any activity in the MTL. Thus, the results of the parametric analysis support the prediction that the neural correlates of temporal-order memory decisions differ according to shorter and longer time lags, irrespective of how “short” or “long” conditions are categorized.

To confirm the hemispheric asymmetry in DL-PFC, we extracted the peak responses in each hemisphere and entered these into a hemisphere (left, right) \times time lag (short, long) repeated ANOVA (only two levels of time lag were used because we were interested in examining the extremes). This analysis yielded significant 2-way interaction, $F(1,16) = 32.23$, $p < .0001$, and follow-up tests revealed that activity was greater for shorter than longer lags in left DL-PFC, $t(16) = 3.13$, $p < .01$, whereas the opposite was true in right DL-PFC, $t(16) = 2.70$, $p < .05$ (see **Figure 7**).

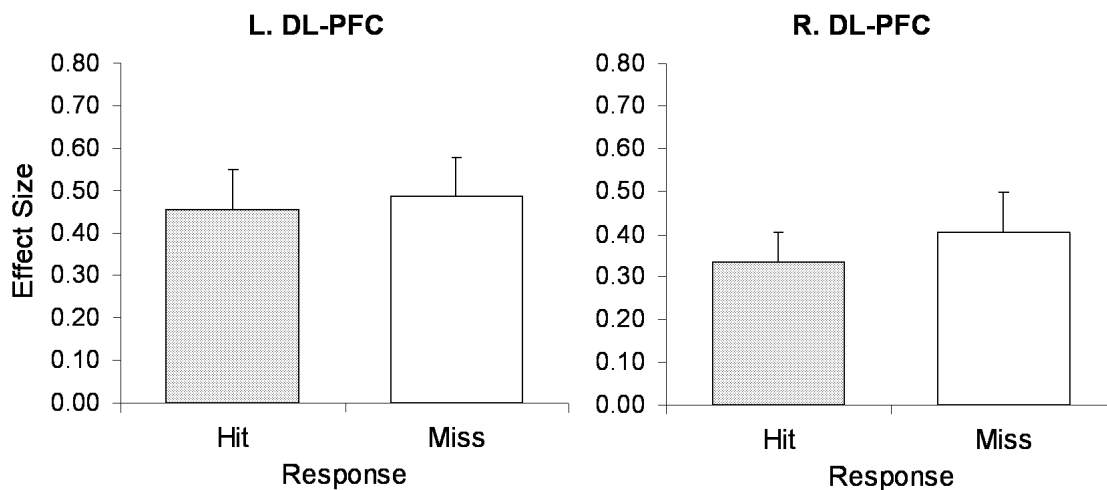


Figure 7: Activity Related to Hits and Misses in Left and Right DL-PFC for Shorter and Longer Time Lags

To investigate the relationship between the hemispheric asymmetry in PFC activity and potential differences in retrieval success and task difficulty, we conducted two ancillary analyses on the regions that showed time lag effects. First, we determined if activity in these regions differed between hits and misses. As illustrated by Figure 7, no significant differences between hits and misses were found either in left or right PFC (main effect of item: $p = .12$, item \times hemisphere interaction: $p = .36$), nor in other brain regions. Second, we determined if activity in the regions showing an effect of time lag varied as a function of task difficulty. Finally, the main findings from the parametric analysis were not affected by entering accuracy or familiarity as covariates.

Discussion

The results of the present study suggest that reconstruction and distance are distinct processes involved in temporal-order memory for autobiographical events, and

that these processes are differentially recruited depending upon the temporal distance between events. The study yielded three main findings. First, when events occurred closer in time, activity in the left DL-PFC, MTL, left parietal, posterior midline, and visual cortices indicated that temporal-order memory involved the recollection of contextual details. Second, when events occurred further away in time, activity in the right DL-PFC and fusiform gyrus indicated that temporal-order memory involved familiarity processes. Finally, the left lateralization of PFC activity for shorter lags coupled with the right lateralization of PFC activity during longer lags yielded a marked hemispheric asymmetry in PFC activity. We discuss these three findings in separate sections below.

Regions Associated with Reconstruction Processes During Shorter Time Lags

At shorter time lags, a network of brain regions were activated, including left DL-PFC, posterior parahippocampal, parietal and visual cortices, suggesting that recollection of contextual details was utilized to temporally parse the events. Several studies have indicated a greater role for left PFC during tasks involving recollection (Dobbins, et al., 2002; Dobbins, et al., 2003; Henson, et al., 1999; Kahn, et al., 2004; Nolde, Johnson, & D'Esposito, 1998; Ranganath, et al., 2000; Rugg, Fletcher, Chua, & Dolan, 1999), with the majority of studies reporting activity in DL-PFC as in the present study (for exceptions see Kahn, et al., 2004; Rugg, et al., 1999). The left DL-PFC involvement in recollection memory is thought to reflect an increase in reflective and evaluative

demands, and greater episodic specificity during the retrieval of contextual information. Left DL-PFC has also been found in laboratory memory studies that have specifically investigated temporal context memory (Cabeza, et al., 1997; Konishi, et al., 2002; Suzuki, et al., 2002). For example, Suzuki et al. (2002) manipulated the temporal distance between pairs of line drawings by as much as 3 hours, which is more similar to the present time frame. Consistent with the results of the present study, Suzuki et al. found greater left DL-PFC activity for temporal judgments made for pairs of drawings separated by shorter temporal distances than those separated by longer distances. The results of the present study allow us to further characterize the involvement of left DL-PFC in temporal memory for autobiographical events involving a richer and extensive temporal context.

As predicted, we found greater activity in posterior parahippocampal cortex for shorter lags, but the hippocampus activity was sub-threshold. These results suggest that although the hippocampus was recruited, suggesting that the photo-paradigm was eliciting recollection of autobiographical events (Cabeza, Prince, et al., 2004), activity in this region did not differentiate the temporal order effects as strongly as the posterior parahippocampal cortex. The finding that the right posterior parahippocampal cortex was associated with reconstruction of temporal context is consistent with three different accounts of parahippocampal function. First, several fMRI studies, including studies using words and objects, have associated the posterior parahippocampal gyrus with

recollection and relational memory (Diana, et al., 2007). In the present study, the parahippocampal activation could have reflected the recollection of the photo-taking episodes, which is required to reconstruct the order of events close in time. Second, the posterior parahippocampal gyrus has been strongly associated with spatial scene perception. In particular, a region dubbed the "parahippocampal place area" has been found to be more activated during the processing of spatial layout than during the processing of objects, faces, and other control stimuli (Epstein & Kanwisher, 1998). The reported parahippocampal activation was near the parahippocampal place area and might have reflected the processing of the spatial aspects of retrieved mental images or the photos used as cues. However, it is not clear why spatial scene processing would differ as a function of decreasing temporal distance. Third, the parahippocampal cortex has been linked to mental navigation and retrieval of topographical information (Aguirre, Zarahn, & D'Esposito, 1998; Maguire et al., 1998; Mellet et al., 2000) (for a review see N. Burgess, Maguire, & O'Keefe, 2002), which might be more important as spatial distance decreases. However, in the present study, temporal distance was not significantly positively correlated with spatial distance. Furthermore, the reported activity in the parametric analysis reflects the unique contribution of temporal lag after covarying out the effects of spatial distance. Thus, of these accounts, the involvement of the posterior parahippocampal cortex in recollection is the most parsimonious within the framework of the present study, in which both spatial and other information linked

to the photo-taking event might contribute to reconstructing the temporal order memory. Future work is needed to clarify the role of the MTL, including the involvement of the hippocampus, in temporal-order memory for autobiographical events relying on reconstructive processes.

In addition to PFC and MTL regions, recollection for temporal judgments involving shorter time lags also engaged intervening posterior parietal, posterior midline (retrosplenial, posterior cingulate, precuneus), and visual cortex regions. Posterior parietal and posterior midline activations are among the most typical findings in functional neuroimaging studies of EM retrieval (for a review see Cabeza, et al., 2000). Several fMRI studies have linked subregions of parietal and posterior midline cortices with recollection (for reviews see Cabeza, 2008; Wagner, et al., 2005). For example, Daselaar, Fleck and Cabeza (2006) found recollection-related activity in left parieto-temporal and retrosplenial regions that was very close to the ones observed here. Damage to the retrosplenial cortex can cause amnesia (Valenstein, et al., 1987), and in the right side it has been found to specifically affect memory for spatial relationships (for a review see Maguire, 2001b). Thus, in our study, this region might contribute to both recollection and spatial memory. As for the precuneus, some evidence has linked its role in memory retrieval to the processing of visual images (Fletcher et al., 1995), and this function might have contributed to the reconstruction of temporal order. Finally, activations in visual cortex and cuneus regions likely reflect the retrieval of visual details

(Buckner & Wheeler, 2001), which is critical for AM retrieval (Rubin & Greenberg, 1998).

In a prior study using the photo-paradigm, Cabeza, Prince et al. (2004) found greater visual cortex and cuneus activity when participants recognized campus photos they took themselves compared to similar photos taken by others.

Regions Associated with Distance Processes During Longer Time Lags

The analysis identifying brain regions where activity increased as a function of lag yielded only two regions: right DL-PFC and right fusiform areas. The finding of right DL-PFC activity in association with long lags is consistent with functional neuroimaging evidence linking this region to familiarity (Dobbins, Kroll, & Yonelinas, 2004; Eldridge, et al., 2000; Henson, et al., 1999). A related interpretation of these right PFC activations is that they reflect an increase in monitoring for items that are close to the response criterion (Henson, et al., 2000). This issue is discussed in the next section. The present right DL-PFC activation is also consistent with several studies investigating temporal context memory that have reported activations in this region (Cabeza, et al., 1997; Dobbins, et al., 2003; Fujii et al., 2004; Konishi, et al., 2002; Suzuki, et al., 2002). Some of these studies also found activations in left PFC (Cabeza, et al., 1997; Konishi, et al., 2002), but these activations might reflect the contributions of recollection to temporal order judgments in some conditions. In fact, when these contributions are controlled by subtracting out activity during source memory from activity during temporal-order

judgments, as done by Dobbins et al. (2003), the resulting pattern of PFC activity is strongly right lateralized.

Turning to the right fusiform gyrus, this is a region that some studies have associated with the processing of specific perceptual information, as opposed with the left fusiform activity, which is assumed to mediate more conceptual or abstract processing (Garoff, Slotnick, & Schacter, 2005; Koutstaal et al., 2001; Simons, Koutstaal, Prince, Wagner, & Schacter, 2003). For example, in one fMRI study (Koutstaal, et al., 2001), priming-related activity in the right fusiform gyrus (but not in the left fusiform) was reduced when the perceptual properties of the items changed between study (e.g., a yellow umbrella) and test (e.g., a striped umbrella). In another fMRI study (Garoff, et al., 2005), encoding activity in the right fusiform gyrus (but not in the left fusiform) predicted memory for specific perceptual properties of stimuli. Thus, the right fusiform gyrus seems to be involved in processing item-specific perceptual information, which might underlie familiarity processes (Jacoby & Dallas, 1981; Whittlesea & Williams, 2000) (although see Voss & Paller, 2006). The role of the right fusiform gyrus in temporal-order decisions for longer lags might reflect greater reliance on perceptual aspects of the information during distance judgments. For instance, participants could have ordered the two photos in time by paying attention to their perceptual details. Although we predicted greater activity for longer lags in the perirhinal cortex, a region important for familiarity processes (e.g., Eichenbaum, Yonelinas, & Ranganath, 2007),

the results of the present study suggest instead that perceptual fluency via the fusiform gyrus is involved in temporal order memory judgments for autobiographical events separated by longer time lags and that activity in this region might underlie distance processes. Further work is needed to clarify the role of the perirhinal cortex and other regions that might mediate distance processes.

Hemispheric Asymmetry in Prefrontal Cortex Activity

The main finding of the present study was a hemispheric asymmetry in DL-PFC during temporal-order memory such that left PFC showed greater activity for shorter than longer time lags and right PFC showed greater activity for longer than shorter lags. The hemispheric asymmetry we observed is consistent with our hypothesis that reconstruction vs. distance processes are similar to recollection vs. familiarity processes, respectively, which have been previously associated with left vs. right PFC activations (Dobbins, Kroll, et al., 2004; Eldridge, et al., 2000; Henson, et al., 1999). For example, Henson et al. (1999) used the “remember-know” procedure (Tulving, 1985) to determine when memory is accompanied by contextual details (“remember” judgment) versus when it is not (“know” judgment), as based on participant introspections. The study yielded greater left DL-PFC activity for remember responses (recollection), but greater right DL-PFC activity for know responses (familiarity). Thus, the hemispheric asymmetry in the present study extends this finding to the temporal-order memory domain, supporting the hypothesis that temporal-order decisions for shorter vs. longer

lags are based on reconstruction (recollection) vs. distance (familiarity) processes, respectively.

