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Neural Mechanisms of Real-World Episodic Memory Retrieval:  
Investigations using functional neuroimaging, brain stimulation, and wearable camera  
technology

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

by

Tiffany Chow

2017



## ABSTRACT OF THE DISSERTATION

Neural Mechanisms of Real-World Episodic Memory Retrieval:  
Investigations using functional neuroimaging, brain stimulation, and wearable camera  
technology

by

Tiffany Chow

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2017

Professor Jesse A. Rissman, Chair

Advancements in neuroimaging and brain stimulation techniques have provided unique opportunities to further understand the neural mechanisms of episodic memory retrieval. The act of retrieving information about a past experience is known to depend on the coordinated engagement of a broad networks of regions, including frontal lobe regions such as the rostralateral prefrontal cortex (RLPFC) and medial temporal lobe areas such as the hippocampus (Cabeza & St. Jacques, 2007; Maguire & Mummery, 1999; Reynolds, McDermott, & Braver, 2006). Although much of the field's extant knowledge has been derived from studies assessing memories formed in laboratory-based settings, the incorporation of life-logging technology – such as wearable digital camera devices – can assist with the nonintrusive photographic capture of everyday life events, which can later be employed as mnemonic probes. The experiments in

this dissertation aim to assess the neural mechanisms mediating real-world episodic retrieval by employing naturalistic stimuli to elicit memories for personal experiences.

This dissertation begins with a broad overview of the behavioral and neural findings derived from memory experiments incorporating wearable camera technology, followed by novel examinations of the neural correlates underlying real-world events through the use of functional magnetic resonance imaging (fMRI) and high-definition transcranial direct current stimulation (HD-tDCS). Chapter 2 featured an in-depth review of prior applications of wearable digital cameras to behavioral and neuroimaging assessments of autobiographical memory retrieval as well as how their contributions expand knowledge of such processes to naturalistic settings. Chapters 3-5 report the results of a series of fMRI investigations examining recall of events from the real world and how they may differ across mnemonic features related to the original experiential source of the event, the recognition of the event based on previously encountering photographs of those experiences, and the temporal order of the event details. Chapter 3 found that dissociable patterns of neural activation were evoked in brain networks previously implicated in either autobiographical or laboratory-based memory retrieval (McDermott, Szpunar, & Christ, 2009), such that the autobiographical memory network was preferentially sensitive to whether or not the depicted events had been personally experienced, while the laboratory-based network was preferentially sensitive to whether or not photographs of the depicted events had been previously encountered. These findings suggest that these networks contribute to different retrieval processes and showcase how memories for first-hand experiences have distinctive neural signatures from memories for second-hand event knowledge. Chapter 4 focused on the hippocampus, with an emphasis on the division of labor along the hippocampal long-axis. The findings revealed that the posterior hippocampus was disproportionately sensitive

to the source of the photographs, whereas the anterior hippocampus reacted more strongly to whether the photographs themselves had been previously seen, as well as whether their temporal order was intact. Chapter 5 assessed hemispheric differences in RLPFC responsivity to violations of temporal order during retrieval. The left RLPFC exhibited greater activation for temporal order violations only when events were novel, while the right RLPFC demonstrated greater activation for temporal order violations only when events had been previously encountered as photographs. These results suggest that the RLPFC is capable of differentially determining whether events are consistent with either prior schemas or memories. To further examine the left RLPFC and evaluate its causal involvement in mnemonic processes, Chapter 6 applied HD-tDCS methodology to this region in order to determine its impact on event recognition and temporal order processing. The targeted application of anodal current to the left RLPFC produced an increased likelihood of false recognition and – relative to sham stimulation – led to a shift in response bias, which may indicate the RLPFC’s role in memory monitoring. Together, these findings from fMRI and HD-tDCS experiments help clarify the contributions and characteristics of the neural substrate supporting episodic memory retrieval, particularly with regards to how these processes may occur in the real world.

The dissertation of Tiffany Chow is approved.

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2017

## **DEDICATION**

To my family, whose encouragement fostered a love for learning and scientific inquiry.

To my Mother, who provided me with the motivation and drive.

To my Father, who gave me endless support and guidance.



## TABLE OF CONTENTS

<b>LIST OF FIGURES</b>	<b>ix</b>
<b>LIST OF TABLES</b>	<b>x</b>
<b>ACKNOWLEDGMENTS</b>	<b>xi</b>
<b>VITA</b>	<b>xiii</b>
<b>CHAPTER ONE</b>	
Background	<b>1</b>
<b>CHAPTER TWO</b>	
Neurocognitive mechanisms of real-world autobiographical memory retrieval: Insights from studies using wearable camera technology	<b>4</b>
Abstract	5
Introduction	6
Wearable digital cameras	8
Research in clinical contexts	10
Behavioral research in nonclinical populations	17
Neuroimaging research in nonclinical populations	19
Discussion	29
<b>CHAPTER THREE</b>	
Multi-voxel pattern classification differentiates personally experienced event memories from secondhand event knowledge	<b>43</b>
Abstract	44
Introduction	46
Methods	52
Results	63
Discussion	68
<b>CHAPTER FOUR</b>	
Representation of distinct dimensions of event retrieval along the hippocampal long axis	<b>79</b>
Abstract	80
Introduction	81
Methods	87
Results	98
Discussion	104
<b>CHAPTER FIVE</b>	
Differential responsivity of the left and right rostrolateral prefrontal cortex to temporal order violations during the retrieval of real-world memories	<b>114</b>
Abstract	115
Introduction	117
Methods	120
Results	128
Discussion	133

## **CHAPTER SIX**

High-definition transcranial direct current stimulation of the left rostrolateral prefrontal cortex induces shifts in recognition bias through increased false recognition **141**

Abstract 142

Introduction 143

Methods 147

Results 153

Discussion 160

## **CHAPTER SEVEN**

Conclusion **169**

**REFERENCES 178**

## LIST OF FIGURES

<b>Figure 2.1</b>	<b>34</b>
<b>Figure 2.2</b>	<b>35</b>
<b>Figure 2.3</b>	<b>36</b>
<b>Figure 2.4</b>	<b>38</b>
<b>Figure 2.5</b>	<b>39</b>
<b>Figure 3.1</b>	<b>73</b>
<b>Figure 3.2</b>	<b>74</b>
<b>Figure 3.3</b>	<b>74</b>
<b>Figure 3.4</b>	<b>75</b>
<b>Figure 3.5</b>	<b>76</b>
<b>Figure 3.6</b>	<b>77</b>
<b>Figure 4.1</b>	<b>109</b>
<b>Figure 4.2</b>	<b>110</b>
<b>Figure 4.3</b>	<b>111</b>
<b>Figure 4.4</b>	<b>112</b>
<b>Figure 5.1</b>	<b>137</b>
<b>Figure 5.2</b>	<b>138</b>
<b>Figure 5.3</b>	<b>139</b>
<b>Figure 5.4</b>	<b>140</b>
<b>Figure 6.1</b>	<b>164</b>
<b>Figure 6.2</b>	<b>165</b>
<b>Figure 6.3</b>	<b>166</b>
<b>Figure 6.4</b>	<b>167</b>
<b>Figure 6.5</b>	<b>168</b>

## LIST OF TABLES

**Table 2.1**

**41**

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- Rissman, J., Chow, T.E., Reggente, N., & Wagner, A.D. (2016). Decoding fMRI signatures of real-world autobiographical memory retrieval. *Journal of Cognitive Neuroscience*, 28(4), 604-620.
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- Chow, T.E., & Rissman, J. (2017). Neurocognitive mechanisms of real-world autobiographical memory retrieval: Insights from studies using wearable camera technology. *Annals of the New York Academy of Sciences*, 1396(1), 202-221.

### Presentations (Selected)

- Rissman, J., Chow, T., Hardekopf, K., & Wagner, A.D. (2011). Decoding real-world autobiographical retrieval experiences with fMRI multi-voxel pattern analysis. Presented at the *Society for Neuroscience Annual Meeting*, Washington, DC.
- Uncapher, M.R., Chow, T., Rissman, J., Eberhardt, J., & Wagner, A.D. (2012). Strategic influences on memory expression: Effects of countermeasures and memory strength on the neural decoding of past experience. Presented at the *Society for Neuroscience Annual Meeting*, New Orleans, LA.
- Chow, T.E., Westphal, A.J., Storozuk, L.A., Medina, B.V., Ngoy, C.D., & Rissman, J. (2014). Multi-voxel pattern classification differentiates personally experienced event memories from second-hand event knowledge. Presented at the *Society for Neuroscience Annual Meeting*, Washington, DC.

- Westphal, A.J., Ngoy, C.D., Chow, T.E., Storozuk, L.A., Liao, V., Peters, M.A.K., Wu, A., Shams, L., & Rissman, J. (2016). Transcranial direct current stimulation to left rostrolateral prefrontal cortex results in divergent effects on memory and reasoning. Presented at the *International Conference on Memory*, Hungary.
- Chow, T.E., Westphal, A.J., Ngoy, C.D., & Rissman, J. (2016). Representation of distinct dimensions of episodic retrieval along the hippocampal long-axis. Presented at the *International Conference on Memory*, Hungary.
- Chow, T.E., Westphal, A.J., & Rissman, J. (2016). Assessing fMRI-based memory detection: Can personally experienced event memories be differentiated from second-hand event knowledge? Presented at the *International Neuroethics Society Annual Meeting*, San Diego, CA.  
[“Top Abstract” award, published in *The American Journal of Bioethics Neuroscience*.]
- Chow, T.E., Westphal, A.J., & Rissman, J. (2016). Differential responsivity of left and right rostrolateral prefrontal cortex to temporal order violations during the retrieval of real world memories. Presented at the *Society for Neuroscience Annual Meeting*, San Diego, CA.

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## CHAPTER ONE

### Background

Advancements in neuroscientific techniques have provided a unique opportunity to further understand the neural mechanisms of learning and memory. In particular, these approaches have been instrumental in clarifying the neural correlates associated with episodic memory, which has been described as a form of long-term memory for events and experiences that possess specific spatiotemporal contexts (Tulving, 1972). Critically, a defining feature of episodic memory is autonoetic consciousness, where individuals are consciously aware of previous recollection and learning episodes (Tulving, 1989). These characteristics differentiate episodic memory from other types of memory.

Autobiographical memory is closely related to episodic memory and involves the recollection of personally experienced events and episodes (Cabeza & St. Jacques, 2007; Gilboa, 2004). Although autobiographical memory and episodic memory are associated, the exact relationship between the mnemonic processes is still unclear. While some researchers propose that autobiographical memory is synonymous with episodic memory, others suggest that autobiographical memory is a specific subsystem of episodic memory processes (Nyberg et al., 1996; Piefke, Weiss, Zilles, Markowitsch, & Fink, 2003). However, both perspectives concur that these mnemonic processes include the conscious retrieval of events and experiences along with their associated contextual details (Burianova & Grady, 2007). Consequently, autobiographical and episodic memories should typically be mediated by similar neural mechanisms and recruit activation in comparable neural networks (Burianova & Grady, 2007).

Both episodic and autobiographical memory retrieval recruit a distributed network of brain regions (Cabeza & Nyberg, 2000; Cabeza & St. Jacques, 2007; Svoboda, McKinnon, & Levine, 2006). Specifically, brain regions in the default mode network mediate long-term episodic memory retrieval, and thus, also support autobiographical recall (Buckner, Andrews-Hanna, & Schacter, 2008). The default mode network – which includes areas such as lateral and midline parietal areas, midline frontal structures, and lateral temporal lobes – supports not only memory retrieval, but also other internally oriented tasks such as prospection and theory of mind (Buckner et al., 2008; Spreng & Grady, 2010). Although several cognitive operations also engage a subset of these regions, the pattern of activation in these areas during episodic memory retrieval differs from that of other internally-oriented tasks and even other types of memory (Burianova & Grady, 2007; Cabeza, Dolcos, Graham, & Nyberg, 2002; Spreng & Grady, 2010).

However, episodic memory research presents major methodological challenges, and the ecological validity of existing paradigms has been a concern in the field for numerous years (Finley, Brewer, & Benjamin, 2011). This is particularly true with regards to studies of autobiographical recall (Finley et al., 2011). The vast majority of extant neuroscientific experiments examine laboratory-based experiences, rather than those derived from the real world. Laboratory-based experimental paradigms are constrained in several ways, which may not accurately reflect the phenomenological properties of autobiographical memories (Cabeza & St. Jacques, 2007; McDermott et al., 2009). The utilization of such paradigms to assess memory retrieval may result in the engagement of brain regions that diverge from the episodic memory literature, particularly for autobiographical recall: previous research has indicated several differences between the areas recruited during the retrieval of autobiographical memories and laboratory-based memories (Cabeza & St. Jacques, 2007; Gilboa, 2004; McDermott et al., 2009).

Some studies have even discovered minimal overlap in regions associated with these memories (McDermott et al., 2009). As such, it is imperative for studies of autobiographical memory to reflect the retrieval of real-world events and not simply those generated within a laboratory environment. Therefore, to better understand the neural correlates underlying episodic memory retrieval as it occurs in the real world, more ecologically valid paradigms must be used to assess such processes.

Wearable camera technology provides an opportunity to incorporate naturalistic stimuli derived from the real world into episodic and autobiographical memory research, which may result in greater ecology validity (St. Jacques, Conway, Lowder, & Cabeza, 2011). This novel technology provides several potential advantages, as these camera devices automatically capture hundreds of photographs each day and allow unobtrusive, objective assessment of naturally-encoded memories (Hodges, Berry, & Wood, 2011; Hodges et al., 2006). Attempts to better capture participants' real-world experiences have prompted the inclusion of these wearable camera technologies in experiments of episodic memory, such as their use in generating photographs for utilization as retrieval cues. The application of these methods to investigate episodic memory retrieval has provided an innovative means to explore the mnemonic processes underlying real-world events and experiences. The following studies of episodic memory retrieval are motivated by developments in the literature as well as the extension of this research to the real world.

## CHAPTER TWO

### Neurocognitive mechanisms of real-world autobiographical memory retrieval:

#### Insights from studies using wearable camera technology<sup>1</sup>

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<sup>1</sup> This section was previously published as: Chow, T.E., & Rissman, J. (2017). Neurocognitive mechanisms of real-world autobiographical memory retrieval: Insights from studies using wearable camera technology. *Annals of the New York Academy of Sciences*, 1396(1), 202-221.

## **ABSTRACT**

In recent years, the investigation into the cognitive and neural mechanisms of autobiographical memory has been aided by the use of experimental paradigms incorporating wearable camera technology. By effortlessly capturing first-person images of one's life events, these cameras provide a rich set of naturalistic stimuli that can later be used to trigger the recall of specific episodes. Here, we chronicle the development and progression of such studies in behavioral and neuroimaging examinations of both clinical and non-clinical adult populations. Experiments examining the effects of periodic review of first-person images of life events have documented enhancements of autobiographical memory retrieval. Such benefits are most pronounced in patients with memory impairments, but there is mounting evidence that cognitively healthy individuals may benefit as well. Findings from functional magnetic resonance imaging experiments using wearable camera stimuli as retrieval probes have produced results that, although largely consistent with the broader episodic memory literature, have significantly extended prior findings concerning the underlying mnemonic processes and the neural representation of autobiographical information. Taken together, wearable camera technology provides a unique opportunity for studies of autobiographical memory to more closely approximate real-world conditions, thus offering enhanced ecological validity and opening up new avenues for experimental work.

## INTRODUCTION

The ability to recollect detailed information about past events is a hallmark of episodic memory (Tulving, 2002). The vast majority of behavioral and neuroimaging studies of episodic retrieval have used laboratory-encoded stimuli, such as words or pictures, as memory probes. While such stimuli provide researchers with tight experimental control over the perceptual qualities, exposure duration, and retention interval of the events being probed, laboratory stimuli lack the richness of most real-world experiences. When events are encoded in a naturalistic setting, it is more likely that the details will have personal relevance, including information about the visuospatial context (event location), temporal context (timing of the event along with its relation to other life occurrences), cognitive context (what one was thinking about and/or trying to accomplish at the time), social context (who one was with), and emotional context (how one was feeling). Thus, it is perhaps unsurprising that neuroimaging studies comparing the profile of brain activity during the retrieval of stimuli learned in a laboratory context to that associated with the retrieval of autobiographical memories (i.e., memories for one's own life events) typically find marked differences. For instance, autobiographical memory retrieval evokes much greater activation of default mode network regions implicated in introspective cognition and self-referential processing – such as the medial prefrontal cortex (mPFC) – as well as medial temporal lobe (MTL) regions associated with recollection of visuospatial contextual details, such as the hippocampus and parahippocampal cortex (Cabeza et al., 2004; Chen, Gilmore, Nelson, & McDermott, 2017; Kim, 2012). Indeed, a meta-analysis of functional magnetic resonance imaging (fMRI) studies of episodic retrieval revealed only limited anatomical overlap in the neural correlates associated with the retrieval of laboratory-encoded and autobiographical memories (McDermott et al., 2009). Moreover, performance on standard laboratory-based

memory tasks can be largely unrelated to one's autobiographical retrieval abilities, as demonstrated by individuals with either "highly superior autobiographical memory" or "severely deficient autobiographical memory" (LePort et al., 2012; LePort, Stark, McGaugh, & Stark, 2017; Palombo, Alain, Söderlund, Khuu, & Levine, 2015; Patihis et al., 2013). Dissociations like these have led some to propose that retrieving autobiographical event knowledge is fundamentally different from other forms of episodic retrieval (Chen et al., 2017; Roediger & McDermott, 2013).

Efforts to understand the neural mechanisms of real-world autobiographical memory retrieval have utilized a variety of experimental techniques to evoke recall. These include prospective methods, which document life events as they occur and thus allow for increased experimental control (Cabeza & St. Jacques, 2007). Such studies have benefited from the use of naturalistic stimuli, particularly photographs, to probe participants' memories (Cabeza et al., 2004; St. Jacques, Rubin, LaBar, & Cabeza, 2008). While photographs can serve as effective retrieval cues that allow individuals to recollect experiences, the use of handheld cameras in autobiographical memory retrieval research presents potential methodological concerns as well. This is primarily due to participant involvement in the act of documenting personal events, which may result in modifications or biases in the resultant memories (Henkel, 2014). This same limitation applies to studies in which written diary entries (Barclay & Wellman, 1986; Burt, Kemp, & Conway, 2003) or voice recordings (Levine et al., 2004; Svoboda & Levine, 2009) are used to log daily experiences. However, recent technological advancements have facilitated the development of camera-based memory paradigms that avoid the need for participants' explicit input. Namely, studies have begun to incorporate the use of wearable digital camera devices to automatically capture images of the wearer's life events, which can later be used as probes to

assess behavioral and neural processes related to the retrieval of these real-world autobiographical memories. This novel, nonintrusive approach provides objective measures of autobiographical details and occurrences while increasing the ecological validity of experimental tasks.

The goal of this review is to summarize and evaluate the growing set of behavioral and fMRI studies published in peer-reviewed journals that have incorporated wearable cameras as a tool to assess memories encoded in naturalistic contexts. This includes detailing how such camera devices have been utilized in experimental paradigms on clinical and nonclinical adult populations, with an emphasis on what this work has revealed about the mechanisms of autobiographical memory retrieval.

## **WEARABLE DIGITAL CAMERAS**

The first notable wearable camera device to be adopted by memory researchers was the SenseCam from Microsoft Research Cambridge (<http://research.microsoft.com/en-us/um/cambridge/projects/sensecam>), developed in 2003 as a tool for keeping a visual record of one's life experiences without the need for user intervention (Hodges et al., 2006). The SenseCam is most commonly worn on a lanyard around the neck and automatically takes relatively low-resolution (0.3 megapixel), wide-angle photographs from the wearer's perspective every 30 seconds (although the user can configure this interval to be shorter or longer). Moreover, the camera will capture additional photographs when its electronic sensors detect salient variations in the wearer's external environment, including changes in ambient temperature, light intensity and color, infrared (to detect body heat), and acceleration. The SenseCam was designed to operate for long periods of time without recharging or uploading



photographs to the computer for review and storage. These characteristics allow the SenseCam to unobtrusively capture a large number of time-stamped images of its wearer's life events, providing a wealth of content that researchers can use in autobiographical memory experiments.

A commercial version of the SenseCam, marketed as the Vicon Revue<sup>®</sup>, became available in 2010 due to increasing public interest in life-logging devices (Bell & Gemmell, 2009), and the technology was later licensed to OMG Life, who released a higher-resolution and global positioning system (GPS)-enabled wearable camera product in 2012 called the Autographer<sup>®</sup> (**Figure 2.1**). While memory researchers have benefitted from these newer iterations of the original SenseCam (Chow et al., 2014; Rissman, Chow, Reggente, & Wagner, 2016; Svanberg & Evans, 2014), these products have struggled to achieve commercial success, and, as of 2016, all manufacturing and sales operations have ceased. Given recent technological advances, the market for life-logging devices has since shifted towards wearable video cameras, such as the GoPro HERO<sup>®</sup>, Narrative Clip<sup>®</sup>, MeCam HD<sup>®</sup>, iON SnapCam<sup>®</sup>, and Snapchat Spectacles<sup>®</sup>. To our knowledge, no scientific studies of human memory have yet incorporated these latest video-enabled devices, but we anticipate that they will soon become a valuable research tool. Additionally, several memory studies have used necklace-mounted smartphones to document the lives of research participants (De Leo, Brivio, & Sautter, 2011; Nielson, Smith, Sreekumar, Dennis, & Sederberg, 2015). Although the overall number of published memory studies utilizing wearable camera technology is still quite limited, the SenseCam and its immediate successor, the Vicon Revue, remain the most prevalent devices in the literature. The majority of studies have utilized this technology for behavioral experiments, particularly in clinical contexts, but an increasing number of fMRI studies examining real-world autobiographical event recall in healthy individuals have emerged in recent years.

## RESEARCH IN CLINICAL CONTEXTS

External memory aids can be effective tools for assisting individuals with memory impairments (Kapur, Glisky, & Wilson, 2004). Although patients with memory deficits can experience difficulties with the retrieval of personal memories, there are few external memory aids intended to bolster memory for such autobiographical events. Wearable digital camera devices offer a promising method to help compensate for mnemonic difficulties due to their automaticity in capturing photographs of one's day-to-day activities (Berry et al., 2007). A number of experiments, many conducted as case studies on individual patients, have evaluated the SenseCam's efficacy in supporting autobiographical memory retrieval.

The first such study to appear in a peer-reviewed journal was a behavioral experiment by Berry and colleagues (2007) on a 63-year-old patient with limbic encephalitis. This patient's bilateral hippocampal lesions, although relatively mild, resulted in difficulty retrieving both recent and remote autobiographical events. The researchers sought to evaluate whether the patient's ability to recall details about her life experiences could be improved by having her wear a SenseCam and periodically review the photographic record of any notable (i.e., non-routine) events. Of particular interest was whether SenseCam-based rehearsal could outperform a more traditional written diary-based approach; these two life-logging methods were employed sequentially, each for at least 1 month. Throughout the study, the patient's husband periodically tested her ability to recall the details of recent life events, with each recall test followed by an opportunity to review the SenseCam photographs or diary entries that recorded these events. Although these two forms of life-logging are impossible to equate on all attributes, an effort was made to match the review procedure and manner of testing. Relative to the diary entries,

rehearsal of SenseCam photographs was associated with substantial improvements in the patient's ability to recall the recorded events, even over long durations of time (e.g., 3 months) without the patient reviewing photographs between testing sessions. Moreover, her memory for events significantly increased with successive viewings of SenseCam photographs, but no such progressive benefit was observed in the diary condition. Despite a number of methodological shortcomings, this proof-of-concept case study provided support for the notion that the photographs captured by wearable cameras might be particularly efficacious as cues for triggering recall of autobiographical event details and bolstering the long-term retention of these memories. When fMRI data were later collected from this same patient (Berry et al., 2009), greater activity was observed across a network of brain regions typically associated with autobiographical retrieval when the patient reported recognition of photographs of an event that she had previously rehearsed using the SenseCam reviewing procedure, relative to recognition of SenseCam photographs for an event that had been exclusively rehearsed using the written diary procedure. Although such results cannot prove that SenseCam photographs helped this memory-impaired patient recollect her actual life events as originally experienced, rather than remembering the repeatedly viewed photographs of the events, these encouraging demonstrations of mnemonic benefits and heightened retrieval-related brain activity motivated a series of follow-up investigations.

Similarly encouraging results were obtained in another research team's case study of an amnesic patient with a large right-lateralized MTL lesion caused by herpes simplex viral encephalitis (Loveday & Conway, 2011). SenseCam cues were found to promote the recollection of significantly more contextual details for autobiographical events, relative to cues derived from written diary entries. Importantly, these memory improvements were observed even when the

SenseCam photographs were only used as cues for prompting episodic recall and not also used as opportunities for rehearsal. This suggests that the beneficial effects can extend beyond the strengthening of autobiographical memory traces through repeated study and retrieval practice. SenseCam-induced memory improvements were also apparent in a contemporaneous case study of a patient with mild cognitive impairment (Browne et al., 2011). While this study provided the patient with opportunities to review the photographs captured by her camera (or, in the control condition, to review diary entries written by her husband) during the first 2 weeks, the advantages of the SenseCam procedure were well apparent even after 6 months had elapsed since her last event review session, with a twofold increase in the number of event features recalled. Relatedly, a study of six older patients diagnosed with mild-to-moderate Alzheimer's disease found that review of events through SenseCam images, in comparison with a written diary, resulted in the majority of patients being able to recall more event details in both the short term (2 weeks after the event) and long term (1 and 3 months afterwards); **Figure 2.2** (Woodberry et al., 2015). It is notable that all of the aforementioned studies reported that SenseCam photographs led patients to recall event details that were not themselves apparent in the images. This suggests that these automatically captured first-person snapshots might be particularly effective at triggering mnemonic pattern-completion processes (Horner, Bisby, Bush, Lin, & Burgess, 2015; Liu, Gould, Coulson, Ward, & Howard, 2016), perhaps by harnessing the functional contribution of any intact portions of the patients' hippocampi to bring associated event details back to mind. Indeed, Loveday and Conway (2011) reported that their amnesic patient would occasionally experience a "Proustian moment" – a powerful flood of recollected details – when encountering her SenseCam photographs.

By virtue of enhancing patients' ability to remember events from their daily lives, use of the SenseCam may potentially bestow additional quality-of-life benefits. For example, rehearsal of events using SenseCam photographs resulted in diminished anxiety and stress as well as increased confidence for a patient with mild cognitive impairment (Browne et al., 2011). Relatedly, the SenseCam can be used within the context of psychotherapy for emotional events: for a patient with memory deficits and an anxiety disorder following acquired brain injury, the SenseCam was superior in evoking autobiographical memory retrieval, including the specific recall of anxiety-producing events and internal state information critical for cognitive-behavioral therapeutic intervention (Brindley, Bateman, & Gracey, 2011). SenseCam review also decreased apathy and increased sense of self in an older patient with moderate Alzheimer's disease (Crete-Nishihata et al., 2012; Massimi et al., 2008). Similarly, a patient with memory impairment stemming from Korsakoff's syndrome demonstrated better recall for events captured and reviewed with the SenseCam, along with improved subjective ratings of identity (Svanberg & Evans, 2014). In a larger study of 51 patients with mild Alzheimer's disease who were randomly assigned to one of three cognitive training programs, including a written diary and a SenseCam intervention, the SenseCam group showed significantly improved functional capacity and reduced depressive symptomology when measures were compared before the program and 1 week afterwards (Silva et al., 2017). However, these beneficial effects were transient and decreased when measured 6 months later, suggesting that continued SenseCam use might be necessary to maintain these subjective quality-of-life enhancements. In comparison with the SenseCam, anecdotal reports from patients and caregivers suggest that the written diary method was not as rewarding or effective and could even cause stress or tension with its use (Berry et al., 2007; Browne et al., 2011; Silva et al., 2017; Woodberry et al., 2015).

It is important to consider what qualities of the photographs captured by wearable cameras make them so effective at cuing episodic recall and strengthening the later accessibility of event details. One advantage of photographs over verbal diary entries is the fact that pictorial stimuli are known to be associated with better memory than verbal stimuli (Maisto & Queen, 1992; Snodgrass, Volvovitz, & Walfish, 1972). Even if the people, objects, or landmarks depicted within a given photograph are insufficient to elicit recall of the specific episode, the high degree of perceptual correspondence between a first-person perspective photograph and the visuospatial context in which the event was encoded may facilitate recollection. Ample research has shown that mental reinstatement of a context, typically through the use of visual imagery, aids in the recovery of information that had been acquired in that context (Smith, Handy, Angello, & Manzano, 2014; Smith & Vela, 2001). By providing potent visual cues to promote context visualization, photographs may accelerate the initial phase of the mental time travel process that is considered to be the hallmark of autobiographical recollection (Brewer, 1996; Tulving, 2002; Williams, Healy, & Ellis, 1999). Furthermore, camera-based studies typically present participants with multiple images depicting the temporal unfolding of an event, which provides additional contextual information and increases the likelihood of there being sufficient cues for retrieval (Barnard, Murphy, Carthery-Goulart, Ramponi, & Clare, 2011) while easing the demands on the executive system to engage in self-initiated episodic search processes. Indeed, it has been suggested that the viewing of brief, ordered sequences of photographs captured by wearable cameras may roughly approximate the time-compressed and fragmentary characteristics of actual endogenously retrieved autobiographical memories (Loveday & Conway, 2011). That said, a recent study that probed participants' memories with sequences of SenseCam photographs depicting events unfolding in either their original forward order or in a

random order found only a small advantage in recall for the forward-order condition (Mair, Poirier, & Conway, 2017). This could suggest that the overall amount of detail contained within the set of images is more consequential than the temporal dynamics conveyed in the sequence.

When SenseCam photographs are periodically shown to memory-impaired patients to help them remember recent events, the accessibility of these memory traces may be progressively strengthened through the well-documented memory enhancing effects of spaced retrieval practice (Roediger & Butler, 2011; Sekeres et al., 2016; Soderstrom, Kerr, & Bjork, 2016). It is also possible, if not likely, that the details of the event memories will be altered to some degree by each viewing of the photographs. Reminder cues are thought to return stored memories to a labile state in which they are briefly amenable to updating – and distortion – before reconsolidation mechanisms act to stabilize the trace (Schwabe, Nader, & Pruessner, 2014). Although some efforts have been made to understand the mechanisms and long-term consequences of memory reactivation and updating in wearable camera paradigms (St. Jacques, Montgomery, & Schacter, 2015; St. Jacques, Olm, & Schacter, 2013; St. Jacques & Schacter, 2013), more work will be needed to evaluate the contributions of retrieval practice and reconsolidation in memory-impaired patients using photographic review procedures as an external memory aid.

One significant limitation of studies comparing SenseCam-based review to diary-based review is the inherent difficulty of equating the event-logging and review procedures. Diary entries can differ wildly in composition, ranging from basic outlines or notes of important details (Berry et al., 2007; Woodberry et al., 2015) to more expansive entries recording event information in addition to associated emotions and thoughts (Browne et al., 2011; Silva et al., 2017). While cameras are worn by the patient, diary entries are typically (although not always,

see Loveday and Conway (2011) as well as Silva et al. (2017)) written by someone else – such as the patient’s spouse (Berry et al., 2009; Berry et al., 2007; Browne et al., 2011; Woodberry et al., 2015) or the experimenter (Woodberry et al., 2015) – owing to concerns that memory-impaired patients would be unable to accurately log their daily events or that their efforts to do so would potentially alter their memories and bias the results. In an apparent trade-off between ease of implementation and precise experimental control, many experiments have opted to involve patients’ spouses in reviewing or testing procedures (Berry et al., 2009; Berry et al., 2007; Browne et al., 2011; Loveday & Conway, 2011; Woodberry et al., 2015). One study even had the experimenter assist some patients while other patients were assisted by their spouses (Loveday & Conway, 2011). Future camera studies incorporating diary review as a comparison condition should require that the same individual, preferably an experimenter, record diary entries to ensure consistency and should also limit spousal involvement in testing procedures to prevent potential subjectivity. Furthermore, most of the case studies reviewed above have probed patients’ memories with a relatively limited number of life events. It would be useful for future studies to record and test a larger number of unique events to better understand wearable cameras’ potential to cue retrieval for a broader range of memories.

In summary, studies examining the consequences of SenseCam use in memory-impaired patients have reported promising benefits for the accessibility and vividness of memories for personal events, often with concomitant improvements in subjective well-being. However, given that many of the results were derived from case studies on individual patients with heterogeneous memory disorders, caution is warranted in evaluating the robustness and generalizability of these effects. It is our hope that, as wearable cameras become more widely adopted as a tool for patient



rehabilitation, psychologists and clinicians will continue to collaborate on larger-scale studies aimed at evaluating the factors that maximally affect the efficacy of this approach.

## **BEHAVIORAL RESEARCH IN NONCLINICAL POPULATIONS**

Although wearable camera studies have demonstrated marked improvements in autobiographical recall for memory-impaired patients, an important question is whether this technology would also offer benefits to cognitively healthy individuals. Relatively few studies have examined unimpaired participants, but those that have done so have largely reported positive outcomes. One early study assessed whether young adults would show enhanced long-term retention of events that they rehearsed using an end-of-day SenseCam photograph review procedure (Finley et al., 2011). Although substantial forgetting occurred across the 8-week interval of the experiment, participants' memories for reviewed events were more accurate in comparison with non-reviewed events, even when no explicit instructions were given to memorize the images.

Another study compared SenseCam and diary review protocols in groups of healthy younger and older adults and found that the SenseCam method enhanced autobiographical memory performance in both age groups (Silva, Pinho, Macedo, & Moulin, 2013). Intriguingly, this study also found that the SenseCam condition was associated with broader enrichment of participants' cognitive function, as assessed by a battery of neuropsychological tests. The largest effects were observed for both memory and executive function tasks, including measures of semantic, verbal, and working memory. Participants' subjective reports indicated that reviewing photographs not only cued more memories than reviewing diary entries, but also produced a better sense of reliving. This is in line with previous SenseCam studies of clinical populations

(Berry et al., 2009; Berry et al., 2007; Browne et al., 2011). To explain the performance gains on neuropsychological measures, the researchers speculated that SenseCam-based rehearsal may serve as a short-term cognitive stimulant, potentially by virtue of the photographs being interesting and pleasurable to look at, which in turn can heighten alertness (Silva et al., 2013). While potentially promising, these findings of generalized cognitive enhancement should be replicated to confirm whether the benefits of SenseCam use are as far-reaching as these researchers have claimed. A more recent study also compared the effects of SenseCam use in younger and older adults to examine the benefits of SenseCam images as retrieval cues (Mair et al., 2017). Relative to cuing memories with participant-generated event titles, cuing with SenseCam photographs led to improved recall (including of details not apparent in the images) in both age groups, with no significant effects of aging. The apparent lack of age differences in these two studies is surprising, given other work showing age-related changes in behavioral performance and neural engagement during autobiographical recall (St. Jacques, Rubin, & Cabeza, 2012). Further exploration will be helpful to evaluate what experimental design considerations might impact the degree to which younger versus older adults' memories benefit from photographic rehearsal and cuing. Indeed, the data indicating memory improvements in younger adults are somewhat mixed. Although others have reported a similar benefit of SenseCam-based memory cuing over verbal cuing in younger adults (St. Jacques, Conway, & Cabeza, 2011), one large study examining the effects of SenseCam review procedures – versus diary review or no review – found no improvements in memory recall when participants were tested 1 week later (Seamon et al., 2014). Given the methodological differences in these various experiments, more research is needed to delineate the boundary conditions that determine the utility of wearable cameras as a memory aid for cognitively healthy individuals.

## NEUROIMAGING RESEARCH IN NONCLINICAL POPULATIONS

The integration of wearable cameras into fMRI studies has helped to elucidate the neural mechanisms underlying autobiographical memory retrieval by incorporating naturalistic stimuli to assess participants' memories for real-world events. After briefly reviewing the neuroimaging literature on autobiographical memory, we will discuss the insights that have emerged from the seven fMRI experiments published to date that have used wearable camera photographs as memory probes in cognitively healthy adults. With the exception of the case study by Berry and colleagues (2009) discussed above, wearable cameras have yet to be incorporated into neuroimaging studies of memory-impaired patients or other clinical populations.

Autobiographical memory retrieval involves recruiting a predominately left-lateralized network of distributed brain regions (Cabeza & St. Jacques, 2007; Svoboda et al., 2006). These include MTL areas such as the hippocampus and parahippocampal cortex, which are critically important for recollection processes, as well as regions of the temporoparietal junction, lateral temporal cortex, and posterior parietal cortex (Cabeza & St. Jacques, 2007; Svoboda et al., 2006). Medial regions of the prefrontal cortex (PFC) contribute to the representation of one's self as an agent in the memory, as well as the broader schema of the event, while more lateral PFC regions mediate episodic search processes and the selection and maintenance of search results (Cabeza & St. Jacques, 2007; Gilboa, 2004; Gusnard, Akbudak, Shulman, & Raichle, 2001; Svoboda et al., 2006). Additionally, occipital regions, the precuneus, and the amygdala contribute to the retrieval of mnemonic representations through processes involving visual imagery and emotion (McDermott et al., 2009). The posterior cingulate cortex and retrosplenial cortex are also thought to support recollection by facilitating mental reconstruction of the

visuospatial reference frame (Marchette, Vass, Ryan, & Epstein, 2014; Svoboda et al., 2006; Vann, Aggleton, & Maguire, 2009). This set of regions has been consistently associated with autobiographical memory retrieval throughout the neuroimaging literature (Cabeza & St. Jacques, 2007; Chen et al., 2017; Gilboa, 2004; Gusnard et al., 2001; McDermott et al., 2009; Svoboda et al., 2006), although some studies have suggested more bilateral (Graham, Lee, Brett, & Patterson, 2003; Vandekerckhove, Markowitsch, Mertens, & Woermann, 2005) or right-lateralized involvement (Fink et al., 1996; Markowitsch et al., 2000).

Neuroimaging studies have used photographic stimuli derived from the SenseCam to assess the neural correlates of recollection and familiarity during autobiographical recall of real-world events. Milton and colleagues evaluated these processes as a function of memory remoteness (Milton, Muhlert, Butler, Benattayallah, & Zeman, 2011; Milton, Muhlert, Butler, Smith, et al., 2011). The researchers first studied recent memories, where participants were scanned approximately 36 hours after photograph acquisition (Milton, Muhlert, Butler, Benattayallah, et al., 2011). A modified Remember/Know paradigm was used during the fMRI scan session to assess recall as participants were shown SenseCam images generated from their own lives as well as the lives of other participants. Recollected and familiar events evoked activity in overlapping brain regions previously associated with autobiographical retrieval, including the posterior cingulate, right inferior parietal lobe, and right dorsolateral PFC. However, recollection elicited greater activity in the right posterior and anterior parahippocampal gyrus as well as the mPFC, whereas familiarity elicited greater activity in the right ventrolateral PFC and bilateral cingulate gyrus. These findings are broadly consistent with previous studies of recollection and familiarity (Diana, Yonelinas, & Ranganath, 2007; Yonelinas, Otten, Shaw, & Rugg, 2005). Moreover, the activity of the right hippocampus and posterior parahippocampal

gyrus increased parametrically as participants' retrieval experiences increased from weakly familiar to strongly recollected. It is unclear whether these effects should be attributed to quantitative differences in memory strength or qualitative differences in the subjective attributes of retrieval (e.g., the degree of contextual reinstatement). However, the fact that these regions' activity increased between weak recollection and strong recollection trials supports the notion that recollection may not be an all-or-none phenomenon, but rather may operate as continuously varying or graded retrieval process (Mickes, Wais, & Wixted, 2009; Slotnick, 2013).

Milton and colleagues (2011) then scanned the same participants 5 months after last wearing the SenseCam in the original study (Milton, Muhlert, Butler, Benattayallah, et al., 2011) while they performed the same recognition memory task in order to evaluate the neural mechanisms of recollection and familiarity for remote autobiographical memories. Compared to the previous 36-hour retention interval, photographs depicting events that had transpired approximately 5 months earlier showed decreased neural activation related to both recollection and familiarity in the right hippocampus and parahippocampal gyrus. Indeed, for these remote memories, recollection-related MTL activity no longer exceeded that observed during familiarity-based responses or correctly rejected novel images. Consistent with the standard consolidation model, which predicts reduced MTL involvement and increased neocortical involvement as memories become more temporally remote (Squire, Genzel, Wixted, & Morris, 2015), the researchers only found recollection-related activity for 5-month-old memories in neocortical regions, such as the mPFC. However, it should be noted that Milton and colleagues' second fMRI experiment had a relatively small sample ( $n = 10$ ), limiting their experimental power (Milton, Muhlert, Butler, Smith, et al., 2011). Additionally, owing to the small number of unique events captured by the cameras, they opted to use the same stimuli for both the short-

delay and long-delay scanning sessions, so the neural representations of the remote memories may have been somewhat altered by this retrieval practice. Fortunately, more work is underway to investigate the effects of both temporal remoteness and retrieval practice on the neural correlates of real-world memories (Uncapher, Boyd-Meredith, Rissman, & Wagner, 2014).

St. Jacques and her collaborators have also used wearable cameras to conduct a set of fMRI studies assessing the neural mechanisms of autobiographical memory retrieval for real-world events. Their first study investigated how the processes associated with mentally projecting oneself into specific events from one's past differ from those supporting simulation of another individual's perspective (St. Jacques, Conway, Lowder, et al., 2011). Participants wore the SenseCam while concurrently keeping a written record of daily activities. One week after last wearing the SenseCam, participants underwent fMRI scanning and were presented with photographs from their own lives as well as from the lives of other individuals and instructed to either retrieve the depicted events or comprehend the depicted event from another individual's perspective. Overall, SenseCam photographs allowed participants to strongly re-experience their personal past as well as understand another individual's perspective. Not surprisingly, projection into one's own past evoked greater activity in areas previously implicated in autobiographical memory retrieval, including the bilateral ventrolateral PFC, left hippocampus, posterior midline regions, and lateral temporal regions. However, an interesting dissociation was observed within the mPFC, such that projection into one's own past preferentially recruited a ventral component of the mPFC, whereas projection into someone else's past preferentially recruited a more dorsal component of the mPFC (Gusnard et al., 2001; St. Jacques, Conway, Lowder, et al., 2011). Task-related functional connectivity further established the different contributions of dorsal and ventral mPFC regions: the ventral mPFC showed greater connectivity with regions of the

hippocampus and precuneus associated with episodic retrieval memory processes, whereas the dorsal mPFC demonstrated greater connectivity with areas of the frontoparietal network associated with control processes. These results provided novel evidence that ventral and dorsal mPFC regions support dissociable forms of self-projection.

Data collected from the aforementioned study were also used to examine putative gender differences in autobiographical recall evoked by visual versus verbal retrieval cues (St. Jacques, Conway, & Cabeza, 2011). During the fMRI scanning session, memories were cued by either a sequence of SenseCam photographs (dynamic visual cue) or a short textual description (verbal cue). Men demonstrated greater neural activity during the reliving of memories elicited by the visual cues, relative to the verbal ones, in regions associated with autobiographical memory, including the left hippocampus, left inferior frontal gyrus, right occipital cortex, and retrosplenial cortex. In comparison, women were equally sensitive to both types of cues, such that neural activity did not differ significantly in response to reliving prompted by verbal or visual stimuli. These results could have important implications for studies using camera-based life-logging procedures to bolster autobiographical retrieval in patient populations, as males and females may experience differences in the relative efficacy of photographs versus diary entries as memory prompts.

In another cleverly designed fMRI experiment incorporating wearable cameras, St. Jacques and colleagues (2013) investigated how the neural mechanisms associated with the cued reactivation of event memories can contribute not only to the subsequent strengthening of these memories, but also, under certain circumstances, to their distortion. Participants in their study were given Vicon Revue cameras to wear as they completed a self-guided museum tour (**Figure 2.3**). Two days later, participants underwent fMRI scanning while they were presented with

photographs from their own camera to trigger memory reactivation for events they had experienced during their museum tour, with a subset of these images followed by a new lure photograph derived from an alternative version of the museum tour that participants had not actually experienced. Then, 2 days after the scan, participants completed a recognition memory task where they were presented with photographs of reactivated targets and lures that had been previously encountered in addition to novel photographs of targets and lures. Not surprisingly, events that had been reactivated received a boost in subsequent memory. However, participants also reported increased recognition of photographs depicting event elements that they had not actually experienced in real life but which had become falsely woven into their memories of real events through the presentation of lure images during the reactivation session. This reactivation-induced memory distortion was consistent with the findings of the researchers' previous behavioral experiment (St. Jacques & Schacter, 2013), setting the stage for their investigation into the neural correlates of this robust and putatively adaptive (Schacter, Guerin, & St. Jacques, 2011) quirk of episodic memory.

When these researchers examined the fMRI activity associated with photographs that participants would subsequently claim to remember, they found a number of regions that showed increases in activation (relative to subsequently forgotten events), regardless of whether these memories were true or false. These regions – which included the bilateral posterior inferior parietal cortex, left posterior parahippocampal cortex, and bilateral retrosplenial cortex – also showed sensitivity to the degree of reliving reported by participants during the scanning session. Further examination of these regions' responses during lure trials revealed that the lure photographs that went on to later be correctly rejected by participants (indicating that they were not falsely integrated into the original memory trace) were associated with low activity levels at



the time the lure appeared on the screen, whereas the lure photographs that went on to be falsely remembered as real experiences were associated with sustained involvement of these areas during both initial reactivation and lure presentation. In addition to finding that these regions' activity predicted both true and false subsequent memories, the analyses also identified regions that were uniquely associated with true or false subsequent memories. For trials with high reliving ratings, comparing target presentation relative to lure presentation demonstrated that subsequently true memories evoked greater activity in the posterior cingulate and rostromedial PFC whereas subsequently false memories evoked greater activity in the ventrolateral PFC, ventral mPFC, lateral temporal cortex, and right anterior hippocampus. Taken together these findings help to clarify the neural processes at work when revisiting photographs of a past event, showcasing how some of the same regions involved in strengthening the representation of a true memory can also contribute toward the creation of a (at least partially) false one due to the inherent malleability of memory traces immediately following reactivation.

On the basis of the success of this experimental paradigm, it was later adapted in a behavioral study to assess differences in reactivation processes between healthy younger and older adults (St. Jacques et al., 2015). Consistent with prior findings (St. Jacques et al., 2013; St. Jacques & Schacter, 2013), reactivation quality affected subsequent memory such that photographs that evoked greater reliving ratings during the reactivation phase were more likely to lead to subsequent hits or, in the case of lure stimuli, subsequent false alarms during the recognition phase. Furthermore, in line with the broader literature on age-related increases in the frequency of false remembering (Devitt & Schacter, 2016), older adults exhibited significantly more false alarms than younger adults. But despite this overall increase in false memories, older adults showed a smaller impact of reactivation on subsequent recognition performance.

Accordingly, aging appears to diminish the ease with which episodic memories can be updated. Although this property likely has negative consequences in many circumstances in which it is desirable to update one's memory based on new information, it also has the somewhat counterintuitive positive consequence of making the memories of older adults less vulnerable to reactivation-induced distortions. These data thus help to advance our understanding of how the critical process of memory updating changes over the lifespan.

In another innovative investigation into the brain mechanisms that support memory for real-world events, Nielson and colleagues (2015) gave their participants customized neck strap-mounted smartphones to record photographs, along with corresponding GPS coordinates, of their experiences over a period of roughly 1 month (**Figure 2.4**). The participants then underwent fMRI scanning, during which each was presented with individual photographs from their smartphone's camera and instructed to mentally relive each experience. The resulting fMRI data were analyzed using multi-voxel pattern analysis (MVPA), a methodological technique that differs from traditional univariate analyses by assessing the spatial pattern of brain activation, rather than the peak of activation, which can allow for greater sensitivity (Norman, Polyn, Detre, & Haxby, 2006; Rissman & Wagner, 2012; Tong & Pratte, 2012). Using a variant of MVPA known as representational similarity analysis, the fMRI activity patterns from individual trials were compared with one another and their dissimilarity (i.e., "neural distance") was computed. When the researchers attempted to relate the neural distance between pairs of events to the spatial distance between them (i.e., how much geographic distance separated the locations where the probe photographs were captured), they found that activity patterns within the left anterior hippocampus could be used to predict spatial distances between events, ranging from 100 meters to 30 kilometers. Strikingly, this same region was found to also carry information about the

temporal distance between events, such that events that took place further apart in time (e.g., 1 month) showed greater neural distance than events that occurred closer together in time (e.g., 15 hours). These results demonstrate lateralization in the hippocampal computations supporting the recall of autobiographical event details, with the left anterior hippocampus playing a particularly important role in representing and integrating the spatiotemporal characteristics of personal episodes. This study nicely illustrates the potential for wearable camera technology to provide valuable information, such as geographical and temporal tagging of real-world experiences over many weeks, which could not be easily ascertained through other methods. This in turn allows for an enriched understanding of how the spatial and temporal features of event knowledge are represented in the brain.

Most recently, Rissman and colleagues (2016) examined the degree to which an individual's level of memory for personally experienced events can be decoded based on distributed fMRI activity patterns measured in response to wearable camera photographs (**Figure 2.5**). After wearing a Vicon Revue camera for 3 weeks, participants were scanned while viewing brief sequences of photographs depicting events from their own lives or from other participants' lives. Participants indicated their subjective retrieval experience with one of eight response options, which included varying levels of novelty, familiarity, and recollection. Using MVPA methodology, the neural activation patterns associated with individual trials were used to train a logistic regression classifier algorithm, which learned the distributed patterns of activity most capable of distinguishing between each of the subjective retrieval outcomes. The classifiers were then used to predict the mnemonic state of trials on which the model had not been trained. The results revealed extraordinarily accurate classification (>90% correct) of whether or not each probed memory was from one's own life or someone else's life. Classifiers could also decode

more nuanced information about the subjective qualities of one's remembrance, such as whether the photographs evoked a strong or moderate sense of recollection, familiarity, or novelty. These neural signatures of autobiographical retrieval were found to be stable across retention intervals of up to 1 month, as well as highly consistent across participants. Assessment of the classifier-based "importance maps" provided insights into which brain regions provided diagnostic signals for each mnemonic classification scheme. For instance, when classifying hits versus correct rejections, an extensive set of lateral frontoparietal regions were highly predictive of participants' own events, whereas activity in visual regions, such as occipital and inferior temporal areas, tended to be predictive of novel photographs from someone else's life. When classifying between trials where participants reported recollection of contextual details versus trials associated with only familiarity-based recognition, regions most diagnostic of recollection included the hippocampus and parahippocampal cortex, as well as medial frontal areas and parietal regions, such as the retrosplenial cortex and posterior cingulate cortex, along with the left angular gyrus. These results build upon earlier efforts to decode memory retrieval states associated with laboratory-encoded visual stimuli (Rissman, Greely, & Wagner, 2010) by extending such effects to real-world events, and showcase the ability of fMRI to differentiate between subtle gradations in the strength and subjective quality of one's memory.

Taken together, wearable cameras have been utilized by memory researchers to capture photographs of real-world experiences that can later be presented in the fMRI scanner to probe various aspects of autobiographical memory (the main findings of these fMRI studies are summarized in **Table 2.1**). The results have largely corroborated the field's prior characterization of the neural substrates of autobiographical recall, as derived from studies using laboratory-based techniques for probing participants' memories for past events. In this sense, rather than upending

our understanding of the core cortical and MTL brain systems that support event retrieval, camera-based fMRI paradigms have helped confirm that these mechanisms can generalize to the retrieval of real-world memories encoded in naturalistic settings. That said, this emerging literature contains a number of novel findings, including the dissociation between ventral and dorsal mPFC contributions to the reliving of a personally-experienced event memory versus projecting oneself into an event experienced by someone else (St. Jacques, Conway, Lowder, et al., 2011), the graded nature of neural representations of episodic recollection and familiarity (Milton, Muhlert, Butler, Benattayallah, et al., 2011; Milton, Muhlert, Butler, Smith, et al., 2011; Rissman et al., 2016), hippocampal lateralization in the representation of spatiotemporal information associated with personal events (Nielson et al., 2015), the differential sensitivity of men and women to verbal versus visual retrieval cues (St. Jacques, Conway, & Cabeza, 2011), and the mechanisms of reactivation-induced distortion of real-world event memories (St. Jacques et al., 2013). Although there are certainly circumstances in which the enhanced experimental control over exposure duration, attentional allocation, and event content provided by laboratory stimuli can outweigh the enhanced ecological validity provided by wearable camera stimuli, we believe that the fMRI studies reviewed above have provided an important first step towards showcasing the viability of more naturalistic paradigms for cataloging people's day-to-day experiences and characterizing the brain processes evoked during their retrieval.

## **DISCUSSION**

Wearable camera technology has not only been used to enhance individuals' memories, but has also been instrumental as a tool for studying the cognitive and neural processes that support autobiographical memory. The integration of wearable camera technology into

behavioral and fMRI experiments permits more ecologically valid assessments of autobiographical memory retrieval by providing detail-rich, personally-relevant cues that evoke specific experiences. As such, wearable camera photographs may better capture the complex phenomenological properties of real-world memories than laboratory-based stimuli. Like other prospective experimental methods for logging one's day-to-day experiences, these nonintrusive camera devices allow for some degree of experimental control, but critically avoid other techniques' potential for interfering with the encoding process (Cabeza & St. Jacques, 2007). Although integration of wearable camera technology with neuroimaging approaches to assess healthy adult populations has only occurred recently, these techniques have been effectively used to evaluate the contributions of various cortical and MTL regions to the recollection of events from one's personal past. While several other review articles on wearable cameras have recently appeared, they predominately focus on the devices' rehabilitative applications and do not comprehensively cover extant neuroimaging experiments (Allé et al., 2017; Dubourg, Silva, Fitamen, Moulin, & Souchay, 2016; Silva, Pinho, Macedo, & Moulin, 2016). The combination of wearable camera technology and neuroimaging methods may prove to be a powerful approach that helps further elucidate the complexities of autobiographical recall for real-world events.

Despite the many promising findings highlighted in our review, this still-small body of research suffers from a number of limitations that will be important to address as the field moves forward. Many of the clinical studies investigating the use of wearable cameras as a therapeutic tool for bolstering retention of autobiographical memories in memory-impaired patients have derived their results from single cases or very small cohorts. Given the heterogeneity of these patients, as well as of the experimental procedures of individual studies, it is hard to specify which types of patients will be most amenable to the benefits of wearable cameras and which

protocol for photographic review will be most effective. These limitations could begin to be addressed by larger-scale clinical trials featuring more careful control over the procedures for selecting photographs for patients to review, as well as the structure and timing of the memory rehearsal and testing sessions. Efforts should also be made to address the demographic disparity in the wearable camera literature. The majority of clinical experiments have focused on older adults with memory impairments, whereas non-clinical experiments have primarily assessed healthy, younger adults. In order to evaluate the generalizability of extant findings, it would be helpful to know whether memory-impaired younger adults could benefit from wearable cameras, and more behavioral and neuroimaging studies should be done using wearable cameras in cognitively healthy older adults.

On the basis of our own experiences, as well as those described in other studies, there are many practical challenges inherent in the implementation of camera-based experimental paradigms. One difficulty is participant compliance: even with careful instructions, participants may not wear their cameras in the “on” mode for long enough to generate a sufficient number of photographs or capture enough unique events. Even if cameras were worn as instructed, it is possible to capture repetitive and generic daily events that may not be memorable or personally relevant (De Leo et al., 2011; Milton, Muhlert, Butler, Benattayallah, et al., 2011; Rissman et al., 2016). Given the variability of life experiences across participants, or even variability within participants across days, it can be hard to adopt universally applicable guidelines for selecting photographs for use as memory probes. Furthermore, in some experimental paradigms, participants’ cameras can generate several thousand photographs (Finley et al., 2011; Kelly et al., 2013; Rissman et al., 2016), so combing through these images in search of optimal stimuli can be an incredibly labor-intensive process. Other issues pertain to image quality. Despite ongoing

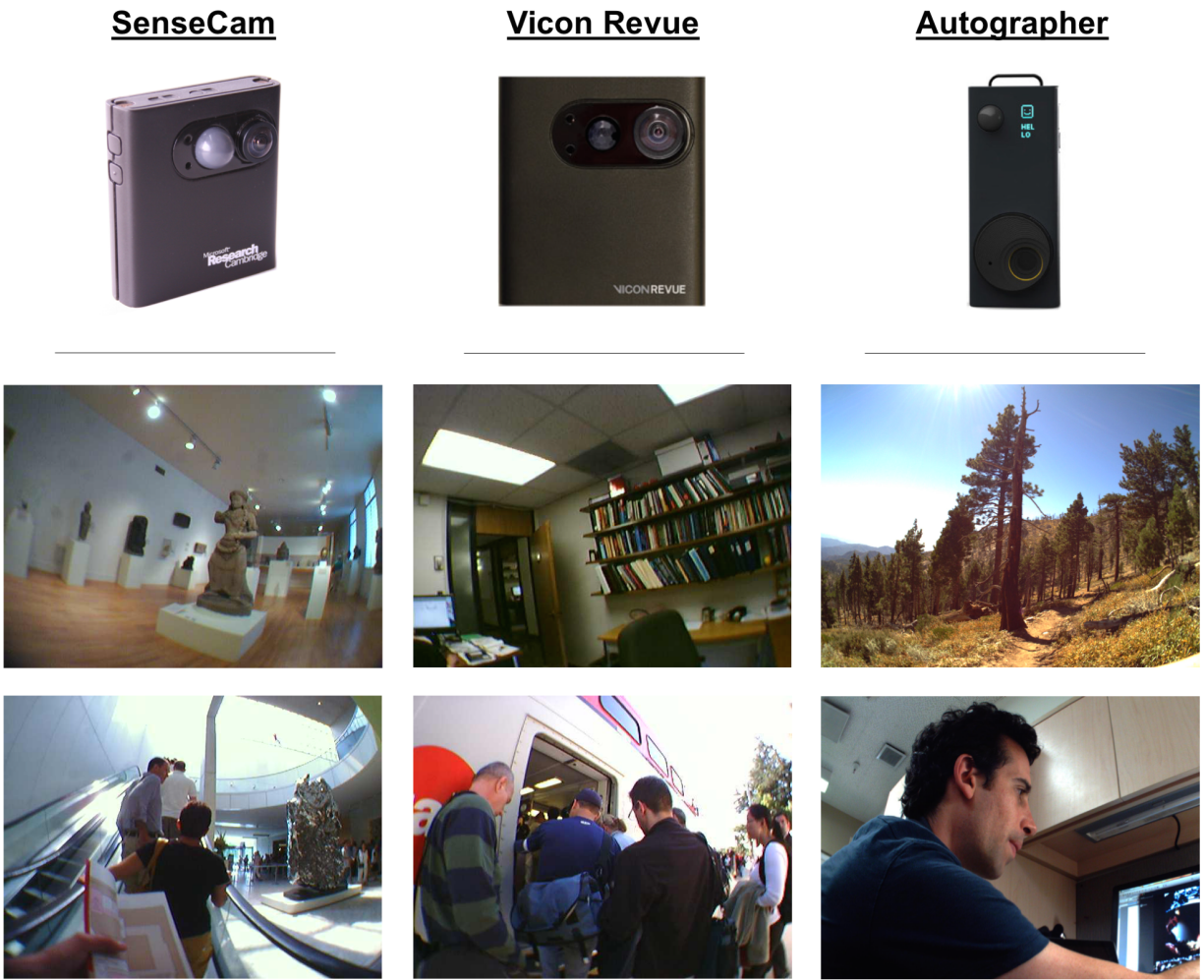
improvements in wearable camera technology, it can be difficult to capture photographs under low-light conditions (Berry et al., 2007; De Leo et al., 2011; Mair et al., 2017; Nielson et al., 2015) or during periods of movement (Milton, Muhlert, Butler, Benattayallah, et al., 2011; Nielson et al., 2015). One study estimated that 93% of their smartphone images were unusable due to image quality or repetitiveness (De Leo et al., 2011), but even uneventful photographs may be able to cue memory retrieval (Hodges et al., 2011). It is also hard to know whether a camera-wearer was paying attention to his or her surroundings at the time that a given photograph was recorded; a seemingly interesting event could have been captured by a camera while its wearer was looking elsewhere or consumed by unrelated thoughts. Although these issues may make camera-based studies more challenging to implement than other memory experiments, the advantages provided by such paradigms in facilitating the study of real-world autobiographical memories – for which the details can be verified by photographs, timestamps, and even sometimes GPS coordinates – may outweigh the obstacles.

As video-enabled wearable camera devices achieve increasingly greater storage capacity and battery life, researchers should explore what added utility video might provide for clinical applications and cognitive neuroscience research studies. Furthermore, if audio recordings are also collected, then this combination may provide additional contextual details (e.g., recognizable voices, interpersonal dialogue, environmental sounds) to aid retrieval. Indeed, audiovisual stimuli typically evoke better recognition memory performance than either modality individually (Meyerhoff & Huff, 2016). However, legal issues and privacy concerns pertaining to the surreptitious recording of conversations may ultimately limit the viability of audio and audiovisual life-logging technology. Future research efforts should remain mindful of such user-experience considerations (Doherty et al., 2012; Harvey, Langheinrich, & Ward, 2016).



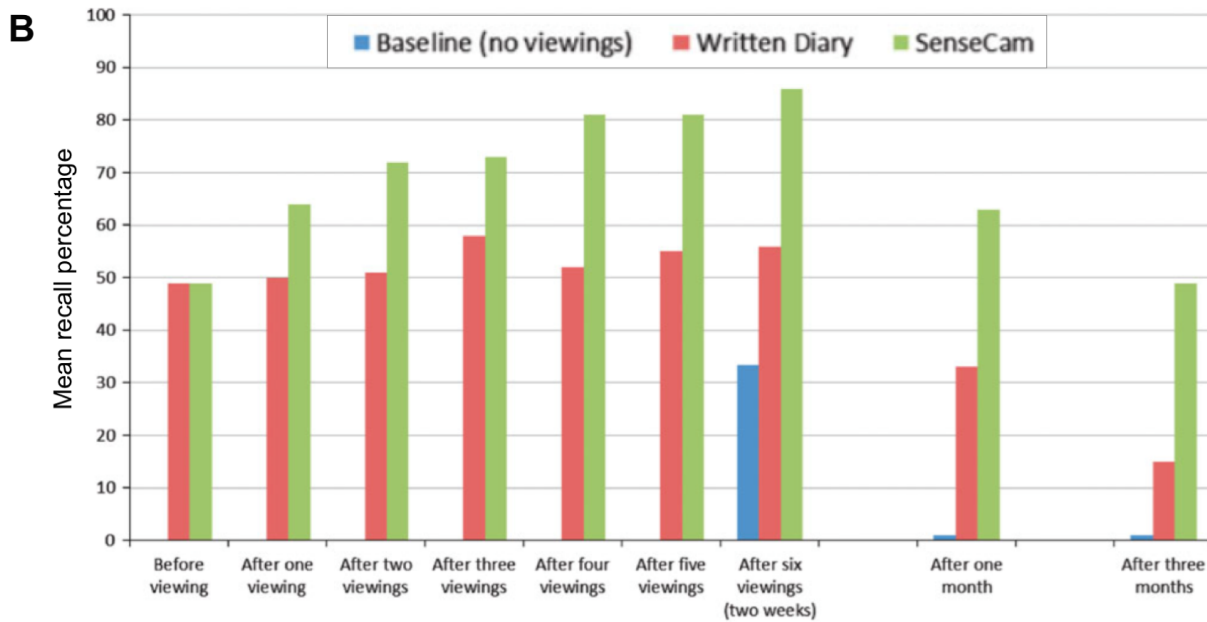
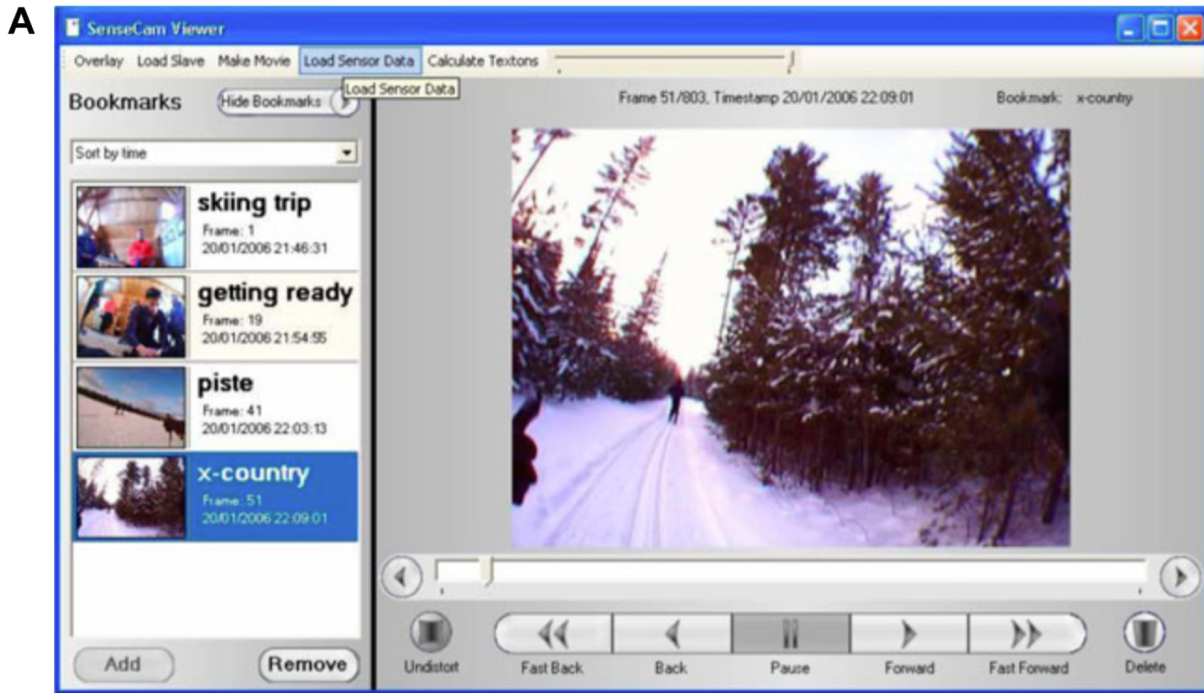
Since the literature regarding camera-based investigations of autobiographical memory retrieval is still nascent, the field is ripe with underexplored research questions that could be approached with this technology. For instance, it could be informative to deploy wearable cameras to examine how people's memories may be affected through social interactions with other individuals, including the effects of photograph sharing (e.g., through social media applications) on memory accuracy and retention. Studies could also provide cameras to groups of individuals who experience the same events from different vantage points. The resulting photographs could provide a unique opportunity to assess the viewpoint specificity of real-world memories. This research direction may be of particular interest in applied settings concerned with the detection of autobiographical memories for specific past experiences (Agosta & Sartori, 2013; Bles & Haynes, 2008; Meegan, 2008; Meixner & Rosenfeld, 2014; Rissman et al., 2016). In sum, although wearable camera technology has already been productively used to further our understanding of autobiographical memory retrieval – and in some circumstances, to rehabilitate its deficiencies – we hope that these devices will provide many exciting opportunities for future research into the recall of real-world events.

## FIGURES



**Figure 2.1**

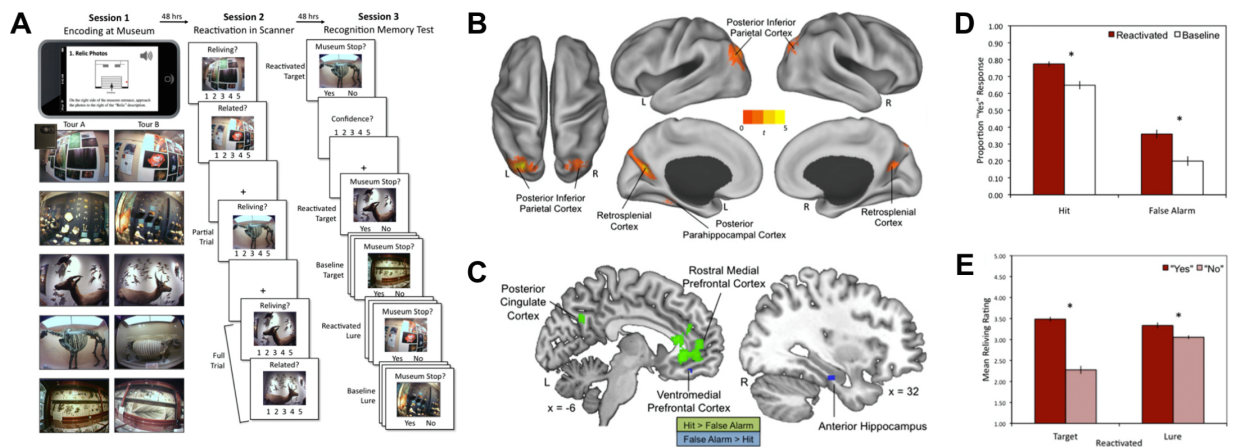
The SenseCam wearable camera device and its commercial successors, the Vicon Revue and the Autographer, with example photographs from each product. Images adapted from Microsoft Research, Vicon Motion Systems Ltd., and OMG Life. SenseCam photographs provided courtesy of Peggy St. Jacques; Vicon Revue and Autographer photographs provided by the authors.



**Figure 2.2**

A comparison of autobiographical recall in patients with Alzheimer’s disease when using different forms of external memory aids to review events. (A) Multiple experiments, particularly

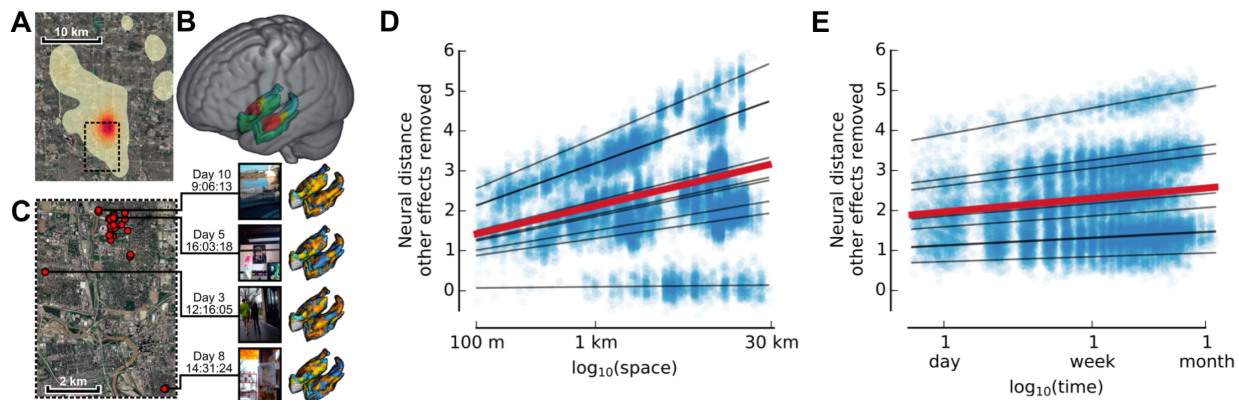
clinical ones, have included the process of revisiting event photographs captured by wearable camera devices. This study in particular allowed participants to review images using a software program called the SenseCam Viewer (Microsoft Research Cambridge). (B) Over the course of several months, participants with Alzheimer’s disease were tested on their recall for experienced events. Their performance, in terms of mean recall percentage, is shown for the SenseCam condition, written diary condition, and the baseline condition (in which no review of the events was conducted). Memory for events rehearsed with the SenseCam review method steadily improved across successive viewings and outperformed diary-based rehearsal, with lasting improvements even after several months had elapsed since the last review opportunity. Figure adapted, with permission, from Woodberry et al. (2015).