Importantly, the hemispheric asymmetry in PFC activity cannot be attributed to differences in retrieval success. Although PFC activity varied as a function of time lag, it did not differ as a function of accuracy; in both left and right DL-PFC, activity was similar for hits and misses. This finding is consistent with several fMRI studies showing that during episodic retrieval some PFC regions are sensitive to retrieval orientation rather than to retrieval success (Dobbins, et al., 2002; Dobbins, et al., 2003; Kahn, et al., 2004; Ranganath, et al., 2000; for a review see Rugg & Wilding, 2000). For example, in Dobbins et al. (2003), recollection-related left PFC activity and familiarity-related left PFC activity did not differ between correct and incorrect memory decisions. The results of the present study are consistent with retrieval orientation accounts of PFC function whereby activity reflects the processes involved during the attempt to retrieve irrespective of retrieval success. Moreover, including accuracy as a covariate did not affect the results of the parametric analysis, which further supports the suggestion that activity in these regions is independent of retrieval effort and task difficulty.

Beyond the recollection-familiarity distinction, another account that explains the hemispheric asymmetry finding is the distinction between systematic and heuristic processes (Nolde, Johnson, & Raye, 1998). Systematic processes involve the retrieval of more detailed information that engages greater reflection and evaluation, such as during

source memory attributions, and relies on left PFC. In contrast, heuristic processes involve the simple maintenance of information and comparison of that information to a response criterion, such as during simple item-recognition tasks, and relies on right PFC. Like the recollection-familiarity distinction, the systematic-heuristic distinction is supported by a substantial amount of evidence (e.g., Dobbins, et al., 2002; Nolde, Johnson, & D'Esposito, 1998; Ranganath, et al., 2000). The present hemispheric asymmetry finding can be easily explained in terms of the systematic-heuristic distinction because making temporal-order decisions for shorter lags requires the systematic evaluation of available source information. Conversely, temporal-order decisions for longer lags can be based on a simple heuristic evaluation of memory strength. The systematic/heuristic distinction has been typically investigated by contrasting different memory tasks (e.g., source memory vs. item recognition; although see Dobbins, et al., 2002; Dobbins & Wagner, 2005), but in the present study, we found differences consistent with this distinction within the same task (shorter vs. longer lags). This result provides further support for the idea that the critical factor determining PFC activity is not the type of task but the type of memory processes recruited by the task. These results are consistent with the source-monitoring framework (M. K. Johnson, et al., 1993), which proposes that performance in source memory tasks involves both systematic and heuristic processes (also see Dobbins & Wagner, 2005).

In contrast, our results are less consistent with the post-retrieval monitoring account of lateralization differences in the PFC activity. Post-retrieval monitoring refers to the evaluation of items retrieved from memory in accordance with their accuracy and relevance to the task (Burgess & Shallice, 1996; Koriat & Goldsmith, 1996; Norman & Bobrow, 1979). Evidence from both neuropsychology (Curran, Schacter, Norman, & Galluccio, 1997; Schacter, Curran, Galluccio, Milberg, & Bates, 1996) and neuroimaging (e.g., Henson, et al., 2000; Rugg, et al., 1999) have suggested a role for right PFC in post-retrieval monitoring (also see Fleck, et al., 2006). In the present study we found that activity in right and left PFC that varied as a function of time lag was not affected by task difficulty. At the same time, the lateralization of PFC varied as a function of recollection vs. familiarity (or systematic vs. heuristic) demands but not as a function of retrieval success, suggesting that retrieval orientation is the critical factor determining PFC lateralization in our task rather than effort or monitoring demands.

Conclusions

In the present study we employed a novel photo paradigm to investigate temporal order memory for autobiographical events, in which we were able to control for the order of when events occurred along with other factors (e.g., Cabeza, Prince, et al., 2004). Although a controlled way to elicit AMs, the photo paradigm replicates the common experience of taking photographs during sightseeing. Unlike typical laboratory stimuli, the use of the photo paradigm also allowed us to manipulate the

temporal distance between events over longer intervals, which was important for separating the processes involved in temporal context memory. Furthermore, in the photo paradigm participants were also personally familiar with the campus, and thus, recall of these events might have been influenced by the autobiographical salience associated with particular locations (e.g., Westmacott & Moscovitch, 2003). Although we did not find that differences in overall familiarity affected the main results, the interaction between autobiographical significance and temporal context memory will be interesting for future research.

Our results are consistent with behavioral evidence in AM suggesting that there are two distinct processes which are involved in temporal context memory: 1) *reconstruction*, based on the rich recollection of contextual details, and 2) *distance*, based on differences in the familiarity signal (Friedman, 1993, 2004). Reconstruction and distance processes are similar to recollection and familiarity but not identical. For example, Friedman (1993, 2004) proposed that distance processes are the preferred method for determining temporal context, with reconstruction processes accessed only when accuracy is important (such as in the present study), but not all models of recollection and familiarity make this same assumption (for a review see Yonelinas, 2002). While we found parahippocampal activity for shorter lags suggesting the use of reconstruction processes in this condition, activity in the hippocampus was not as strong a predictor of temporal order memory. Furthermore, although we found activity in

fusiform gyrus for longer lags consistent with the use of distance processes, we did not observe the predicted perirhinal activity. Future research is needed to better characterize how the distance-reconstruction distinction differs from the recollection-familiarity distinction, such as determining the characteristics and content of the AMs that are retrieved via self-report measures. In particular, the interaction of distance-reconstruction processes and the retrieval of episodic versus semantic autobiographical events is an important issue (Cabeza & St. Jacques, 2007). Despite possible differences between the two constructs, by characterizing these temporal processes within the framework of recollection and familiarity we were able to make predictions about lateralization differences in the PFC and activity in posterior regions, which were not directly discernable in the behavioral model of reconstruction and distance (Friedman, 1993, 2004).

The results of the present study are consistent with prior evidence from lesion and neuroimaging suggesting that the PFC is important for temporal information. However, we extend these findings by showing that the left DL-PFC is particularly implicated in reconstruction-based temporal judgments, whereas the right DL-PFC is involved in distance-based judgments. Furthermore, we found that posterior brain regions were also important in these temporal processes, especially in the case of reconstruction. To our knowledge, this is the first fMRI study to investigate temporal context memory for autobiographical events. In the present study the time lag between

the events took place within a single day; future studies should probe longer lags between autobiographical events to determine if the findings generalize to broader temporal distances in memory.

7. Study 2: Neural Differences in Self-Projection of Self Versus Other Perspectives

Functional neuroimaging studies have linked self-projection to the medial prefrontal cortex (mPFC; Mitchell, 2009). The medial PFC is involved in abstract forms of mentalizing (Amodio & Frith, 2006; Gallagher & Frith, 2003) such as integrating social information about the stable dispositions of others and the self across time (Van Overwalle, 2009). Subregions within the mPFC, however, may differentially contribute to self-projection. Ventral mPFC is sensitive to the ability to re-experience the self in time during AM (Levine, et al., 2004; Maguire & Mummery, 1999), and focal lesions that overlap here impair the subjective experience of re-experiencing the personal past (M. A. Wheeler & Stuss, 2003). Moreover, resting-state functional connectivity has shown that subregions of the mPFC comprise separable networks. Ventral mPFC is linked to the hippocampus and other regions associated with the medial temporal lobe (MTL) network (Kahn, Andrews-Hanna, Vincent, Snyder, & Buckner, 2008; Vincent et al., 2007), a system of brain regions important for internally directed processes, such as memory. In contrast, dorsal mPFC is linked to dorsolateral PFC and lateral parietal cortices associated with the frontoparietal network (Vincent, Kahn, Snyder, Raichle, & Buckner, 2008), a system of brain regions associated with controlled processes. Ventral mPFC has been associated with inferences about one's own self and dorsal mPFC with inferences about another individual (Krueger, Barbey, & Grafman, 2009; Mitchell, 2009; Van

Overwalle, 2009). However, there is considerable debate regarding the functional specialization of the mPFC with respect to self versus other processing (Northoff et al., 2006).

The goal of the present fMRI study was to examine self-projection of self vs. other elicited by naturalistic stimuli within the same individuals by employing a novel camera technology. We tested three main predictions regarding the role of mPFC, which were based on the evidence regarding ventral and dorsal subregions in self versus other processing (Krueger, et al., 2009; Mitchell, 2009; Van Overwalle, 2009). First, ventral mPFC will be preferentially recruited during self-projection of self, whereas dorsal mPFC will be recruited to a greater extent for self-projection of other. Second, ventral vs. dorsal mPFC will be sensitive to variability in the ability to re-experience the personal past and to understand another's perspective. Third, ventral vs. dorsal mPFC will be functionally connected to separable neural networks contributing to self-projection of self vs. other.

Methods

Participants

There were twenty-three participants (12 females; Mean Age = 23.7, SD = 3.6) who were healthy, right-handed, and without history of neurological or psychiatric episodes. Participants gave written informed consent for a protocol approved by the Duke University Institutional Review Board.

Materials and Procedure

SenseCam. SenseCam (<http://research.microsoft.com/en-us/um/cambridge/projects/sensecam/>) is a small wearable digital camera that has electronic sensors (i.e., light, heat, and motion) that can automatically and silently trigger thousands of photographs in a single day (see **Figure 8A**). This differs considerably from the normal way in which we can use a camera to generate retrieval cues (Cabeza, Prince, et al., 2004; St.Jacques, Rubin, Labar, & Cabeza, 2008), because it does not disrupt the ongoing experience of events through the act of taking a photograph (also see Levine, et al., 2004). Several photographs taken from a particular event (e.g., eating ice-cream; see **Figure 8B**) can be consecutively viewed to create a dynamic visuospatial cue (<http://www.youtube.com/watch?v=sr1i-sICafs>). The SenseCam lens also maximizes the field of view to better capture the perspective of the wearer by incorporating a wide-angle (fish-eye) lens. In sum, the SenseCam captures dynamic images taken from the first person perspective, which provide highly effective cues for self-projection to alternative self vs. other perspectives.

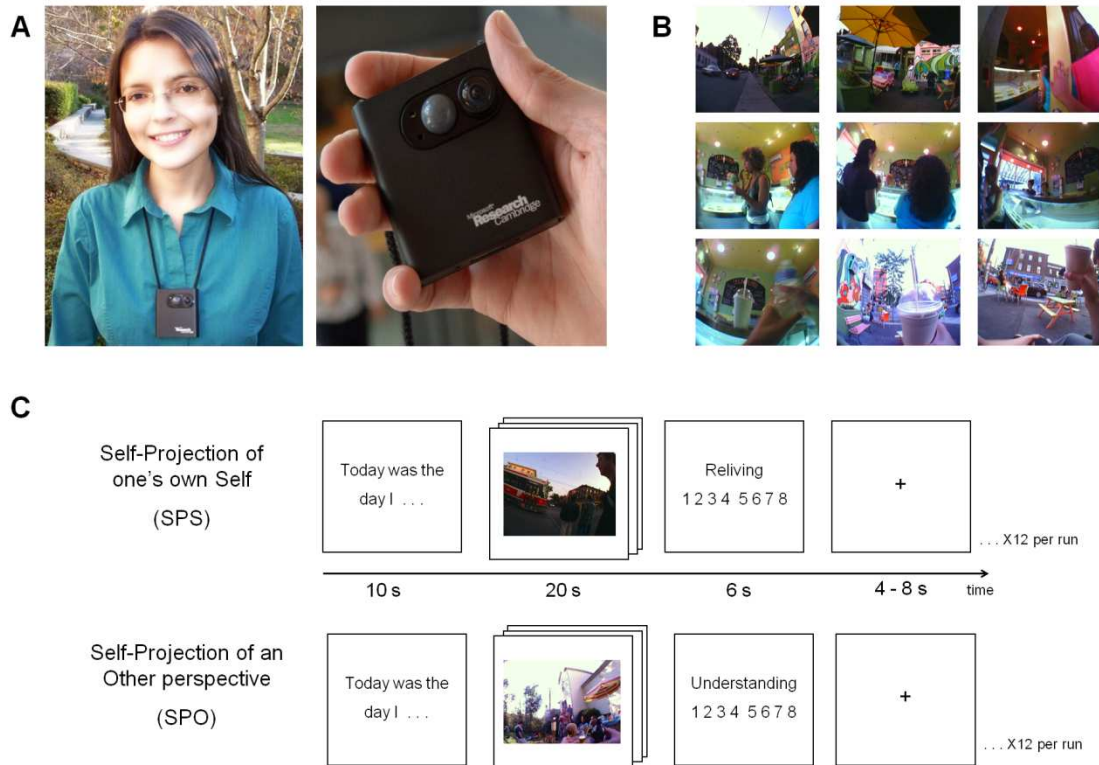


Figure 8: SenseCam and Study Design

(A) The SenseCam is a small wearable device that takes photographs automatically, without input from the user, **(B)** SenseCam images acquired during a trip to the ice-cream shop, and **(C)** The experimental design depicting the study

Prospective Collection. Retrieval cues were prospectively collected, such that participants were asked to keep a record of their lives prior to the scanning session by wearing the SenseCam. Participants wore the SenseCam for 6 days and kept a schedule of each day's activities to be used to parse the SenseCam images into events. The daily schedule was recorded at the end of each day along with a unique identifier to distinguish that particular day from others (e.g., "Today was the day I had lunch with Ben"). Participants were instructed to write about 10-15 brief sentences, one for each

major event during the day (e.g., "Had breakfast", "went to the grocery store . . .") which were used to segregate the images into events.