**Figure 2.3**

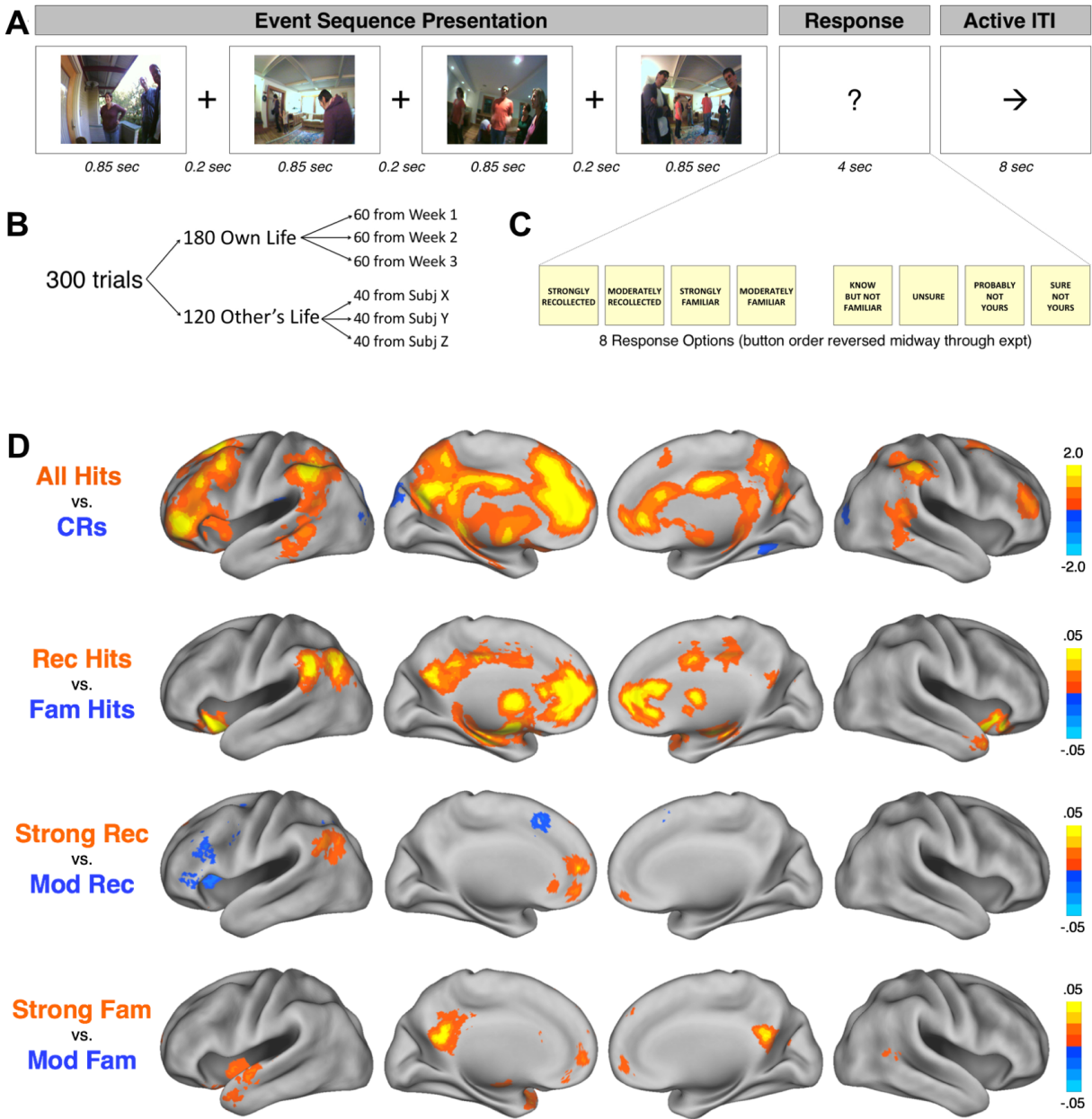
Common and distinct neural areas associated with subsequent true and false autobiographical memories. (A) The experimental design included three phases. Session 1 involved the encoding task, where participants engaged in a museum tour. Session 2 involved reactivation during the fMRI scan session, where participants were presented with images from museum stops they had

visited (“targets”) and prompted to make ratings of their sense of reliving (“partial trial”). A subset of trials in the second session (“full trial”) also presented an image from an alternate museum tour (“lure”) and prompted participants to rate the relatedness of the two images. Session 3 involved the recognition memory test: participants were presented with targets and lures that were either from the second session or were completely novel (“baseline”) and prompted to indicate whether the images contained a museum stop that had been visited. (B) Subsequent true memories (target images that were later recognized) and subsequent false memories (lure images that were later reported as recognized) were associated with activation in several common brain areas, including the left parahippocampal cortex, bilateral retrosplenial cortex, and bilateral posterior inferior parietal cortex. (C) However, different brain regions were associated with reactivation quality for subsequent hits and false alarms. For memories with high reliving ratings during target presentation relative to lure presentation, subsequent hits showed greater reactivation-related activity in regions like the rostral mPFC and posterior cingulate cortex, while subsequent false alarms showed greater reactivation-related activation in the right hippocampus and ventral mPFC. (D) Behavioral results from the recognition memory test demonstrated increased rates for hits and false alarms for reactivated images, relative to baseline ones. (E) Behavioral results indicated that the quality of memory reactivation differed based on recognition memory performance. Mean reliving ratings were greater for hits (responding “yes” to a target) relative to misses (responding “no” to a target). Mean reliving ratings were also greater for false alarms (responding “yes” to a lure) in comparison to correct rejections (responding “no” to a lure). Figure adapted, with permission, from St. Jacques et al. (2013).



**Figure 2.4**

The spatial and temporal distance between autobiographical events scales with the dissimilarity of neural activity patterns (“neural distance”) in the left anterior hippocampus. (A) A heat map representing locations in Columbus, Ohio where participants’ images were captured by wearable GPS-enabled smartphones. (B) Regions of interest in the medial temporal lobe: anterior hippocampus (red), intermediate hippocampus (yellow), posterior hippocampus (blue), and parahippocampal cortex (green). (C) Select event locations for a single participant, where each red marker indicates a photograph that was presented during the fMRI scan session. The time and corresponding location of four sample photographs are included, along with the associated heat maps of the single-trial activation parameter estimates in the right and left hippocampus. (D and E) When the effects of other factors were eliminated from the model, neural distance within the left anterior hippocampus was correlated with both spatial distance (D) and temporal distance (E). Each blue marker indicates a pair of photographs shown to participants, with the black lines representing the estimated neural distance from each participant’s regression results and the red lines indicating the averaged estimated neural distance across all participants. Figure adapted, with permission, from Nielson et al. (2015).



**Figure 2.5**

Decoding neural signatures of autobiographical event retrieval. (A) On each trial of the fMRI session, participants viewed a sequence of four photographs depicting the temporal unfolding of an event and then made a judgment indicating their level of memory for the event. (B) For each participant, experimental trials included photographic sequences from their own life, across the

span of the three weeks they wore their camera device, as well as sequences from the lives of three other participants. (C) The response options for participants during the scan session range from reporting strong recollection of the depicted event to expressing high confidence that the event was not from one's own life. (D) Maps of classifier importance values associated with four different binary classification analyses, averaged across participants. Warm colors depict voxels where increased activation biased the classifier to predict that a trial was associated with the condition listed in orange print, whereas cool colors depict voxels where increased activation biased the classifier to predict that a trial was associated with the condition listed in blue print. For each classification, decoding performance is reported as the mean area under the receiver operating characteristic curve (AUC). [CRs = Correct Rejections; Rec = Recollection; Fam = Familiarity; Mod = Moderate]. Figure adapted, with permission, from Rissman et al. (2016).



**Table 2.1**

Neuroimaging research in non-clinical populations.

Experiment	Camera Protocol	Memory Protocol	Main Findings
Milton, Muhlert, Butler, Benattayallah, et al. (2011)	<ul style="list-style-type: none"> <li>• 15 healthy participants (18-25 years old)</li> <li>• 2-day SenseCam capture of daily events</li> </ul>	<ul style="list-style-type: none"> <li>• fMRI scan occurred ~36 hours after camera was worn.</li> <li>• Modified Remember/Know paradigm used to test recognition memory in response to presentations of participants' own photos or photos from other individuals.</li> </ul>	<ul style="list-style-type: none"> <li>• Recollection elicited greater activity in the mPFC and right parahippocampal gyrus.</li> <li>• Familiarity elicited greater activity in the right ventrolateral PFC and bilateral cingulate gyrus.</li> <li>• Regions including the right hippocampus, right parahippocampal gyrus, and mPFC were parametrically modulated by the subjective strength of recollection.</li> </ul>
Milton, Muhlert, Butler, Smith, et al. (2011)	<ul style="list-style-type: none"> <li>• 10 healthy participants (18-25 years old)</li> <li>• 2-day SenseCam capture of daily events</li> </ul>	<ul style="list-style-type: none"> <li>• fMRI scan occurred ~5 months after camera was worn.</li> <li>• Extension of Milton, Muhlert, Butler, Benattayallah, et al. (2011) using the same memory protocol with identical photos presented in both scan sessions.</li> </ul>	<ul style="list-style-type: none"> <li>• Relative to recently encoded memories, remote memories showed decreased recollection and familiarity-related activity in the right hippocampus and parahippocampal gyrus.</li> <li>• Neocortical regions, including the mPFC, continued to be recruited during retrieval of remote memories.</li> </ul>
St. Jacques, Conway, & Lowder (2011)	<ul style="list-style-type: none"> <li>• 23 healthy participants (18-35 years old)</li> <li>• 6-day SenseCam capture of daily events</li> </ul>	<ul style="list-style-type: none"> <li>• fMRI scan occurred ~1 week after the last day the camera was worn.</li> <li>• Each trial presented a dynamic sequence of 40 photos depicting an event from the participant's life or someone else's life.</li> <li>• Participants were instructed to mentally project themselves into each event, rating either reliving for their own life events or understanding for other's life events.</li> </ul>	<ul style="list-style-type: none"> <li>• Self-projection preferentially engaged the ventral mPFC, while projection into another's perspective preferentially engaged the dorsal mPFC.</li> <li>• Ventral mPFC showed greater task-related functional connectivity with regions of the MTL network associated with memory processes.</li> <li>• Dorsal mPFC demonstrated greater task-related functional connectivity with areas of the frontoparietal network associated with control processes.</li> </ul>
St. Jacques, Conway, & Cabeza (2011)	<ul style="list-style-type: none"> <li>• 23 healthy participants (18-35 years old)</li> <li>• 6-day SenseCam capture of daily events</li> </ul>	<ul style="list-style-type: none"> <li>• fMRI data collected at the same time as St. Jacques, Conway, &amp; Lowder (2011).</li> <li>• Trials were comprised of either photo sequences or verbal retrieval cues describing events from the participant's life.</li> <li>• Participants were given instructions to recall each event and rate their reliving.</li> </ul>	<ul style="list-style-type: none"> <li>• Women were sensitive to both visual and verbal cues, with no significantly different activity.</li> <li>• Men were more sensitive to visual cues, which evoked greater activity in areas associated with autobiographical memory retrieval, including the left hippocampus.</li> </ul>

<b>Experiment</b>	<b>Camera Protocol</b>	<b>Memory Protocol</b>	<b>Main Findings</b>
St. Jacques, Olm, & Schacter (2013)	<ul style="list-style-type: none"> <li>• 35 healthy participants (18-30 years old); 26 included in the fMRI analysis</li> <li>• ~4-5 hour Vicon Revue capture of a self-guided museum tour</li> </ul>	<ul style="list-style-type: none"> <li>• The experiment included 3 sessions with 48 hours between each: 1) museum tour while wearing camera, 2) fMRI scan session (reactivation phase), and 3) recognition test.</li> <li>• During fMRI scan, participants' camera photos were used to cue recall of museum tour stops and participants rated their reliving.</li> <li>• On some fMRI trials, after a participant's own photo was shown, a lure photo from an alternate version of the museum tour was presented and the participant judged how related the depicted exhibit was to the one in their own photo.</li> </ul>	<ul style="list-style-type: none"> <li>• Reactivated events increased both true and false subsequent memories, depending on reactivation quality.</li> <li>• Common regions associated with true and false subsequent memories included the left posterior parahippocampal cortex, bilateral posterior parietal cortex, and retrosplenial cortex</li> <li>• Subsequently true memories were associated with greater activation in regions such as the rostromedial PFC while subsequently false memories were associated with greater activation in areas including the ventrolateral PFC, ventral mPFC, and right hippocampus.</li> </ul>
Nielson et al. (2015)	<ul style="list-style-type: none"> <li>• 9 healthy female participants (19-26 years old)</li> <li>• Participants wore smartphones for ~1 month to record daily events as well as their time and GPS coordinates</li> </ul>	<ul style="list-style-type: none"> <li>• fMRI scan took place 1-3 weeks after the camera-wearing period concluded.</li> <li>• Photos from participant's camera were presented one at a time to cue retrieval, with participants indicating whether they recalled the depicted event and how vividly.</li> </ul>	<ul style="list-style-type: none"> <li>• Representational similarity analysis searched for MTL areas where the "neural distance" between pairs of events was related to the spatial or temporal distances between pairs.</li> <li>• The left anterior hippocampus was found to represent recalled autobiographical events' spatial features for distances ranging from 100 meters to 30 kilometers.</li> <li>• The left anterior hippocampus was also found to represent the temporal features of recalled autobiographical events for times ranging from 15 hours to 1 month.</li> </ul>
Rissman et al. (2016)	<ul style="list-style-type: none"> <li>• 16 healthy participants (18-22 years old)</li> <li>• 3-week Vicon Revue capture of daily events</li> </ul>	<ul style="list-style-type: none"> <li>• fMRI scan occurred 6-9 days after the camera-wearing phase concluded.</li> <li>• Participants were presented with sequences of 4 photos depicting events from their own life or from other participants' lives.</li> <li>• Participants used one of eight response options – which included levels of recollection, familiarity, and novelty – to indicate their retrieval experience.</li> </ul>	<ul style="list-style-type: none"> <li>• Participants' subjective retrieval experience could be reliably decoded from fMRI activity patterns.</li> <li>• The neural signatures associated with autobiographical retrieval were highly consistent across participants and were stable up to a 1-month retention interval.</li> <li>• Regions most diagnostic of recollection (vs. familiarity) included the hippocampus, parahippocampal cortex, left angular gyrus, medial frontal areas, and parietal regions.</li> </ul>

## **CHAPTER THREE**

**Multi-voxel pattern classification differentiates personally experienced event memories**

**from secondhand event knowledge**

## **ABSTRACT**

Studies of autobiographical memory retrieval often use photographs as a means to probe participants' memories for past events. Recent neuroimaging work has shown that viewing a set of photographs depicting an event from one's own life evokes a characteristic pattern of brain activity across a network of frontal, parietal, and medial temporal lobe regions that is easily distinguished from the brain activity associated with viewing photographs from someone else's life (Rissman et al., 2016). However, it is unclear whether the neural signatures associated with remembering a personally experienced event are distinct from those associated with recognizing previously encountered photographs of an event. The present experiment used a novel functional magnetic resonance imaging (fMRI) paradigm to investigate putative differences in brain activity patterns associated with these distinct expressions of memory retrieval. Eighteen participants wore necklace-mounted digital cameras to capture the events of their everyday lives over the course of three consecutive weeks. One week later, participants underwent fMRI scanning, where on each trial they viewed a sequence of eight photographs depicting either an event from their own life or from another participant's life and judged their memory for this event. Importantly, half of the trials featured photographic sequences that had been shown to participants during a laboratory session administered the previous day. We used multi-voxel pattern analyses to assess the sensitivity of two brain networks of interest – as identified by a meta-analysis of prior autobiographical and laboratory-based memory retrieval studies – to the original source of the photographs (own life vs. other's life) and their experiential history as stimuli (previewed or non-previewed). The results revealed a striking dissociation, such that activity patterns within the autobiographical memory network were most diagnostic of whether the photographs depicted one's own personal experience (regardless of whether they had been

previewed), whereas activity patterns within the laboratory-based memory network were most diagnostic of whether the photographs had been previewed (regardless of whether they were from the participant's own life). These results not only show dissociable patterns of neural activation across two putative memory networks, but also that these neural signatures are differentially associated with the photographic source and pre-exposure of real-world events.

## INTRODUCTION

Photography has become a ubiquitous means for documenting the events of our lives, and the images captured by cameras provide potent cues for later triggering recollection of event details. Many cognitive neuroscientific studies of autobiographical memory have capitalized upon this by incorporating photographs as memory probes to assess the retrieval of personally experienced events (Chow & Rissman, 2017; St. Jacques & De Brigard, 2015). However, the mnemonic processes evoked during the viewing of a photograph can be multifaceted, and it is important for researchers to appreciate the distinction between memories for the originally experienced event and memories for having previously viewed photographs of the event. These memories may often go hand in hand, but they are theoretically dissociable, in that a novel photograph can trigger the recollection of the depicted event or a previously viewed photograph depicting someone else's life experience can be recognized as visual stimulus that has been encountered in one's past. Although neuroimaging investigations of autobiographical memory have provided valuable insights into the contributions of cortical and medial temporal lobe regions in various aspects of retrieval (Cabeza & St. Jacques, 2007; Svoboda et al., 2006), it remains unclear whether the act of remembering a real-world event can be neurobiologically dissociated from the recognition of a photograph of an event.

The vast majority of extant functional magnetic resonance imaging (fMRI) studies examining episodic memory have utilized laboratory-based experiences, rather than those derived from the real world. Although paradigms studying autobiographical and laboratory-generated memories tend to elicit comparable memory retrieval demands (Kim, 2012), these experimental methods often differ in several ways (Gilboa, 2004; McDermott et al., 2009). Studies of autobiographical and laboratory-based memories typically differ with regards to the

temporal remoteness of the probed memories and the vividness of retrieval (McDermott et al., 2009; Svoboda et al., 2006). Laboratory-based memory studies generally involve encoding and retrieving a set of homogenous stimuli with limited personal relevance and context (Gilboa, 2004). The memories used in these laboratory-based paradigms are often formed over a short period of time, with memory performance typically assessed shortly after encoding (McDermott et al., 2009; Svoboda et al., 2006). In contrast, autobiographical memory studies often utilize contextually rich, salient stimuli that are inherently self-referential; these stimuli are derived from participants' own lives and may be more likely to trigger the retrieval of memories entailing the re-experience of various sensory and emotional qualities (Gilboa, 2004; McDermott et al., 2009). Autobiographical memory studies often involve the retrieval of remote events: the autobiographical memories probed in these paradigms are typically older, with their initial encoding ranging from weeks to years prior, and the age of the tested memories may also be less homogenous than laboratory-based studies (Cabeza & St. Jacques, 2007; McDermott et al., 2009). These differences between autobiographical and laboratory-based tasks may evoke different qualitative retrieval experiences, and result in the engagement of different neural correlates.

Several studies have previously implicated differences in the brain regions engaged by autobiographical memory and laboratory-generated memories (e.g., Burianova & Grady, 2007; Cabeza et al., 2004). To characterize the potential differences between these two purportedly distinct aspects of memories, McDermott, Szpunar, and Christ (2009) conducted an Activation Likelihood Estimation (ALE) meta-analysis that compared studies evaluating the retrieval of memories encoded in a laboratory setting with those assessing the retrieval of autobiographical memories. Their results indicated that recalling memories encoded in these settings engaged

different brain regions, with overlapping activations only found in a few small areas, including the right thalamus, left inferior frontal cortex, and posterior cingulate cortex. This is consistent with other studies that have found minimal overlap between autobiographical and laboratory-based memories in areas involved in general memory retrieval processes (Burianova & Grady, 2007). The McDermott et al. (2009) meta-analysis found that laboratory-generated memories exclusively recruited a set of regions including the bilateral middle frontal gyrus, bilateral inferior parietal cortex, and left inferior frontal gyrus. In contrast, autobiographical memories uniquely engaged areas including the medial prefrontal cortex and bilateral medial temporal lobe. These results implicate differential activation of regions in an “Autobiographical Network” and “Laboratory-based Network,” corresponding to the retrieval of memories encoded in naturalistic and laboratory settings, respectively. This broadly concurs with other studies comparing the two putative forms of memories (Cabeza et al., 2004). Moreover, performance on standard laboratory-based memory tasks can be largely uncorrelated with one’s performance on assessments of autobiographical recall, as demonstrated by recent reports of exceptional individuals exhibiting a phenomenon known as “highly superior autobiographical memory,” (LePort et al., 2012; LePort et al., 2017; Patihis et al., 2013) as well as those exhibiting the converse phenomenon known as “severely deficient autobiographical memory” (Palombo et al., 2015). Dissociations like these have led some to propose that retrieving autobiographical event knowledge is fundamentally different from other forms of episodic retrieval (Chen et al., 2017; Roediger & McDermott, 2013).

However, the exact reason for the disparity between autobiographical and laboratory-based memories is still unclear. It may be due to differences in the evoked mnemonic processes (e.g., recognition as based on either contextual recollection or item familiarity), methodology



(e.g., perceptual qualities of the stimuli used to probe memories), or even characteristics of the tested memories themselves (e.g., personal relevance or temporal remoteness). Additional research is necessary to clarify what conditions drive these differences between memories formed in laboratory-based and naturalistic settings.

One relatively new experimental approach attempts to increase the ecological validity of autobiographical memory retrieval studies by incorporating naturalistic stimuli derived from wearable digital cameras that capture photographs of participants' lives. Previous studies have used wearable camera technology to investigate various aspects of memory for everyday occurrences and events (e.g., Milton, Muhlert, Butler, Benattayallah, et al., 2011; Milton, Muhlert, Butler, Smith, et al., 2011; Nielson et al., 2015; Rissman et al., 2016; St. Jacques, Conway, Lowder, et al., 2011; St. Jacques et al., 2013). However, of these experiments, few have utilized multivariate analytical techniques such as multi-voxel pattern analysis (MVPA) methods (Norman et al., 2006; Tong & Pratte, 2012) to characterize the neural signatures of retrieval processes evoked by different types of photographs, particularly images associated with naturalistic settings. Previous applications of MVPA have shown an ability to differentiate and decode the neural activation patterns associated with photographically-triggered memories for real-world events (Rissman & Wagner, 2012). MVPA can be used to provide information regarding both the process of autobiographical memory retrieval as well as the content of the retrieved memories (e.g., Chadwick, Hassabis, Weiskopf, & Maguire, 2010; Polyn, Natu, Cohen, & Norman, 2005; Rissman et al., 2016; Rissman et al., 2010; Uncapher, Boyd-Meredith, Chow, Rissman, & Wagner, 2015). As such, MVPA offers a powerful approach to assess various types of mnemonic distinctions.

Only two extant fMRI experiments have combined MVPA methods with camera-based

experimental paradigms to examine naturalistic autobiographical memory retrieval (Nielson et al., 2015; Rissman et al., 2016). Nielson and colleagues (2015) assessed hippocampal representations of temporal and spatial information during real-world autobiographical memory retrieval through the use of customized smartphones that collected both photographs and GPS data. Participants wore a smartphone over the course of a month, with their resultant photographs shown during the fMRI scanning sessions as cues to recall specific events. Both the spatial and temporal distances between events were correlated with neural activity patterns within the left anterior hippocampus during retrieval. This demonstrates that MVPA approaches can be used to detect the neural signatures of autobiographical information, even when limited to certain regions.

In addition to assessing specific regions, the integration of MVPA techniques with wearable digital camera paradigms can be leveraged to examine the retrieval of autobiographical memories and their corresponding subjective characteristics. A recent study by Rissman and colleagues (2016) utilized wearable digital cameras to assess the whole-brain patterns of neural activation accompanying real-world recall and participants' associated retrieval experiences. Participants wore a digital camera device for a period of three weeks, and were scanned a week later while making mnemonic judgments concerning brief photographic sequences portraying their own life events or events from other individuals' lives. Not only could MVPA methods reliably differentiate the neural signatures of novel events that were correctly rejected from experienced events that were correctly recognized, but such techniques could also distinguish between the activity patterns of different levels of recognition, corresponding to the subjective strengths of novelty, familiarity, and recollection. Importantly, this study demonstrated dissociable activity patterns for subjective characteristics of real-world autobiographical memory

retrieval.

Although these two experiments have provided valuable information about the patterns of brain activity during autobiographical memory retrieval under naturalistic conditions, much remains unknown about the specifics of real-world recognition. This includes whether or not different aspects of retrieval – for instance, the differences between recollection of an event and recognition of particular photographic representations – can be identified based on patterns of neural activation. If experiments employing naturalistic stimuli are to be used to study autobiographical memory retrieval in an ecologically valid manner, then it is critical to understand the potential differences in recognition processes that may occur during such a paradigm.

The present fMRI experiment sought to extend Rissman and colleagues' (2016) findings by examining the differences in the neural activity patterns associated with event characteristics. The current study assessed retrieval as a function of different sources of event photographs and whether or not these images had been previously encountered. To accomplish this, wearable camera technology was employed to capture photographs of participants' daily life events, and these images were subsequently used as memory probes during the fMRI scan sessions. The resulting patterns of neural activity were then assessed for differences in photographic source (i.e., photographs from the subject's own life or from another individual's life) and pre-exposure (i.e., photographs that were either previously encountered or novel). Of particular interest was assessing whether MVPA techniques could be leveraged to distinguish between retrieval processes elicited by event photographs and how they were experienced. That is, whether MVPA methods could reliably differentiate between recall associated with photographic source and pre-exposure status, which may help clarify how personally experienced events may be distinguished

from secondhand event knowledge. MVPA techniques were applied to brain areas corresponding to the autobiographical memory retrieval and laboratory-based memory retrieval networks identified by McDermott et al.'s (2009) meta-analysis, which suggested that memories encoded in either laboratory-based settings or naturalistic ones were associated with certain brain regions. This methodology examines whether the distributed patterns of neural activity evoked in these regions during autobiographical memory retrieval may provide differential information regarding the photographic source and pre-exposure of events.

If brain regions associated with retrieval in naturalistic and laboratory-based settings do not differ significantly in terms of their ability to decode different event attributes, then this would indicate that these areas may be jointly involved in processing at least certain kinds of mnemonic qualities. If these two networks differ in their ability to decode event features, then this would not only suggest differences in the sensitivity of these regions to specific memory characteristics, but also that these mnemonic processes are dissociable from one another and associated with different neural correlates. This experiment may hold implications for the understanding of the neural correlates associated with real-world autobiographical memories and their respective characteristics.

## **METHODS**

### **Participants**

Eighteen participants (9 females; 18 – 22 years old) with no prior history of neurological or psychiatric issues completed the experiment. Two other individuals initially took part in the experiment, but their participation was discontinued prior to the fMRI scan session (one due to loss of interest and one due to non-compliance). All participants were right-handed native

English speakers with normal or corrected-to-normal vision. Additionally, participants were screened for MRI compatibility and contraindications. Participants gave written informed consent in accordance with the Institutional Review Board procedures at the University of California, Los Angeles (UCLA). Participant enrollment was limited to UCLA undergraduate students in an effort to limit the variance in the types of life experiences and environmental settings captured by their wearable digital cameras. Participants consented for their camera's photographs to be viewed by the experimenters and by other participants in the experiment. Participants were remunerated with \$215 for their time and effort.

## **Procedure**

### ***Wearable Cameras***

All participants were provided with a necklace-mounted Autographer digital camera device (OMG Life, Oxford, UK) and wore them daily over the course of three consecutive weeks. This small 5-megapixel camera contains electronic sensors that detect variations in the external environment, including changes in ambient light and movement. When the Autographer's sensors are triggered, it automatically takes color still-photographs (2592 x 1936 pixels) using its forward-facing, wide-angle lens with a 136° field of view. The Autographer does not include a display screen, so participants were unable to review any of their photographs. Participants retained complete discretion over when and where their cameras were actively taking photographs; participants were able to turn off their Autographer whenever they desired.

### ***Stimuli***

Experimental stimuli consisted of image sequences created from the photographs

captured by participants' Autographer cameras. After the completion of the three-week camera-wearing interval, 40 unique events per week were identified for each participant. For each unique event, eight photographs were selected based on their ability to best depict the temporal progression of that experience. These eight photographs formed one "event sequence." The amount of time elapsing between the first and last photograph of each event sequence was constrained to be no more than 15 minutes. A total of 120 event sequences were created from photographs of each participant's life. In selecting these events, an effort was made to sample a wide variety of experiences and avoid overrepresentation of specific activities, individuals, and locations that tended to recur day after day. Minor edits were performed on some images to ensure that the photographs did not contain visual cues that could immediately enable self-identification, such as cropping to remove participants' visible body parts. All stimuli were standardized to the same dimensions (460 x 345 pixels) and presented against a gray background (1440 x 900 pixels) during both the photograph pre-exposure session and the fMRI scan session.

### ***Experimental Phases***

This study consisted of three phases: a three-week camera-wearing phase, a photograph pre-exposure phase, and an fMRI scan phase.

#### *Phase 1: Camera Wearing.*

In the first phase of the experiment, participants wore Autographer cameras over the course of three weeks. Participants were instructed to wear their camera devices, at their discretion, for at least eight hours a day to ensure that a sufficient number of photographs were captured and that these photographs depicted a reasonably diverse set of life events. Participants

made weekly visits to the laboratory where the experimenters downloaded their photographs. The Autographer cameras were returned to the experimenters after 21 days. The number of viable photographs per week ranged between 1,620 and 10,594 images (median = 4,332), depending on participants' camera-wearing habits. Participants were unaware of the goals of our research study and had no knowledge of how the photographs captured by the camera would be used in the upcoming experimental task.

*Phase 2: Pre-exposure of Stimuli.*

The second phase of the experiment consisted of the photograph pre-exposure session, which was conducted in the laboratory one week after the conclusion of the camera-wearing phase. The purpose of this session was to expose participants to a subset of their own event sequences as well as a subset of another participant's event sequences in order to subsequently measure the behavioral and neural consequences of this pre-exposure. Participants were presented with 120 event sequences (60 from their own life and 60 from another participant's life; evenly sampled from the three weeks of camera-wearing) in random order, with the constraint that no more than three sequences in a row were from their own life or another participant's life. For each event sequence, participants were asked to rate the distinctiveness of the depicted event on a 4-point scale. This task was used to ensure attentive processing and incidental encoding of the stimuli. Participants were not explicitly informed as to which event sequences were derived from their own cameras and which were derived from other individuals' cameras. Event sequences that appeared during the pre-exposure phase will be referred to as "Previewed" sequences, whereas event sequences that did not appear during this phase will be referred to as Non-previewed sequences.

The trial structure of the pre-exposure session was equated with that of the subsequent fMRI scan session as closely as possible. The timing of each trial was identical. All trials began with the presentation of an eight-photograph event sequence, where each individual photograph within a sequence was shown for 0.8 s, with a 0.2-s fixation interval between successive images. Presentation of the event sequence was followed by a 4-s response period for participants to indicate their distinctiveness rating and then a 6-s inter-trial interval (ITI) with fixation.

### *Phase 3: fMRI Scanning.*

The last phase of the experiment occurred one day after the pre-exposure session was administered. Participants underwent fMRI scanning while viewing and making judgments about 240 event sequences (120 from their own life and 120 from another participant's life, with 50% of the sequences from each condition previously encountered during the pre-exposure session). During each trial, an eight-photograph sequence was presented with the same timing as used during the pre-exposure session (0.8 s per image with a 0.2-s fixation interval between successive images), and then participants were given 4 s to make their response, followed by a 6-s ITI (**Figure 3.1**). Participants were required to make two judgments about each event sequence: (1) a judgment about the source of the photographs indicating whether the depicted event was captured by one's own camera ("Self") or whether it was from another person's life ("Other"), and (2) a judgment about whether the photographs were presented in their originally acquired temporal order ("Intact") or whether some of the photographs were presented in a temporally scrambled order ("Scrambled"). The inclusion of temporally scrambled sequences in this experiment, which comprised 50% of all trials (evenly distributed across conditions) and involved the rearrangement of the final four photographs of a sequence, was intended to facilitate



an analysis of temporal order memory and schema-based prediction error, which is beyond the scope of the present investigation and will be featured in a separate report. Thus, for the purposes of the present report, we have elected to collapse across Intact and Scrambled trials and focus our analyses on the neural signatures of the two other critical experimental factors of photographic source (Self vs. Other) and pre-exposure (Previewed vs. Non-previewed).

Participants were instructed to indicate their judgments by pressing one of four keys on an MRI compatible button-box using the fingers of their right hand. The two judgments required on each trial (photographic source and temporal order) were combined into a single response with the following options: “Self and Intact,” “Self and Scrambled,” “Other and Intact,” and “Other and Scrambled.” Although participants were informed that some trials would feature event sequences that they had encountered in the laboratory on the previous day, they were not asked to make judgments indicating whether or not each trial’s event sequence had been pre-exposed.

### **fMRI Data Acquisition**

All neuroimaging data were acquired on a Siemens 3.0 Tesla Tim Trio MRI scanner at the UCLA Staglin IMHRO Center for Cognitive Neuroscience. Functional volumes were obtained with T2\*-weighted whole-brain echo-planar imaging (EPI) sensitive to blood-oxygen-level-dependent (BOLD) contrast. Each EPI volume consisted of 35 axial slices acquired in an interleaved manner (TR = 2000 ms, TE = 27 ms, flip angle = 75°, FoV = 192 mm voxel size = 3.0 x 3.0 x 3.5 mm). The experiment included 10 functional runs, each with 221 volumes, where the first 3 volumes of each run were discarded to account for T1 stabilization. A whole-brain high-resolution anatomical scan (T1-weighted structural MPRAGE) and a T2-weighted in-plane

anatomical scan were also collected for each participant to aid in spatial registration and normalization. Additionally, a field map image was acquired for each participant to assist in unwarping procedures for areas susceptible to distortion.

### **fMRI Preprocessing and Univariate Analyses**

Prior to analysis, EPI timeseries data were preprocessed using conventional procedures from SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>) including slice time correction, motion correction with a six-parameter rigid-body realignment procedure, unwarping, co-registration, segmentation, and normalization to MNI stereotactic space. Co-registration aligned all images to the T2 in-plane anatomical, followed by the MPRAGE anatomical. Following co-registration, the MPRAGE was segmented into cerebrospinal fluid (CSF), white matter, and gray matter. Nonlinear warping parameters were computed to normalize each participant's grey matter image to a grey matter template in MNI space, and these warping parameters were applied to all functional images, which were resampled into 3-mm isotropic voxels. Finally, potential artifacts in the EPI data were mitigated using the GLMdenoise procedure (<http://kendrickkay.net/GLMdenoise/>) (Kay, Rokem, Winawer, Dougherty, & Wandell, 2013). This denoising procedure begins by identifying task-unrelated brain voxels from a univariate general linear model (GLM), and then uses the timeseries of these “noise pool” voxels to develop a set of nuisance regressors, which we then regressed out of the timeseries of all voxels to generate a denoised timeseries. To ensure independence of data across runs, a 5-fold cross-validation procedure was performed where the 10 runs of the study were split into 5 pairs and the GLMdenoise cross-validation procedure was implemented within each of the pairs.

## Networks of Interest

Networks of interest were obtained from McDermott, Szpunar, and Christ's 2009 ALE meta-analysis. Their meta-analysis identified one set of brain regions consistently associated with autobiographical memory, derived from peak coordinates reported in 14 prior fMRI studies in which activation associated with retrieval of personal events (typically cued with words, sentences, or pictures) was compared to that of a control task. They also identified another largely non-overlapping set of regions associated with the retrieval of laboratory-based memories, derived from peak coordinates reported in 18 prior fMRI studies in which participants made recognition judgments on either word, picture, object, or face stimuli that had been studied in a laboratory setting (the activation maps in these studies were typically derived from contrasts of hits > correct rejections). The "Autobiographical Network" included areas such as the medial prefrontal cortex, posterior cingulate/retrosplenial cortex, angular gyrus, and bilateral medial temporal lobe (hippocampus/parahippocampal gyri). The "Laboratory-based Network" included areas such as the left inferior frontal gyrus, bilateral middle frontal gyri, bilateral frontal operculum, precuneus, bilateral inferior parietal cortex, posterior cingulate cortex, and left medial temporal lobe (posterior parahippocampal gyrus). Overlap between the Autobiographical Network and the Laboratory-based Network was very limited – indeed, the only shared regions were a few small clusters in the lateral inferior frontal gyrus, posterior cingulate cortex, and thalamus.