Cue Selection. Three days were randomly assigned to elicit self-projection of one's own self (SPS). The content of the remaining three days was used for an analysis that was not the main focus of the present investigation (St Jacques, Conway, & Cabeza, 2010). For each day, 12 events were selected to be tested in the scanner. To elicit self-projection of other perspectives (SPO), images were collected by three volunteers who wore a SenseCam in locations at least 100 miles away from Duke University and whose lifestyles differed from the participants. Images in the SPO condition depicted events that would have been familiar to the participants (e.g., going to the going to the grocery store, eating at a restaurant, going to Wal-Mart, renting a movie from Blockbuster, etc.) but which were not self-relevant, thus minimizing the likelihood that the other-perspective condition would include pictures of self-relevant people, places, and activities, which might inadvertently trigger AMs. Debriefing following the scanning session indicated that the SPO images were familiar to many of the participants, but did not trigger personal memories. The SPO images were also carefully selected to be similar to the SPS images (e.g., indoor/outdoor, time of day, etc.). Images in both conditions were selected to ensure good picture quality.

FMRI Scanning. The scanning session took place one week following the last day the SenseCam was worn (mean length of delay = 8 days, $SD = 1.2$). There were a

total of nine fMRI runs blocked by condition and presented in an alternating order (i.e., ABCABCABC), counterbalanced across participants based on a Latin square design. Three of the separate runs consisted of another condition, which was included for a separate analysis. The structure of the remaining six runs was similar in each condition (see **Figure 8C**). Each of these runs began with a 10-second title screen (i.e., “Today was the day I...”) and consisted of 12 cues presented in chronological order from that day, for a total of 36 events per condition across 3 runs. Cues were presented for 20 seconds, and participants were instructed to recall the events depicted from their own perspective or to understand the events being depicted from another person’s perspective. The cues in each condition consisted of 40 SenseCam pictures depicting a single event and presented at a rate of two pictures per second.

Following each cue presentation, participants indicated their subjective experience. In the SPS condition participants rated the subjective experience of recollection, reliving, which refers to how much they were able to re-experience the event depicted as if it were happening right now or as if they were mentally traveling back to the time when the event occurred. It is important to note that reliving is similar to other subjective measures of recollection, such as the remember/know paradigm (for a review see Yonelinas, 2002). For example, in the remember/know paradigm, participants are asked to use introspection to classify items as recollected (vivid re-experiencing of the original event and its context) or merely familiar. Although introspection has its

limitations, the results of hundreds of remember/know studies are highly consistent with findings of hundreds of studies using objective measures of recollection, such as source memory (Yonelinas, 2002). However, there are some critical differences between the reliving scale and remember/know paradigm, which make the reliving scale a better measure for AM. First, the reliving scale could be considered a better subjective measure of recollection in AM than remember/know because it does not require the assumption of a dual-process model (Wixted, 2007; Yonelinas, 2002). Second, reliving is a better predictor of recollection in AMs compared to the remember/know scale, which is a better predictor of confidence in AMs (Rubin, Burt, et al., 2003; Rubin, Schrauf, & Greenberg, 2004). In the SPO condition participants were asked to indicate the amount of understanding of the other person's perspective. While taking another person's perspective, participants were instructed to try to understand what was happening, where the event was taking place, and why the event was occurring. Ratings were conducted on an 8-point scale from low to high, and were self-paced (up to 6 seconds). Following a response, a fixation cross was presented for a jittered interval between 4 and 8 seconds plus any remaining time from the response period.

fMRI Methods

Image Acquisition. Scanning was conducted using a 4T GE magnet.

Anatomical scanning included a T1-weighted sagittal localizer series and 3D fast spoiled gradient echo recalled structural images were acquired in the coronal plane (256² matrix,

TR = 12.3 ms, TE = 5.4 ms, flip angle = 20°, FOV = 240, 68 slices, 1.9 mm slice thickness). Coplanar functional images were acquired using an inverse spiral sequence (64² image matrix, TR = 2000 ms, TE = 6 ms, FOV = 240, flip angle = 60°, 34 slices, 3.8 mm slice thickness).

fMRI Analyses. Image processing and analyses were performed using SPM software in Matlab (SPM5; Wellcome Department of Imaging Neuroscience). Functional images were corrected for slice acquisition order, realigned to correct for motion artifacts, spatially normalized to a standard stereotactic space, and spatially smoothed using an 8-mm isotropic Gaussian kernel. Coordinates are reported in Talairach space using a transformation from the Montreal Neurological Institute coordinates (Brett, Christoff, Cusack, & Lancaster, 2001).

Self-Projection of Self vs. Other. To examine activation differences between self vs. other self-projection during the presentation of the SenseCam images, we used a Finite Impulse Response (FIR) basis function. The FIR approach allowed us to examine potential activation differences without assuming a particular canonical hemodynamic response function, and thus, was appropriate for the complex and temporally protracted processes elicited in the present study. The FIR model included 16 regressors of peristimulus time bins of 2s duration (equal to the TR) for each condition, yielding estimates of fMRI signal change across the entire trial period (SenseCam presentation and Rating).

We conducted a Condition (SPS, SPO) x Time (0 to 20s) ANOVA implemented in SPM5 in order to isolate activation differences in the self vs. other conditions across the FIR timepoints associated with the presentation of the SenseCam images. We examined the Main Effect of Condition at an FDR corrected threshold of $P = .05$ using a 2 voxel extent threshold, and inclusively masked with the effect of interest (SPS > SPO or SPO > SPS) at $P = .05$ to determine the direction of the effect. An extent threshold of 2 voxels was chosen here because the ROI approach combined with a corrected threshold was considered very conservative. Further, we took a region of interest (ROI) approach to examine brain regions associated with self vs. other self-projection in the present study based on a previous quantitative metaanalysis which generated activation likelihood estimation maps corresponding to statistically significant concordance of activated voxels in 19 AM and 50 ToM studies (Spreng, Mar, & Kim, 2009).

Parametric Modulation by Behavior. To examine the neural correlates associated with self vs. other self-projection that was sensitive to online behavioral responses we employed a parametric approach. To identify increases in activity as a function of increasing behavioral responses on each trial, we created a GLM in which temporal vs. mental self-projection was modulated by reliving and understanding using the first-order parametric modulation option integrated in SPM5. Subsequently, random-effects analyses were performed on the parameter estimate of the parametric regressor for the behavioral response. We used the results of the one-sample t-test ($p =$

.05) reflecting activity modulated by reliving or understanding as an inclusive mask to determine whether the regions showing activation differences in self vs. other self-projection were also sensitive to behavior.

Task-Related Functional Connectivity Analysis. Seed voxels in the ventral vs. dorsal medial PFC that were identified in our previous analysis on self vs. other self-projection were further interrogated to examine the task-related network of brain regions functionally connected with dissociable medial PFC regions. We should note that in the present article we refer to dorsal mPFC (z-axis on Talaraich atlas: > 20 mm) and ventral mPFC (z-axis on Talaraich atlas: < 20 mm to > -15 mm) (e.g., Krueger, et al., 2009; Van Overwalle, 2009), however, the particular naming convention may differ among authors (e.g., Buckner, Andrews-Hanna, & Schacter, 2008; Northoff & Bermpohl, 2004). To find these functional connectivity maps, we employed a second analysis based on individual trial activity (Rissman, Gazzaley, & D'Esposito, 2004). Specifically, we first created a GLM in which each individual trial was modeled by a separate covariate, thus yielding different parameter estimates for each individual trial and for each individual subject. The resulting correlation maps were fisher transformed to allow for statistical comparison. Then, to examine differences in functional connectivity of ventral vs. dorsal medial PFC regions associated with temporal vs. mental self-projection we conducted a two-sample t-test in SPM5 using a false discovery rate corrected threshold of $P = .05$ and a 2 voxel extent threshold.

Results

Behavioral Results

SPS was associated with a mean reliving rating of 5.04 ($SD = .56$; $RT = 1.42$ s, $SD = .67$), whereas SPO was associated with a mean understanding rating of 4.50 ($SD = .86$; $RT = 1.35$ s, $SD = .61$). There were no significant differences in the reaction time across the two conditions (Cohen's $d = .11$). The behavioral results suggest that the SenseCam images evoked a strong ability to re-experience the personal past and to comprehend another individual's perspective.

fMRI Results

Self-Projection of Self vs. Other. The results of the self vs. other self-projection revealed a dorsal vs. ventral distinction in the mPFC (see **Table 5** and **Figure 9**). There was greater activity in the dorsal mPFC during SPO compared to SPS. Additionally, the SPO > SPS contrast revealed greater recruitment of right DL-PFC and ventral parietal cortices. In contrast, there was greater recruitment of the ventral mPFC during self vs. other self-projection. Additionally, the SPS > SPO contrast revealed greater recruitment in several regions associated with AM retrieval (Cabeza & St. Jacques, 2007), including the left hippocampus, lateral temporal, posterior midline and bilateral VL-PFC. Interestingly, the difference between SPS vs. SPO was reflected by less deactivation in ventral mPFC but greater activity in dorsal mPFC, which is a pattern of findings consistent with others (Gusnard, Akbudak, Shulman, & Raichle, 2001) and linked to a

default state of cognitive processing (Gusnard, Raichle, & Raichle, 2001). In sum, these results suggest that ventral vs. dorsal subregions of the PFC contribute to separable forms of self-projection.

Table 5: Self-Projection of Self vs. Other

Region	BA	x	y	z	F	Voxels
<u>SPO > SPS</u>						
Dorsal mPFC	9	-7	38	33	14.17	12
	9	-11	56	25	13.67	5
Dorsolateral PFC	9	19	49	33	30.51	12
Ventral Parietal Cortex	39	-45	-67	38	15.26	5
	40	-56	-57	27	12.59	7
	40	52	-53	34	10.93	5
<u>SPS > SPO</u>						
Ventral mPFC	10	-7	54	-3	53.56	51
Frontopolar Cortex	10	-37	48	12	80.47	18
Ventrolateral PFC	45	-41	23	16	17.94	9
	47	-45	14	-7	6.79	2
	47	-41	29	-8	6.73	3
	47	52	29	-5	17.06	3
Anterior Cingulate	24	-7	30	20	32.01	7
Supplemental Motor Area	6	4	10	52	16.61	7
Thalamus	--	4	-7	0	42.34	8
Temporopolar Cortex	38	-37	17	-26	24.59	12
Middle Temporal Cortex	21	-52	-15	-12	27.71	17
	21	41	-8	-9	17.46	5
Superior Temporal Cortex	22	-45	-57	17	25.61	22
Hippocampus	--	-22	-12	-15	28.68	71
Retrosplenial Cortex	29	0	-51	6	20.00	10
Posterior Cingulate	31	-7	-31	33	19.20	2
Ventral Parietal Cortex	39	-37	-75	25	14.31	11

Talaraich Coordinates Reported

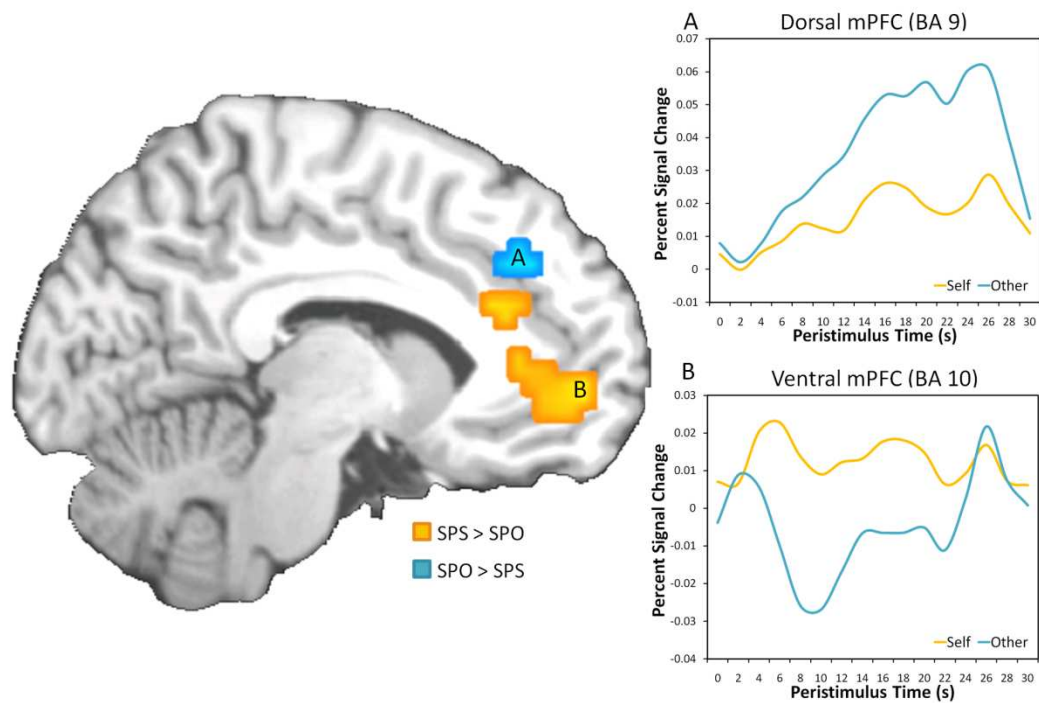


Figure 9: Self-Projection of Self vs. Other in the Ventral vs. Dorsal mPFC

Parametric Modulation of Behavior. In order to directly link activation

differences in self-projection to behavior, we examined activity in the above regions that was modulated on each trial by the extent of reliving in the case of SPS, and understanding in the case of SPO (see **Table 6** and **Figure 10**). We found greater modulation of ventral mPFC during highly relived trials for SPS, but no modulation by understanding in this same region for SPO. In contrast, there was greater modulation of dorsal mPFC by better understanding for SPO, but no modulation in this region by reliving for SPS. In sum, these results show that activity in the ventral mPFC is sensitive to reliving when taking one's own past perspective during memory retrieval, whereas

activity in dorsal mPFC is sensitive to better understanding when projecting one's self onto a different mental perspective.

Table 6: Parametric Modulation of Behavior

Region	BA	x	y	z	F	Voxels
<u>SPS: Understanding</u>						
Dorsal mPFC	9	-7	38	33	14.17	6
	9	19	49	36	26.63	4
Ventral Parietal Cortex	39	-45	-67	42	13.38	4
<u>SPO: Reliving</u>						
Ventral mPFC	10	-7	47	-6	21.66	8
Anterior Cingulate	24	-4	34	16	31.90	6
	24	0	37	5	24.70	12
Supplemental Motor Area	6	4	10	52	16.61	5
Thalamus	--	4	-7	0	42.34	6
Temporopolar Cortex	38	-37	17	-26	24.59	7
Middle Temporal Cortex	21	-56	-15	-15	22.29	6
Superior Temporal Cortex	22	-45	-57	17	25.61	22
Hippocampus	--	-22	-12	-15	28.68	33
Retrosplenial Cortex	29	0	-51	6	20.00	9

Talaraich Coordinates Reported

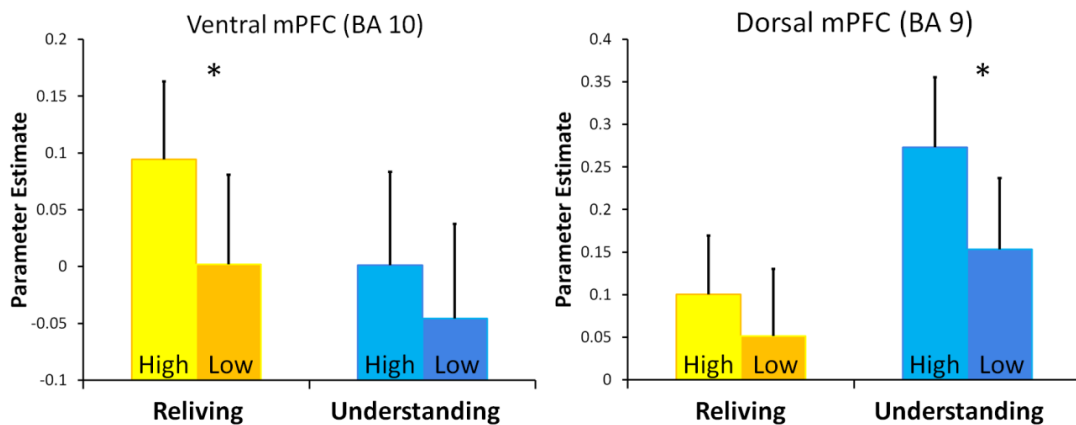


Figure 10: Parametric Modulation of Behavior in Ventral vs. Dorsal mPFC

Task-Related Functional Connectivity Analysis. For examining functional connectivity we used the peak voxels identified in the ventral and dorsal mPFC regions engaged by self vs. other self-projection as seed voxels in individual trial-based analyses. These analyses revealed that ventral vs. dorsal mPFC showed task-related functional connectivity with MTL and Frontoparietal Networks (see **Table 7** and **Figure 11**). Ventral mPFC showed greater co-activation with the left hippocampus and precuneus, compared to dorsal mPFC. In contrast, dorsal mPFC showed greater co-activation with bilateral frontal and parietal regions, compared to ventral mPFC. The pattern of functional connectivity of these ventral vs. dorsal mPFC regions is consistent with previous studies examining spontaneous patterns of coherent activity during passive resting state, which have revealed an MTL network (Kahn, et al., 2008; Vincent et al., 2006) and Frontoparietal Network (Vincent, et al., 2008). In sum, the findings from the functional connectivity analysis provide strong support for the dissociable role of dorsal vs. ventral mPFC in self vs. other self-projection.

Table 7: Task-Related Functional Connectivity of the mPFC during Self-Projection

Region	BA	x	y	z	T	Voxels
<u>SPO > SPS</u>						
Dorsal mPFC	9	-7	38	30	17.08	645
Dorsolateral PFC	9	-52	24	34	4.8	132
	9	45	35	37	3.35	2
	46	48	37	16	3.29	4
Ventrolateral PFC	47	-52	36	-2	4.84	29
	47	-52	18	-4	4.19	11
Orbitofrontal Cortex	11	-45	43	-18	4.32	30
	11/47	48	43	-9	3.72	5
Frontopolar Cortex	10	26	51	-3	3.61	2
Clastrum	--	-22	21	-7	4.55	11
	--	22	21	-7	5.71	48
Middle Temporal Cortex	21	-56	-30	-11	3.4	4
	21	63	-33	-14	3.46	14
	21	67	-26	-8	3.23	2
Superior Temporal Cortex	41	41	-33	5	3.66	3
Precuneus	7	15	-78	46	3.82	2
Dorsal Parietal Cortex	7/40	-45	-48	55	6.04	300
	7/40	48	-49	48	5.02	162
Cerebellum	--	-37	-60	-29	4.54	83
	--	-15	-81	-22	3.79	5
	--	37	-67	-25	4.67	42
<u>SPS > SPO</u>						
Ventral mPFC	10	-7	55	1	17.3	277
Hippocampus	--	26	-22	-12	4.11	2
Precuneus	7	-11	-49	48	5.09	2
Talaraiich Coordinates Reported						

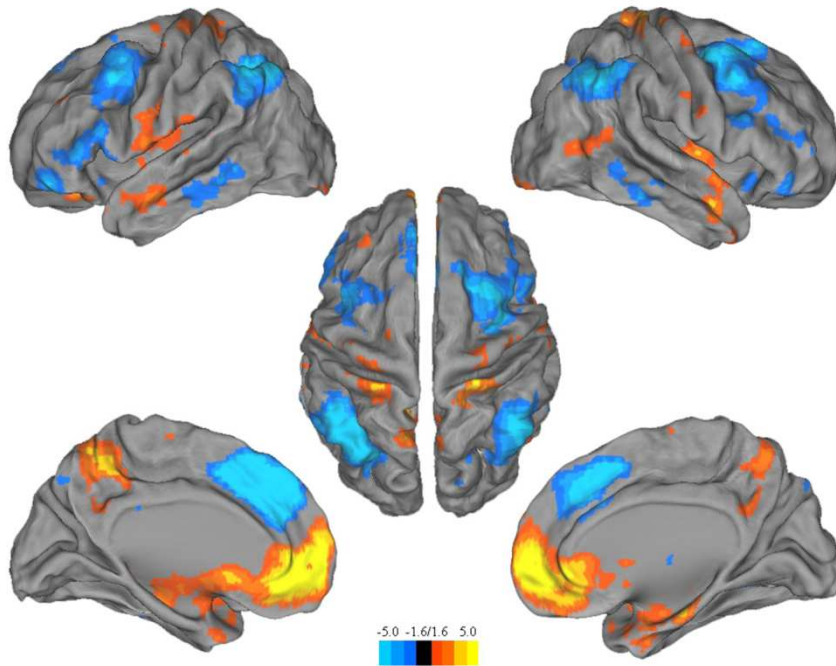


Figure 11: Task-Related Functional Connectivity of the Ventral vs. Dorsal mPFC during Self-Projection

Discussion

The present fMRI study investigated the neural mechanisms underlying self-projection to the personal past and into the life of another person within the same individuals via naturalistic stimuli that were prospectively generated using a novel camera technology. Our data indicate that there is a ventral vs. dorsal distinction in the mPFC during self-projection relying on shifts in perspective from one's own self vs. another individual. There were three main findings supporting this result. First, we found that temporal self-projection into the personal past recruited greater ventral mPFC, whereas mental self-projection into another person's perspective recruited greater dorsal mPFC. Second, activity in ventral vs. dorsal mPFC was sensitive to

parametric modulation on each trial by the ability to relive the personal past or to understand another's perspective. Third, task-related functional connectivity analysis revealed that ventral mPFC contributed to the MTL network linked to memory processes, whereas dorsal mPFC contributed to the frontoparietal network linked to controlled processes.

mPFC is a critical node in the network of regions supporting tasks relying on self-projection such as AM retrieval (Buckner & Carroll, 2007a; Mitchell, 2009; Spreng, et al., 2009) and ToM (Buckner & Carroll, 2007a; Mitchell, 2009; Spreng, et al., 2009). Here we show that ventral vs. dorsal mPFC may differentially support self vs. other forms of self-projection during these tasks. The mPFC coordinates reported here also overlap with those found by a previous meta-analysis on social cognition (Van Overwalle, 2009) and one on self-referential processing (Northoff, et al., 2006). The exact role of particular subregions within the mPFC has been a matter of considerable debate, with some studies observing recruitment of ventral mPFC when making inferences about one's own self and dorsal mPFC when mentalizing about others (Krueger, et al., 2009; Van Overwalle, 2009; also see Spreng, et al., 2009), and other studies observing that both dorsal and ventral mPFC recruited during self-referential processes (Northoff, et al., 2006). The recruitment of particular subregions of the mPFC during self-projection may vary according to the degree of personal relevance. Consistent with this idea, in a series of studies Mitchell and colleagues (Ames, Jenkins, Banaji, & Mitchell, 2008; Jenkins,

Macrae, & Mitchell, 2008; Mitchell, Banaji, & Macrae, 2005; Mitchell, Macrae, & Banaji, 2006) found that ventral mPFC was recruited to a greater extent when mentalizing about similar others (e.g., people with the same political beliefs), presumably because they could rely more on the retrieval of information from their own life. In contrast, dorsal mPFC was recruited more when making inferences about dissimilar others. In the case of the current study, we found dorsal mPFC for a dissimilar other and ventral mPFC for a very similar other- one's own past self. Two previous studies investigating self-projection within the same individuals also found greater recruitment of ventral mPFC for AM versus ToM, but they did not observe differences in the recruitment of the dorsal mPFC (Rabin, Gilboa, Stuss, Mar, & Rosenbaum, 2009; Spreng & Grady, 2009). Control over the use of the first-person perspective during self-projection (e.g., D'Argembeau et al., 2007), employment of naturalistic dynamic visuospatial cues and other methodological differences may potentially account for the observed difference between the current and previous studies.

The recruitment of the mPFC also modulated the extent of self-projection to the personal past or into the life of another person. Ventral mPFC was recruited to a greater extent when temporal self-projection involved greater re-experience of the personal past as measured by subjective ratings of the amount of reliving. These results are consistent with prior functional neuroimaging studies showing that the ventral mPFC is sensitive to the ability to re-experience the self in time during AM (Levine, et al., 2004; Maguire &

Mummery, 1999), and with patient studies showing that lesions with overlap here impair the subjective experience of re-experiencing the personal past (M. A. Wheeler & Stuss, 2003). In contrast, dorsal mPFC was recruited to a greater extent when mental self-projection involved better understanding of another person's perspective. Dorsal mPFC is recruited during tasks that rely on evaluation (Northoff, et al., 2006) such as during impression formation of another individual (Mitchell, Neil Macrae, & Banaji, 2005). The sensitivity of dorsal mPFC to better understanding of a dissimilar other may reflect increased engagement of reliance on rule-based strategies to infer an alternative perspective.

Ventral vs. dorsal mPFC were functionally connected to separate neural networks, which differentially contributed to self-projection. Ventral mPFC showed greater functional connectivity with the hippocampus and precuneus, a pattern of results consistent with the MTL network supporting memory (Kahn, et al., 2008; Vincent, et al., 2006), whereas dorsal mPFC showed greater functional connectivity with lateral frontal, frontopolar, and dorsal parietal cortices, a pattern of functional connectivity which is consistent with the frontoparietal network supporting controlled processes (Vincent, et al., 2008). The MTL network is a subsystem of the default network, the set of brain regions that are coactive during passive resting states and associated with internally directed processes such as memory (Buckner, et al., 2008). Greater involvement of the MTL network during self-projection to the personal past is consistent

with the idea that the ability to take one's own perspective may rely upon the recovery of memory details. In contrast, the frontoparietal network supports the initiation and flexible adjustment of controlled processes (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008). Vincent et al. (2008) suggested that the frontoparietal network may contribute to the integration between externally directed attention and internally directed thought, given that it is anatomically juxtaposed between the dorsal attention and default networks. These types of controlled processing may be particularly important during self-projection into the life of another person, which potentially involves greater integration between an externally presented perspective and internally directed processes. The functional dissociation between the neural networks supporting self-projection observed in the present study is also consistent with evidence that AM and ToM are independent (Rosenbaum, Stuss, Levine, & Tulving, 2007).