The FDR-corrected ALE maps were obtained from McDermott and colleagues (2009) and resampled to 3 mm<sup>3</sup> voxel resolution to create two networks of interest to use as masks in the following analyses (**Figure 3.2**). The Autobiographical Network (originally 2580 voxels) and Laboratory-based Network (originally 1536 voxels) were then modified to ensure coverage in all

of our participants, to exclude all overlapping voxels (94 voxels), and to equate their total size. The latter was done to ensure that any differences in classification performance between the two networks could not be attributable to a greater number of features (i.e., voxels) in one network. These procedures resulted in an Autobiographical Network with 1432 voxels and a laboratory-based mask with 2484 voxels. Subsequently, the most significant 1432 voxels in the Laboratory-based Network were retained, and the ALE values of the voxels within each network were binarized to create masks.

### **Multi-Voxel Pattern Analysis (MVPA)**

MVPA was applied within each network of interest to evaluate the sensitivity of the BOLD activation patterns to photographic source (Self vs. Other) and pre-exposure status (Previewed vs. Non-previewed). MVPA was conducted in MATLAB with the Princeton MVPA Toolbox (<http://code.google.com/p/princeton-mvpa-toolbox>) and custom code. The unsmoothed timeseries data were detrended to eliminate both linear and quadratic trends and then z-scored. No feature selection was implemented (i.e., all voxels with a given network-of-interest mask were used as features). For each trial, BOLD signal was averaged across the 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, and 7<sup>th</sup> TRs, which correspond to 6-14 s after event sequence onset and thus capture the window of peak activation associated with stimulus processing and evaluation. The resulting single trial activity patterns were then used to train a regularized logistic regression (RLR) algorithm to classify between trials of two different conditions. We have found this classification algorithm to perform well in similar experimental paradigms (Rissman et al., 2016; Rissman et al., 2010; Uncapher et al., 2015). This algorithm implemented a multi-class logistic regression function using a softmax transformation of linear combinations of features (i.e., voxels) with an additional ridge penalty

term as a Gaussian prior on the feature weights. This penalty term provided  $L_2$  regularization, enforcing small weights. During classifier training, the RLR algorithm learned the set of weights ( $\beta$  values) that maximized the log likelihood of the data; weights were initialized to zero, and optimization was implemented with conjugate gradient minimization using the gradient of the log likelihood combined with the  $L_2$  penalty. The  $L_2$  penalty was set to be half of the additive inverse of a user-specified parameter (which we set to a fixed value of 100), multiplied by the square of the  $L_2$  norm of the weight vector for each class, added over classes.

Within-subjects pattern classification was run using a 5-fold cross-validation procedure, with each fold comprised of the data from two runs (corresponding to the same two-run subsets used for GLMdenoise procedure). Within each fold, if the number of trials from each condition were unequal, the trial counts were balanced by randomly discarding trials from the more plentiful condition. Trials from four of the folds were used to train the classifier, and its performance was then assessed by having the classifier predict the condition labels of each trial from the held-out fold. These probabilistic predictions were tabulated across all testing trials and ranked to allow the calculation of receiver operating characteristic (ROC) curves, reflecting the relationship between the classifier's true positive and false positive rate across a range of potential decision boundaries. Our primary classification performance metric was the area under the curve (AUC). This measure, widely used in the machine learning literature and considered more informative than overall accuracy (Bradley, 1997), can be interpreted as the probability that a randomly chosen member of one class has a smaller estimated probability of belonging to the other class than has a randomly chosen member of the other class. In other words, AUC indexes the mean accuracy with which a randomly chosen pair of Class A and Class B trials could be assigned to their correct class (0.5 is random performance; 1.0 is perfect performance). Because

our trial count balancing procedure involved discarding random subsets of trials, we repeated the entire 5-fold cross validation procedure 20 times for each participant and saved the mean AUC. Group-level analyses were implemented as one-sample *t*-tests (two-tailed) comparing the AUC results from a given classification against a theoretical null hypothesis value of 0.5, and these results were subsequently Bonferroni corrected to account for the two comparisons of the AUC results against chance. An additional set of analyses using shuffled class labels confirmed that the empirical chance-level indeed converged on  $AUC = 0.5$ , indicating that no insidious biases were present in our classification workflow.

Although our primary analyses focused on the comparison of classification performance for our two meta-analytically defined networks-of-interest, we also conducted an exploratory whole-brain searchlight mapping analysis (Kriegeskorte, Goebel, & Bandettini, 2006) to provide a more complete portrait of the anatomical distribution of regions sensitive to photographic source and pre-exposure. The searchlight analysis was implemented by training and testing a series of RLR classifiers, each using the voxels within a small spherical mask (radius = 3 voxels; maximum volume = 123 voxels). This process was repeated with spheres centered at all brain voxels within an 80,126-voxel whole-brain mask. Each classification was performed using the same 5-fold cross-validation procedures described above; the only difference was that instead of re-running each classification 20 times with different balanced trial selections, each classification was repeated 5 times (due to the computationally-intensive nature of this analysis), and the mean AUC across iterations was saved at each sphere center. Group-level *t*-maps were created by comparing the mean AUC across subjects to the null hypothesis of 0.5 for each voxel. The resulting maps were corrected for multiple comparisons using AFNI's 3dClustSim, which employs Monte Carlo simulations to calculate the requisite cluster size

needed to achieve a whole-brain corrected threshold of  $p < 0.05$ . This procedure requires an estimate of the empirical smoothness of the data under null hypothesis conditions, which we derived by re-running the searchlight classifications 20 times using shuffled class labels and averaging the resulting maps; smoothness was computed using AFNI's 3dFWHMx. Using this method, we determined that the combination of a voxel height threshold of  $p < 0.005$  (one-tailed) and a minimum cluster size of 36 voxels yielded appropriate correction at  $p < 0.05$ .

## RESULTS

### Behavioral Results

Overall, participants were 89.0% correct in indicating the photographic source (Self vs. Other) of the depicted event sequences, which was well above chance ( $t_{(17)} = 24.506, p < 10^{-13}$ ). Although the experimental task did not prompt subjects to indicate the pre-exposure status of events, participants' performance can be further separated based whether the photographs of an event had been previously encountered during Phase 2 (Previewed) or whether they were being encountered for the first time (Non-previewed); **Figure 3.3A**. A repeated measures ANOVA on the accuracy revealed no main effect of photographic source (Self events: 89.8%, Other events: 88.1%;  $F_{(1,17)} = 0.744, p = 0.401$ ), but there was a main effect of pre-exposure (Previewed events: 90.9%, Non-previewed events: 87.0%;  $F_{(1,17)} = 19.348, p < 10^{-3}$ ). There was also a significant interaction between photographic source and pre-exposure ( $F_{(1,17)} = 22.624, p < 10^{-3}$ ) such that Self events were more successfully labeled as "Self" when they had been Previewed (93.7%) than when they were Non-previewed (85.9%) ( $p < 10^{-4}$ ), whereas Other events were equally likely to be successfully labeled as "Other" when they had been Previewed (88.1%) as when they were Non-previewed (88.1%) ( $p = 0.934$ ).

We also analyzed the mean reaction times of trials with correct photographic source judgments; **Figure 3.3B**. A repeated measures ANOVA revealed no main effect of photographic source (Self events: 2.108 s, Other events: 2.905 s;  $F_{(1,17)} = 0.231, p = 0.637$ ). However, there was a main effect of pre-exposure (Previewed events: 2.065 s, Non-previewed events: 2.141 s;  $F_{(1,17)} = 14.026, p < 10^{-2}$ ). There was also a significant interaction ( $F_{(1,17)} = 14.026, p < 10^{-2}$ ), such that Self events more rapidly labeled as “Self” when they had been Previewed (2.040 s) than when they were Non-previewed (2.183 s) ( $p < 10^{-3}$ ), whereas Other events had comparable RTs whether they had been Previewed (2.091 s) or Non-previewed (2.098 s) ( $p = 0.784$ ).

### **MVPA Results**

We assessed the performance of separate classifier models trained and tested using the voxel activity patterns within either the Autobiographical Network or within the Laboratory-based Network. Only trials for which participants indicated the correct photographic source (Self/Other status) of the event were used in the classification analyses. While analyses of the incorrectly performed trials (e.g., false memories and forgotten experiences) could potentially be of interest, participants’ generally high accuracy levels resulted in low trial counts for these conditions, rendering classification too underpowered. Our MVPA analyses first examined the ability of each network to decode the photographic source of individual events (i.e., to discriminate Self events from Other events); **Figure 3.4A**. This classification was highly accurate for both the Autobiographical Network (mean AUC = 0.841;  $t_{(17)} = 21.642, p < 10^{-12}$ ) and the Laboratory-based Network (mean AUC = 0.790;  $t_{(17)} = 13.027, p < 10^{-9}$ ). A direct comparison between the classification performance of each network revealed that the Autobiographical Network outperformed the Laboratory-based Network ( $t_{(17)} = 6.513, p < 10^{-5}$ ).



This robust decoding of photograph source held up when we separately analyzed trials containing only Previewed events or only Non-previewed events, despite analytical power being reduced by around 50% in each case. When the analysis was restricted to Previewed events, classification of Self/Other status remained well above chance in both the Autobiographical Network (mean AUC = 0.796;  $t_{(17)} = 16.261, p < 10^{-10}$ ) and the Laboratory-based Network (mean AUC = 0.746;  $t_{(17)} = 9.998, p < 10^{-7}$ ), with the Autobiographical Network showing significantly better performance ( $t_{(17)} = 3.986, p < 10^{-3}$ ). When the analysis was restricted to Non-previewed events, classification of Self/Other status remained well above chance in both the Autobiographical Network (mean AUC = 0.817;  $t_{(17)} = 16.181, p < 10^{-10}$ ) and the Laboratory-based Network (mean AUC = 0.785;  $t_{(17)} = 11.210, p < 10^{-8}$ ), with the Autobiographical Network again showing significantly better performance ( $t_{(17)} = 2.217, p < 0.05$ ). Finally, we examined whether the Self/Other status of events could be decoded even when never-before-seen photographs of one's own life events (i.e., Self, Non-previewed) were compared to previously seen photographs of someone else's life events (i.e., Other, Previewed). This analysis pits memories for first-hand experiences of an event against second-hand knowledge of someone else's experiences, allowing a critical test of whether a brain-based classifier is capable of distinguishing between these two forms of event recognition. As with the prior analyses, this classification was found to be highly accurate in both the Autobiographical Network (mean AUC = 0.813;  $t_{(17)} = 14.345, p < 10^{-9}$ ) and Laboratory-based Network (mean AUC = 0.772 and  $t_{(17)} = 9.993, p < 10^{-7}$ ), with the former network outperforming the latter ( $t_{(17)} = 4.284, p < 10^{-3}$ ).

We next examined the ability of brain activity patterns within each network to decode the pre-exposure status of individual events (**Figure 3.4B**). We anticipated that this distinction might be harder to decode, given that photograph pre-exposure was not a task-relevant variable (i.e.,

participants were not explicitly asked to judge whether photos were Previewed or Non-previewed). This was indeed the case for the Autobiographical Network, where classification of Previewed vs. Non-previewed trials was no better than chance (mean AUC = 0.519;  $t_{(17)} = 1.512$ ,  $p = 0.298$ ). However, activity patterns within the Laboratory-based Network showed pre-exposure decoding performance that was reliably above-chance (mean AUC = 0.585;  $t_{(17)} = 6.300$ ,  $p < 10^{-4}$ ). Direct comparison of classification performance in the two networks showed a significant advantage for the Laboratory-based Network ( $t_{(17)} = 5.193$ ,  $p < 10^{-4}$ ). We next repeated this analysis separately for Self events and for Other events. When restricting the analysis to Self events, classification performance within the Autobiographical Network improved slightly but remained non-significant relative to chance (mean AUC = 0.539;  $t_{(17)} = 2.057$ ,  $p = 0.111$ ). Classification within the Laboratory-based Network remained above-chance (mean AUC = 0.596;  $t_{(17)} = 6.389$ ,  $p < 10^{-4}$ ) and significantly better than that of the Autobiographical Network ( $t_{(17)} = 2.810$ ,  $p < 0.05$ ). When restricting the analysis to Other events, classification within the Autobiographical Network was at chance (mean AUC = 0.507;  $t_{(17)} = 0.513$ ,  $p = 1.229$ ). Classification within the Laboratory-based Network (mean AUC = 0.554) was significantly better than that of the Autobiographical Network ( $t_{(17)} = -2.231$ ,  $p < 0.05$ ), but when tested against chance, it did not reach significance after correction for multiple tests ( $t_{(17)} = 2.251$ ,  $p = 0.076$ ).

These findings suggest that the Autobiographical and Laboratory-based Networks are preferentially sensitive to different mnemonic characteristics, with the Autobiographical Network being better than the Laboratory-based Network at decoding whether a depicted event is from one's own life and the Laboratory-based Network being better than the Autobiographical Network at decoding whether the photographs of an event have been previously encountered. A

repeated measures ANOVA confirmed this interaction ( $F_{(1,17)} = 73.537, p < 10^{-6}$ ; **Figure 3.5**).

Importantly, this interaction remained significant when the classification analyses were re-run using only the data from the temporally intact event sequences ( $F_{(1,17)} = 19.179, p < 10^{-3}$ ).

While our network-based classification analyses demonstrated a clear dissociation, presumably reflecting the differential contributions of these two networks to memory retrieval, we next used a whole-brain searchlight analysis to evaluate whether the anatomical distribution of decoding effects would roughly adhere to these networks (**Figure 3.6**). As with the network-based analyses, group-level searchlight maps revealed that decoding of photographic source (Self vs. Other) was much more robust than decoding of pre-exposure status (Previewed vs. Non-previewed). This was true throughout much of the brain, and indeed no regions showed significantly greater decoding performance for pre-exposure than photographic source. That Self/Other status was more readily decodable is not surprising, given that this distinction was task-relevant to participants and highly salient. The more interesting question pertains to the relative anatomical distribution of peak decoding performance. The strongest effects for the Self vs. Other classification were observed in regions that overlapped heavily with the Autobiographical Network, including the ventral and posterior aspect of lateral parietal cortex (bilaterally, but with preferential effects in the left hemisphere), medial parietal cortex (including the posterior cingulate and retrosplenial cortex), anterior ventromedial prefrontal cortex, and regions of the medial temporal lobe (including parahippocampal cortex). We note that the robust classification performance observed in the left dorsal motor cortex is likely linked to participants' use of their right hand to make different finger presses for Self and Other trials. In contrast, regions exhibiting significant decoding of Previewed/Non-previewed status showed notable overlap with the regions of the Laboratory-based Network, including prominent

involvement of the left lateral prefrontal cortex and bilateral posterior parietal cortex (including regions concentrated along the lateral bank of the intraparietal sulcus). Interestingly, several of the regions that McDermott, Szpunar, and Christ's 2009 meta-analysis had identified as being associated with both autobiographical and laboratory-based retrieval (i.e., the regions depicted in magenta in **Figure 3.2**, which were excluded from our networks-of-interest analysis) showed significant decoding of both photographic source and pre-exposure in our searchlight analyses. Overall, even though the searchlight mapping procedure was not confined to the regions that comprised the networks used in our core MVPA analyses, we found that decoding of the photographic source and pre-exposure status of events was predominately associated with regions of the Autobiographical Network and Laboratory-based Network respectively. Despite the strong convergence across analytic approaches, we acknowledge that the peak searchlight effects did not map perfectly onto the boundaries of the two networks, nor was the dissociation absolute. Nonetheless, these findings suggest that the brain regions whose activity patterns most strongly code for retrieval of self-relevant life experiences are largely distinct from those that code for one's experiential history with visual stimuli such as photographs.

## **DISCUSSION**

This fMRI experiment utilized wearable digital cameras to assess real-world autobiographical memory retrieval with MVPA methods. Importantly, this approach increased ecological validity by allowing the incorporation of participants' daily life events as retrieval cues without the need for explicit encoding of these autobiographical experiences. As such, this approach may be better than laboratory-based methods in approximating the process of retrieving memories, particularly those that had been formed in naturalistic settings. The experimental

paradigm consisted of participants wearing a camera device for three weeks to automatically photograph life events. Participants then returned to the laboratory a week later where they encountered a subset of photographic event sequences from their lives and the lives of other individuals. Participants were scanned the following day while making mnemonic judgments about the event sequences drawn from their own lives and from the lives of other participants.

MVPA was used to characterize the amount of photographic source and pre-exposure information present in the neural activity patterns of the Autobiographical and Laboratory-based Networks, as identified by McDermott and colleague's 2009 meta-analysis. Even when the networks were matched in size and all overlapping regions were excluded, the Autobiographical Network and the Laboratory-based Network were superior at decoding different mnemonic characteristics. The Autobiographical Network, which included regions such as the medial temporal lobe and medial prefrontal cortex, was better able to decode the photographic source of a given event, whereas the Laboratory-based Network, which consisted of regions such as the left lateral prefrontal cortex, was more accurate at decoding whether photographs of an event had been previously encountered.

Remarkably, the activation patterns associated with pre-exposure could be decoded even though participants were not explicitly instructed to evaluate whether photographs of events were novel. The Laboratory-based Network specifically supported the neural correlates of stimuli recognition. Not only did this network classifier outperform the Autobiographical Network, but the Laboratory-based Network also was significantly better than the Autobiographical Network when restricting analyses to events from other individuals' lives. As such, this showed that the neural signatures of pre-exposure were dissociable from that of photographic source determinations. This is consistent with previous findings that the regions within the Laboratory-

based Network were sensitive to old/new effects (McDermott et al., 2009). In comparison, the Autobiographical Network was associated with photographic source. This is consistent with previous work, which found that several areas within this network have been associated with source and self-referential processes, including the medial prefrontal cortex and medial temporal lobe regions such as the hippocampus (Addis, Moscovitch, Crawley, & McAndrews, 2004; Cabeza & St. Jacques, 2007; Gilboa, 2004; Maguire & Mummery, 1999; Rissman et al., 2016; Svoboda et al., 2006). Critically, these results demonstrate that personally experienced event memories are capable of being distinguished from previously encountered depictions of events, which can be considered secondhand event knowledge. Hence, although recognition of a photograph can involve multiple experiences – where it is possible to remember an event as well as a specific image – these results suggest that it is possible to robustly differentiate between these similar mnemonic processes.

Both the Autobiographical Network and the Laboratory-based Network were able to successfully decode the source of photographs. This indicates that differentiation of events' photographic source involved regions associated with memories formed in both laboratory and naturalistic settings, which could also be discerned from the searchlight maps. This may be due to the cognitive processes involved with the experimental task, as the Self events vs. Other events distinction might require the recollection of personally experienced events as well as recognition of photographic details. Accordingly, in this study, the processes involved in laboratory-based recall and autobiographical retrieval may not be mutually exclusive. Previous work provides evidence of the similarity of these processes. Rissman and colleagues' 2016 experiment assessed whether a MVPA classifier that was trained to distinguish between mnemonic retrieval states for laboratory-based memories from a previous face memory

experiment would be capable of differentiating between the same states for real-world memories. Their results suggest that real-world autobiographical memories and laboratory-based ones are similar enough to generalize predictions from one dataset to another. However, Rissman and colleagues' 2016 experiment differs from the present study in several ways and did not examine the neural activity patterns of previous encounters with stimuli or how they may relate to those of laboratory-based memories.

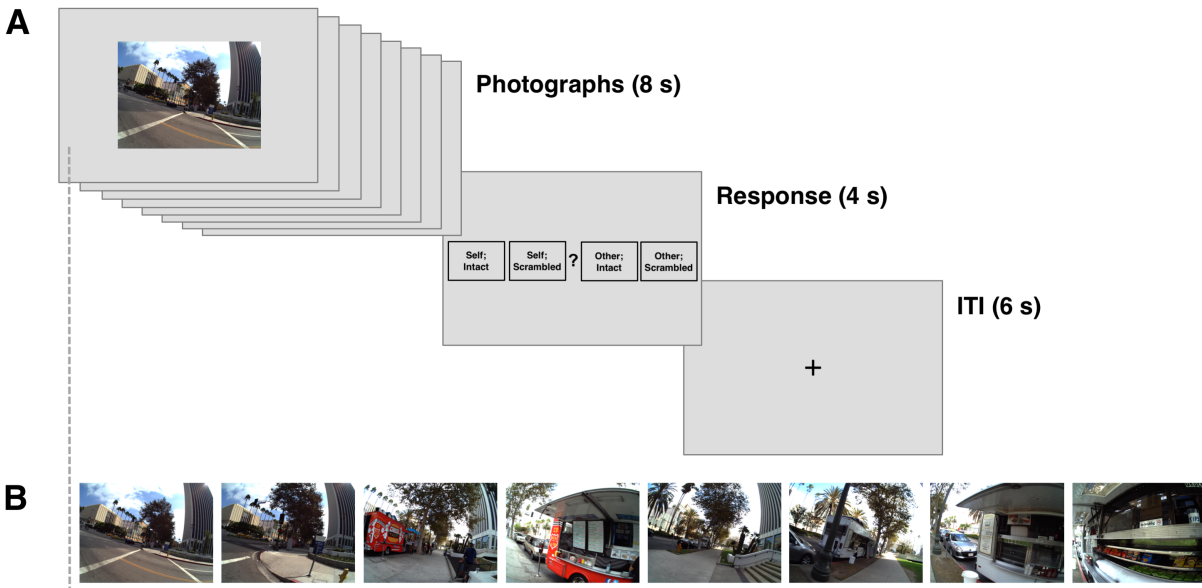
Furthermore, all participants were UCLA undergraduate students, so it was expected that their photographs would reflect some degree of similarity based on their experiences around the university campus. Although the exact extent of overlap in participants' photographs is unclear, the overall novelty of events is expected to be greater for photographs from other individuals' lives. It may be possible that this overlap in photographic content between participants would help the Laboratory-based Network successfully differentiate between the photographic source conditions just based on recognition of similar images. However, while this study did not control for the extent of event overlap between participants' photographs, this experimental paradigm was able to document real-world experiences for use as retrieval cues and increase its ecological validity. Further work is required to delineate the differences in the neural correlates associated with autobiographical memories and laboratory-based memories, especially with regards to the representations of different mnemonic characteristics.

With respect to applied contexts, the use of fMRI techniques and tools may hold important societal implications due to the remarkable accuracy with which brain activity patterns can be used to distinguish recognized stimuli from novel stimuli (Meegan, 2008; Rissman & Wagner, 2012). The growing use of neuroscience evidence in the United States legal system suggests that fMRI-based experiential memory detection approaches could be greatly influential,

especially in the criminal justice system (McCabe, Castel, & Rhodes, 2011; Meegan, 2008). However, before neurotechnologies can be utilized for applied purposes, such as in forensic settings, it is imperative to determine whether scientific evidence legitimately justifies and supports such applications. Rigorous empirical investigation is needed to evaluate both the capabilities and limitations of fMRI memory measurements in order to prevent potentially detrimental or unforeseen consequences. Prior fMRI experiments have demonstrated robust MVPA-based decoding of specific mnemonic states – including novelty or recognition – even on single trials (Rissman et al., 2016; Rissman et al., 2010; Uncapher et al., 2015). The results of the present experiment demonstrated that a MVPA classifier could dissociate critical mnemonic features of real-world autobiographical memories, even for more specific distinctions. The MVPA classifier’s ability to distinguish participants’ own photographs from previously encountered images of other individuals’ lives indicates the possibility that the distributed neural activity patterns evoked during the retrieval of a personally experienced event may be differentiated from those evoked during secondhand event knowledge. Furthermore, the MVPA classifier was capable of differentiating whether or not photographs of events were novel, irrespective of their original source, even in the absence of explicit memory judgments. Therefore, the findings of the study not only further current understanding of autobiographical memory retrieval in naturalistic settings, but may also inform the utilization of fMRI methodology in applied contexts as well.

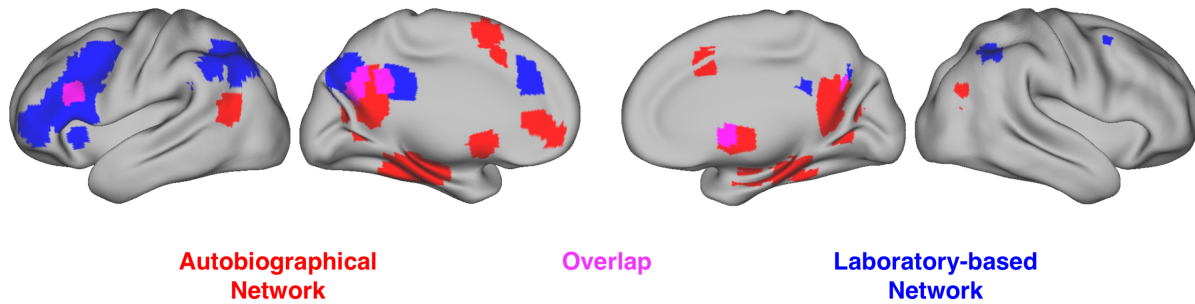


## FIGURES



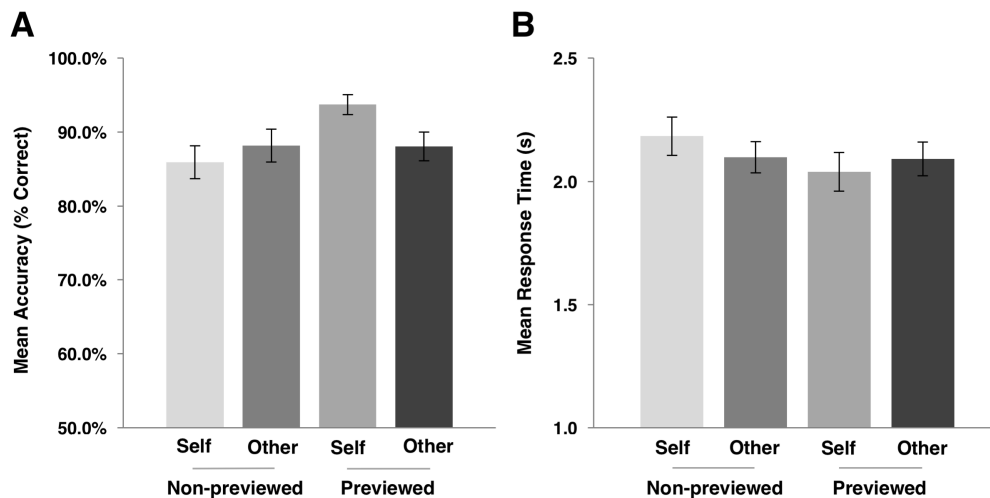
**Figure 3.1**

(A) Schematic of an experimental trial from the fMRI session. In each trial, the eight photographs of an event sequence were presented for 0.8 s each, separated by 0.2-s fixation intervals. Presentation of the event sequence was followed by a 4-s response period. An inter-trial interval (ITI) of 6 s of resting fixation separated trials from one another. (B) An example of an event sequence that might be presented during one trial.



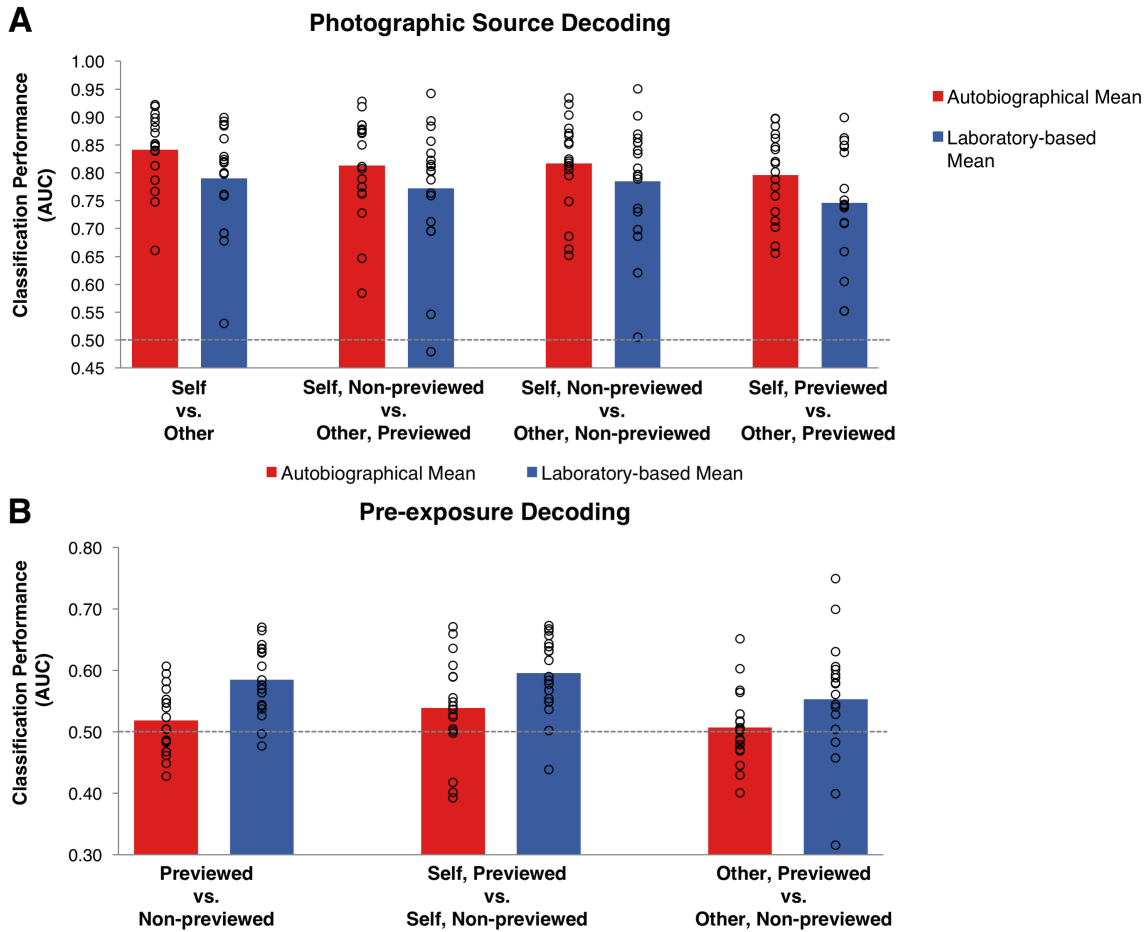
**Figure 3.2**

Networks of interest used for our multi-voxel pattern analyses. These networks were derived from McDermott et al.'s (2009) meta-analysis of fMRI studies of autobiographical memory (red regions) and laboratory-based memory (blue regions). Prior to analysis, areas of overlap (magenta regions) were excluded, and networks were equated for voxel size, with only the top 1432 voxels included in each network of interest.



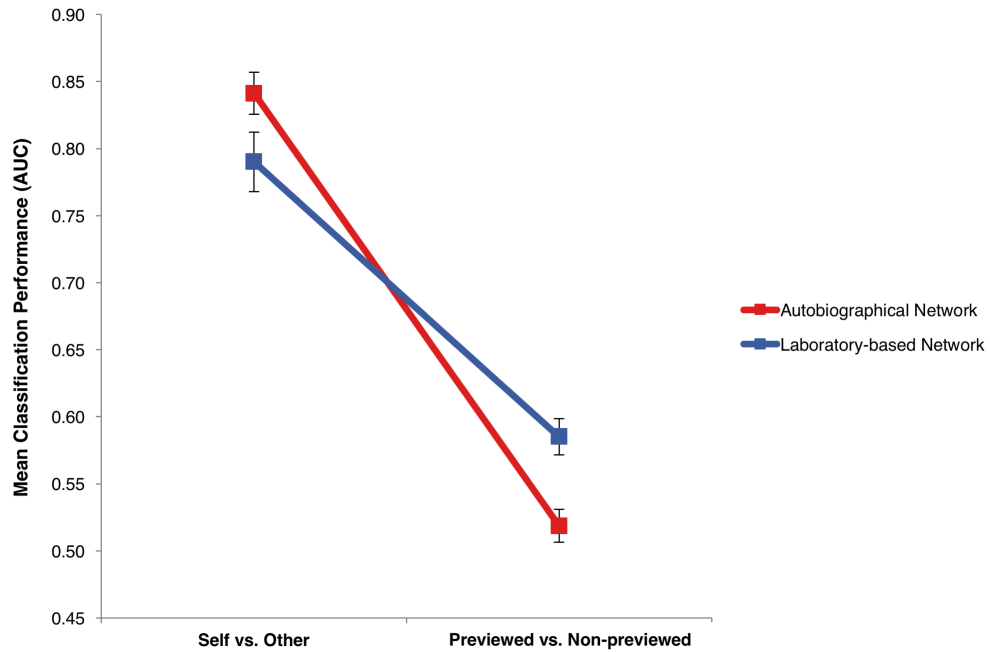
**Figure 3.3**

Behavioral results. Mean accuracy of photographic source judgments (A) and mean response times to correctly performed trials (B) are shown for the individual photographic source and pre-exposure conditions. The error bars represent the standard error.



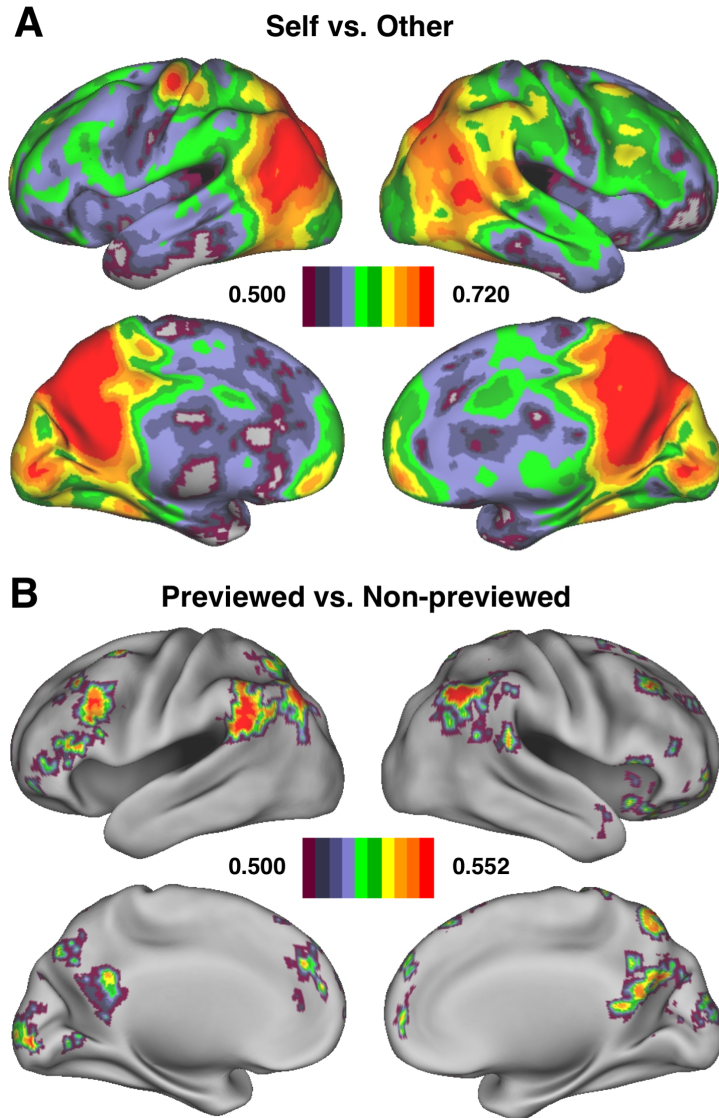
**Figure 3.4**

Classification performance within the Autobiographical Network (red bars) and Laboratory-based Network (blue bars). A) Decoding of photographic source (Self vs. Other) across all trials and for analyses restricted to subsets of trials based on their pre-exposure status. B) Decoding of pre-exposure status (Previewed vs. Non-previewed) across all trials and for analyses restricted to subsets of trials based on their photographic source. The bars depict mean AUC across subjects, and the markers depict the AUC values of individual subjects. The dashed line indicates chance-level performance.



**Figure 3.5**

The interaction between the Autobiographical Network and Laboratory-based Network’s ability to classify photographic source and pre-exposure. Relative to the Laboratory-based Network, the Autobiographical Network demonstrated better decoding of photographic source (Self vs. Other), but poorer decoding of pre-exposure (Previewed vs. Non-previewed). The error bars indicate the standard error.