Although mPFC is frequently observed in tasks relying on self-projection (Spreng, et al., 2009) it is also one of the most frequent regions observed during emotional tasks (Phan, Wager, Taylor, & Liberzon, 2002). Very few studies have controlled for both self-reference and emotion within the same individuals, thus it is difficult to definitively distinguish these processes (for a meta-analysis see Gilbert et al., 2006). However, one study found that ventral mPFC was sensitive to the self-relevance of stimuli irrespective of emotion (Moran, Macrae, Heatherton, Wyland, & Kelley, 2006). In the present study, the elicitation of emotional responses during self-projection was

minimized, because the SenseCam images depicted very recent, everyday events (e.g., attending class, studying, etc.). Moreover, the dorsal vs. ventral distinction observed in the current study would be difficult to explain based on the role of these mPFC subregions in emotion (e.g., Dolcos, LaBar, & Cabeza, 2004). Thus, the pattern of results observed in the present study is more consistent with the suggestion that the ventral vs. dorsal distinction in mPFC is related to differences in the nature of self-projection rather than emotion. Future studies, however, should directly manipulate the elicitation of emotion during self-projection for self vs. other.

Conclusions

The dynamic visuospatial cues employed in the current study provided a novel way to investigate self-projection of one's own life or the life of another individual. We found a ventral vs. dorsal distinction in the recruitment of the mPFC for self vs. other shifts in perspective. Further, ventral mPFC modulated the extent to which one's own perspective was re-experienced, whereas dorsal mPFC modulated the ability to understand an alternative perspective. Supporting the dissociable role of these mPFC subregions during different forms of self-projection, task-related functional connectivity analysis revealed that ventral vs. dorsal mPFC were nodes in different neural networks. Ventral mPFC contributed to the MTL network linked to memory processes, whereas dorsal mPFC contributed to the frontoparietal network linked to controlled processes. In

sum, the results of the current study suggest that the mPFC contributes to shifts from the present moment to alternative self and other perspectives.

8. Study 3: Age-Related Differences in Autobiographical Memory

The main effect of healthy aging on *autobiographical memory* (AM) retrieval is a deficit in *episodic richness*, which refers to a decrease in the ratio of specific episodic details compared to broad semantic information. Although this behavioral effect has been observed in several studies (Levine, et al., 2002; Piolino, et al., 2002; St. Jacques & Levine, 2007) its neural mechanisms are largely unknown. In particular, it is unknown *when* the age effect occurs during retrieval. A memory cue (*Where did I see these data before?*) triggers effortful search process guided by semantic knowledge of one's own life (*...the Cognitive Neuroscience Society meeting? ...Society for Neuroscience?*), which eventually lead to successful recovery of a target memory (*in an SfN poster...*). Memory for the target might be elaborated by recovering additional episodic details (*...it was early in the morning...*). In the case of AM, search and elaboration processes can take as long as 15-30 seconds, which allows the use of functional MRI (fMRI) to disentangle the activations associated with these two phases (Addis, Wong, & Schacter, 2007; Daselaar, et al., 2008). The present fMRI study investigated age-effects on search and elaboration processes during AM retrieval.

It is not clear whether the age-related deficit in episodic richness occurs early during retrieval, while one is searching for the target memory, or late during retrieval, while one elaborates upon recovered information. Elaboration processes might be very sensitive to aging because they depend on an interaction between the recovery of specific details mediated by the hippocampus and effortful control processes mediated by the PFC, and both processes, and their associated brain regions, are known to decline with aging (for a review see Dennis & Cabeza, 2008). For example, fMRI studies have shown that hippocampal activity related to recollection is attenuated by aging, such that older adults rely more on familiarity processes associated with other MTL regions (e.g., Cabeza, Daselaar, et al., 2004; Daselaar, Fleck, Dobbins, et al., 2006). Aging also involves changes in frontal activation, with under-recruitment observed during memory conditions that lack environmental support (e.g., Logan, Sanders, Snyder, Morris, & Buckner, 2002; Paxton, Barch, Racine, & Braver, 2008), as well as compensatory over-recruitment (Cabeza, 2002). Furthermore, episodic richness is mediated by activations that occur late during AM retrieval (Cabeza & St. Jacques, 2007; Svoboda, et al., 2006), and relies on the recruitment of additional self-initiated retrieval processes (Daselaar, et al., 2008). An age-related deficit in early search processes might be less likely because AM search tends to be guided by semantic memory (Conway & Pleydell-Pearce, 2000), which is a memory function relatively well preserved in older adults (Craik & Jennings, 1992).

To investigate the neural basis of age-related differences episodic richness by parsing the spatiotemporal dynamics of AM retrieval we used a self-paced design in which young and older adults searched for an AM elicited by a generic cue word, pressed a key when the memory was found, and then elaborated on the memory until the end of the trial. After scanning, participants verbally described the memories they recalled in the scanner and objective analysis of these descriptions of recall were used to determine episodic richness. We investigated the hypothesis that age-related declines in episodic richness are associated with reduced recruitment of the hippocampus and PFC during elaboration.

Methods

Participants

There were seventeen young (18 - 35 years of age) and sixteen older participants (60 – 75 years of age), who were healthy, right-handed and without history of neurological or psychiatric episodes. All participants reported that they were not taking medication known to affect cognitive function, and older adult participants were screened for uncontrolled hypertension. Participants gave written informed consent for a protocol approved by the Duke University Institutional Review Board. One young adult and one older adult were excluded due to symptoms of depression as indicated by scores > 13 on the Beck Depression Inventory (BDI; Beck & Steer, 1978). Furthermore, two young adults and one older adult were excluded from the analyses because of

problems with completing the task as instructed. Thus, the reported results are based on data from fourteen young (7 females; mean Age = 24.43, $SD = 3.73$) and fourteen older (6 females; mean Age = 64.21, $SD = 2.86$) participants.

Demographic and psychometric data (see **Table 8**) were obtained in a separate session within one week of the scanning session. All participants had obtained at least a secondary school education (12 years). Participants scored a minimum of 28 on the Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975) and a maximum of 11 on the BDI. There were no age-related differences in the number of years of education, MMSE, BDI, the Weschler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), verbal fluency (FAS), or categorical fluency (animal names and supermarket items).

Table 8: Participant Variables by Age Group

	M		SD		t (27)
	Young	Older	Young	Older	Y vs. O
Age (years)	24.43	64.21	3.73	2.86	31.79**
Education (years)	16.50	17.43	2.28	1.91	1.17
MMSE	28.71	28.50	0.61	0.76	- 0.82
BDI	3.93	5.07	3.29	3.47	0.89
WASI-Full IQ	122.36	126.00	7.66	10.07	1.08
WASI-Verbal IQ	120.93	123.79	7.87	7.37	0.99
WASI-Performance IQ	118.14	122.00	7.49	11.79	1.03
Verbal Fluency	47.43	42.79	10.87	16.12	- 0.89
Categorical Fluency	48.79	41.21	13.55	11.78	- 1.58

* $p < .05$, ** $p < .0001$

Materials and Procedures

Materials. Memory cues consisted of 60 emotionally arousing words selected from the affective norms for English words database (Bradley & Lang, 1999), such that there were 30 positive (Valence mean = 7.93, $SD = 0.45$; Arousal Mean = 5.96; $SD = 0.83$) and 30 negative (Valence Mean = 2.17, $SD = 0.52$; Arousal Mean = 6.00; $SD = 1.03$) words that were equally arousing. In order to create auditory cues the words were recorded in a female voice and constrained to an equal duration of 1 s.

Procedure. The procedure was similar to Daselaar et al. (2008; also see Greenberg, et al., 2005). During scanning participants were asked to search for AMs

triggered by the auditory cue words. Participants were instructed to retrieve an AM with specific spatiotemporal coordinates. They indicated when a specific AM was found by making a response on the button-box and then continued to elaborate on the retrieved event in as much detail as possible for the rest of the trial. Thirty seconds following the onset of the auditory cue participants were given auditory instructions to rate the amount of emotion (negatively arousing to positively arousing) and reliving (low to high) associated with the memory on an 8-point scale. Rating responses were self-paced (up to 6 s) and separated by at least 0.5 s. There were 6 functional runs, with 10 memory cues in each run (5 positive words and 5 negative word), and an inter-trial interval at least 1.5 to 7.5 s. Participants were instructed to keep their eyes closed for the duration of each run.

Immediately following the scanning session participants were asked to provide a short title for the memory retrieved during scanning and to answer additional questions on a subset of the AM questionnaire (e.g., Rubin, Schrauf, et al., 2003). Participants were asked to date when the event had occurred (e.g., last day to > 10 years ago), to indicate the amount of vividness or how clearly the event was remembered, the perspective or whether the memory was seen through their own eyes or through the eyes of an outside observer, the significance of the memory, and the physiological response during retrieval (e.g., heart pounding, etc.). Also, given that AM comprises many different types of events (Brewer, 1986; St. Jacques & Cabeza, In Press) we asked participants to

indicate whether the type of memory retrieved was a unique event (referring to a particular time and place), repeated event (memory for an event with multiple occurrences), extended event (occurring longer than one day), or semantic information (long-standing facts about one's own life).

Within two days of the scanning session, participants returned for an additional session in which they were asked to verbally recall the memories retrieved during scanning, cued using the title participants had provided following the scanning session. Participants were instructed to freely recall for at least one minute and were not provided with retrieval support from the experimenter. Following transcription each memory was coded for the number of episodic details and semantic details (e.g., Levine, et al., 2002). Details were tallied for each category and the proportion of episodic details to the total details (episodic + semantic) was calculated for each memory in each subject as an estimate of the amount of episodic re-experiencing unbiased with respect to differences in protocol length.

fMRI Methods

Image Acquisition. Scanning was conducted using a 4T GE magnet. Auditory stimuli were presented using headphones and behavioral responses were recorded using an eight-button fiber optic response box (Resonance Technology, Northridge, CA). Head motion was minimized using foam pads and a headband. Anatomical scanning started with a T1-weighted sagittal localizer series, and then 3D fast spoiled gradient

echo recalled structural images were acquired in the coronal plane (256² matrix, TR = 12.3 ms, TE = 5.4 ms, flip angle = 20°, FOV = 240, 68 slices, 1.9 mm slice thickness).

Coplanar functional images were subsequently acquired using an inverse spiral sequence (64² image matrix, TR = 2000 ms, TE = 6 ms, FOV = 240, flip angle = 60°, 34 slices, 3.8 mm slice thickness).

Image Processing. Image processing and analyses were performed using SPM software in Matlab (SPM5; Wellcome Department of Imaging Neuroscience).

Functional images were corrected for slice acquisition order, realigned to correct for motion artifacts, and then spatially normalized to a standard stereotactic space, using the template implemented in SPM5. Subsequently, the functional images were spatially smoothed using an 8 mm isotropic Gaussian kernel.

fMRI Analyses. To account for the fact that we used a self-paced paradigm in which participants indicated when they recalled a specific event, we implemented a flexible fMRI design in the context of the GLM. The design distinguished six components in each trial: four transient and two sustained regressors. Transient regressors included the memory cue (immediately at onset of the trial), response-related decision processes (750 ms before the response indicating a memory was recalled), and the two ratings (second and third response). Sustained regressors included the memory search period (from trial onset to response) and the elaboration period (from response to the first rating). The transient regressors were modeled by convolving a canonical

hemodynamic response function with a vector representing period onsets, while the sustained regressors were modeled with a boxcar function representing both period onsets and offsets. In order to account for differences in the timing of activations due to the self-paced design, the response indicating that a memory was accessed determined the duration of the memory access period as well as the onsets of the response and elaboration periods. The use of the self-paced design reduced potential issues of multi-collinearity between the regressors, and as an additional check we directly evaluated this by calculating the variance inflation factor (VIF; J. Cohen, Cohen, West, & Aiken, 2003). For each regressor in each run and each participant, we extracted R^2 , the squared multiple correlation between a single regressor and the other regressors, using Design Magic (<http://www.matthijs-vink.com/tools.html>) and computed the VIF ($1/(1-R^2)$). The standard cut-off value of 10 (J. Cohen, et al., 2003) was used to exclude potential runs where multi-collinearity between the regressors was an issue (e.g., Scheibe et al., 2006). On the basis of these results, only 4 runs were potentially problematic and these runs were excluded from the analysis. Data were high pass filtered using a cutoff of 128 Hz, and global effects were removed (non-proportional scaling). Head motion was assessed prior to pre-processing, and no individual moved more than 3 mm in any direction, in any run.

To assess the validity of our flexible fMRI design, we investigated the time courses for fast and slow responses with respect to the self-paced button press indicating

that a memory was formed. First, fast and slow responses were determined with respect to the mean reaction time in each subject. Second, a GLM was created in which trial onsets time-locked to the cue were modeled with a Finite Impulse Response basis set of peristimulus time bins of 2 s duration (equal to the TR). The resulting parameter estimates were subsequently averaged for each peristimulus time bin, yielding estimates of fMRI signal change across the whole 48 s trial period for both fast and slow bins. Finally, for the actual validation, we used a ROI approach, focusing on auditory and motor cortex defined using the Talaraich Daemon Atlas (Lancaster, Summerin, Rainey, Freitas, & Fox, 1997; Lancaster et al., 2000) implemented with PickAtlas software (Maldjian, Laurienti, Kraft, & Burdette, 2003). The clusters showing significant ($p < 0.005$, cluster size > 10) cue-related activity in the auditory cortex or response-related activity in the motor cortex based on the GLM analysis were defined as ROIs. These results show that, in both age groups, cue-related activity was not modulated by response time, whereas the peak of response-related activity shifted depending on whether it was a fast or a slow response (see **Figure 12**). Furthermore, the young and older adults showed similar peaks in auditory cortex, and a similar average peak response in the motor cortex. These findings are important because they suggest that age-related differences in other brain regions, such as the hippocampus and the frontal lobes, are not simply due to a global effect of aging on the hemodynamic response.