**Figure 3.6**

Group-averaged searchlight maps for decoding of (A) photographic source and (B) pre-exposure. Only regions achieving whole-brain corrected significance at  $p < 0.05$  are shown. The color intensity of a given voxel indicates the mean decoding performance (AUC) of a classifier trained and tested using activity patterns localized to a 3-voxel radius sphere centered around that voxel. For visualization purposes, the AUC values associated with the upper-bound of the color scale

differs between the two classification maps in order to showcase the dynamic range as well as the peak magnitudes of the respective effects.

## **CHAPTER FOUR**

### **Representation of distinct dimensions of event retrieval along the hippocampal long axis**

## **ABSTRACT**

A number of mnemonic attributes can be simultaneously elicited when viewing photographs of real-world experiences. These include whether the depicted event was from an individual's own life, whether the photographs themselves were novel or familiar, and whether the depicted event was shown to be unfolding in its original temporal order. While the hippocampus has been implicated in retrieval processes, it is still unclear how the hippocampal long axis is sensitive to these three dimensions of memory retrieval. This functional magnetic resonance imaging (fMRI) study utilized wearable camera technology to assess the mnemonic experiences associated with photographic probes in order to assess hippocampal long-axis sensitivity to different facets of memory retrieval. Participants wore necklace-mounted digital cameras to photograph daily life occurrences during a three-week period. Participants underwent fMRI scanning while viewing photographic sequences varying in whether the depicted event was from one's own life (photographic source), whether the photographs were familiar or viewed for the first time (pre-exposure), and whether the event details were unfolding in their veridical sequence (temporal order). The findings of this study demonstrated differential sensitivity to photographic source, pre-exposure, and temporal order along the hippocampal long axis. Anterior hippocampal regions were primarily sensitive to pre-exposure status and temporal order; intermediate regions were predominately sensitive to photographic source and temporal order; and posterior regions are primarily sensitive to photographic source. Taken together, these results reveal dissociable activation along the hippocampal long axis corresponding to different memory dimensions.



## INTRODUCTION

The recall of real-world experiences can be elicited in numerous ways, including through photographs of a particular event. Previous studies of episodic memory retrieval have employed a variety of stimuli – such as photographs – to prompt the recall of mnemonic experiences and further understand their neural correlates. Although a broad network of regions facilitates memory retrieval, medial temporal lobe areas – especially the hippocampal formation – are crucial for the recollection of episodic experiences (Cabeza & St. Jacques, 2007; Maguire & Mummery, 1999). Neuroimaging techniques such as functional magnetic resonance imaging (fMRI) have confirmed the importance of the hippocampus in episodic memory recall, particularly for autobiographical events (Cabeza & St. Jacques, 2007; Kim, 2012; McDermott et al., 2009; Svoboda et al., 2006). Indeed, the hippocampus has been found to contain sufficiently robust representations of episodic details such that its fMRI activity patterns can be used to decode the retrieval of specific autobiographical memories, regardless of their temporal remoteness (Bonnici et al., 2012).

But, while photographs can provide powerful cues that allow individuals to relive and reminisce about events, the use of these stimuli may unintentionally evoke different types of mnemonic processes. It is unclear to what extent the recognition signals elicited by such stimuli in autobiographical memory experiments are due to the recognition of previously encountered photographs or to the reliving of the depicted experience. These processes are often confounded in extant studies. If all the photographic probes in an experiment are novel, then this may elicit encoding of the new photograph as a visual stimulus in addition to prompting the recollection of an old memory (e.g., Gilboa, Winocur, Grady, Hevenor, & Moscovitch, 2004). However, if photographs had been previously encountered prior to the study, then this may evoke both

recognition of that photograph as well as recollection of an event (e.g., Finley et al., 2011). As such, the present study attempts to disentangle the hippocampal contributions to distinct aspects of memory retrieval, including differences between the recall of a personally experienced event and the recognition of the photographs depicting an event.

Neuroimaging assessments have found hippocampal involvement in different retrieval processes. This includes instances where memories contain a self-referential dimension (Addis et al., 2004; Fink et al., 1996; Maguire & Mummery, 1999). Comparisons of personal and impersonal memories have found greater hippocampal activation during the retrieval of personal events (Fink et al., 1996). Furthermore, this activation may be dependent on the level of self-relevance for a memory. One fMRI experiment found that hippocampal activity was modulated by the personal significance of autobiographical memories when the effect of memory recency was covaried out: the greater the events' personal significance, the greater the hippocampal activation (Addis et al., 2004). Overall, hippocampal studies generally suggest that such self-referential effects were located in intermediate and posterior regions along the long axis (Addis et al., 2004; Fink et al., 1996; Maguire & Mummery, 1999).

However, the hippocampus also contributes to other mnemonic processes, such as the detection and encoding of novel stimuli (Ranganath & Rainer, 2003). Neuroimaging experiments have consistently found anterior hippocampal activity in response to novelty, particularly with regards to stimulus novelty (Daselaar, Fleck, & Cabeza, 2006; Strange & Dolan, 2006; Strange, Fletcher, Henson, Friston, & Dolan, 1999; Tulving, Markowitsch, Craik, Habib, & Houle, 1996). Some of these studies have even suggested a functional dissociation between anterior and posterior hippocampal regions. One fMRI study found novelty responses in the left anterior hippocampus and familiarity responses in bilateral posterior areas (Strange et al., 1999). Another

study found similar results in the anterior hippocampus, but recollection effects in the posterior hippocampus (Daselaar et al., 2006). Despite differences in the posterior hippocampus, stimulus novelty effects in the hippocampus seem to be preferentially localized to more anterior regions (Daselaar et al., 2006; Strange et al., 1999).

Additionally, the hippocampus may be involved in processing the temporal features of learned sequences of events during retrieval (Hsieh, Gruber, Jenkins, & Ranganath, 2014; Lehn et al., 2009; Tubridy & Davachi, 2011). Although animal studies have previously shown that the hippocampus contains representations of temporal order, neuroimaging studies have just begun to find effects in the human hippocampus for memory regarding temporal features (Fortin, Agster, & Eichenbaum, 2002; Hsieh et al., 2014; Kesner, Gilbert, & Barua, 2002; Lehn et al., 2009). One fMRI experiment found that anterior hippocampal areas may mediate the retrieval of information pertaining to temporal order: anterior hippocampal regions were more active when the temporal order of sequences from a previously viewed movie were reconstructed based on memory, relative to when inferences alone were made about the temporal order of sequences (Lehn et al., 2009). Furthermore, research has also implicated the hippocampus in temporal order mismatch detection, with greater activation when chronological order mismatches were detected in previously encountered sequences (Kumaran & Maguire, 2006b, 2007). Not only is the hippocampus important for the temporal organization of mnemonic retrieval processes, including mismatch detection of sequential order, but it may also be important for related cognitive processes as well, such as sequence processing and disambiguating sequences with shared commonalities (Kumaran & Maguire, 2006a, 2006b, 2007). However, the majority of hippocampal studies have only assessed the temporal organization of events and sequences that are not necessarily autobiographical in nature. While attempts to remedy this situation have

employed the use of more naturalistic stimuli and paradigms, hippocampal contributions to the temporal organization of episodic and autobiographical memory retrieval are still unclear (Lehn et al., 2009; St. Jacques et al., 2008).

To better understand the contributions of different regions within the hippocampus, experiments have assessed the functions of its longitudinal axis. Previous studies have examined different partitions of the hippocampus along its long axis, with distinct specializations and attributes proposed for each of the constituent regions. Several investigations have divided these regions to form an anterior and posterior split of the hippocampus (e.g., Fanselow & Dong, 2010; Poppenk, Evensmoen, Moscovitch, & Nadel, 2013). Other approaches have segmented the long axis into three portions in order to assess the hippocampal head, body, and tail. Prior studies have utilized percentile-based segmentation to divide the hippocampus based on its medial axis, which is equivalent to the Y axis of anterior commissure-posterior commissure (AC-PC) space (Poppenk et al., 2013). One such experiment used coronal slices to assess the volumes of these regions by defining the anterior 35% of the long axis as the head, the intermediate 45% as the body, and the posterior 20% as the tail (Hackert et al., 2002). In contrast, other experiments have investigated the hippocampal head, body, and tail through percentile-based divisions of equal length (e.g., Collin, Milivojevic, & Doeller, 2015; Greicius et al., 2003). Some studies have even utilized spherical regions of interest placed along the length of the hippocampus – corresponding to the anterior, middle, and posterior portions – to assess functional differences (e.g., Qin et al., 2015). As such, multiple methods have been applied to better understand the functional organization of the human hippocampus. Although these various approaches have provided insights into the long-axis specialization of the hippocampus, the differences along more subtle

gradations of the hippocampal long axis remain unclear, particularly with regards to the relationship of these different regions to distinct aspects of memory retrieval.

Extant fMRI studies that investigate mnemonic engagement of different hippocampal regions typically utilize experimental paradigms where stimuli were encoded in laboratory settings. However, laboratory-based memory paradigms may not be entirely representative of real-world memory retrieval, as they differ in several crucial aspects from autobiographical memory paradigms involving the encoding of personal events. In particular, the two types of experimental paradigms differ in terms of contextual details as well as self-referential information: laboratory-based experimental paradigms are typically not as multifaceted or contextually-detailed as paradigms investigating the retrieval of autobiographical events (McDermott et al., 2009; Rissman et al., 2016). Furthermore, comparisons of the neural correlates facilitating autobiographical and laboratory-based memory retrieval have found few regions in common; the retrieval of laboratory-based and autobiographical events can be distinguished through differential activation, including greater activation of the hippocampus during autobiographical memory retrieval (Cabeza et al., 2004; McDermott et al., 2009). As such, due to these disparities, it is important to determine the involvement of different hippocampal regions not just for laboratory-encoded events, but also for events from the real world.

To increase the ecological validity of current fMRI autobiographical memory paradigms and assess memories formed in naturalistic settings, one experimental approach incorporates wearable digital cameras to photograph participants' life events and utilize the resulting images as mnemonic cues (for review, see Chow & Rissman, 2017). The results of such studies have provided a better understanding of the neural correlates facilitating the retrieval of real-world

events (e.g., Milton, Muhlert, Butler, Benattayallah, et al., 2011; Milton, Muhlert, Butler, Smith, et al., 2011; Nielson et al., 2015; Rissman et al., 2016; St. Jacques, Conway, Lowder, et al., 2011; St. Jacques et al., 2013). One recent study by Rissman, Chow, Reggente, and Wagner (2016) utilized this method to study the neural correlates underlying subjective mnemonic experiences associated with real-world autobiographical memory retrieval. Participants wore digital camera devices to automatically photograph daily life events and underwent fMRI scanning while making explicit memory judgments about photographs from their lives as well as from other participants' lives. This experiment found that the patterns of neural activity in several regions, including the hippocampus, were consistently informative about different mnemonic states: the neural activation patterns within the hippocampus were not only diagnostic of correctly-identified events from participants' lives, but were also diagnostic of recollected events that were recalled with a high level of detail. The present study aimed to expand upon Rissman and colleagues' 2016 experiment, and builds upon previous work by the authors to investigate the representation of mnemonic characteristics corresponding to real-world memories.

The present study was interested in utilizing wearable camera devices to assess hippocampal responses to distinct mnemonic attributes in an experimental paradigm involving naturalistically-encoded events. Although previous experiments using real-world elements have found hippocampal involvement in various aspects of episodic memory retrieval, few have focused on how the hippocampus may support different facets of recall, particularly mnemonic experiences evoked by viewing photographs. A recent study by Nielson, Smith, Sreekumar, Dennis, and Sederberg (2015) is one of the few experiments with naturalistic paradigms that specifically examine multiple aspects of hippocampal activity during memory retrieval by incorporating wearable camera devices to record autobiographical events and using the resultant

photographs as retrieval cues. Participants in the study wore customized smartphones to photograph their life events and document their location with GPS data. During the fMRI scan session, participants were shown photographs from their lives and asked to retrieve the depicted events. This study found that the anterior hippocampus contained both spatial and temporal information. Despite this, much remains unknown regarding the hippocampus' contributions to various dimensions of episodic memory retrieval, and whether such mnemonic experiences are differentially coded along the hippocampal long axis.

To clarify the involvement of the hippocampus during the retrieval of mnemonic features, the current study utilized wearable digital camera devices to examine activation along the hippocampal long axis in terms of the photographic source, pre-exposure, and temporal order of real-world memories. Participants in the study wore a digital camera device for three weeks to automatically photograph their daily life occurrences. A week later, participants were shown brief photographic sequences derived from their own events as well as other participants' events. The next day, participants were scanned while viewing sequences obtained from the same photographic sources and making explicit memory judgments. This study was interested in subtle gradations of activation changes along the hippocampal long axis, so each hippocampus was divided into six equal lengths that were assessed for activity regarding different memory features. Accordingly, the present experiment examined the hippocampal long axis to determine its contributions to distinct mnemonic dimensions derived from real-world memories.

## **METHODS**

With the exception of the temporal order manipulation applied to the experimental stimuli, the study paradigm has been described in detail in Chow, Westphal, & Rissman (In

Preparation). The temporal order manipulation will be described below, in addition to the generalities of the study procedure.

## **Participants**

All 18 participants in this study (9 females; 18 - 22 years old) were healthy individuals with no previous psychiatric or neurological issues. Two additional individuals took part in the study, but their participation was discontinued before being scanned. Participants consisted of University of California, Los Angeles (UCLA) undergraduate students that were native English speakers, right-handed, and had normal or corrected-to-normal vision. All participants were determined to be MRI compatible, with no contraindications. Written informed consent was obtained from participants following the procedures of the UCLA Institutional Review Board.

## **Procedure**

### ***Wearable Cameras***

Participants wore necklace-mounted, 5-megapixel Autographer digital cameras over a period of three consecutive weeks (Autographer, 2015). These small Autographer camera devices contain forward-facing, wide-angle lenses that encompass a 136° field of view. Additionally, the Autographer contains electronic sensors capable of detecting changes in the surrounding environment; these sensors prompt the Autographer device to automatically take color photographs (2592 x 1936 pixels) in response to environmental variations. Participants were in complete control over the use of the cameras, but were unable to review their photographs due to the Autographers' lack of display screens.



## ***Stimuli***

### *Event Sequences*

Experimental stimuli consisted of photographic sequences generated from participants' Autographer images. Forty unique events were identified for each of the three weeks that participants wore their Autographers. For each of these episodes, eight photographs were selected to best represent the temporal unfolding of the given experience within a 15-minute time frame. Each set of eight photographs made up an "event sequence," and 120 event sequences in total were derived from photographs of each participant's life. All event sequences were presented with the same dimensions against a gray background during both the pre-exposure and fMRI scan sessions. Minor edits were applied to certain photographs to standardize stimuli. Event sequences were chosen to avoid overrepresentation of experiences. As a result, event sequences contained a range of different situations, including depictions of various individuals, locations, and activities.

### *Temporal Order of Event Sequences*

During the fMRI scan session, the temporal order of events was manipulated. Participants were presented with event sequences that were temporally unaltered (the "Intact" condition) or temporally altered (the "Scrambled" condition). Half of the event sequences from a participant's life, as well as half of the event sequences from another individual's life, were presented in a temporally intact form. The eight photographs within an intact sequence depicted the event as it originally occurred (i.e., in an A-B-C-D-E-F-G-H order). The other event sequences were presented in a temporally scrambled fashion. To implement these scrambled sequences, the last four photographs within a given event sequence would be temporally rearranged in either an A-

B-C-D-G-E-H-F order or an A-B-C-D-F-H-E-G order. These two temporal alterations were selected to ensure no backward or forward associations in the sequences (Kumaran & Maguire, 2007). An equal number of scrambled sequences consisting of the A-B-C-D-G-E-H-F order and the A-B-C-D-F-H-E-G order were created for each experimental condition. Event sequences were randomly selected to be intact or scrambled at presentation.

Regardless of whether an event sequence was presented in an intact or a scrambled form, the temporal order of the first four photographs within an event sequence was always preserved. This temporal preservation of the first four photographs within a scrambled event sequence created associative mismatch conditions, where the first half of an event sequence was identical to the original experience but the second half of the sequence was novel (Kumaran & Maguire, 2006b, 2007). This associative mismatch condition has been found to elicit hippocampal activity in studies without explicit memory demands (Kumaran & Maguire, 2006b, 2007). The intact event sequences created match conditions, where the temporal progression of an event sequence was identical to that of the original experience. This match condition has been shown to elicit hippocampal activation in experiments utilizing explicit memory demands (Duncan, Ketz, Inati, & Davachi, 2012; Hannula & Ranganath, 2008). As such, the temporal order of an event sequence allowed the assessment of hippocampal engagement during this experimental paradigm.

### ***Experimental Phases***

The experimental paradigm involved three phases: a camera-wearing phase that lasted for three weeks, a photograph pre-exposure phase where participants encountered a subset of stimuli, and an fMRI data collection phase.

### *Phase 1: Camera Wearing*

Participants wore Autographer cameras for a period of three weeks, during which they were instructed to wear the devices for at least eight hours each day in order to document sufficient representative life events. Participants retained full discretion over the time and location of which to use their camera devices. The Autographers were returned after 21 days, with participants capturing a median of 4,332 images per week across the camera-wearing period (range: 1,620 to 10,594 images per week). Participants gave permission for their resulting Autographer photographs to be used in the study, but were unaware of the mnemonic tasks involved in the experimental paradigm.

### *Phase 2: Stimuli Pre-exposure*

The pre-exposure session took place one week after participants last wore their Autographers. During this phase, participants were shown 120 event sequences (the “Previewed” condition), comprised of 60 events from participants’ own lives and 60 from another participant’s life. Participants were tasked with making judgments about the distinctiveness of each sequence using a 4-item scale, from “Non-distinctive,” “Somewhat Non-distinctive,” “Somewhat Distinctive,” and “Distinctive.” Participants were not provided with information regarding the original source of the event sequences. Participants were also not told to encode the depicted sequences. The Previewed condition consisted of an equal number of event sequences that had been selected at random from each of the three weeks that the Autographer cameras were worn. The remaining 60 event sequences from participants’ own images and the remaining

60 sequences from the other individual's life were not shown to participants prior to the fMRI scan; these event sequences constituted the "Non-previewed" condition.

As with the fMRI scan session the following day, event sequences were randomly presented during the pre-exposure session without more than three consecutive sequences belonging to the same condition. The timing of event sequence presentation was the same for the pre-exposure session and the fMRI session: each photograph in an event sequence was presented for 0.8 s, followed by a 0.2-s fixation after each image. Participants were allotted 4 s to respond after the presentation of an event sequence. Trials were separated by a 6-s interstimulus interval. The pre-exposure session and fMRI scan session were equated as closely as possible.

### *Phase 3: fMRI Scan Session*

The day after the pre-exposure session, participants underwent fMRI scanning. During this session, participants were tasked with making explicit judgments about the photographic source and temporal order of the event sequences: the photographic source variable concerns whether images in an event sequence were originally from a participant's own camera or from another individual's camera while the temporal order variable concerns whether event sequences were presented in their original order. Participants were instructed on the task immediately preceding the fMRI scan. Participants were instructed that images within an event sequence were obtained entirely from their own camera (the "Self" condition) or from a camera belonging to another individual (the "Other" condition), and they should indicate their photographic source judgment as such. Participants were also instructed to determine whether event sequences were presented in a temporally intact or a temporally scrambled manner. Additionally, participants were informed that they had previously encountered event sequences during the pre-exposure

session, but were not tasked with indicating whether events were Previewed or Non-previewed. Participants indicated their photographic source and temporal order responses using a 4-item response scale that consisted of “Self and Intact,” “Self and Scrambled,” “Other and Intact,” and “Other and Scrambled.” Prior to the fMRI task instructions, participants should have been unaware of the experiment's memory component. Accordingly, participants should not have been purposely encoding events while wearing their Autographer camera devices. Moreover, participants should not have been exposed to their event sequences before the pre-exposure session. Overall, this approach allows for the approximation of autobiographical memory processes as utilized in the real world.

During fMRI data acquisition, participants were scanned while making mnemonic judgments about 240 event sequences. These 240 event sequences were evenly distributed across the eight experimental conditions, which were derived from the factorial combination of the photographic source (Self vs. Other), pre-exposure (Previewed vs. Non-previewed), and temporal order (Intact vs. Scrambled) variables. Event sequences were randomly assigned to the different conditions. Behavioral indices, including reaction times, were collected. Missing responses as well as incorrect answers for both the photographic source and temporal order of event sequences were removed for the following analyses such that only trials in which both variables were correctly identified were utilized.

As with the pre-exposure session, event sequences in the fMRI scan session were randomly presented such that only three consecutive sequences would include identical conditions. The timing of each trial in the fMRI scanning session was equivalent to that of the pre-exposure phase. Each event sequence was presented for 8 s, where constituent images were shown for 0.8 s followed by a 0.2-s fixation screen. After event sequence presentation,

participants had 4 s to indicate a response. Trials were separated by a 6-s inter-trial interval (ITI) to prevent hemodynamic response overlap. The structure and timing of the experiment can be seen in **Figure 4.1**.

### **fMRI Data Acquisition**

A Siemens 3.0 Tesla Tim Trio whole body human MRI scanner at the UCLA Staglin IMHRO Center for Cognitive Neuroscience was used to collect all fMRI data. Functional images were acquired with a whole-brain T2\*-weighted echo-planar imaging (EPI) sequence (TR = 2000 ms, TE = 27 ms, flip angle = 75 degrees, FoV = 192 mm, and resolution = 3.0 x 3.0 x 3.5 mm voxels). EPIs were collected in an interleaved sequence with 35 axial slices. Each of the 10 runs in the study consisted of 221 volumes, where the first 3 volumes were removed on account of T1 stabilization. In addition, a whole-brain high-resolution T1-weighted magnetization prepared rapid gradient echo (MPRAGE) image (resolution = 1.0 x 1.0 x 1.0 mm voxels) and a T2-weighted in-plane anatomical image were obtained for each participant. To aid with unwarping procedures for regions liable to distortion, a field map image of magnetic field inhomogeneities was also collected for each participant.

### **fMRI Data Analysis**

Preprocessing and analysis of fMRI data were performed with Statistical Parametric Mapping 8 software (SPM8; <http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>). Functional images were preprocessed with conventional techniques, including slice time correction for differences in slice acquisition timing, motion correction using a six-parameter rigid-body realignment procedure, unwarping with the field map, co-registration, segmentation, and

normalization to Montreal Neurological Institute (MNI) stereotactic space. Co-registration of images involved first registering the T2-weighted coplanar anatomical image to the mean functional image, with the MPRAGE then being registered to the T2-weighted coplanar anatomical image. The MPRAGE was segmented by tissue type into cerebrospinal fluid (CSF), white matter, and gray matter. The gray matter image was subsequently warped to the Montreal Neurological Institute (MNI) gray matter template image. The resultant nonlinear transformation parameters were applied to the functional images, which were then resampled into 3-mm isotropic voxels. Functional images were not smoothed to prevent distortion to the medial temporal lobe. GLMdenoise was applied to denoise the functional images by creating additional noise regressors for a general linear model (GLM) analysis using task-unrelated voxels (Kay et al., 2013).

After preprocessing and denoising, subject-level univariate analyses were conducted on the event-related fMRI data using the GLM framework. The eight experimental conditions were included in the GLM as event regressors, and were convolved with a canonical hemodynamic response function. These experimental conditions were modeled for responses that were correct for both the photographic source and temporal order. All incorrect answers, combined across the eight conditions, and non-responses were modeled as well. Additional GLM regressors included covariates of non-interest, such as linear trend, session mean, and the six movement parameters obtained from the realignment preprocessing procedures. A high-pass filter with a period of 128 seconds was applied. Group-level analyses were conducted on the whole-brain for contrasts of interest using random effects *t*-tests. Data analyses only included trials in which the participant correctly identified both the photographic source and temporal order of an event sequence.

## Regions of Interest (ROIs)

Hippocampal regions of interest were generated from the probabilistic Harvard-Oxford atlas with a 50% tissue probability threshold (Desikan et al., 2006). Each hippocampus was further split into six regions through divisions made perpendicular to the hippocampal long axis. This resulted in the long-axis hippocampal ROIs utilized in this study. To create these ROIs, a pitch transform was first applied to each hippocampus such that its long axis was rotated into a horizontal position. Each hippocampus was subsequently divided along the long axis to form six smaller ROIs of approximately equal lengths. The pitch transform was then reversed for all hippocampal ROIs to rotate them back to their initial X coordinates. As a result, these ROIs were partitioned to take into account the angle of the hippocampal long axis. Subject-specific versions of the 12 hippocampal ROIs were created through intersections of the individual ROIs with each participant's subject-level mask to ensure that the resulting ROIs only contained existing voxels.

This study refers to the ROIs within each hippocampus by a combination of ROI number and hemisphere. ROIs were denoted with “L” for left hemisphere regions and “R” for right hemisphere ones. As such, the left hippocampus consisted of the “L1,” “L2,” “L3,” “L4,” “L5,” and “L6” ROIs while the right hippocampus contained the “R1,” “R2,” “R3,” “R4,” “R5,” and “R6” ROIs. Within each hippocampus, smaller ROI numbers indicated more anterior regions along the long axis, such that L1 and R1 represented the most anterior areas and L6 and R6 represented the most posterior areas. **Figure 4.4A** displays the resulting ROIs used in the study. As such, anterior hippocampal regions consisted of L1 and L2 in the left hippocampus as well as R1 and R2 in the right hippocampus. Intermediate regions included L3 and L4 in the left hippocampus in addition to R3 and R4 in the right hippocampus. Posterior regions included L5 and L6 in the left hippocampus as well as R5 and R6 in the right hippocampus. These ROIs



allowed for more fine-grain examinations of changes in activation along the hippocampal long axis.

### **Parameter Estimates**

To assess activity along the long axis of the hippocampus, a parameter estimate extraction procedure was conducted using the hippocampal ROIs. Estimated parameter values ( $\beta$  values, the condition-specific estimates of activity) were first extracted from all hippocampal ROIs. Parameter estimates of univariate activity were obtained for the different levels of photographic source (Self events and Other events), pre-exposure (Non-previewed events and Previewed events), and temporal order (Intact events and Scrambled events). These parameter estimates were extracted for individual levels when collapsed across all others. For instance, Non-previewed events involved activation during novel photographs, regardless of photographic source or temporal order.

To examine whether a specific region exhibited greater activity for one level over another within a variable, the difference between parameter estimates was calculated for each ROI. These difference calculations included subtracting the parameter estimates of Other events from those of Self events (i.e., Self – Other), subtracting the parameter estimates of Previewed events from Non-previewed events (i.e., Non-previewed – Previewed), and subtracting the parameter estimates of Scrambled events from those of Intact events (i.e., Intact – Scrambled). For instance, the difference in parameter estimates for temporal order would involve subtracting the parameter estimates of Scrambled events from the parameter estimates of Intact events. Accordingly, positive values for the parameter estimate difference between the levels of photographic source represented greater activation for Self events, whereas negative values indicated more activation

for Other events. Positive values for the parameter estimate difference between levels of pre-exposure indicated more activity during Non-previewed events, but negative values indicated more activity during Previewed events. Additionally, positive values for the parameter estimate difference between levels of temporal order indicated more activation for Intact events, while negative values represented greater activation for Scrambled events.

The resulting differences in parameter estimates for photographic source, pre-exposure, and temporal order were utilized to determine regional activation. The mean parameter estimate differences were assessed with repeated measures ANOVAs using the hemisphere and ROIs as factors. Pairwise comparisons were performed using Bonferroni correction. One-sample *t*-tests (two-tailed) with Bonferroni corrections were conducted to compare the parameter estimate differences against the null hypothesis (i.e., zero) to assess whether ROIs were differentially sensitive to mnemonic attributes. Within each of the ROIs, Bonferroni corrections were applied to account for the three *t*-tests of parameter estimate differences against the null hypothesis.

## RESULTS

### Behavioral Results

Participants were given the task of judging the photographic source and temporal order of event sequences during the fMRI scan session. Participants used four possible response options – “Self, Intact,” “Self, Scrambled,” “Other, Intact,” and “Other, Scrambled” – to evaluate the depicted events. The behavioral results are shown in **Figure 4.2**. Repeated measures ANOVAs were used to assess the behavioral results and pairwise comparisons were Bonferroni corrected.

The mean reaction times for correct answers across the four response options were not significantly different ( $F_{(1, 17)} = 0.008, p = 0.930$ ). With regards to the reaction times of the eight

conditions, there was only a significant effect of pre-exposure for correct trials ( $F_{(1, 17)} = 7.375, p < 0.05$ ). Participants were faster when correctly responding to Previewed events than Non-previewed events: participants had a mean reaction time of 2.110 s for Previewed events and a mean reaction time of 2.212 s for Non-previewed events. There was no effect of photographic source ( $F_{(1, 17)} = 0.099, p = 0.757$ ) or temporal order ( $F_{(1, 17)} = 1.831, p = 0.194$ ). There was an interaction between the photographic source of an event and its pre-exposure status ( $F_{(1, 17)} = 6.032, p < 0.05$ ), although no simple effects survived Bonferroni correction.

Participants were fairly accurate in determining the photographic source and temporal order of event sequences. When collapsing across the temporal order judgment, participants were correct on an average of 88.958% of trials for the photographic source of the event sequences, which was well above chance ( $t_{(17)} = 24.506, p < 10^{-13}$ ). In comparison, when collapsing across the photographic source judgment, participants were correct on an average of 75.417% of trials for the temporal order of event sequences and their performance was also better than chance ( $t_{(17)} = 14.473, p < 10^{-10}$ ). One-sample *t*-tests (two-tailed) with Bonferroni correction show that photographic source accuracy was above chance across the different pre-exposure and temporal order conditions: Non-previewed, Intact events ( $t_{(17)} = 16.998, p < 10^{-10}$ ); Non-previewed, Scrambled events ( $t_{(17)} = 20.595, p < 10^{-12}$ ); Previewed, Intact events ( $t_{(17)} = 34.324, p < 10^{-15}$ ); and Previewed, Scrambled events ( $t_{(17)} = 18.603, p < 10^{-11}$ ). The temporal order accuracy across photographic source and pre-exposure conditions was above chance as well, which is shown by one-sample *t*-tests (two-tailed) with Bonferroni correction: Self, Previewed events ( $t_{(17)} = 15.225, p < 10^{-10}$ ); Self, Non-previewed events ( $t_{(17)} = 11.302, p < 10^{-7}$ ); Other, Previewed events ( $t_{(17)} = 11.905, p < 10^{-8}$ ); and Other, Non-previewed events ( $t_{(17)} = 8.167, p < 10^{-5}$ ).

Furthermore, one-sample  $t$ -tests (two-tailed) with Bonferroni correction reveal that participants' performance was also above chance across all eight conditions. This included: Self, Non-previewed, Intact events ( $t_{(17)} = 13.853, p < 10^{-9}$ ); Self, Previewed, Intact events ( $t_{(17)} = 26.799, p < 10^{-13}$ ); Self, Non-previewed, Scrambled events ( $t_{(17)} = 9.125, p < 10^{-6}$ ); and Self, Previewed, Scrambled events ( $t_{(17)} = 12.419, p < 10^{-8}$ ). Similarly, participants' performance was also above chance for: Other, Non-previewed, Intact events ( $t_{(17)} = 16.199, p < 10^{-10}$ ); Other, Previewed, Intact events ( $t_{(17)} = 23.779, p < 10^{-12}$ ); Other, Non-previewed, Scrambled events ( $t_{(17)} = 5.711, p < 10^{-3}$ ); and Other, Previewed, Scrambled events ( $t_{(17)} = 8.480, p < 10^{-5}$ ). As such, participants were adept at performing the mnemonic judgments for photographic source and temporal order across all eight experimental conditions.

When taking into account participants' performance across all eight experimental conditions, there were main effects across each of the three factors. A repeated measures ANOVA reveal that there was an effect of photographic source ( $F_{(1, 17)} = 7.867, p < 0.05$ ) where participants were more accurate for Self events, which had a mean accuracy of 71.806%, than Other events, which had mean accuracy of 64.461%. There was also an effect of pre-exposure ( $F_{(1, 17)} = 36.478, p < 0.05$ ). Participants were more accurate for Previewed events, which had a mean accuracy of 71.574%, than Non-previewed events, which had a mean accuracy of 64.722%. There was also an effect of temporal order ( $F_{(1, 17)} = 32.080, p < 0.05$ ). Participants were more accurate for Intact events, where participants had a mean accuracy of 77.732%, than Scrambled events, which had a mean accuracy of 58.565%. Moreover, there was an interaction between the photographic source and the pre-exposure of events ( $F_{(1, 17)} = 6.917, p < 0.05$ ). For Previewed events, participants were more accurate for Self events, which had a mean accuracy of

77.315%, than Other events, which had a mean accuracy of 65.833% ( $p < 10^{-4}$ ). In sum, participants were overall quite accurate in their mnemonic judgments.

## **fMRI Results**

First, the whole hippocampus was assessed for the mean difference in parameter estimates between levels of the three experimental variables. One-sample  $t$ -tests (two-tailed) with Bonferroni corrections were used to compare parameter estimates within the left and right hippocampi against the null hypothesis to determine if there was greater activation for one level over another. These analyses reveal that the left and right hippocampi were differentially sensitive to levels within photographic source, pre-exposure, and temporal order (**Figure 4.3**). For the left hippocampus, there was greater activation for Self events ( $t_{(17)} = 3.591, p < 10^{-2}$ ), Non-previewed events ( $t_{(17)} = 2.894, p < 0.05$ ), and Intact events ( $t_{(17)} = 5.168, p < 10^{-3}$ ). Likewise, for the right hippocampus, there was greater activation for Self events ( $t_{(17)} = 3.283, p < 0.05$ ), Non-previewed events ( $t_{(17)} = 3.260, p < 0.05$ ), and Intact events ( $t_{(17)} = 4.416, p < 10^{-2}$ ). A repeated measures ANOVA was used to assess the parameter estimate differences, but no lateralization effects were found for photographic source ( $F_{(1, 17)} = 0.200, p = 0.660$ ), pre-exposure ( $F_{(1, 17)} = 0.400, p = 0.536$ ), or temporal order ( $F_{(1, 17)} = 0.376, p = 0.548$ ).

However, examination of regional activation along the long axis of the hippocampus showed dissociable sensitivity to these mnemonic features. The anterior, intermediate, and posterior hippocampal regions were differentially engaged by specific levels of the three experimental variables. These hippocampal findings can be seen in **Figure 4.4**.

Assessments of hippocampal divisions along the long axis found that only a subset of hippocampal regions were differentially sensitive to photographic source. Specifically,

intermediate and posterior regions in both hippocampi demonstrated more activation for Self events, relative to Other events. In the left hippocampus, there was greater activity for Self events than Other events in L3 ( $t_{(17)} = 4.934, p < 10^{-3}$ ), L4 ( $t_{(17)} = 3.008, p < 0.05$ ), and L5 ( $t_{(17)} = 2.893, p < 0.05$ ). The corresponding regions in the right hippocampus demonstrated the same effect. Regions R3 ( $t_{(17)} = 5.548, p < 0.05$ ), R4 ( $t_{(17)} = 3.290, p < 0.05$ ), and R5 ( $t_{(17)} = 2.800, p < 0.05$ ) all showed greater activation for Self events, relative to Other events. Only R6 in the right hippocampus demonstrated greater activation for Other events, although this was not significant ( $t_{(17)} = -0.817, p > 0.05$ ). There was an effect of the ROIs across both hippocampi ( $F_{(2.966, 50.427)} = 3.899, p < 0.05$ , Greenhouse-Geisser corrected). The average activation in L3 and R3 was significantly greater for Self events than the average of L1 and R1 (mean parameter estimate difference =  $0.073, p < 10^{-2}$ ) as well as the average of L6 and R6 (mean parameter estimate difference =  $0.083, p < 0.05$ ). This indicates that intermediate regions across the hippocampi were significantly more active for Self events than the most posterior or most anterior regions. Furthermore, there was also a significant quadratic trend in the anterior to posterior activation of the ROIs ( $F_{(1, 17)} = 14.567, p < 10^{-2}$ ). The amount of greater average activation for Self events changed in a quadratic manner such that it peaked in intermediate regions (L3 and R3) and remained elevated through posterior portions (L5 and R5) before diminishing. There was no effect of hemisphere ( $F_{(1, 17)} = 0.163, p = 0.692$ ) and the interaction between hemisphere and ROIs was not significant ( $F_{(5, 85)} = 0.767, p = 0.576$ ). As a result, intermediate and posterior hippocampal areas showed greater activation for Self events.

In contrast, anterior hippocampal regions were differentially sensitive to pre-exposure. There was significantly more activity for Non-previewed events, in comparison with Previewed events, for L1 ( $t_{(17)} = 3.264, p < 0.05$ ) and L2 ( $t_{(17)} = 2.802, p < 0.05$ ) in the left hippocampus.

Anterior regions in the right hippocampus showed activation for Non-previewed events, relative to Previewed events, that was either significantly greater or strongly trending. This can be seen in R1 ( $t_{(17)} = 2.726, p < 0.05$ ), R2 ( $t_{(17)} = 2.638, p = 0.052$ ), and R3 ( $t_{(17)} = 3.320, p < 0.05$ ). Only L5 in the left hippocampus showed greater activity for Previewed events, although this was not a significant difference ( $t_{(17)} = -1.167, p = 0.778$ ). Altogether, there was an effect of the ROIs across both hippocampi ( $F_{(3.147, 53.504)} = 3.413, p < 0.05$ , Greenhouse-Geisser corrected), but no pairwise comparisons survived correction. However, there was a significant linear trend in the anterior to posterior activation of the ROIs across both hippocampi ( $F_{(1, 17)} = 7.136, p < 0.05$ ). That is, sensitivity for Non-previewed events was greatest in more anterior regions (L1 and R1) but diminished linearly towards more posterior regions along the hippocampal long axis. Additionally, the main effect of hemisphere was not significant ( $F_{(1, 17)} = 0.805, p = 0.382$ ), and neither was the interaction between hemisphere and ROIs ( $F_{(5, 85)} = 1.545, p = 0.185$ ). Therefore, whereas anterior hippocampal areas showed greater activation for Non-previewed events, intermediate and posterior regions demonstrated greater activity for Self events. This indicates that pre-exposure and photographic source recruited predominately dissociable regions such that photographic recognition and event recall relied on different areas along the hippocampal long axis.

Anterior and intermediate hippocampal regions were also differentially sensitive to temporal order. In the left hippocampus, there was greater activity for Intact events, relative to Scrambled events, in L1 ( $t_{(17)} = 4.205, p < 10^{-2}$ ), L2 ( $t_{(17)} = 3.391, p < 0.05$ ), L3 ( $t_{(17)} = 3.323, p < 0.05$ ), and L4 ( $t_{(17)} = 2.957, p < 0.05$ ). In the right hippocampus, R2 ( $t_{(17)} = 3.173, p < 0.05$ ) and R3 ( $t_{(17)} = 4.406, p < 10^{-3}$ ) demonstrated significantly more activation for Intact events than Scrambled ones. There was greater activity for Scrambled events only in L6 of the left

hippocampus, although this was not significant ( $t_{(17)} = -0.465, p > 0.05$ ). There was an effect of the ROIs across both hippocampi ( $F_{(5, 85)} = 4.178, p < 10^{-2}$ ). The average activation of L3 and R3 was significantly greater from the average of L6 and R6 (mean parameter estimate difference = 0.068,  $p < 0.05$ ), such that activation in intermediate regions was significantly greater than that of posterior regions. Additionally, there was a significant linear trend in the activity of the ROIs ( $F_{(1, 17)} = 7.316, p < 0.05$ ). The average activation across ROIs was greatest for Intact events throughout the first half of the hippocampus, peaking at L3 and R3, but decreased thereafter. There was also no significant effect of hemisphere ( $F_{(1, 17)} = 0.338, p = 0.569$ ) and no significant interaction between hemisphere and ROIs ( $F_{(5, 85)} = 0.779, p = 0.568$ ). As such, anterior and intermediate hippocampal areas were more engaged during Intact events. Taken together, these findings demonstrate that sensitivity towards different mnemonic features changed significantly along the long axis of the hippocampus.

## **DISCUSSION**

In the present study, hippocampal activation was assessed using a naturalistic paradigm employing wearable cameras to facilitate real-world autobiographical retrieval. Participants first wore digital camera devices throughout the course of three weeks to automatically photograph their life events. A week after wearing their cameras, participants were shown photographic sequences derived from their lives as well as the lives of other participants. Participants were scanned the following day while making explicit memory judgments about the events depicted in the photographic sequences. Activity in response to the event sequences' photographic source, pre-exposure, and temporal order were examined in different regions along the hippocampal long axis. The additional divisions of the hippocampus beyond an anterior and posterior split revealed



gradations of activation differences along the long axis. Moreover, this is the first study to examine the relationship of three distinct features of memory within the long axis of the hippocampus for naturalistically encoded memories.

Differences in the parameter estimates for the experimental levels within the photographic source, pre-exposure, and temporal order variables were used to assess activation. Although this experiment examined each factor in isolation – that is, when collapsed across the other factors – the effects of the combined experimental conditions should only minimally influence the assessed factor. When the left and right hippocampi were assessed in their entirety, they were both sensitive to the three experimental factors. There was greater activity in both hippocampi for Self events, Non-previewed events, and Intact events. This established hippocampal engagement during specific mnemonic event features. However, sensitivities to these different experimental factors were not located in the same regions along the hippocampal long axis.

When the left and right hippocampi were each partitioned into six divisions of equal length along the long axis, analyses revealed a dissociable gradation of activation in response to the experimental factors. Anterior hippocampal regions were primarily sensitive to pre-exposure and temporal order. Specifically, these anterior areas showed more activation for Non-previewed events and for Intact events. Intermediate hippocampal regions were predominately sensitive to photographic source and temporal order, with greater activation for Self events and Intact events. In contrast, posterior hippocampal regions were primarily sensitive to photographic source, with more activity for Self events relative to Other events. Importantly, regions sensitive to pre-exposure were primarily different from those sensitive to photographic source. This demonstrates that the recognition of a photograph may evoke different activation than the recall of a given

event. As such, regions of the hippocampal long axis were differentially engaged by mnemonic features.

Hippocampal contributions to the self-referential dimensions of autobiographical memory have been suggested by prior neuroimaging studies (Addis et al., 2004; Fink et al., 1996; Maguire & Mummery, 1999). The present experiment found photographic source sensitivity – as represented by greater activation for Self events – in intermediate and posterior portions of the hippocampus. These results concur with those of prior findings regarding self-referential engagement of the hippocampus, such as those of Addis, Moscovitch, Crawley, and McAndrews (2004). While their results differed from those of the current study in finding left anterior hippocampal activation, this may be due to the influence of the other mnemonic characteristics that were also assessed in their study, such as emotionality and detail. However, Addis and colleague's findings of hippocampal activity were also bilateral, with activation present in left intermediate hippocampal areas and right posterior hippocampal areas, which roughly correspond with the findings of the current study.

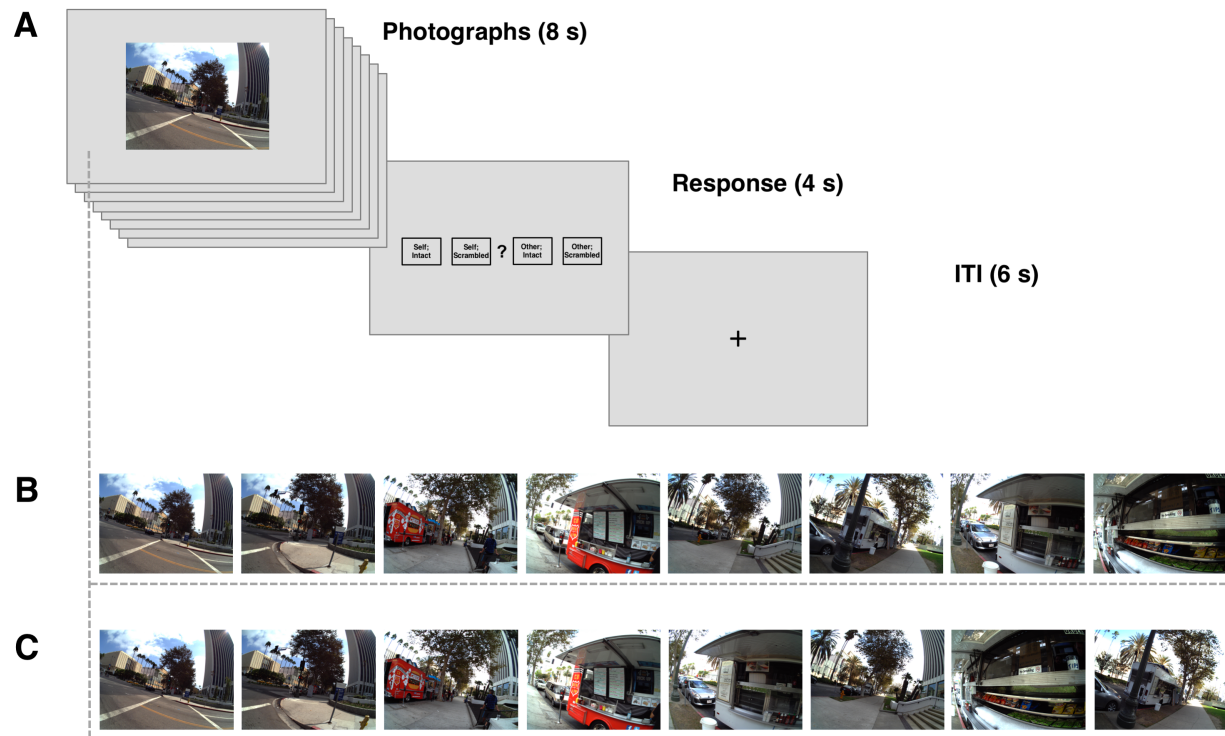
Novelty effects have also been previously demonstrated in the hippocampus (Ranganath & Rainer, 2003). In the current experiment, more anterior regions of the hippocampus were found to be sensitive to pre-exposure by demonstrating greater activation for novel, Non-previewed event sequences, which was similar to the stimulus novelty effects found in this region by Strange, Fletcher, Henson, Friston, and Dolan (1999). However, unlike Strange and colleagues, the present findings did not demonstrate a familiarity effect in the posterior hippocampus. This may be due to the limited number of event sequence presentations in the experiment: whereas Strange and colleague's 1999 study included eight presentations of the same stimuli, participants in the current experiment could maximally encounter event sequences

only once during the pre-exposure session and again in the fMRI scan session. Although Strange and colleague's novelty findings were localized to the left anterior hippocampus, this left lateralized activation may be due to their use of word stimuli (Daselaar et al., 2006; Kopelman, Stevens, Foli, & Grasby, 1998; Milner, 1972). Other experiments utilizing picture stimuli have demonstrated novelty effects in the right anterior hippocampus, which may contribute to the explanation of bilateral anterior hippocampal novelty effects in the findings of the present study (Tulving et al., 1996).

Moreover, the hippocampus has been implicated in temporal aspects of episodic memory, particularly with regards to retrieving sequences of events and their respective temporal order (Lehn et al., 2009; Tubridy & Davachi, 2011). The current study's findings of anterior hippocampal sensitivity to the temporal order of event sequences concur with previous findings regarding this region's involvement in the retrieval of the temporal sequences for prior events (Lehn et al., 2009). However, although previous studies have incorporated the use of naturalistic stimuli to assess hippocampal contributions to temporal aspects of memory retrieval, very few have successfully demonstrated significant hippocampal involvements during these paradigms (Lehn et al., 2009; St. Jacques et al., 2008). One of the few fMRI experiments that assessed hippocampal contributions to autobiographical memories derived from the real world found representations of temporal information in left anterior hippocampus, which coincide with the present results (Nielson et al., 2015). However, their findings specifically concerned the temporal distance between events, and not the sequential order of such occurrences (Nielson et al., 2015). These results suggest that the hippocampus is broadly sensitive to the temporal dimensions of autobiographical memory. Additionally, the results of the present study differed from those of Nielson and colleagues (2015) by demonstrating how activation in response to temporal order

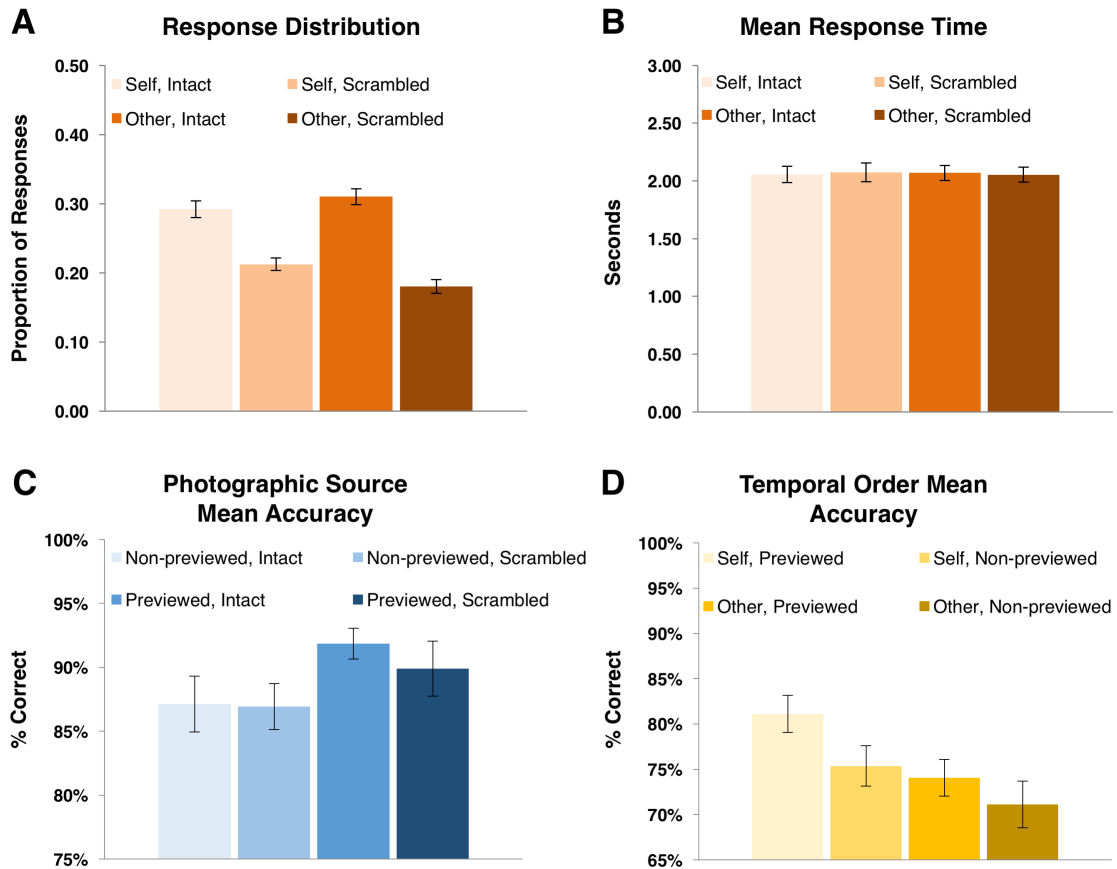
changed along the hippocampal long axis, especially relative to other mnemonic features. The present experiment helps clarify hippocampal involvement in the temporal aspects of real-world autobiographical memories, and is one of the few to successfully assess hippocampal contributions to the temporal organization of such mnemonic processes using naturalistic stimuli. In summary, the current experiment revealed subtle changes in activity along the long axis of the hippocampus with regards to distinct event dimensions. The results of the study suggest that anterior hippocampal areas were sensitive to event pre-exposure and temporal order, intermediate regions were sensitive to event temporal order and photographic source, and posterior areas were sensitive to photographic source. Moreover, this dissociation along the long axis indicates differential hippocampal contributions during the recognition of a personal event in comparison with the recall of a previously encountered photograph. These findings expand upon previous hippocampal research, and extend such results to the recall of autobiographical experiences derived from naturalistic settings. As such, this experiment helps elucidate the contributions of the hippocampal long axis towards the retrieval of real-world, multidimensional autobiographical events.

## FIGURES



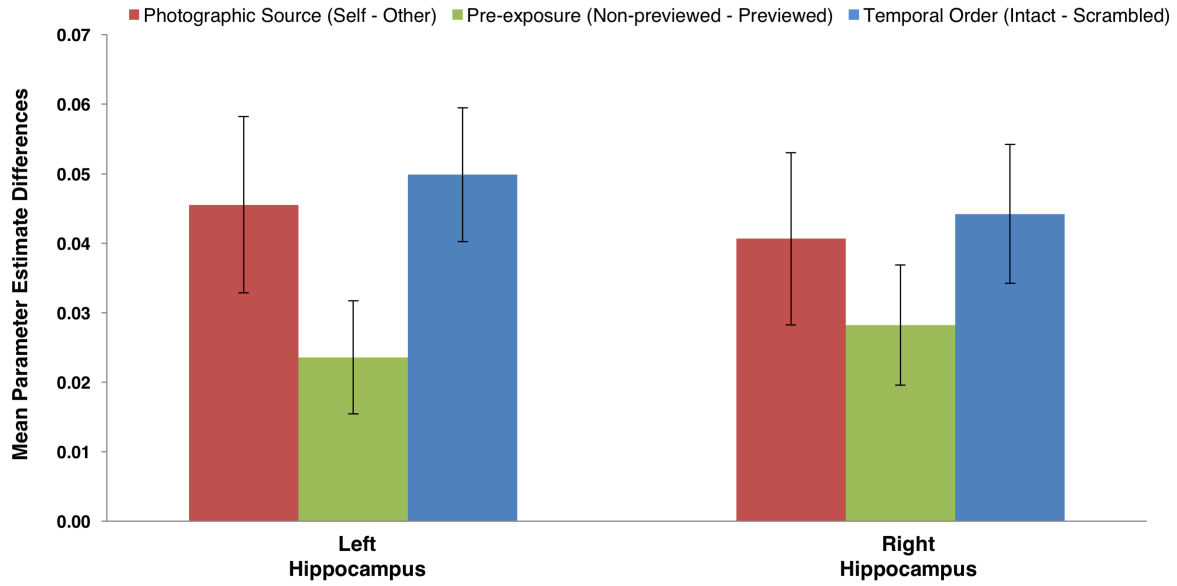
**Figure 4.1**

(A) Depiction of an individual experimental trial during the fMRI session. Event sequences within each trial were presented for 8 s; event sequences consisted of eight constituent images that were each shown for 0.8 s, followed by a 0.2-s fixation. Participants were given 4 s to respond with their mnemonic judgment. There was a 6-s inter-trial interval (ITI) separating each trial. These event sequences could be presented in (B) a temporally intact order or (C) a temporally scrambled order.



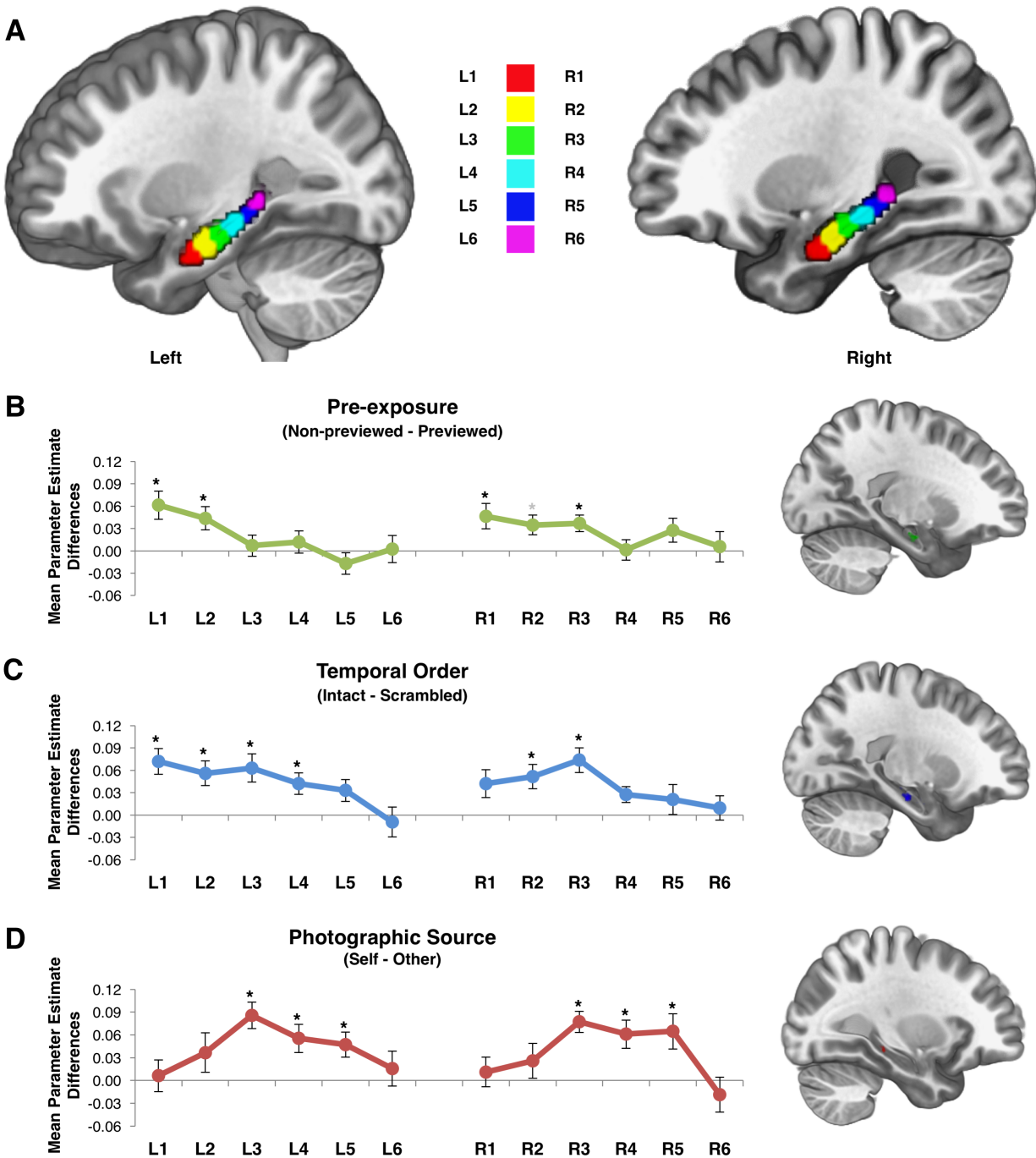
**Figure 4.2**

Behavioral findings with regards to the response options and the experimental conditions. Across the four response options, the resulting (A) response distribution and (B) mean response time are shown. (C) The mean photographic source accuracy is shown as a function of the pre-exposure and temporal order conditions. (D) The mean temporal order accuracy is depicted as a function of the photographic source and pre-exposure conditions. The error bars show the standard error.



**Figure 4.3**

Univariate parameter estimates of activity for the whole hippocampus. Both the left and right hippocampi demonstrated sensitivity to the photographic source, pre-exposure, and temporal order of events. Specifically, both hippocampi demonstrated greater activity for: Self events in comparison with Other ones, Non-previewed events relative to Previewed ones, and Intact events compared with Scrambled ones. The error bars indicate the standard error.



**Figure 4.4**

Univariate parameter estimates across all 12 hippocampal ROIs for the different mnemonic effects. Hippocampal activations for the pre-exposure, temporal order, and photographic source effects are depicted to illustrate the peak clusters. (A) Hippocampal ROIs used in the study. Each



hippocampus was divided into six constituent regions perpendicular to the long axis. The naming schematic for each region denotes its hemisphere and its position on the long axis relative to the anterior of the hippocampus. Left hippocampal ROIs were denoted with an “L” whereas right hippocampal ROIs were indicated with an “R.” Smaller numbers in ROI names indicate closer proximity to the anterior hippocampus. (B) The pre-exposure effects, which were primarily located in anterior regions. (C) The temporal order effects, which were primarily located in anterior and intermediate regions. (D) The photographic source effects, which were primarily located in intermediate and posterior regions. The error bars for the pre-exposure, temporal order, and photographic source effects represent the standard error.

## **CHAPTER FIVE**

### **Differential responsivity of the left and right rostrolateral prefrontal cortex to temporal order violations during the retrieval of real-world memories**

## **ABSTRACT**

The rostralateral prefrontal cortex (RLPFC) critically supports higher cognitive processes, including episodic and autobiographical memory. In particular, this region has been implicated in a variety of retrieval processes, such as retrieval monitoring (e.g., Cruse & Wilding, 2009). However, it is still unclear how the RLPFC supports the retrieval of real-world memories, and whether the left and right RLPFC perform the same mnemonic functions during event recall. In the present investigation, we used a novel experimental paradigm to further elucidate the contributions of RLPFC regions during autobiographical memory retrieval as well as related mnemonic attributes, such as temporal order information. Eighteen subjects wore necklace-mounted digital cameras to photograph their daily lives over the course of three consecutive weeks. A total of 120 photographic sequences, each consisting of eight unique images, were selected to represent distinctive events in participants' lives. Participants underwent functional magnetic resonance imaging (fMRI) scanning while making mnemonic judgments about these events, half of which had been previously encountered during a laboratory session that occurred the day before. Furthermore, half of all events in the fMRI scan session were also presented in a temporally scrambled manner, where the last four images within a photographic sequence were shown in a different order than originally experienced. Brain activity was interrogated as a function of photograph pre-exposure status (previewed vs. non-previewed) and temporal order (intact vs. scrambled). Analyses revealed a striking dissociation in the activation profile of left and right hemisphere RLPFC regions. The left RLPFC showed greater activity for temporally scrambled photograph sequences relative to intact event sequences, but only when such sequences were being experienced for the first time. Since temporal order violations in these sequences could not be detected based on comparison with

one's memory-derived expectations, this result suggests that left RLPFC may play a role in evaluating whether each successive photograph is consistent with one's schema for how events of the type depicted tend to unfold. Interestingly, the right RLPFC also showed greater activation for scrambled than intact photograph sequences, but only when the sequences had been pre-exposed. This suggests a role in monitoring for a memory-based prediction error (i.e., detecting when the photograph sequence was inconsistent with the way it was experienced the prior day). Taken together, this dissociation provides evidence that the left and right RLPFC may be sensitive to distinct facets of temporal order violations and may contribute in different ways during autobiographical memory retrieval.

## INTRODUCTION

The recall of real-world events and experiences is characterized by complex phenomenological qualities, including specific spatiotemporal contexts, that distinguish it from other forms of memory (Tulving, 1972, 1989). Such episodic and autobiographical memory retrieval processes are mediated by a widely-distributed network of brain regions, which consist of areas like the prefrontal cortex (PFC) whose subregions have been implicated in various mnemonic functions (Cabeza & St. Jacques, 2007; Gilboa, 2004; Lepage, Ghaffar, Nyberg, & Tulving, 2000; Ranganath, Johnson, & D'Esposito, 2000; Svoboda et al., 2006). In particular, an anterior portion of the PFC, the rostralateral prefrontal cortex (RLPFC), critically supports a range of higher cognitive processes, including the control and monitoring of episodic retrieval (Dobbins & Wagner, 2005; Gilbert et al., 2006; Ranganath et al., 2000; Reynolds et al., 2006; Simons, Henson, Gilbert, & Fletcher, 2008; Westphal, Reggente, Ito, & Rissman, 2016). This area has also been associated with several other episodic memory retrieval processes – for instance, the assessment of specific contextual details at retrieval (Ranganath et al., 2000) – as well as component operations like retrieval success (McDermott, Jones, Petersen, Lageman, & Roediger, 2000). RLPFC involvement also occurs in related functions such as the integration of relational information or knowledge, particularly in the context of analogical reasoning (Watson & Chatterjee, 2012; Wendelken, Nakhachenko, Donohue, Carter, & Bunge, 2008). Thus, episodic memory retrieval encompasses multiple cognitive functions that rely on the RLPFC.

Intriguingly, prior studies have also suggested hemispheric lateralization of PFC functions (Cabeza, Locantore, & Anderson, 2003; Dobbins, Simons, & Schacter, 2004). The left RLPFC has been implicated in relational memory, particularly in evaluating and integrating relationships between items (Prince, Daselaar, & Cabeza, 2005). More generally, the left RLPFC

has been associated with both reasoning and episodic memory retrieval processes (Westphal et al., 2016). In contrast, the right RLPFC has been implicated in retrieval monitoring (Henson, Rugg, Shallice, Josephs, & Dolan, 1999). Other studies have linked the left RLPFC to the recollection of conceptual details and the right RLPFC to the recollection of perceptual details, with asymmetric sensitivity to novelty between the hemispheres (Dobbins & Wagner, 2005). Given these dissociations, the left and right RLPFC might also show differential sensitivity to other related mnemonic attributes, such as temporal order information. It is unclear how temporal information may interact with novelty detection in RLPFC areas, but such an understanding would help clarify the results of prior studies.

Consistent with its role in a wide range of cognitive tasks, the RLPFC can exhibit differential functional connectivity profiles. That is, the RLPFC is capable of interacting with varying sets of brain areas in order to mediate different processes. For instance, the left RLPFC demonstrated different coupling with regions, as well as networks, depending on whether episodic memory, analogical reasoning, or perception tasks were being performed (Westphal et al., 2016). More generally, the RLPFC itself is part of the frontoparietal control network that helps facilitate processes related to cognitive control and decision-making (Dosenbach et al., 2007; Power et al., 2011; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). Despite differences in functional connectivity across distinct tasks, RLPFC activation has been found to be correlated with regions of the broader frontoparietal control network (Wendelken et al., 2008). However, the RLPFC interacts with other networks as well. This region has also been found to communicate with the ventral attention network, which is involved in stimulus-driven attention (Corbetta & Shulman, 2002; Fox, Corbetta, Snyder, Vincent, & Raichle, 2006). Although previous studies have found distinct functional connectivity profiles of the left and right RLPFC

regions, little is known about hemispheric differences across memory processes within the same study.

The current functional magnetic resonance imaging (fMRI) study aimed to better characterize contributions of RLPFC regions during the retrieval of real-world memories by interrogating brain activity as a function of whether photographs of events were novel or familiar and whether the temporal sequence of events unfolded in the proper order. To accomplish this, wearable digital camera devices were employed to capture photographs of participants' daily life events, which were then used as memory probes in the experiment. A number of memory retrieval studies have used wearable camera technology to capture detailed photographic probes in order to evoke the recall of specific experiences (e.g., Chow & Rissman, 2017; Rissman et al., 2016). Indeed, individuals have reported recalling event details not explicitly depicted in such photographs during these types of studies (e.g., Berry et al., 2007; Finley et al., 2011). Such characteristics lend themselves well to study episodic and autobiographical memory retrieval processes, particularly when these photographs are captured without participants' input so as to avoid biasing memories (Henkel, 2014). This use of naturalistic stimuli may provide a better method in which to assess memories by incorporating life events drawn from individuals' lives, in contrast to laboratory-based tasks that typically involve more generic cues that are not personally-relevant (Gilboa, 2004). As extant neuroimaging methods predominantly use laboratory-based stimuli to assess memory processes, this novel approach has the benefit of offering increased ecological validity and extending such findings to actual life experiences, without sacrificing experimental control.

Previous neuroimaging studies utilizing wearable digital cameras have assessed the functions of other PFC regions during the retrieval of personal memories. This includes areas

such as the medial PFC (St. Jacques, Conway, Lowder, et al., 2011). PFC activation has also been found in other wearable digital camera experiments that investigated topics such as the neural correlates underlying gradations of episodic retrieval (Milton, Muhlert, Butler, Benattayallah, et al., 2011; Milton, Muhlert, Butler, Smith, et al., 2011; Rissman et al., 2016). However, experiments utilizing naturalistic stimuli have never specifically focused on RLPFC regions and their contributions to episodic memory processes, including whether or not the left and right RLPFC perform similar mnemonic functions. If the left and right RLPFC regions are differentially responsive to specific facets of episodic retrieval experiences – such as whether photographs of events were familiar and whether the events were depicted in their original temporal order – then these areas would be associated with separate activation and functional connectivity profiles, which would provide evidence supporting lateralization of PFC function and sensitivity. As such, the use of real-world personal memories to examine the RLPFC’s sensitivity to the recognition of photographs and the depicted events’ temporal order offers a unique approach to help further understand the contributions of this region, particularly with regards to potential hemispheric differences.

## **METHODS**

The experimental paradigm has been previously described in Chow, Westphal, & Rissman (In Preparation). The general procedure will be described below.

### **Participants**

Participants in this study consisted of 18 healthy undergraduate students (9 females; 18 – 22 years old) without prior neurological or psychiatric issues from the University of California,



Los Angeles (UCLA). Two additional individuals participated in the experiment as well, but were discontinued prior to undergoing the fMRI scan session. All participants were right-handed native English speakers with normal or corrected-to-normal vision that were screened for MRI compatibility. In accordance with the procedures of the UCLA Institutional Review Board, written informed consent was obtained from all participants.

## **Procedure**

### ***Wearable Cameras***

Autographer digital cameras were employed to capture still color photographs (2592 x 1936 pixels) of participants' lives, with a subset of the resulting images utilized as naturalistic stimuli to elicit mnemonic judgments (Autographer, 2015). The Autographer is a 5-megapixel camera capable of capturing a 136° field of view using a forward-facing, wide-angle lens. It also includes electronic sensors to detect changes in the external environment, which prompt the camera to automatically take photographs. These necklace-mounted camera devices were worn by the participants over the course of three consecutive weeks, with the participants completely able to control when photographic capture occurred. The Autographer does not have a display screen, so participants were unable to view their own photographs prior to the experimental sessions. Moreover, participants were not informed of the study's memory component, which should minimize purposeful encoding of events captured by the Autographers. As such, incorporating the use of wearable digital cameras may better allow for the study of real-world autobiographical memories.

## ***Stimuli***

### *Event Sequences*

Sequences of eight photographs (referred to as “event sequences”) were derived from participants’ resulting Autographer images and used as the experimental stimuli. A total of 120 event sequences were drawn from each participant’s photographs: 40 unique events were selected for each week the participants wore their Autographer cameras, and for each experience eight photographs that best exemplified the temporal unfolding of these episodes within a 15-minute time period were identified. Event sequences depicted a range of experiences and were selected to minimize overrepresentation of life episodes. Stimuli were standardized through the application of minor edits to specific photographs. All event sequences were presented at the same dimensions against a gray background.

### ***Experimental Phases***

The study paradigm consisted of three phases: the three-week camera-wearing phase, the photograph pre-exposure phase where participants viewed a subset of the event sequence stimuli, and the fMRI data acquisition phase. Participants received instructions prior to each session. Event sequences were randomly assigned to the experimental conditions. During both the pre-exposure session and the fMRI scan session event sequences were presented randomly, with no more than three consecutive event sequences assigned to the same condition. Event sequences were presented in their original, unaltered temporal order during the pre-exposure session, but the temporal order of the event sequences was manipulated during the fMRI scan session. Event sequences were presented using the same timing during both the pre-exposure and fMRI scan sessions: each individual photograph within an event sequence was displayed for 0.8 s with a

0.2-s fixation interval afterwards. After each event sequence was shown, participants were given 4 s to respond accordingly, depending on the session's task. A 6-s inter-trial interval (ITI) followed each trial. The structure of the pre-exposure and fMRI sessions were equated to be as close as possible.

### *Phase 1: Camera Wearing*

Participants were instructed to wear their Autographer cameras for at least eight hours each day over the duration of three weeks in order to photograph an adequate number of representative life events. Depending on participant usage, the Autographer cameras generated between 1,620 and 10,594 photographs each week, with a median of 4,332 photographs produced per week. Participants returned their Autographer cameras after 21 days, and gave permission for their photographs to be utilized as stimuli (although they were not informed of the mnemonic aspect of the study paradigm).