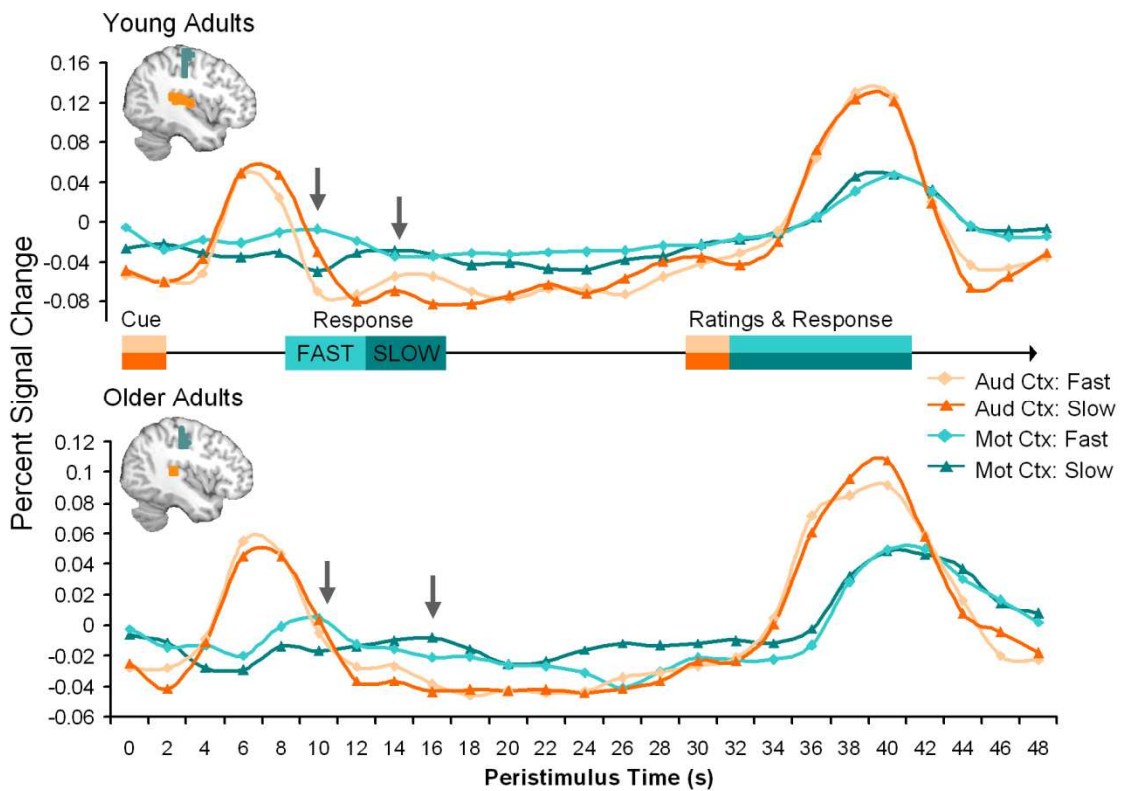


Figure 12: Time Course for Fast and Slow Responses

The time courses for fast and slow responses were nearly identical in the auditory cortex (aud ctx, orange/peach lines), and did not differ between age groups. In contrast, the time course for fast and slow responses was very different in the motor cortex (mot ctx, blue lines). The differences in peak latency in the motor cortex (gray arrows) for fast trials (light colors) and slow trials (dark colors) shows similar peaks in each age group, although there was a trend for slower responses in the older adults.

Age-Related Effects During AM Retrieval. In order to determine the impact of aging on search and elaboration phases of AM retrieval we examined both age-invariant effects and age-related differences in each phase. For assessing age-invariant effects associated with the search and elaboration phases, a conjunction map was created thresholding each age group's random effects separately for each contrast at $p = .005$ and

10 voxels and then exclusively masking with the age-related differences at $p = .005$. This procedure yielded an activation map containing only those voxels that showed age-invariant effects during the search and elaboration phases. We assessed brain areas showing age-related differences by using a two sample t-test to compare young and older adults separately during the search and elaboration phases ($p = .005$, with a cluster size > 10 voxels), and then inclusively masked this statistical image with the corresponding statistical map for the group of interest at $p = .005$. Thus, the resulting pattern of age-related differences in activity had to pass two hurdles: 1) the difference should be significant within one group, and 2) the difference should be significantly larger within one group compared to the other group. Given the *a priori* role of the hippocampus in AM (Cabeza & St. Jacques, 2007; Maguire, 2001a; McDermott, Szpunar, & Christ, 2009; Spreng, et al., 2009; Svoboda, et al., 2006), we conducted an additional ROI analysis ($p = .01$) to examine both age-invariant and age-related differences using the Talarach Daemon Atlas (Lancaster, et al., 1997; Lancaster, et al., 2000) implemented with PickAtlas software (Maldjian, et al., 2003).

Hippocampal-PFC Coupling. In order to examine the effective connectivity between the hippocampus and VLPFC, we used dynamic causal modeling (DCM) implemented in SPM5 (Friston, et al., 2003). First, we created two volumes of interest (VOIs) in the hippocampus and VLPFC based on the peaks from the age-related differences during elaboration using a sphere with an 8 mm radius, which were adjusted

for the task design. It is important to note that the level of activity is not directly dependent upon coactivation among brain regions (Nyberg, McIntosh, Cabeza, Nilsson, et al., 1996). Although the right hippocampus and left VLPFC showed less activity during elaboration in the older adults, there was sufficient variance within each of these regions for effective connectivity analysis, as indicated by the observation of age-invariant effects here for highly episodically rich AMs. Then, for each individual subject and replicated over the six sessions, we created a model space that included iterations for the location of the driving input and modulatory inputs by episodic richness on possible intrinsic connections between each region. Episodic richness was determined as those trials with a greater proportion of episodic to semantic details (i.e., > 50%). Plausible models included combinations of the following manipulations: driving inputs (in the hippocampus, VLPFC or both regions), intrinsic connections (reciprocal, bottom-up only, top-down only) and modulatory inputs (reciprocal, bottom-up only, top-down only). The final model space included 27 models that were estimated for each participant and replicated over the six sessions. We used a Bayesian Model Selection (BMS) implemented in SPM8 to select an optimal model separately within each age-group using random effects (Stephan, Penny, Daunizeau, Moran, & Friston, 2009). Finally, to assess group effects, the resulting individual participant coefficients were submitted to a two-sample t-test at $p < .05$.

Results

Behavioral Results

Participants were able to recall an event matching the cue on more than 95% of trials (see **Table 9** for mean behavioral scores, standard deviations, t-scores, p-values, and effect sizes). There were no age-related differences in the online ratings of reliving or emotional arousal. However, older adults were slower to make emotional ratings and there was a trend for slower retrieval of AMs compared to young adults.

Table 9: Mean Behavioral Responses by Age Group

	M		SD		t (26)	Effect Size
	Young	Older	Young	Older	Y vs. O	Cohen's D
<u>Scanning</u>						
% AMs	0.99	0.80	0.02	0.03	1.45	0.57
Reaction Time (s)	6.55	8.68	2.11	3.62	- 1.90	- 0.72
Reliving						
Rating	5.03	5.26	1.07	0.93	- 0.62	- 0.23
Reaction Time (s)	2.49	2.96	0.60	0.66	- 2.00	- 0.75
Emotion						
Rating	2.53	2.28	0.33	0.37	1.74	0.71
Reaction Time (s)	2.14	2.67	0.67	0.63	- 2.09 *	- 0.81
<u>Post-Scanning Ratings</u>						
Vividness	4.69	4.70	0.78	1.01	- 0.42	- 0.01
Significance	3.00	3.23	0.79	0.95	- 0.68	- 0.26
Physiological Response	2.31	1.73	0.99	0.77	1.74	0.65
Perspective						
Own Eyes	5.78	5.44	0.83	0.91	- 1.02	0.39
Observer	2.37	2.38	0.92	0.90	0.05	- 0.01
Date of Memory (%)						
day	0.05	0.03	0.04	0.04	0.92	0.50
week	0.09	0.06	0.06	0.05	1.50	0.54
month	0.12	0.06	0.08	0.07	2.29 *	0.80
year	0.26	0.15	0.09	0.08	3.20 ***	1.29
5 years	0.25	0.13	0.11	0.09	2.93 **	1.19
10 years	0.14	0.15	0.08	0.11	- 0.16	- 0.10
> 10 years	0.09	0.41	0.06	0.19	- 6.07 ****	- 2.27
Memory Type (%)						
Unique	0.81	0.62	0.15	0.19	2.96 **	1.11
Repeated	0.14	0.24	0.09	0.14	- 2.22 *	- 0.85
Extended	0.05	0.12	0.06	0.15	- 1.66	- 0.61
Fact	0.002	0.02	0.01	0.03	- 1.93	- 0.80
<u>Verbal Recall</u>						
Episodic Richness (%)	0.72	0.51	0.09	0.17	4.05 ****	1.54

* p < .05, ** p < .01, *** p < .005, ****p < .0005

As predicted the older adults showed a reduction in the episodic richness, the proportion of episodic details to the total number of episodic and semantic details, during the retrieval of AMs, $t(26) = 4.05, p < .0005$. Memories retrieved by the older adults ($mean = 0.51$ $SD = 0.17$) were 20% less episodically rich compared to young adults

($mean = 0.72$, $SD = 0.09$), and the effect size, $d = 1.54$, is large according to Cohen's standards (Cohen, 1988). The large effect size of the age-related differences in episodic richness compared to the small effect size of the reliving ratings ($d = -.23$) suggests that the latter were not sensitive enough to detect age effects. Consistent with the finding of an age-related reduction in episodic richness, the older adults reported that they recalled a smaller proportion of unique AMs and a greater proportion of repeated AMs and semantic information compared to young adults. There were no age-related differences in post-scan ratings of vividness, significance of the memory, physiological responses or memory perspective. Although there were no age-related differences in the proportion of memories retrieved from the most recent period (i.e., day, week), older adults retrieved more remote memories (i.e., > 10 years), and young adults recalled more events from other periods (i.e., month, year, 5 years). The age-related difference in episodic richness could be related to the observed age-related differences in remoteness (Cabeza & St. Jacques, 2007; Moscovitch, et al., 2005). However, there was no intra-individual correlation between remoteness and episodic richness when collapsed across age, $r = -.04$, $t(26) = -1.20$, $p = .24$, or separately in young adults, $r = -.05$, $t(13) = -.03$, $p = .54$, or older adults, $r = -.05$, $t(13) = -1.32$, $p = .21$, which suggests that more remote memories were not less episodically rich. This result might seem unexpected, because remote memories are sometimes associated with less episodic richness (Alvarez & Squire, 1994; Moscovitch, et al., 2005). However, in the present study, remote memories

were also self-selected, very accessible, and potentially more detailed than if retrieval was constrained to a specific lifetime and remote period (e.g., Cohen & Faulkner, 1988; Dijkstra & Kaup, 2005; Rubin & Schulkind, 1997); thus, it is not so surprising that these remote events would vary in episodic richness. In sum, the behavioral results show that the episodic richness of AMs was greatly reduced in older adults. Below, we turn to the fMRI results to elucidate the potential neural bases underlying this age-related reduction in episodic richness.

fMRI Results

Age-invariant effects during AM retrieval. During AM retrieval several several age-invariant effects were observed during the search phase (see **Table 10**). During search, both young and older adults recruited a number of the regions frequently found in AM retrieval (e.g., Cabeza & St. Jacques, 2007; Svoboda, et al., 2006) including the left VLPFC, left hippocampus, bilateral temporopolar cortex, bilateral retrosplenial cortex, and left parahippocampal cortex. During elaboration, a subset of these age-invariant search regions continued to remain online in both groups including the left parahippocampal cortex and the left retrosplenial cortex, and there was additional age-invariant recruitment of the left VPC. However, the pattern of age-related differences during elaboration suggested that the overall amount of activity recovered by the older adults was reduced when compared to the young adults.