### *Phase 2: Stimuli Pre-exposure*

The pre-exposure session was used to manipulate participants' exposure to select stimuli and was implemented one week after the Autographer cameras were last worn. During this session, participants were presented with 60 event sequences from their own lives and 60 event sequences from another individual's life, for a total of 120 event sequences (the "Previewed" condition). An equal number of event sequences were randomly selected from each of the three weeks the participants wore their Autographers. Participants were asked to indicate the distinctiveness of each event sequence in the Previewed condition using a 4-item scale consisting of "Non-distinctive," "Somewhat Non-distinctive," "Somewhat Distinctive," and "Distinctive."

Participants were not instructed to encode the event sequences, and information about the original source of the photographs was not provided. Participants were not presented with the remaining event sequences (60 event sequences from their own lives and 60 sequences from another individual's life) until the fMRI scan session (the "Non-previewed" condition).

### *Phase 3: fMRI Scan Session*

The fMRI data collection session occurred the day after the pre-exposure session. The session's structure and timing are depicted in **Figure 5.1**. Participants were presented with event sequences and asked to explicitly indicate the corresponding photographic source and temporal order characteristics. The photographic source determination was based on whether the photographs within a sequence were originally captured by participants' own cameras (the "Self" condition) or another individual's camera (the "Other" condition). The temporal order determination was based on whether the images in an event sequence were shown in their original order: the eight photographs within an event sequence were presented in either a temporally unaltered format corresponding to their original A-B-C-D-E-F-G-H order (the "Intact" condition) or a temporally altered format, where the order of the last four photographs were rearranged in an A-B-C-D-G-E-H-F order or an A-B-C-D-F-H-E-G order (the "Scrambled" condition). An equal number of event sequences were presented in the two temporally altered formats of the Scrambled condition, which were chosen to avoid forward or backward associations (Kumaran & Maguire, 2007). Half of the event sequences from each participant's life and half of the event sequences from another individual's life were presented in a temporally scrambled form. Event sequences were randomly assigned to be in either the Intact or the Scrambled condition at presentation during the fMRI scan session. Participants indicated their

determination of event sequences' photographic source and temporal order through the use of four responses, consisting of "Self and Intact," "Self and Scrambled," "Other and Intact," and "Other and Scrambled." Participants did not make a judgment about whether event sequences were in the Previewed or Non-previewed condition, but were informed that a subset of event sequences had been encountered the previous day. In total, participants made mnemonic judgments about 240 event sequences during the fMRI scan session. An equal number of these event sequences were assigned to each of the experiment's eight conditions, which resulted from the factorial combination of the photographic source (Self vs. Other), pre-exposure (Previewed vs. Non-previewed), and temporal order (Intact vs. Scrambled) variables.

### **fMRI Data Acquisition**

All fMRI data were collected with the Siemens 3.0 Tesla Tim Trio whole body human MRI scanner at the UCLA Staglin IMHRO Center for Cognitive Neuroscience. Functional images were obtained using a whole-brain T2\*-weighted echo-planar imaging (EPI) sequence that was acquired through 35 interleaved axial slices (TR = 2000 ms, TE = 27 ms, flip angle = 75 degrees, FoV = 192 mm, and resolution = 3.0 x 3.0 x 3.5 mm voxels). Each of the 10 scanning runs contained 221 volumes, with the first 3 volumes later removed due to T1 stabilization. For each participant, a field map image of magnetic field inhomogeneities was obtained to help with unwarping procedures, in addition to a whole-brain high-resolution T1-weighted magnetization prepared rapid gradient echo (MPRAGE) image (resolution = 1.0 x 1.0 x 1.0 mm voxels) and a T2-weighted in-plane anatomical image.

## **fMRI Data Analysis**

All neuroimaging data were preprocessed and analyzed with Statistical Parametric Mapping 8 software (SPM8; <http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>). Preprocessing of fMRI data were conducted using conventional procedures, including slice time correction for the order of slice acquisition, motion correction utilizing a six-parameter rigid-body realignment procedure, unwarping, co-registration, segmentation, and normalization to Montreal Neurological Institute (MNI) stereotactic space. Co-registration first aligned the T2 in-plane anatomical to the mean function image, followed by registering the MPRAGE to the T2 in-plane anatomical. The MPRAGE was subsequently segmented into gray matter, white matter, and cerebrospinal fluid (CSF). The resulting gray matter image was normalized into MNI space, with the corresponding nonlinear warping parameters applied to the functional images. The data were subsequently resampled into 3-mm isotropic voxels and denoised using GLMdenoise, which utilized task-unrelated voxels to create additional noise regressors for a general linear model (GLM) analysis (Kay et al., 2013). Functional images were smoothed using a 6-mm full width at half maximum Gaussian kernel, and a high-pass filter with a period of 128 seconds was applied.

### ***Univariate fMRI Analyses***

A GLM framework was utilized to conduct subject-level univariate analyses on the event-related fMRI data. GLM event regressors included the experiment's eight conditions – which were only modeled for correct photographic source and temporal order responses – and were convolved with a canonical hemodynamic response function. Incorrect responses were combined across all experimental conditions and modeled separately from non-responses. Other GLM regressors included covariates of non-interest, such as the six movement parameters, linear

trend, and session mean. Whole-brain group-level analyses were implemented for contrasts of interest through the use of random effects  $t$ -tests.

All of the current analyses focus on the pre-exposure and temporal order variables, but were conducted using trials with correct responses to both the photographic source and temporal order of event sequences. A cluster size threshold was applied to data such that  $p < 0.05$ . Monte Carlo simulations from AFNI's 3dClustSim were used to calculate the requisite cluster sizes, based on spatial smoothness estimates from AFNI's 3dFWHMx. For the univariate contrasts to reach a corrected  $p < 0.05$  cluster-level significance, a minimum cluster size of 10 voxels was required for a voxel height threshold of  $p < 0.005$  (two-tailed).

### ***Task-Dependent Functional Connectivity fMRI Analyses***

Task-dependent functional connectivity of the left and right RLPFC was assessed using the generalized psychophysiological interactions (gPPI; <http://www.nitrc.org/projects/gppi>) toolbox, which implements a generalized form of context-dependent psychophysiological interactions (McLaren, Ries, Xu, & Johnson, 2012). Additional GLMs were created in accordance with the same procedure used for the univariate analyses in order to model only a single variable of interest at a time (e.g., only temporal order trials). Multiple regression was performed within each of these separate GLM frameworks using regressors that included the psychological tasks, the seed region's blood-oxygen-level-dependent (BOLD) signal, the psychophysiological interaction term, and covariates of non-interest. The same cluster thresholding procedure applied to the univariate analyses was also utilized to correct the functional connectivity results to  $p < 0.05$ , such that a voxel height threshold of  $p < 0.005$  (one-tailed) required a minimum cluster size of 31 voxels.

## RESULTS

### Behavioral Results

During the fMRI scan session, participants were tasked with indicating the photographic source and temporal order of event sequences. Response options consisted of “Self, Intact,” “Self, Scrambled,” “Other, Intact,” and “Other, Scrambled.” Participants’ performance on the photographic source and temporal order judgments is shown in **Figure 5.2**. Behavioral results were assessed with repeated measures ANOVAs with the post-hoc comparisons of simple effects Bonferroni corrected.

Participants were proficient at performing both the photographic source and temporal order judgments. Participants accurately answered an average of 88.958% of trials for the photographic source judgment alone, which was better than chance ( $t_{(17)} = 24.506, p < 0.05$ , Bonferroni corrected). Participants accurately answered an average of 75.417% of trials based on the temporal order judgment alone and their performance was also better than chance ( $t_{(17)} = 14.473, p < 0.05$ , Bonferroni corrected).

Each experimental variable demonstrated a main effect. There was a main effect of photographic source ( $F_{(1, 17)} = 7.867, p < 0.05$ ). Participants were more accurate for events from their own lives, where they were correct on an average of 71.806% of Self events and 64.461% of Other events. There was also a main effect of pre-exposure ( $F_{(1, 17)} = 36.478, p < 0.05$ ), where participants were more accurate for events that had been previously seen: on average, participants were correct on 71.574% of Previewed events and 64.722% of Non-previewed events. Lastly, there was a main effect of temporal order ( $F_{(1, 17)} = 32.080, p < 0.05$ ). Participants were more accurate for events that were temporally intact, such that they were correct for an



average of 77.732% of Intact events and 58.565% of Scrambled events. Additionally, there was an interaction between photographic source and pre-exposure ( $F_{(1, 17)} = 6.917, p < 0.05$ ): participants were correct on a greater number of Self, Previewed events – with an average accuracy of 77.315% – in comparison to Other, Previewed events, which had an average accuracy of 65.833% ( $p < 0.05$ ).

There was no significant difference in the mean reaction times (RTs) for correct responses ( $F_{(1, 17)} = 0.008, p = 0.930$ ; **Figure 5.2B**). Across the eight experimental conditions, only pre-exposure resulted in a significant effect for the RTs of correct trials: RTs were faster for events that had been previously seen such that the mean RT for Previewed events was 2.110 s and the mean RT for Non-previewed events was 2.212 s ( $F_{(1, 17)} = 7.375, p < 0.05$ ). There was no significant effect for either the photographic source RT ( $F_{(1, 17)} = 0.099, p = 0.757$ ) or the temporal order RT ( $F_{(1, 17)} = 1.831, p = 0.194$ ). While there was an interaction between the RTs of the photographic source and the pre-exposure variables ( $F_{(1, 17)} = 6.032, p < 0.05$ ), none of the simple effects survived Bonferroni correction.

### **Univariate fMRI Results**

Univariate analyses were first utilized to assess neural activation in response to different pre-exposure and temporal order conditions. Two sets of univariate contrasts were designed to identify regions exhibiting two putatively distinct types of prediction error signaling (i.e. sensitivity to temporal order violations). Group-level maps from these results are shown in **Figure 5.3**.

The first set of univariate contrasts isolated regions showing increased activity when the temporal order of an event sequence violated one's schema-driven expectations (“schema-based

prediction error signal”). Such regions must demonstrate greater activation for Scrambled events, relative to Intact events, but only for Non-previewed events (two-tailed  $t$ -test with  $p < 0.005$ ) and not for Previewed events (two-tailed  $t$ -test with  $p > 0.1$ ). This set of contrasts identified left-lateralized activation in frontal regions, including the left RLPFC (**Figure 5.3A**). That is, the left RLPFC only exhibited a temporal order mismatch detection effect for event sequences viewed for the first time. Since these temporal order violations were unable to be determined based on comparison to a past memory, this finding suggests that the left RLPFC may evaluate whether photographs are consistent with pre-existing schemas for how events like the ones depicted tend to unfold.

The second set of univariate contrasts detected areas demonstrating increased activation when the temporal order of an event sequence violated one’s memory-based expectations (“memory-based prediction error signal”). These regions must exhibit greater activation for Scrambled events, relative to Intact events, but only for Previewed events (two-tailed  $t$ -test with  $p < 0.005$ ) and not for Non-previewed events (two-tailed  $t$ -test with  $p > 0.1$ ). This set of contrasts identified a diverse set of regions, including the right RLPFC (**Figure 5.3B**). While the left PFC also demonstrated this same type of activation, this region was closer to the dorsolateral PFC rather than the RLPFC. As such, only the right RLPFC exhibited a temporal order mismatch detection effect for event sequences that had been previewed in their intact order one day before the scan. This region may be involved in generating predictions, in addition to monitoring for prediction errors based on the retrieval of a memory for how the event sequence had previously unfolded.

Importantly, the RLPFC is the only cortical region to display this differential sensitivity to temporal order violations across hemispheres, as identified by the univariate contrasts. The

RLPFC is uniquely involved in determining whether temporally scrambled sequences were entirely novel or if they had been previously seen before and consistent with an existing memory trace. This suggests that these regions are critical in processing the mnemonic features of real-world events.

Although this study was interested specifically in the RLPFC, other cortical areas did demonstrate bilateral sensitivity towards one set of the univariate contrasts. This includes other regions in the frontal lobe. While bilateral regions in the inferior frontal gyrus and middle frontal gyrus were also sensitive to the two sets of univariate contrasts, activation in these areas were not homologous. Dorsolateral PFC areas in the bilateral inferior frontal gyrus and bilateral middle frontal gyrus were sensitive to temporal order violations of memory-based expectations (the memory-based prediction error signal). Only one region bordering the insula and left inferior frontal gyrus was also sensitive to temporal order violations of schemas-based expectations (the schema-based prediction error signal), although this area was not located in the dorsolateral PFC. Additionally, bilateral inferior parietal lobule and bilateral inferior occipital gyrus regions demonstrated sensitivity for the memory-based prediction error signal, which also indicates a more distributed set of brain regions involved in the determination of temporal order violations for previously experienced events.

### **Task-Dependent Functional Connectivity fMRI Results**

To further understand how the functional contributions of these left and right RLPFC areas may differ during scrambled events, task-related functional connectivity was used to characterize the interactions between each RLPFC region and the rest of the brain. Two spherical regions of interest, each with a radius of 9 millimeters, were centered on the coordinates of the

left and right RLPFC cluster's center of mass (MNI coordinates for left RLPFC [-42 49 -7] and right RLPFC [48 35 1]) in order to spatially encompass as much as the identified regions as possible. These left and right RLPFC seeds were used to determine the interactions of RLPFC areas and how they may differ across events when they were temporally out of order. The functional connectivity profiles resulting from the single-condition connectivity contrasts can be seen as group-level maps in **Figure 5.4**.

Although both the left and right RLPFC showed coupling with one another, these seeds demonstrated predominant connectivity with ipsilateral frontal and parietal regions. The left RLPFC seed showed coupling with regions of the left frontoparietal control network: the left RLPFC exhibited connectivity with areas such as the left lateral PFC – including the dorsolateral PFC – and the left inferior parietal lobule. In contrast, the right RLPFC seed showed coupling with areas of the right ventral attention network, such that it displayed connectivity with regions including the right lateral PFC and right temporoparietal junction. Importantly, the right RLPFC seed also showed coupling with the left posterior hippocampus/parahippocampal gyrus. Additionally, both the left and right RLPFC coupled with the dorsomedial prefrontal cortex. However, the left and right RLPFC coupled with predominately different regions of the dorsomedial PFC, with only 17 voxels of overlap. As such, not only did the left and right RLPFC demonstrate distinct activation during temporal order violations in response to different types of event pre-exposure, but these areas were also associated with different profiles of functional connectivity with other regions during temporally scrambled events.

## DISCUSSION

This study utilized wearable digital cameras to capture naturalistic stimuli from real-world events in order to assess the sensitivity of the left and right RLPFC to temporal order and novelty information. Participants wore digital cameras to capture photographs of their daily lives for three consecutive weeks. A week later, participants viewed a subset of photographic sequences, which consisted of events from their own lives as well as those of other individuals' lives. Participants then underwent fMRI scanning a day later while indicating explicit memory judgments in response to different photographic sequences varying by photographic source, pre-exposure, and temporal order. This experiment evaluated neural activation in response to the pre-exposure and temporal order of event sequences, which allowed for whole-brain examination of regions with different activation profiles during temporal order violations of Non-Previewed and Previewed event sequences. To detect brain areas sensitive to such conditions, regions were identified depending on whether they were responsive to temporal order violations of either one's schema-driven expectations or one's memory-driven expectations. These assessments provide a better understanding of regions' specific contributions to the pre-exposure status and temporal order of episodic memories, and how they may differ across the hemispheres.

Importantly, only the RLPFC demonstrated differential hemispheric sensitivity to temporal order violations across the pre-exposure status of events. Analyses revealed a dissociation in both the activation profile and functional connectivity properties of left and right RLPFC regions in response to temporal order violations. The left RLPFC showed greater activity for temporally scrambled photographic sequences, but only when the sequences were novel. In contrast, the right RLPFC also showed greater activity for temporally scrambled photographic sequences, but only when the sequences were familiar. That is, the left RLPFC was sensitive to

temporal order violations of schema-based expectations while the right RLPFC was sensitive to temporal order violations of memory-based expectations. These two regions also demonstrated distinctive interactions with different networks during temporally scrambled event sequences. The left RLPFC was associated with areas of the frontoparietal control network, including the dorsolateral PFC as well as the inferior parietal lobule. In comparison, the right RLPFC was associated with those of the ventral attention network, including areas of the lateral PFC and temporoparietal junction. The only areas that coupled with both the left and right RLPFC were the contralateral RLPFC homologues as well as the dorsomedial PFC. As such, during episodic memory retrieval, the RLPFC demonstrates hemispheric differences not only in activation, but also in regards to interactions with the rest of the brain.

The left RLPFC has been shown to be involved in relational reasoning, including analogical reasoning (Westphal et al., 2016), particularly through the integration and comparison of relationship representations (Watson & Chatterjee, 2012; Wendelken et al., 2008). Left RLPFC regions are engaged during the integration of multiple retrieved relations (Bunge, Wendelken, Badre, & Wagner, 2005), with the number of visuospatial relationships influencing activation (Christoff et al., 2001; Wendelken, Chung, & Bunge, 2012). As such, the left RLPFC in this present experiment may play a role in comparing novel sequences to pre-existing schemas, potentially through the use of inferential reasoning mechanisms. Moreover, the distinct functional connectivity profile across the two RLPFC regions concurs with prior research indicating that these areas can differentially couple with other brain regions depending on the cognitive process (Westphal et al., 2016) or even the specifics of the task being undertaken, such as the type of relational reasoning (Wendelken et al., 2012). The current study found that the left RLPFC coupled with frontoparietal regions during temporally scrambled events. Prior studies

have indicated that the RLPFC is a member of the frontoparietal control network, and it is commonly used to localize the other regions in the network based on correlated activity (Dosenbach et al., 2007; Power et al., 2011; Vincent et al., 2008). Although this present study used single-condition functional connectivity analyses, functional connectivity analyses of left RLPFC seeds during relational and analogical reasoning tasks have demonstrated similar coupling with the frontoparietal control network (Wendelken et al., 2012; Westphal et al., 2016), suggesting that communication with frontoparietal regions is necessary for these processes. However, the current findings only indicate communication with primarily ipsilateral regions of the frontoparietal control network, and further examination must be undertaken to determine why this is the case.

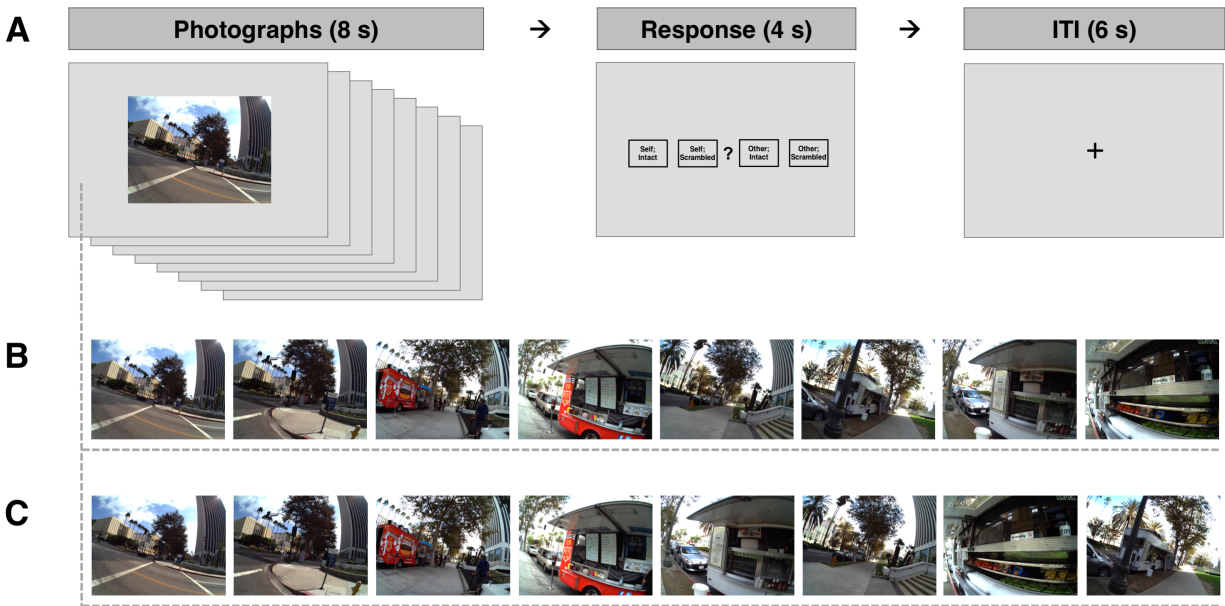
The present right RLPFC findings are also in line with prior studies. The right RLPFC has been associated with episodic memory retrieval tasks (Buckner, Koutstaal, Schacter, Wagner, & Rosen, 1998). This includes retrieval monitoring during episodic memory retrieval (Cruse & Wilding, 2009; Dobbins et al., 2004; Henson, Rugg, et al., 1999; Henson, Shallice, & Dolan, 1999). In particular, Reynolds, McDermott, and Braver (2006) demonstrated that regions of the right RLPFC were sensitive to both episodic retrieval and relational integration processing demands (while left RLPFC regions were sensitive to only one or the other). These prior findings suggest that, while the right RLPFC is also implicated in a variety of cognitive functions, it has a role in processes associated with episodic recall, particularly those related to the monitoring of retrieved information. Accordingly, the right RLPFC in the present study may assist in monitoring and detecting memory-based prediction errors. The current study found right RLPFC connectivity with ipsilateral regions of the ventral attention network. Previous connectivity studies utilizing right RLPFC seeds have found engagement of frontoparietal control network

regions during rest (Vincent et al., 2008). This suggests that the current functional connectivity analyses were indeed measuring task-related connectivity effects, despite the use of single-condition analyses. While the ventral attention network may be a more right-lateralized network (Fox et al., 2006), further assessments should also be conducted in order to determine why right RLPFC connectivity was primarily demonstrated for ipsilateral areas in this network. In addition, the right RLPFC also coupled with the left hippocampus. Prior studies have previously found left PFC connectivity with the left hippocampus, a region critical for memory retrieval (Cabeza & St. Jacques, 2007; Maguire & Mummery, 1999); however, this connectivity only occurred during episodic memory conditions and not for other cognitive processes, such as spatial tasks (Robin et al., 2015). This connectivity further suggests that the right RLPFC contributes to retrieval-related processes.

Overall, the current study demonstrates distinctive differences in the left and right RLPFC's activation and functional connectivity for different facets of retrieval experiences. Although previous experiments have specifically assessed the RLPFC's involvement across several laboratory-based tasks, this study uniquely used wearable digital cameras in order to assess how RLPFC contributions may apply to real-world events. Moreover, this is one of the few studies to examine left and right RLPFC differences in response to the same set of event dimensions: this experiment provides novel information about this area's involvement in temporal order violations, which varies by hemisphere depending on the events' novelty. As such, the present experiment clarifies the RLPFC's contributions and expands them to real-world experiences.

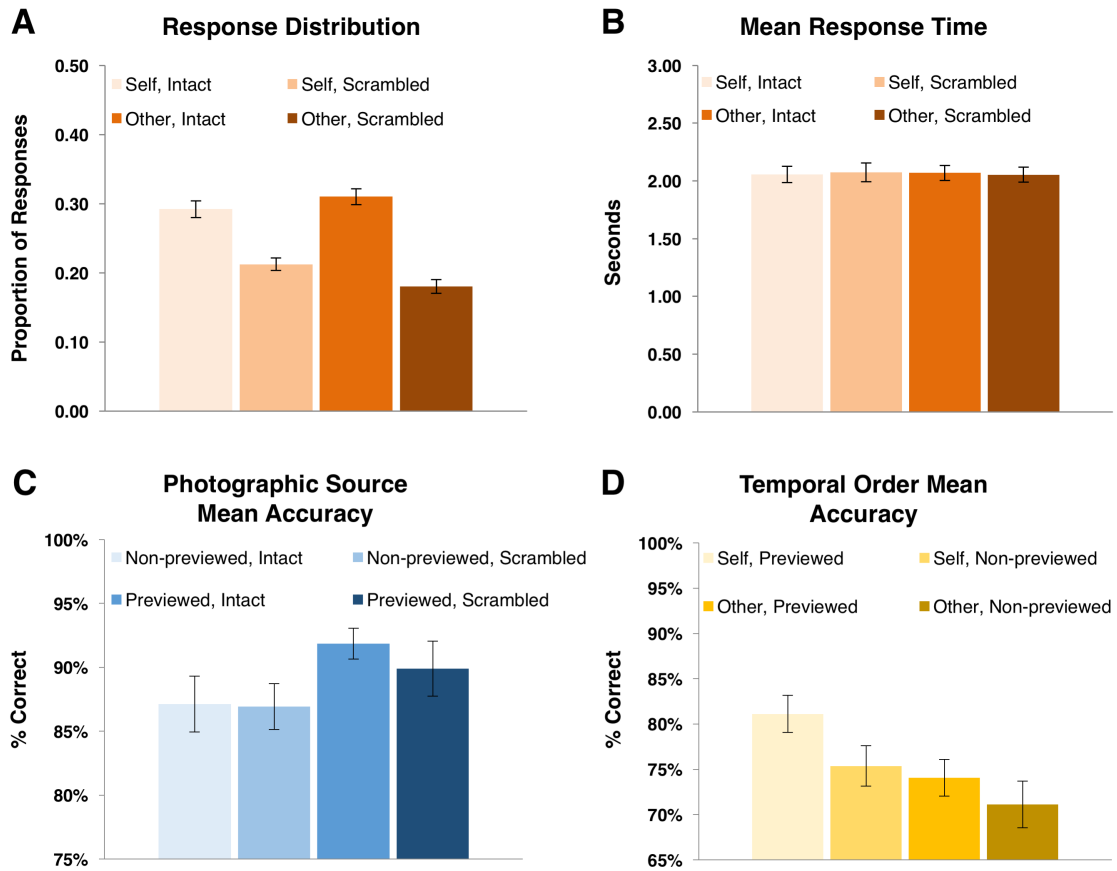


## FIGURES



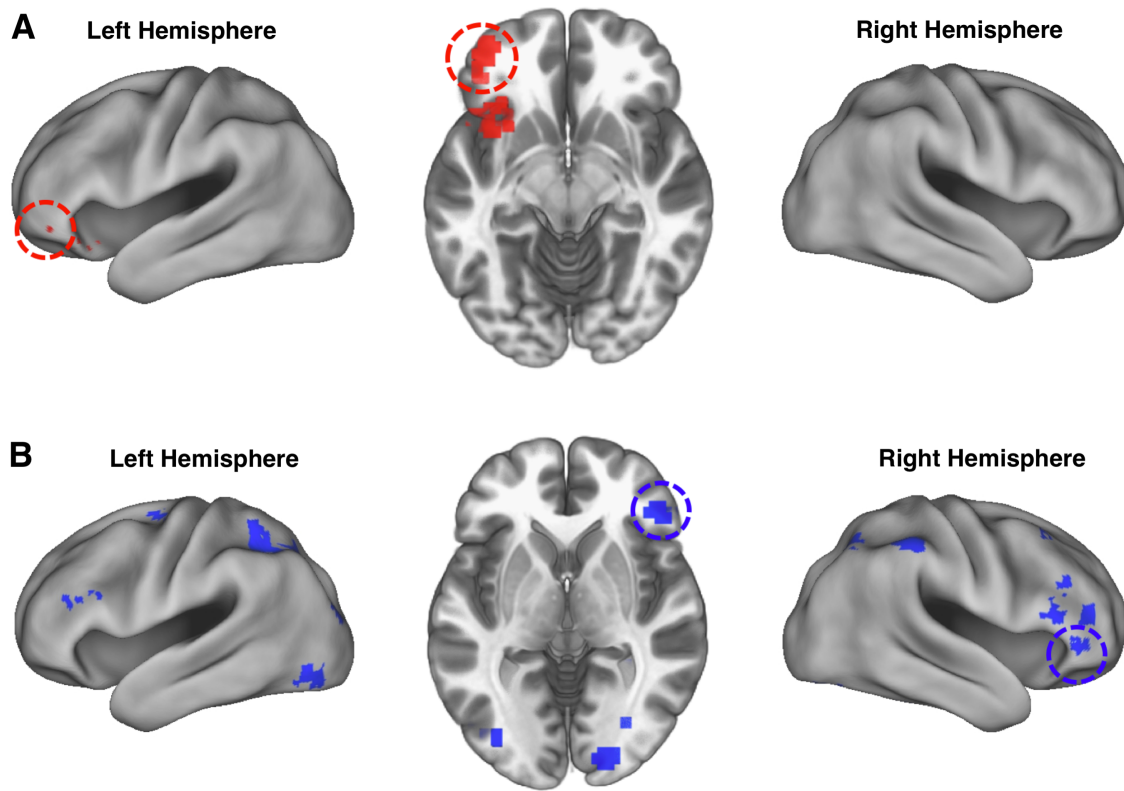
**Figure 5.1**

(A) Diagram of a single trial during the fMRI portion of the experiment. Each of the eight photographs comprising an event sequence was presented for 0.8 s, followed by fixation lasting for 0.2 s. After all photographs within an event sequence were presented, participants were given a 4-s period to respond, with a subsequent 6-s inter-trial interval (ITI) to separate trials. Examples of event sequences presented in a (B) temporally intact manner or a (C) temporally scrambled manner.



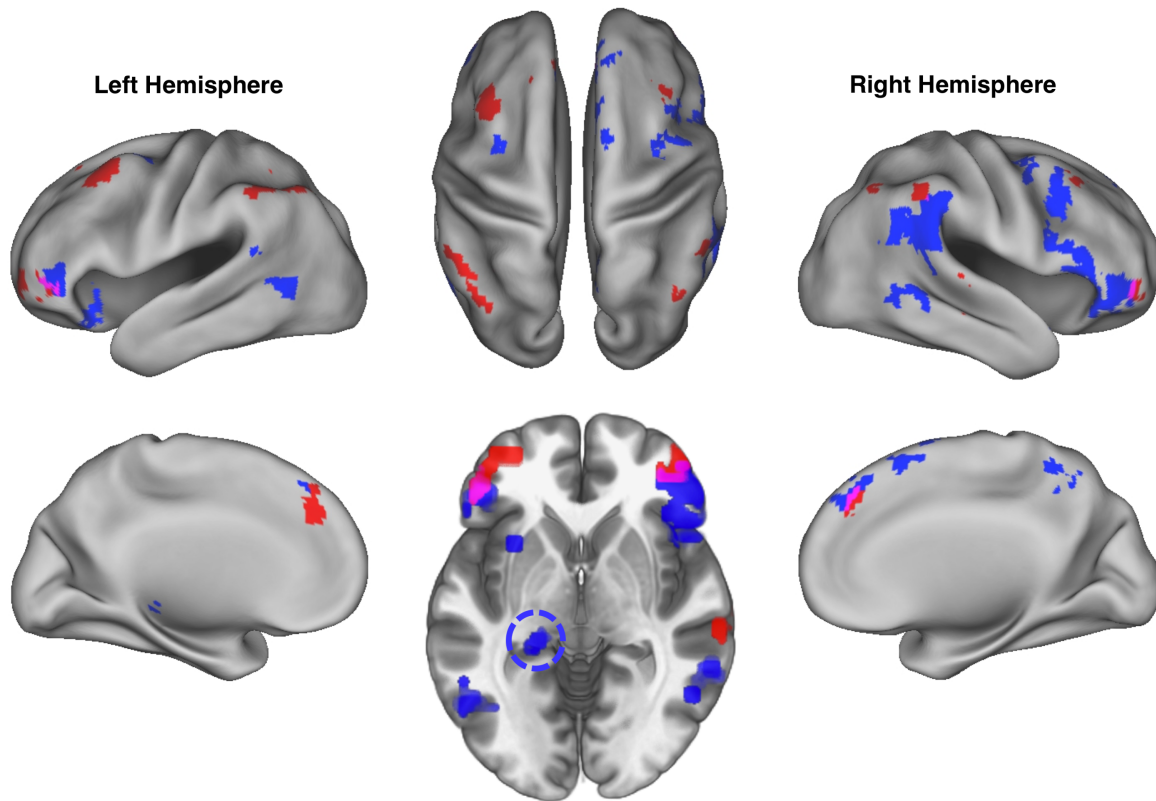
**Figure 5.2**

Behavioral findings for performance across the experimental conditions. The (A) response distribution and (B) mean response time are depicted for the four response options. The mean accuracy is depicted for both the (C) photographic source and (D) temporal order. The error bars represent the standard error.



**Figure 5.3**

Group-level activation identified by the two sets of univariate contrasts. Both contrasts identified regions based on demonstrating more activation for Scrambled events, in comparison with Intact ones. However, the first set of contrasts identified the left RLPFC (shown in red) based on regions that exhibited this type of activity for only Non-previewed events, while the second set of contrasts identified the right RLPFC (shown in blue) based on areas that showed this activation for only Previewed events.



**Figure 5.4**

Group-level task-dependent functional connectivity resulting from 9-millimeter spherical regions of interest centered on the center of mass coordinates in the left and right RLPFC, as identified by the univariate contrasts. Both the left and right RLPFC demonstrated coupling with each other, as well as with ipsilateral regions in the frontal and parietal lobes. Left RLPFC (red; MNI coordinates [-42 49 -7]) demonstrated coupling with the left frontoparietal control network while right RLPFC (blue; MNI coordinates [48 35 1]) exhibited coupling with the right ventral attention network and the left hippocampus/parahippocampal gyrus.

## **CHAPTER SIX**

**High-definition transcranial direct current stimulation of the left rostralateral prefrontal cortex induces shifts in recognition bias through increased false recognition**

## **ABSTRACT**

The rostralateral prefrontal cortex (RLPFC) plays an important role in episodic memory processes, including retrieval monitoring (e.g., Cruse & Wilding, 2009), but a limited number of experiments in humans have investigated its causal contributions to memory task performance. The present study aimed to address this by utilizing high-definition transcranial direct current stimulation (HD-tDCS) to focally modulate the left RLPFC during episodic memory retrieval and assess this region's role in novelty and temporal order determinations. This was a one-day study that used photographic sequences – drawn from the lives of previous participants – to depict a variety of life events. Participants were first exposed to a subset of these images. This was followed by application of HD-tDCS while participants viewed photographic sequences and performed a mnemonic judgment task to determine both the recognition (whether events had been previously seen) and temporal order (whether the temporal order of the last four photographs in a sequence was scrambled) corresponding to each set of images. Application of anodal stimulation to the left RLPFC resulted in participants demonstrating a heightened propensity to make false alarm errors (endorsing novel events as having been previously seen) during the recognition memory task. This was reflected in a significant shift in recognition bias. In contrast, participants who only received sham stimulation experienced no significant changes in response bias. No significant effects of HD-tDCS were observed on participants' temporal order judgments. Taken together, these findings suggest that anodal facilitation of neural processing in the left RLPFC can make novel events seem more familiar to participants, potentially by modulating episodic memory monitoring processes.

## INTRODUCTION

Episodic memory retrieval pervades everyday life. This critical cognitive process entails the recall of specific events and their contexts – such as their spatiotemporal specificity – but is susceptible to errors and distortions (Schacter & Slotnick, 2004). Although many brain areas contribute to episodic retrieval, regions of the prefrontal cortex (PFC) are thought to play an especially important role in controlling memory search processes and monitoring the content that comes back to the mind to facilitate memory-guided behavior (Cabeza & St. Jacques, 2007; Gilboa, 2004; Lepage et al., 2000; Ranganath et al., 2000; Svoboda et al., 2006). A number of studies have highlighted the role of an anterior segment of the PFC, known as the rostralateral prefrontal cortex (RLPFC) in the maintenance of an attentional state that is conducive to episodic retrieval (known as “retrieval mode”), as well as in supporting the recollection of contextual details (e.g., Dobbins & Wagner, 2005; Kahn, Davachi, & Wagner, 2004; Lepage et al., 2000; Ranganath et al., 2000). In a recent functional magnetic resonance imaging (fMRI) experiment utilizing photographs of real-world experiences as mnemonic cues, the authors found evidence for RLPFC involvement in conditions related to novelty and temporal order during retrieval (Chow, Westphal, & Rissman, In Preparation). Specifically, the left RLPFC was identified through univariate contrasts as demonstrating increased activation for temporally scrambled sequences that were entirely novel. This suggests that the left RLPFC plays a critical role in episodic memory retrieval by assessing the mnemonic features of recalled events (Dobbins & Wagner, 2005; Lepage et al., 2000; Ranganath et al., 2000).