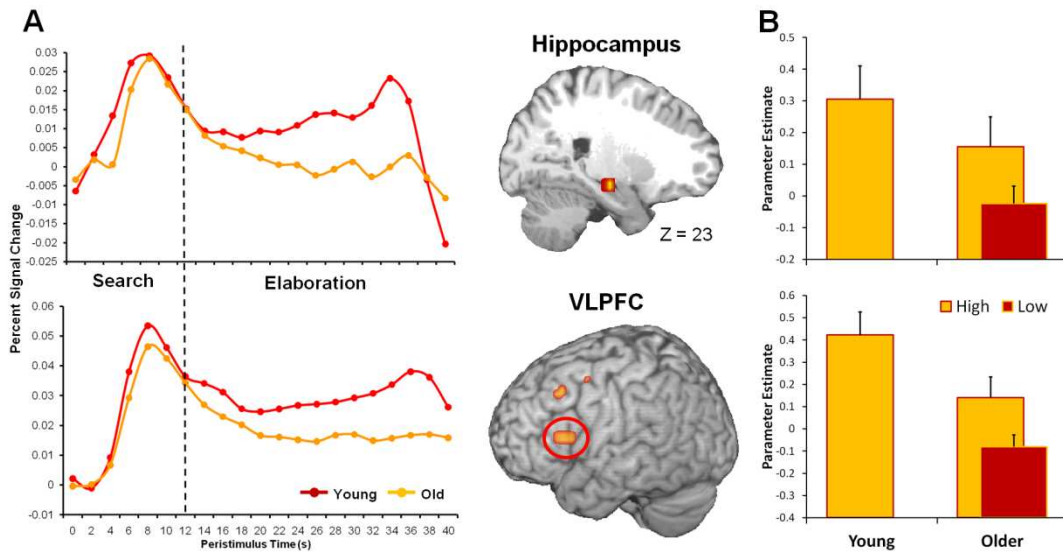


Figure 13: Age Effects during Autobiographical Memory Retrieval
(A) Age-invariant activity was observed in the right hippocampus and left ventrolateral prefrontal cortex (VLPFC) during search, but older adults showed less sustained activity here during elaboration **(B)** Age-effects were attenuated for highly episodic rich AMs. Dotted line represents the peak of the average motor cortex response for the button press.

Table 10: Age-Invariant Effects

Region	BA	H	Young				Older				Voxels
			x	y	z	T	x	y	z	T	
Search											
Ventrolateral PFC	45	L	-45	19	17	8.22	-41	23	13	5.55	276
	47	L	-33	22	-4	7.14	-48	29	-11	5.34	276
Anterior Cingulate	32	L	-7	20	41	10.47	-15	13	38	6.50	48
Temporopolar Cortex	38/21	L	-52	3	-16	6.06	-52	3	-19	4.61	73
	38/21	R	52	-1	-16	6.71	56	3	-19	5.06	75
*Hippocampus	--	L	-26	-22	-9	3.70	-19	-26	-8	4.35	21
Parahippocampus	--	L	-19	-37	-8	3.43	-15	-37	-8	6.49	39
Retrosplenial Cortex	30	L	-22	-51	10	5.37	-11	-54	10	5.34	83
	30	R	15	-44	2	4.91	11	-47	2	5.86	18
Cuneus	17/18	R	4	-94	5	5.81	11	-94	5	5.34	20
Midbrain		L	-4	-33	-14	4.83	-7	-30	-14	5.00	39
Elaboration											
Retrosplenial Cortex	29/23	L	-7	-58	13	9.24	-11	-54	13	3.72	50
*Hippocampus	--	L	-26	-15	-19	4.71	-26	-19	-15	4.12	6
Parahippocampus	--	L	-26	-37	-11	6.82	-26	-30	-14	4.17	19
Ventral Parietal Cortex	39	L	-48	-71	32	5.25	-48	-68	24	3.88	20

Talarach Coordinates Reported. *Region of Interest

Age-related differences during AM retrieval. Age-related differences were primarily observed during elaboration (see **Table 10**). Compared to the age-invariant activity observed during the search phase, older adults showed less activity in the right hippocampus, left posterior cingulate and left VLPFC (see **Figure 13A**). The reduction in recruitment of the VLPFC suggests that fewer details may have been generated during elaboration in the older adults. Consistent with this idea, there was an age-related reduction in the additional recruitment of the right hippocampus and right VPC, suggesting less internal attention driven by the recovery of memory details (Cabeza, et al., 2008). Furthermore, there were additional age-related reductions observed in the recruitment of the left posterior cingulate, a region associated episodic memory retrieval and self-referential processes (Buckner & Carroll, 2007b; Wagner, et al., 2005), and left DLPFC, associated with manipulation of the products of retrieval (Petrides, 2005). These results suggest an alteration in the recruitment of the AM retrieval network during elaboration of AMs in older adults, which might contribute to reductions in episodic richness. In sum, these findings are consistent with the idea that aging strongly impacts the rich elaboration of AMs.

Table 11: Age-Related Differences

Region	BA	H	x	y	z	T	Voxels
<u>Search</u>							
<i>Young > Older</i>							
Dorsomedial PFC	8/32	L	-7	20	44	4.39	47
<i>Older > Young</i>							
No Significant Voxels							
<u>Elaboration</u>							
<i>Young > Older</i>							
Ventrolateral PFC	45	L	-56	19	10	3.34	11
Dorsolateral PFC	9	L	-33	24	37	3.96	18
Dorsomedial PFC	8/6	C	0	21	55	3.54	11
Premotor Cortex	6	L	-41	-1	46	3.15	11
Middle Temporal Cortex	21	R	56	-12	-12	3.44	15
Ventral Parietal Cortex	40/22	R	52	-43	16	4.42	22
*Hippocampus	--	R	26	-15	-12	3.01	6
Posterior Cingulate	31	L	-11	-46	34	5.44	175
<i>Older > Young</i>							
No Significant Voxels							

Talaraich Coordinates Reported. *Region of Interest

We conducted two ancillary analyses in order to confirm that the age-related reduction during elaboration was linked to older adults' overall reduction in episodic richness and to confirm the role of the VLPFC in strategic retrieval processes. First, we examined activity only on those trials associated with higher episodic richness, which included AMs containing more episodic details than semantic details (i.e., > 50% episodic richness). Thus, this additional analysis included the majority of AMs recalled in young adults (81%), but only a subset of the memories recalled by older adults (55%). The fMRI analysis revealed that when both groups recalled higher episodically rich AMs

there were fewer age-related differences during elaboration. Along with the regions previously showing age-invariant activity across all trials during elaboration (see **Table 10**), episodically rich AMs were associated with additional age-invariant effects in the right hippocampus and left VLPFC. These results suggest that the aforementioned age-related reductions in the right hippocampus and left VLPFC were related to older adults' overall difficulty in recovering highly episodically rich AMs during elaboration. A few regions continued to show age-related reductions during the elaboration of episodically rich AMs, including the left posterior cingulate, left DLPFC, and dorsomedial PFC (see **Table 11**). Additional age-related differences were also observed in the left anterior PFC (Brodmann's Area 9; Talaraich coordinates: X = -15, Y = 53, Z = 32; T = 3.31, 11 voxels). In sum, these findings show that older adults recruited the right hippocampus and left VLPFC to a greater extent, which was equivalent to activation levels in young adults, on those trials in which they recalled more episodically rich AMs.

Second, we examined whether strategic retrieval processes could account for group differences in the recruitment of the VLPFC during elaboration of AMs, by including fluency as a covariate. The results of the covariate analysis revealed that both categorical and phonological fluency accounted for the age effect in the recruitment of the VLPFC. In contrast, the fluency measures did not account for the age-related effects observed in the DLPFC, hippocampus or the posterior cingulate. These results show that recruitment of the VLPFC during the elaboration of AMs is sensitive to individual

differences in fluency, suggesting that the age-related reduction observed in this region is linked to strategic retrieval processes. In sum, these results support the interpretation that older adults rely less on strategic retrieval processes, as reflected by age-related reductions in the VLPFC during elaboration, which potentially contribute to the reduced episodic richness of AM.

Hippocampal-PFC Coupling. Given that our first fMRI analysis yielded significant age-related reductions in two brain regions that interact during episodic retrieval, the hippocampus and VLPFC, our second fMRI analyses investigated the effect of aging on the coupling between these regions using DCM in order to distinguish potential differences in bottom-up vs. top-down influence and the influence of episodic richness. Bayesian Model Selection revealed that the optimal model within each age group was identical. A DCM (see **Figure 14** and **Table 12**) with a driving input on the VLPFC, reciprocal intrinsic connections between the hippocampus and the VLPFC, and modulation of episodic richness on the top-down influence of the VLPFC on the hippocampus, was optimal in both young adults (exceedance probability = 0.63) and older adults (exceedance probability = 0.15). These results show that in both age-groups it is the top-down rather than bottom-up influence of the PFC on the hippocampus that modulates episodic richness of AMs, which suggests that strategic controlled retrieval processes potentially underlie the ability to recall additional details during elaboration. Although the identical model was observed in both age groups, there were age-related

differences in the strength of the parameters. Further analysis, revealed that there was a significant age-related reduction in the modulation of episodic richness by top-down influence of the VLPFC on hippocampus, $t(26) = 2.28, p < .05$. Additionally, there was also age-related reductions in the driving input on the VLPFC, $t(26) = 2.28, p < .05$. These results support the hypothesis that the age-related reduction in episodic richness is associated with a decrease in the top-down modulation of the hippocampus by the VLPFC.

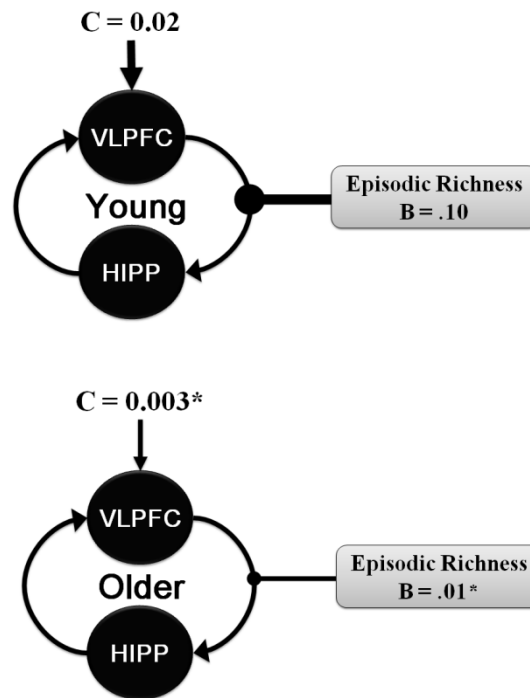


Figure 14: Age-Related Differences in the Dynamic Causal Model

Table 12: Additional Parameter Values in the Dynamic Causal Model

Connection	Young	Older	t (26)
HIPP to VLPFC	0.047	0.018	-1.67
VLPFC to HIPP	0.089	0.043	-1.77

HIPP = Hippocampus

VLPFC = Ventrolateral Prefrontal Cortex

Discussion

The results of the present study suggest that the age-related attenuation in the episodic richness of AMs is associated with difficulty in the strategic retrieval processes underlying recovery of information during elaboration. There were two main findings supporting this idea. First, age-related differences in functional activations were greater during elaboration than during search in the hippocampus and VLPFC, and these differences were attenuated for highly episodically rich AMs. Second, there was an age-related reduction in the amount of top-down modulation of the PFC on the hippocampus by episodic richness during elaboration. These findings are discussed in separate sections below.

Age-Related Effects During Autobiographical Memory Retrieval

To our knowledge this is the first fMRI study to examine age-invariant and age-related differences in search and elaboration processes underlying AM retrieval. We found that aging had less of an impact on functional activations during the initial search process, but a greater impact on later elaboration processes. The results of the present

study are consistent with evidence from event-related potential studies showing that aging effects later retrieval processes in EM (Trott, Friedman, Ritter, & Fabiani, 1997; Trott, Friedman, Ritter, Fabiani, & Snodgrass, 1999; Wegesin, Friedman, Varughese, & Stern, 2002; although see Li, Morcom, & Rugg, 2004; Mark & Rugg, 1998), and to functional neuroimaging studies showing age-invariant effects in the retrieval network (Duverne, Habibi, & Rugg, 2008; Maguire & Frith, 2003a; Morcom, Li, & Rugg, 2007), but they extend these findings by linking the age-related effects to both spatial and temporal components of retrieval.

The current results show preservation in older adults in the recruitment of search processes relying on strategic retrieval guided by semantic information (i.e., VLPFC and temporopolar cortices) and to the access of the memory trace (i.e., hippocampus and retrosplenial cortices; Botzung, et al., 2008; Conway, et al., 2001; Daselaar, et al., 2008). A subset of the age-invariant regions observed during search continued to remain online during elaboration, in the left hippocampus, left parahippocampal cortex and left retrosplenial cortex. Conjointly, these regions have been linked to scene construction, the ability to generate a complex and coherent scene or event, which is commonly engaged across a number of tasks including AM (Hassabis, et al., 2007; Hassabis & Maguire, 2007). Thus, both age groups are potentially able to envision the context of the AM.

Older adults, however, had deficits in the recruitment of additional regions that support the rich elaboration of the constructed scene. First, although age-invariant activity was observed in the left hippocampus, older adults showed a reduction in the additional recruitment of the right hippocampus. In contrast, Maguire and Frith (2003a) found that aging led to a more bilateral pattern of hippocampal activity on an AM recognition task. The segregation of retrieval by search and elaboration processes in the current study, as well as other methodological differences, could potentially account for the observed differences from previous studies. Moreover, several studies have found bilateral recruitment of the hippocampus during AM retrieval in young adults (e.g., Addis, Moscovitch, et al., 2004; Piefke, et al., 2003; Piolino, et al., 2004), and previous functional neuroimaging studies of AM have linked the recruitment of bilateral or right hippocampus to greater episodic richness (e.g., Piolino et al., 2008; Viard, et al., 2007; also see Graham, et al., 2003; Svoboda, et al., 2006). Consistent with these ideas, the age-related reduction in the right hippocampus was also coupled with reductions in posterior regions that support the rich elaboration of AMs, such as the posterior cingulate (Addis, Moscovitch, et al., 2004; Levine, et al., 2004; also see Levine, Svoboda, Turner, Mandic, & Mackey, In Press) and the VPC (e.g., Berryhill, et al., 2007; Levine, et al., 2004). Further, we found age-invariant activity in the right hippocampus when elaboration was restricted to highly episodically rich AMs, suggesting that this region is sensitive to variability in episodic richness.

Second, there was an age-related reduction in the sustained response in the left VLPFC, as well as in the additional recruitment of left DLPFC during elaboration. Lateral ventral and dorsal PFC regions work conjointly during AM retrieval (Cabeza & St. Jacques, 2007) through the controlled recovery and manipulation of information, respectively (Petrides, 2005; also see Miller & Cohen, 2001). Supporting these roles, in the present study the recovery of highly episodic rich AMs resulted in age-invariant VLPFC recruitment, whereas DLPFC continued to show an age-related reduction. Further, individual differences in strategic retrieval ability accounted for the age-related effects in the VLPFC, but not in the DLPFC. These results suggest that the VLPFC potentially contributes to age-related reductions in episodic richness via its role in strategic retrieval processing, but that older adults might have particular difficulty on the controlled manipulation of recovered information during AM retrieval.

In sum, the results of the present study underscore the importance of decomposing the time course of retrieval processes when examining age-related effects by showing a differential pattern of functional activation across search versus elaboration processes in AM retrieval, particularly in the recruitment of the hippocampus and the PFC.

Age-Related Effects on Top-Down Modulation

The findings from the effective connectivity analysis suggest that, despite a similar pattern of coupling between the hippocampus and VLPFC during elaboration,

there was an age-related reduction in top-down modulation associated with episodic richness. The PFC is associated with strategic, controlled processes involving the recovery of information (Petrides, 2005; also see Miller & Cohen, 2001). Here we show that individual differences in strategic retrieval ability as measured by categorical and phonological fluency accounted for age-related effects in the VLPFC. There are several lines of evidence suggesting that aging impacts the strategic, controlled processes mediated by the frontal lobes, possibly as the result of an age-related deficit in dopamine function (for a review see West, 1996). According to the resources deficit theory of cognitive aging (Craik & Byrd, 1982) older adults are impaired on tasks that require self-initiated behavior such that providing environmental support (i.e., retrieval cues) can attenuate age-deficits. Consistent with this latter idea, providing additional retrieval cues during AM recall increases episodic richness (e.g., Levine, et al., 2002). The present findings emphasize that age-related attenuations during elaboration are the result of the interaction between the PFC and hippocampus (cf. West, 1996). The hippocampus and PFC work together during memory retrieval (Moscovitch, 1992), and interactions between these regions are particularly important during more complex recall (for a review see Simons & Spiers, 2003). Further, lesion evidence shows that disconnecting these regions results in AM retrieval deficits (Levine et al., 1998).

The age-related reduction in the top-down modulation of the PFC on the hippocampus for episodically rich AMs is potentially one factor leading to behavioral

differences during AM recall (Levine, et al., 2002; Piolino, et al., 2002; Piolino, et al., 2006; St. Jacques & Levine, 2007). Previous studies have associated the age-related reduction in the episodic richness of AMs with a more general aging phenomenon that tends to impair memory for specific details but not memory for global information and which has been associated with deficits in frontal function (for a review see Craik & Grady, 2002). However, to our knowledge, this is the first study to link the age-related reduction in episodic richness to a decline in the top-down influence of the PFC. Although older adults may recall less episodic information in their AMs, it is important to note that less reliance on specific details may infuse older adults' AMs with a richer narrative that imparts more wisdom or serves a different purpose (Bluck, 2003; James, Burke, Austin, & Hulme, 1998; Labouvie-Vief, 1982) when compared to the AMs of young adults. In sum, the findings demonstrate that elaboration involves the interaction between the recovery of details mediated by the hippocampus and controlled strategic retrieval processes directed by the PFC, and they suggest that older adults recall less episodically rich AM because of a reduction in top-down modulation.

Conclusions

In the present fMRI study, we examined age-related differences in episodic richness on the spatiotemporal dynamics of AM retrieval. Age-related reductions were primarily observed during the later elaboration processes of AM retrieval, with older adults showing a reduction in the recruitment of the hippocampus and PFC. Linking

these results to the behavioral reductions in episodic richness in older adults, we found that functional activity in these regions was attenuated for AMs that were more episodically detailed. Further, we found an age-related reduction in the top-down modulation of the PFC on the hippocampus by episodic richness, possibly reflecting fewer controlled processes operating on the recovery of information in the hippocampus. In sum, the present findings suggest that the age-related deficit in the episodic richness of AMs is associated with an overall reduction in the rich elaboration of these memories, where older adults show less top-down modulation of the PFC on the hippocampus. These findings advance our understanding concerning the age-related differences in neural basis of AM retrieval processes.

9. The AM Retrieval Network Revisited

Functional neuroimaging studies of AM can help to clarify the network of components that orchestrate the recovery and conscious experience of our personal past. The evidence reviewed here suggests that these studies lead to novel insights into the neural mechanisms of memory by allowing the investigation of complex construction processes, qualities of the subjective experience, and issues of remoteness and aging. I will summarize the main findings by considering how they refine the description of the AM retrieval network (see **Figure 3**).

Previous functional neuroimaging studies have emphasized that AM retrieval involves a left-lateralized network, especially regarding the role of left lateral PFC in controlled search and construction processes. However, these studies primarily focused on recollection of AMs, a retrieval process supported by left PFC regions. The results of Study 1 (see Chapter 6) demonstrated that the involvement of left PFC versus right PFC depends upon whether AM retrieval involves greater recollection or familiarity. The exact role of hemispheric asymmetries within the PFC is still unknown and may be due to multiple factors. The current findings suggest that one factor explaining the predominantly left-lateralized recruitment of lateral PFC within AM is the bias towards retrieval tasks that emphasize recollection processes. Future studies of AM retrieval that incorporate retrieval tasks involving familiarity may find greater recruitment of right lateral PFC.

The ability to re-experience the self in time is an integral feature of AM. Previous functional neuroimaging studies of AM have long associated the medial PFC with self-referential processes; however, few studies have directly manipulated this capacity within the same individuals. The results of Study 2 (see Chapter 7) showed that self-projection of self versus other differentially recruited ventral versus dorsal medial PFC subregions. Ventral medial PFC contributed to the ability to relive the personal past through its coactivation with the MTL network and associated memory processes, whereas, dorsal medial PFC supported the ability to understand another individual via controlled processes mediated by the frontoparietal network. In sum, these results suggest that particular subregions of the medial PFC may differentially contribute to separable processes that enable the rich sense of re-experience of the personal past.

Many functional neuroimaging studies of AM have investigated the impact of the remoteness on the neural correlates of retrieval. These studies are invaluable for understanding memory consolidation and storage processes, but they have focused almost exclusively on the role of the hippocampus and they do not consider the impact of the age of the person. Study 3 (see Chapter 8) showed that a similar underlying pattern of activity is observed in older adults during search and construction of AMs, but that activity is of less sustained during elaboration. In particular, age-related reductions associated with less episodically rich AMs were observed in the left VLPFC and the right hippocampus during elaboration, but not during construction. Further,

there was less top-down modulation of the PFC on the hippocampus contributing to episodically rich AMs in older adults. These results emphasize that understanding issues of remoteness and age in AM retrieval demands greater understanding of the temporal components of AM retrieval processes and a greater focus on the multiple regions involved.

The current findings also highlight the importance of using multiple techniques to elicit AMs within the scanning environment in order to answer multifaceted questions about AM retrieval. Prospective methods such as the photo-paradigm (Study 1) and novel camera technology (Study 2) enable control over the properties of memory retrieval and measures of accuracy. The main drawback with prospective methods is that typical paradigms may interfere with the nature encoding of memories. However, as was shown in Study 2, the use of novel technology (e.g., SenseCam/Vicon Revue) can be employed to prospectively collect highly effective cues to elicit AMs without altering the phenomenological experience of retrieval. In contrast to the prospective method, the generic cue method has the least experimental control. Although the generic cue method is frequently criticized for its lack of control it allows memory construction and elaboration processes to be investigated, which may be very important when understanding aging as demonstrated by Study 3.

Future Directions

Many questions remain regarding the neural mechanisms underlying the complex construction, subjective qualities, and remoteness in AM and how these can importantly contribute to our understanding of memory retrieval. First, the mechanisms underlying the complex construction of AMs are not well understood. Functional neuroimaging studies employing the generic cue method to elicit AMs during scanning provide a coarse temporal segregation between construction and elaboration processes (i.e., on the order of seconds), but a finer temporal analysis is needed. In particular, it is difficult to segregate the multiple components that potentially occur during memory construction, such as controlled search processes, selection among multiple events, and monitoring, which are components of retrieval that may occur on the order of milliseconds. Understanding these issues may require the combination of fMRI and EEG techniques to provide both spatial and temporal precision. Further, whether the complex retrieval processes engaged during voluntary AM retrieval are altered during involuntary AM retrieval is unknown.

Second, many subjective qualities of AM retrieval have yet to be explored. For example, functional neuroimaging evidence is missing regarding AMs that involve strong auditory, tactile, or taste sensations and whether memory for these types of sensorial experiences involves activity in corresponding sensory regions. Potential distinctions in the neural mechanisms underlying discrete emotional experiences of

AMs, such as anger, fear, happiness, etc, are largely unknown. Further, self-reference and its close relation to the ability to re-experience the self in time are critical and defining features of AM, yet very few functional neuroimaging studies have directly manipulated this capacity. Subjective qualities of memory experience during AM retrieval are often examined in isolation, but they frequently co-occur and are of correlated. Thus, future studies that employ sophisticated study design and analysis techniques are needed to determine the unique contributions of these subjective qualities of AM retrieval.

Third, studies examining the impact of both age and remoteness on the neural mechanisms of AM retrieval are lacking. In particular, future studies should consider the impact of age and memory remoteness on controlled processes mediated by the PFC, and how this top-down modulation changes according to individual variability (i.e., high versus low functioning individuals), the type of AM retrieved (i.e., episodic vs. semantic), the remoteness of the AM, and how retrieval support may boost top-down modulatory effects during elaboration. Episodic memory shows the earliest and steepest decline in aging. However, older adults' memory complaints are related to difficulties in recalling personal real-world events rather than difficulty with remembering lists of items encoded in the laboratory. An important avenue for future research will be to characterize the functional changes underlying age-related difficulties in retrieval of the

personal past in order to better understand the locus of these changes and potentially provide clinical interventions for pathological aging.

Conclusions

Current studies have established that functional neuroimaging can answer important questions regarding the complex construction, subjective qualities, and remoteness of AM. The challenge for future studies will be to develop new techniques to examine AMs in the scanner that will ask multifaceted questions to consider where these components interact. Ultimately, the goal of all memory research is to understand how memory operates in the real-world. Although the focus here has been on the contribution of functional neuroimaging studies of AM and its advantages compared to LM, the field of cognitive neuroscience of memory would benefit from greater communication between what are often treated as two very separate domains.

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Aging & Emotion in Autobiographical Memory

June 2003

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| 2008-2009 | Philip Jackson Baugh Fellowship, Duke University |
| 2008 | Preparing Future Faculty Fellow, Duke University |
| 2008 | Mathematics of Brain Imaging Award, Institute for Pure and Applied Mathematics, University of California in Los Angeles |
| 2008 | Center for Computational Biology Fellow, University of California in Los Angeles |
| 2007 | Advanced Neuroimaging Summer School Award, UCLA |
| 2007 | Leadership in an Aging Society Award, Duke University |
| 2006-2010 | Graduate School Conference Award |

- 2006 National Sciences and Research Council Post Graduate Scholarship, Canada (declined)
- 2005 American Psychological Society Travel Assistance Award
- 2004 Ontario Graduate Scholar, Canada (declined)

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Publications

- St. Jacques, PL, Lowder, MW, Cabeza, R.** Temporal vs. spatial source memory for autobiographical events: An fMRI study using a novel photo paradigm. Manuscript in Preparation.
- St. Jacques, PL, Conway, MA, Lowder, MW, Cabeza, R.** Watching your life unfold: An fMRI study using a novel photo paradigm to elicit the personal past. Manuscript in Preparation.
- St. Jacques, PL, Botzung, A, Miles, A, Rubin, DC,** Functional neuroimaging of autobiographical memory in post-traumatic stress disorder. Submitted.
- St. Jacques, PL, Kragel, PA, Rubin, DC.** (2010). Dynamic neural networks supporting memory retrieval. Submitted.
- St. Jacques, PL, Rubin, DC, Kragel, PA, Cabeza, R.** (2010). Age-related effects on the neural correlates of autobiographical memory retrieval. Submitted.
- Janssen, SMJ, **St. Jacques, PL** Rubin, DC. (2010). Temporal Distribution of Recollective Memory. *Memory & Cognition*, Under Revision.
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