The left RLPFC has also demonstrated involvement during other tasks. The left RLPFC has been implicated in relational memory with successful retrieval, and this region more generally is engaged during the process of evaluating and integrating relationships between items

(Bunge et al., 2005; Prince et al., 2005; Wendelken et al., 2012). This region may also support reasoning tasks in the same manner. The left RLPFC has been demonstrated to facilitate relational reasoning, which also includes analogical reasoning (Watson & Chatterjee, 2012; Wendelken et al., 2008; Westphal et al., 2016). Indeed, a recent fMRI study found that the left RLPFC supported both episodic memory as well as analogical reasoning (Westphal et al., 2016). Overall, the RLPFC has been consistently implicated as a critical region during episodic memory retrieval, in addition to related cognitive functions, but further research is needed to determine its exact contributions.

PFC functions have been assessed with a variety of methods, including techniques more able to determine causality, such as transcranial direct current stimulation (tDCS). TDCS is a non-invasive method that utilizes weak electrical current to stimulate brain regions and enable better understanding of their involvement in behavioral and cognitive processes (Nitsche & Paulus, 2000). TDCS is a painless experimental methodology, with several advantageous qualities that make it well suited to identify the effects of specific regions (Nitsche & Paulus, 2000). While tDCS effects are relatively localized and transient, this brain stimulation approach reliably causes changes in a variety of cognitive processes (Nitsche et al., 2008; Nitsche & Paulus, 2000; Poreisz, Boros, Antal, & Paulus, 2007). TDCS is thought to accomplish this by evoking changes in neuronal excitability: anodal stimulation induces neuronal depolarization to enhance cortical excitability whereas cathodal stimulation evokes neuronal hyperpolarization to reduce cortical excitability (Fregni et al., 2005; Nitsche & Paulus, 2000). That is, tDCS effects are dependent on the stimulation polarity and corresponding changes in the resting membrane potential (Hummel & Cohen, 2006; Nitsche & Paulus, 2000). Sham stimulation – when applied briefly at a session’s start and end – does not significantly alter cognitive processes (Nitsche et



al., 2008). Moreover, participants are typically unable to differentiate between sham and real stimulation (Nitsche et al., 2008; Poreisz et al., 2007). Additionally, tDCS is not associated with significant adverse effects (Brunoni et al., 2011; Nitsche et al., 2008; Poreisz et al., 2007). TDCS offers an effective and safe brain stimulation approach to examine the effects of specific brain regions, including those involved in the processes of memory retrieval (Datta, Baker, Bikson, & Fridriksson, 2011).

TDCS methods have been previously used to study the PFC and its contributions to various types of memory. Applications of tDCS to the left PFC have previously found working memory enhancements (Fregni et al., 2005; Zaehle, Sandmann, Thorne, Jäncke, & Herrmann, 2011). Only anodal stimulation of the PFC – and not cathodal stimulation – improved working memory performance in comparison to sham stimulation (Fregni et al., 2005; Zaehle et al., 2011). Anodal tDCS of this region has similarly been shown to improve declarative memory (Javadi & Walsh, 2012). Furthermore, tDCS of the left PFC facilitates verbal episodic memory recall: anodal stimulation during retrieval significantly increased memory performance across both young and older participants (Manenti, Brambilla, Petesi, Ferrari, & Cotelli, 2013). The use of anodal tDCS on the left PFC can specifically induce changes in memory performance. However, tDCS studies regarding the effects of the left PFC and its contributions to episodic memory retrieval are not only sparse, but they are also critically missing assessments of this region's involvement in different aspects of event memories. Moreover, conventional tDCS methods utilizing relatively large rectangular sponges have demonstrated diffuse modulatory focus (Datta et al., 2009; Edwards et al., 2013; Lang et al., 2005; Nathan, Sinha, Gordon, Lesser, & Thakor, 1993). This suggests that stimulation impacts both regions of interest as well as

nearby cortices, which may constrain results and interpretation due to the potential modulation of several areas (Nitsche et al., 2007).

To address the restrictions of conventional tDCS techniques, more focal applications of tDCS have recently begun to be employed. For instance, high-definition tDCS (HD-tDCS) methods employ electrode arrays that allow for more precise targeting of brain regions (Datta et al., 2009; Edwards et al., 2013). Critically, HD-tDCS electrode configurations – such as the 4 x 1 ring montage with a central electrode – resulted in the peak electric field magnitude being induced directly below the active electrode and overall greater spatial focus of the modulation (Datta et al., 2009). This was not the case with the conventional rectangular sponges used in traditional tDCS: this approach was more diffuse in its modulatory spatial focus and, critically, did not result in the peak electric field magnitude being induced underneath the sponges (Datta et al., 2009). As such, while conventional tDCS using rectangular sponges is limited in spatial focus, HD-tDCS provides a more precise method of non-invasive stimulation capable of targeting brain regions in a focal manner (Datta et al., 2009; Edwards et al., 2013; Lang et al., 2005; Nathan et al., 1993).

HD-tDCS techniques have been used to further explore the role of the PFC in mnemonic processes. As with convention tDCS experiments, studies utilizing HD-tDCS have predominately assessed regions proximal to the RLPFC, such as the dorsolateral prefrontal cortex (DLPFC). However, few tDCS studies – and no current HD-tDCS experiments – have assessed RLPFC regions, or their involvement in episodic memory retrieval. Given the left RLPFC's critical contributions to a range of cognitive processes, a more causal understanding of its contributions to episodic memory retrieval would better elucidate the findings of prior experiments.

This study utilized HD-tDCS to determine how the left RLPFC contributes to novelty detection and temporal order information during episodic recall, as evoked by photographic sequences. The use of more focal stimulation through HD-tDCS enhances targeting specificity and allows for a better understanding of RLPFC regions without the modulation of other regions that may occur with the conventional form of tDCS. In particular, this experiment was interested in stimulating the left RLPFC in order to examine how it influences the two event characteristics more generally, beyond temporally scrambled events, using a technique that allows for determination of more causal effects. Application of HD-tDCS to the left RLPFC can provide information about its role in retrieval processes if such stimulation impacts the ability to differentiate mnemonic features: if anodal stimulation of the left RLPFC results in behavioral changes that significantly differ from those of sham stimulation alone, this can help characterize the processes underlying important mnemonic functions. As such, this study assessed whether the left RLPFC is involved in determining the temporal order and novelty of events, and how it may more generally support these features during episodic memory retrieval.

## **METHODS**

### **Participants**

Participants consisted of 26 individuals from the University of California, Los Angeles (UCLA) as well as the surrounding location. Of these participants, 13 individuals (4 males and 9 females; average of 20.69 years) received sham stimulation for the entirety of the stimulation session (the “Sham-Sham” condition). The remaining 13 individuals (6 males and 7 females; average of 20.46 years) received sham stimulation followed by anodal stimulation during the

stimulation session (the “Sham-Anode” condition). As this experiment is still in progress, additional participants will be included in the two stimulation groups and matched for gender.

Participants were all 18-30 years old, right-handed native English speakers with normal or corrected-to-normal vision. Additionally, participants did not have a history of brain damage, did not have any neurological or psychiatric disorders, did not consume illegal drugs, and did not consume more than four alcoholic drinks per day. Participants did not possess any HD-tDCS contraindications. Individuals were monetarily remunerated for their participation. Written informed consent was obtained from all participants in accordance with the UCLA Institutional Review Board’s approved protocols.

## **Procedure**

### ***Stimuli***

The current experimental paradigm was modified from a prior fMRI study, described fully in Chow, Westphal, & Rissman (In Preparation). This fMRI study was also assessed in subsequent papers by Chow, Westphal, & Rissman (In Preparation) and Chow, Westphal, & Rissman (In Preparation). The present study paradigm is depicted in **Figure 6.1**.

Experimental stimuli consisted of photographic sequences acquired entirely from the previous participants of the fMRI study in Chow, Westphal, & Rissman (In Preparation). These photographic sequences depict events from previous participants’ lives that were automatically captured by necklace-mounted digital camera devices (Autographer, 2015) worn over the course of three weeks. Each photographic sequence – referred to as an “event sequence” – consisted of eight images, which captured events that occurred within a 15-minute window. Images within event sequences were automatically captured by the digital cameras devices whenever their

electronic sensors were triggered by changes in the environment, which eliminated the need for participants' explicit input to take photographs. These event sequences captured a wide variety of personal experiences, including different locations, activities, and individuals. A total number of 288 event sequences were used throughout the experiment. An equal number of these photographic sequences were selected from each of the 18 previous fMRI participants to minimize repetitious and more generic events. These stimuli were utilized in the current experiment in order to preserve the novelty of the mnemonic probes depicting real-world events.

### *Experimental phases*

This study involved two phases – the pre-exposure session and the HD-tDCS session – which were implemented consecutively on the same day. The study design can be seen in **Figure 6.1D**. Although the two sessions involved different experimental tasks, the timing of trials in both phases were identical. Each run of the experimental task was preceded by 2.5 s of fixation to allow participants to prepare for the oncoming trials. Every trial involved the presentation of an event sequence, where each individual image was shown for 0.8 s and followed by a 0.2-s fixation interval, with a subsequent 4-s response period for participants to answer according to their assigned task. The inter-trial interval (ITI) of both sessions consisted of 2.5 s of fixation. Participants completed a series of practice trials prior to beginning each of the two sessions to become accustomed to the required task and ensure knowledge of the response options.

The pre-exposure session occurred first and was used to expose participants to a subset of event sequences. Of the 288 total event sequences used in the experiment, participants were shown half of all sequences during the pre-exposure session (“Previewed” events). Participants were instructed to rate each event sequence based on their distinctiveness as a whole by

indicating whether they were “Distinctive,” “Somewhat Distinctive,” “Somewhat Non-distinctive,” or “Non-distinctive.” All of the event sequences presented in the pre-exposure session were displayed in their original temporal order, and an equal number of sequences were selected from each of the 18 previous fMRI participants to maintain a variety of life events. The remaining event sequences were not shown during this pre-exposure session (“Non-previewed” events). Participants were not given any explicit instruction to suggest that they should memorize these event sequences. This session allowed for implementation of the recognition memory task by manipulating the pre-exposure status of sequences such that certain events became familiar to participants while maintaining the novelty of other events.

The HD-tDCS session occurred immediately following the pre-exposure session, and participants were tasked with judging both the pre-exposure status and the temporal order of all 288 event sequences. Half of all event sequences were presented in the original temporal order in which events occurred (“Intact” events, i.e. those presented in A-B-C-D-E-F-G-H order). The other half was presented in a temporally scrambled manner (“Scrambled” events) where images were shown in an A-B-C-D-G-E-H-F order to avoid backward and forward associations (Kumaran & Maguire, 2007). The factorial combination of the two within-subject variables – pre-exposure status and temporal order – created four experimental conditions, with an equal number of trials distributed across these resulting conditions. As such, participants were asked to judge whether they had previously encountered event sequences during the pre-exposure session (the recognition memory task) as well as whether event sequences were presented in their original temporal order or in a temporally altered manner (the temporal order task). Participants indicated their response to each event sequence by using the following response options:

“Previewed; Intact,” “Previewed; Scrambled,” “Non-previewed; Intact,” and “Non-previewed; Scrambled.”

The HD-tDCS session was divided in half, with an equal number of trials presented in each, so that different types of stimulation could be administered. One group received only sham stimulation in both halves of the HD-tDCS session (“Sham-Sham”) while the other group received sham stimulation, followed by anodal stimulation (“Sham-Anode”). Accordingly, the first half of the HD-tDCS phase always consisted of sham stimulation, while the second half involved either additional sham stimulation or anodal stimulation. Participants in the Sham-Sham group acted as a baseline measure of behavior across the tasks, and each participant in both groups served as their own control to account for changes over time that may be due to non-experimental factors such as fatigue or practice effects. Participants were randomly assigned to the stimulation condition, but both the Sham-Sham group and the Sham-Anode group performed the same experimental tasks throughout the study. As such, this study included two within-subject variables concerning the pre-exposure status and temporal order of events and one between-groups variable consisting of the stimulation type (Sham-Sham or Sham-Anode).

Counterbalancing of stimuli occurred as a series of steps designed to minimize unwanted effects not related to the experimental task itself. All event sequences were randomly assigned to eight stimuli subsets, consisting of equal numbers of sequences, and these stimuli assignments were kept constant across all participants. Eight counterbalancing lists were then created in which the eight stimuli subsets were assigned different experimental conditions. For instance, the first counterbalancing list designated all event sequences in the first stimuli subsets as belonging to the Previewed and Intact condition, all event sequences in the second stimuli subsets as belonging to the Previewed and Scrambled condition, and so forth. Prior to the start of the study,

participants were assigned one of the eight potential counterbalancing lists, which were used to determine the experimental condition of the event sequences in each trial. The trial order of event sequences was randomized within each half of the HD-tDCS session, so that stimuli that were originally randomly assigned to the first half would never be randomized into the second half and vice versa. Each half consisted of an equal number of trials overall, and an equal number of trials within each of the four experimental conditions. The trial order of event sequences was also randomized in the pre-exposure session.

### ***HD-tDCS Protocol***

HD-tDCS was applied using a battery-driven 1x1 constant direct current stimulator and a 4x1 HD-tDCS adaptor with a 5-electrode montage (Soterix Medical Inc., New York, NY). The central stimulation electrode was placed at AF7, and the remaining electrodes were placed at Fp1, AF3, F7, and F9 in the conventional 10/20 placement system (**Figure 6.2A**). That is, the AF7 electrode determined whether sham or anodal stimulation occurred. Each electrode consisted of a ring with an outside diameter of approximately 1.4 cm and an inside diameter of approximately 0.6 cm. Electrodes were attached onto the scalp using Soterix Medical's HD Cap (Soterix Medical Inc., New York, NY), which was secured using a chinstrap. Placement of electrodes in the experimental montage was modeled using Soterix Medical's HD-Explore™ (Soterix Medical Inc., New York, NY; <http://soterixmedical.com/software/hd-explore>) to maximally stimulate the left RLPFC and minimize field intensities in regions of non-interest. The field intensities resulting from the electrode montage can be seen in **Figure 6.2B**.

The HD-tDCS parameters involved a 40-minute application of either sham, where the current is briefly ramped up and ramped back down at the beginning and end of a given



stimulation period, or 1 milliamp (mA) of anodal stimulation. This stimulation level was selected based on the effectiveness of prior tDCS experiments investigating declarative and working memory (e.g., Andrews, Hoy, Enticott, Daskalakis, & Fitzgerald, 2011; Fregni et al., 2005; Javadi & Walsh, 2012). In each half of the HD-tDCS portion, participants were first given five minutes of stimulation – regardless of sham or anodal stimulation – prior to starting the approximately 35 minutes of task. As such, not only did this stimulation protocol occur for the entire duration of the task performed during each half of the HD-tDCS session, but stimulation of the left RLPFC was already underway once the experimental task was started. Moreover, the current density measurements from these stimulations parameters are less than the commonly-used HD-tDCS protocols applying 2 mA of current for 20 minutes (see Chua, Ahmed, & Garcia, 2017).

## **RESULTS**

Participants' accuracy was assessed in order to clarify the left RLPFC's contributions to the recognition and temporal order of events during episodic memory retrieval. First, each task was assessed separately in order to examine the effects of left RLPFC modulation across the two cognitive processes more broadly. For both the recognition and temporal order tasks, the hit rate and false alarm rate were calculated independent of the other task. For the recognition task, the hit rate consisted of the proportion of Previewed event sequences correctly indicated as such while the false alarm rate entailed the proportion of Non-previewed event sequences that were mistakenly judged as previously seen. For the temporal order task, the hit rate was comprised of the proportion of Scrambled event sequences indicated correctly as such while the false alarm rate involved the proportion of Intact event sequences mistaken as temporally scrambled ones.

Additionally, the corrected recognition (“Pr”) was calculated for each task by subtracting the false alarm rates from the hit rates while the bias index (“Br”) was calculated according to the equation  $Br = (\text{false alarm rate}) / (1 - Pr)$  (Snodgrass & Corwin, 1988). The overall accuracy for each task was also calculated by combining the hit rate and the correct rejection rate: the correct rejection rate for the recognition task consisted the proportion of Non-previewed event sequences that were correctly identified, while the correct rejection rate for the temporal order task comprised of the proportion of Intact event sequences that were correctly identified. Analyses were conducted on the difference scores based on the subtraction of the baseline behavioral measures in the first half of the HD-tDCS session’s sham stimulation condition from those in the second half of the HD-tDCS session. Independent-samples *t*-tests (two-tailed) were utilized to compare performance between stimulation groups while paired-samples *t*-tests (two-tailed) were employed to compare measures within groups.

Overall, participants performed well across the two tasks during the entirety of the HD-tDCS session (**Figure 6.3A**). Performance for both groups was significantly greater than chance (50%) in both tasks. Overall average accuracy in the pre-exposure task was 78.659% for Sham-Sham participants ( $t_{(12)} = 13.089, p < 10^{-7}$ ) and 78.793% for Sham-Anode participants ( $t_{(12)} = 13.228, p < 10^{-7}$ ). Overall average accuracy in the temporal order task was 74.386% for Sham-Sham participants ( $t_{(12)} = 14.071, p < 10^{-8}$ ) and 71.207% for Sham-Anode participants ( $t_{(12)} = 8.721, p < 10^{-5}$ ). Moreover, as the Sham-Sham group provides a measure of baseline behavior across tasks, there was no significant difference between performance across overall accuracy for the pre-exposure and temporal order tasks ( $t_{(12)} = 1.920, p = 0.079$ ). Participants responded to the vast majority of trials, with only an average of 0.16% of trials where no judgment was indicated or a wrong key was pressed across all individuals.

### ***Recognition Memory Task***

Both the Sham-Sham group and the Sham-Anode group experienced a significant decrease in overall accuracy during the recognition memory task when the second half of the HD-tDCS session was compared to the first half. The Sham-Sham group demonstrated an average accuracy of 80.502% in the first half of the HD-tDCS session and an average accuracy of 76.816% in the second half (average decline = 3.686%;  $t_{(12)} = 2.423, p < 0.05$ ). The Sham-Anode group demonstrated an average accuracy of 81.197% in the first half of the HD-tDCS session and average accuracy 76.389% in the second half (average decline = 4.808%;  $t_{(12)} = 3.059, p < 0.05$ ). There was no significant difference between the change scores for the groups' performances ( $t_{(24)} = 0.513, p = 0.613$ ), but data collection is still ongoing. However, these reductions in accuracy were primarily due to separate sources (**Figure 6.3C**). The Sham-Sham group showed a significantly decreased hit rate – averaging a 3.900% reduction in correct trials ( $t_{(12)} = 2.745, p < 0.05$ ) – but there was no significant change in false alarm rate despite an average increase of 3.205% in incorrect trials ( $t_{(12)} = 1.255, p = 0.262$ ). In comparison, while the Sham-Anode group's hit rate decreased by an average of 2.350%, this was not a significant change ( $t_{(12)} = 1.043, p = 0.317$ ). However, the Sham-Anode group's false alarm rate significantly increased by an average of 7.158% ( $t_{(12)} = 4.555, p < 10^{-2}$ ). The Sham-Anode and Sham-Sham groups demonstrated different within-group effects during the recognition memory task.

The Sham-Sham and Sham-Anode groups' performances were mirrored in their Pr and Br scores. Both the Sham-Sham and Sham-Anode groups exhibited significant changes in Pr values due to their overall decrease in accuracy across the two halves of the HD-tDCS session.

The Sham-Sham group showed a significant 0.071 average decrease ( $t_{(12)} = 2.298, p < 0.05$ ), from a Pr of 0.610 in the first half to a Pr of 0.538 in the second half. The Sham-Anode group experienced a significant decrease in Pr ( $t_{(12)} = 3.255, p < 10^{-2}$ ), where the first half of the HD-tDCS session averaged 0.546 while the second half of the session averaged 0.246. Notably, the Sham-Anode group's change in false alarm rate was reflected in their Br values, which indicated a change in response bias that was not seen in the Sham-Sham group: there was a significant increase in the Sham-Anode group's Br values where the first half of the HD-tDCS session averaged 0.327 and the second half averaged 0.406 ( $t_{(12)} = 3.534, p < 10^{-2}$ ). The Sham-Anode participants exhibited a significant average Br increase of 0.079 in the second half of the HD-tDCS session while the Sham-Sham group demonstrated a non-significant Br decrease of 0.014 (first half average = 0.499; second half average = 0.485;  $t_{(12)} = 0.380, p = 0.710$ ). Direct between-group contrast of the Br change scores revealed an effect of stimulation ( $t_{(24)} = 2.189, p < 0.05$ ). This difference in response bias can be seen in **Figure 6.4**. Therefore, with regards to the recognition of event sequences, stimulation of the left RLPFC resulted in increased false alarm rates and a shifted response criterion for the Sham-Anode group that was not present for the Sham-Sham group.

### ***Temporal Order Task***

In comparison, neither the Sham-Sham or the Sham-Anode group demonstrated a significant reduction in overall accuracy for the temporal order task when comparing the second half of the HD-tDCS session with the first half. The Sham-Sham group demonstrated an average accuracy of 75.695% in the first half of the HD-tDCS session and an average accuracy of 73.077% in the second half (average decline = 2.618%;  $t_{(12)} = 1.415, p = 0.182$ ). The Sham-

Anode group demonstrated an average accuracy of 71.538% in the first half of the HD-tDCS session and average accuracy 70.887% in the second half (average decline = 0.641%;  $t_{(12)} = 0.605, p = 0.556$ ). While no between-group differences were found in the change scores for performance ( $t_{(24)} = 0.927, p = 0.363$ ), data from additional participants will be included in the future. However, the Sham-Sham group exhibited a significant decrease in hit rate, averaging a 8.333% reduction in correct trials ( $t_{(12)} = 2.473, p < 0.05$ ), while there was no significant decrease in hit rate for the Sham-Anode group, which averaged a 2.458% reduction in correct trials ( $t_{(12)} = 1.227, p = 0.243$ ; **Figure 6.3D**). This difference is not currently significant between groups ( $t_{(24)} = 1.499, p = 0.147$ ). There was no significant difference in performance for false alarm rates in either the Sham-Sham group (average decrease of 2.991%;  $t_{(12)} = 1.178, p = 0.262$ ) or the Sham-Anode group (average decrease of 1.282%;  $t_{(12)} = 0.985, p = 0.344$ ). Only the performance of the Sham-Sham group differed significantly across the two halves of the HD-tDCS session.

Neither the Sham-Sham group nor the Sham-Anode group demonstrated differences in Pr or Br values. There was also no significant change in Pr values for either the Sham-Sham group ( $t_{(12)} = 1.450, p = 0.173$ ) or the Sham-Anode group ( $t_{(12)} = 0.548, p = 0.594$ ) between the first and second halves of the HD-tDCS session. There was also no significant change in Br values for either the Sham-Sham group ( $t_{(12)} = 1.8659, p = 0.086$ ) or the Sham-Anode group ( $t_{(12)} = 1.085, p = 0.299$ ) across the HD-tDCS session (**Figure 6.4**). As such, for the temporal order of event sequences, stimulation of the left RPFC did not significantly affect the Sham-Anode group although the Sham-Sham group demonstrated differences in performance.

### ***Performance Across both the Recognition Memory Task and the Temporal Order Task***

Next, the recognition and temporal order tasks were analyzed together by assessing only trials with responses that were correct for both. As such, responses were separated into the different trial types: Previewed, Intact trials; Previewed, Scrambled trials; Non-previewed, Intact trials; and Non-previewed, Scrambled trials. Overall accuracy was calculated by combining the correct responses across all trial types. These analyses were also conducted utilizing the difference scores resulting from subtracting baseline performance in the first half of the HD-tDCS session from that of the second half. Independent-samples *t*-tests were used to examine between-group measures and paired-samples *t*-tests were utilized to assess within-group performance.

Participants performed well in terms of overall accuracy when only correct responses for both the recognition memory and temporal order tasks were examined across the two halves of the HD-tDCS session (**Figure 6.3B**). Both the Sham-Sham group and Sham-Anode group performed above chance (25%): the Sham-Sham group averaged 59.348% ( $t_{(12)} = 13.124, p < 10^{-7}$ ) while the Sham-Anode group averaged 56.971% ( $t_{(12)} = 10.378, p < 10^{-6}$ ). As such, participants not only performed well in each individual task, but they were also capable of performing the two tasks in conjunction.

Both the Sham-Sham group and Sham-Anode group demonstrated a significant reduction in overall accuracy for the second half of the HD-tDCS session, based on correct responses for both the pre-exposure status and temporal order of event sequences. The Sham-Sham group's overall accuracy reduced by an average of 4.487% ( $t_{(12)} = 2.470, p < 0.05$ ) while the Sham-Anode group's overall accuracy diminished by 3.365% ( $t_{(12)} = 3.942, p < 10^{-2}$ ). No significant differences were found for performance regarding the Previewed, Intact and Non-previewed,

Scrambled trial types. However, the two groups differed in performance regarding the Previewed, Scrambled and Non-previewed, Intact trials (**Figure 6.5**).

The Sham-Sham group demonstrated a significant reduction in the number of Previewed, Scrambled trial types accurately identified, with an average decrease of 9.615% ( $t_{(12)} = 2.869, p < 0.05$ ). The Sham-Anode group did not demonstrate a significant change in Previewed, Scrambled trial accuracy, although their performance declined by an average of 2.778% ( $t_{(12)} = 0.883, p = 0.394$ ). Of the errors made in response to Previewed, Scrambled trials, the Sham-Sham group demonstrated a significant increase in mistakenly attributing these event sequences to be Non-previewed, Intact trials in the second half of the HD-tDCS session (average increase of 2.077 incorrect trials judged as the Non-previewed, Intact condition;  $t_{(12)} = 2.849, p < 0.05$ , Bonferroni corrected). There were no significant increases in error attributions for the Sham-Anode group with regards to the Previewed, Scrambled trial type (all  $p > 0.05$ ). As such, Sham-Sham participants' errors resulted in misattributions for both the recognition and temporal order of events when judging the features associated with Previewed, Scrambled sequences.

The Sham-Anode group exhibited a significant decrease in the number of Non-previewed, Intact trials that were correctly identified, although this was not seen in the Sham-Sham group's performance: the Sham-Anode group averaged a 6.197% decline ( $t_{(12)} = 2.201, p < 0.05$ ) while the Sham-Sham group averaged a non-significant average reduction of 2.564% ( $t_{(12)} = 0.822, p = 0.427$ ). For errors made in response to Non-previewed, Intact trials, the Sham-Anode group significantly increased the number of incorrect attributions to Previewed, Intact trials in the second half of the HD-tDCS session (average increase of 2.077 incorrect trials indicated as the Previewed, Intact condition;  $t_{(12)} = 3.379, p < 0.05$ , Bonferroni corrected). There were no significant increases in error attributions for the Sham-Sham group in terms of the Non-

previewed, Intact trial condition (all  $p > 0.05$ ). Accordingly, the Sham-Anode group's errors were due to only misattributing the recognition of Non-previewed, Intact sequences.

## **DISCUSSION**

This is the first experiment to utilize HD-tDCS in assessing the left RLPFC's contributions to novelty detection and temporal order information during episodic memory retrieval. Moreover, this is the only study combining wearable camera technology with HD-tDCS methodology. The current study first presented participants with sequences of photographs depicting events from the lives of former participants and then employed HD-tDCS to focally stimulate the left RLPFC as participants made judgments regarding whether sequences had been seen in the immediately preceding pre-exposure session as well as whether sequences were presented in the correct temporal order. As the left RLPFC mediates a variety of cognitive functions, the use of HD-tDCS allows for more targeted modulation of this region and better determination of its causal influence on the retrieval of event characteristics.

The left RLPFC has been implicated in mnemonic processes, including those related to the pre-exposure and temporal order judgments in the current HD-tDCS study. Prior neuroimaging experiments have shown left RLPFC engagement in recognition memory – with greater activation for previously encountered items than novel ones – as well as its contribution during relational memory and the evaluation of contextual mnemonic features (Dobbins & Wagner, 2005; Henson, Rugg, Shallice, & Dolan, 2000; Lepage et al., 2000; Prince et al., 2005; Ranganath et al., 2000; Rugg, Henson, & Robb, 2003; Wendelken et al., 2012). Indeed, previous studies have found that application of anodal tDCS to left PFC regions increased performance on tasks requiring declarative memory retrieval (Javadi & Walsh, 2012; Manenti et al., 2013). Thus,



the left RLPFC appears integral for memory retrieval and anodal stimulation of this region can positively impact its associated mnemonic processes.

Surprisingly, anodal stimulation of the left RLPFC in the current study did not find these expected positive mnemonic effects. Stimulation of this region resulted in different effects across the recognition memory and temporal order tasks. The Sham-Anode group exhibited greater false alarm rates in the recognition memory task during the second half of the HD-tDCS session where anodal stimulation was applied than the first half where sham stimulation was implemented. This change in behavior was reflected in the Sham-Anode's response bias across the two halves of the HD-tDCS session, which was significantly different from that of the Sham-Sham group. There was no significant effect of stimulation for the Sham-Anode group regarding the temporal order task. In comparison, the Sham-Sham group showed significantly poorer performance for both the recognition memory and temporal order tasks in terms of decreased hit rate. Accordingly, anodal stimulation of the left RLPFC led to a significant difference in response bias during the recognition memory task.

As the Sham-Anode group only showed significantly different behavioral changes during the recognition memory task, the effects of stimulating the left RLPFC were limited to the processes mediating this mnemonic function. The current findings of increased false alarms during recognition, and a shift in response bias, may be due to left RLPFC stimulation impacting the ability to effectively monitor episodic memory. This is consistent with lesion studies: patients with lesions in the frontal lobe often demonstrate greater false alarm rates, which is thought to be attributed to problems with memory monitoring (Parkin, Bindschaedler, Harsent, & Metzler, 1996; Schacter, Curran, Galluccio, Milberg, & Bates, 1996; Verfaellie, Rapcsak, Keane, & Alexander, 2004). Previous neuroimaging studies have shown that the RLPFC is involved in the

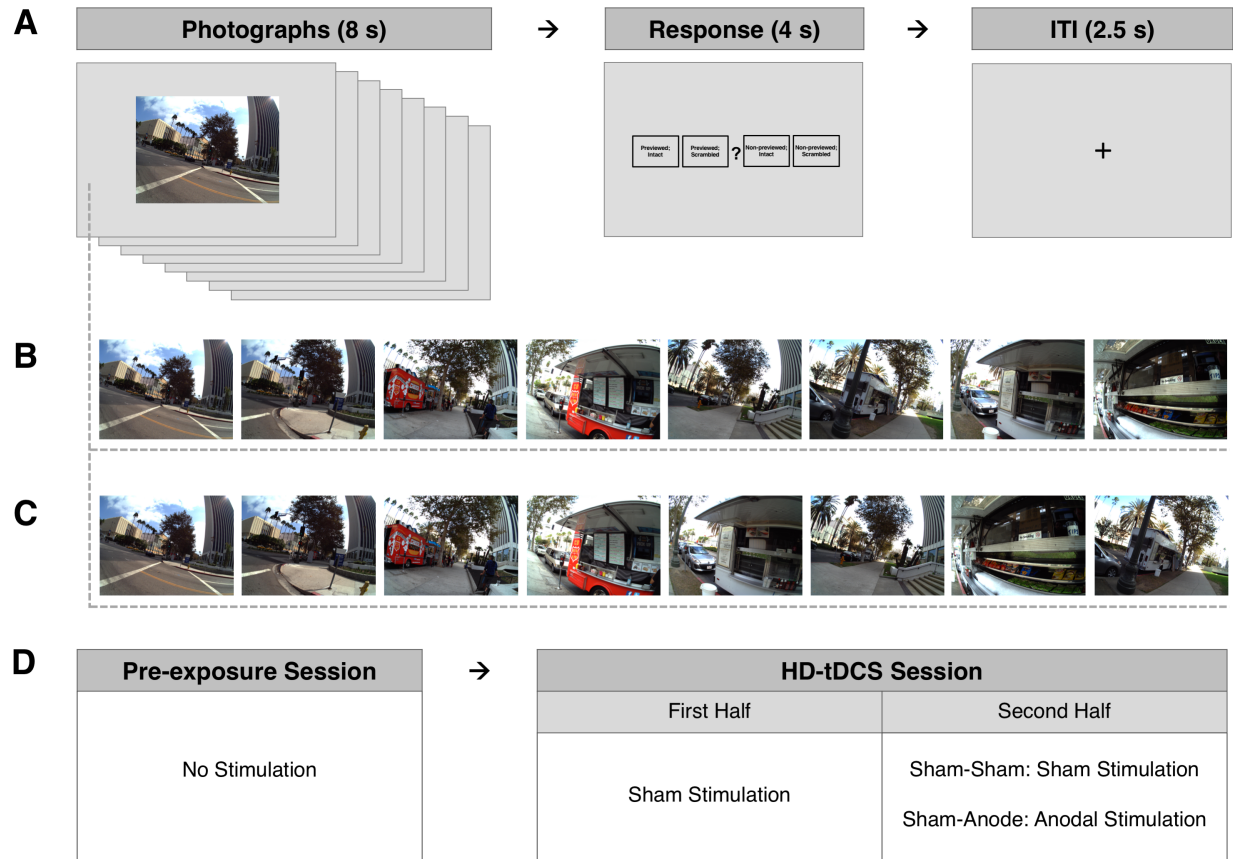
monitoring and control of episodic memory processes (Cruse & Wilding, 2009; Dobbins & Wagner, 2005; Gilbert et al., 2006; Ranganath et al., 2000; Reynolds et al., 2006; Simons et al., 2008; Westphal et al., 2016). Additionally, the left RLPFC has been implicated in response biases during episodic recognition tasks: during recognition, the left RLPFC has demonstrated greater activation when participants shifted between different levels of response bias (liberal or conservative) than when maintaining a single level of response bias (Miller, Handy, Cutler, Inati, & Wolford, 2001). Prior tDCS studies have also found similar results when assessing neighboring regions in the left PFC. Application of anodal tDCS can modulate response bias and effective monitoring of memory retrieval: anodal stimulation of left PFC areas can bias recognition memory judgments (Pergolizzi & Chua, 2017) and even improve memory monitoring accuracy, despite worsened memory performance (Chua & Ahmed, 2016). Additionally, application of anodal tDCS on the left PFC during the encoding of pictures increased the amount of false alarms in a later recognition memory test (Zwissler et al., 2014). Therefore, the left RLPFC may be directly involved in memory monitoring during episodic memory retrieval, resulting in the present findings of significantly shifted response bias. While this study has resulted in notable within-group findings, the lack of power limits current between-group conclusions. However, data collection is ongoing and behavioral measures from additional participants will be included in the final analyses to better address any potential between-group differences.

It is possible that these effects can be partially attributed to fatigue across the experimental session. Both the Sham-Sham and Sham-Anode groups demonstrated decreased overall accuracy during the recognition memory task. However, such an overall decrease was not seen in the two groups during the temporal order task, which only found a significant reduction

in the hit rate for the Sham-Sham group. Additionally, previous tDCS studies utilizing 1 mA of current have found effective modulation across both working memory and declarative memory tasks, even when employing a shorter stimulation duration and less focal, traditional tDCS methods than the present experiment (e.g., Andrews et al., 2011; Fregni et al., 2005; Javadi & Walsh, 2012; Pergolizzi & Chua, 2017). Accordingly, these findings should be primarily due to the application of HD-tDCS to the left RLPFC.

In summary, the present experiment found new evidence for the left RLPFC's causal role in determining events' novelty during episodic memory retrieval. Not only did application of HD-tDCS to the left RLPFC significantly impact episodic memory retrieval by increasing the false alarm rate, but it also resulted in a shifted response bias that was significantly different from that of baseline performance. The current study demonstrates that anodal modulation of the left RLPFC can influence accurate episodic recall, and suggests this may be due to memory monitoring processes. As the present experiment is one of the few tDCS studies examining the RLPFC – including the only one utilizing HD-tDCS – during recall, further research should be conducted in order to better understand this region's causal influence on episodic memory retrieval processes.

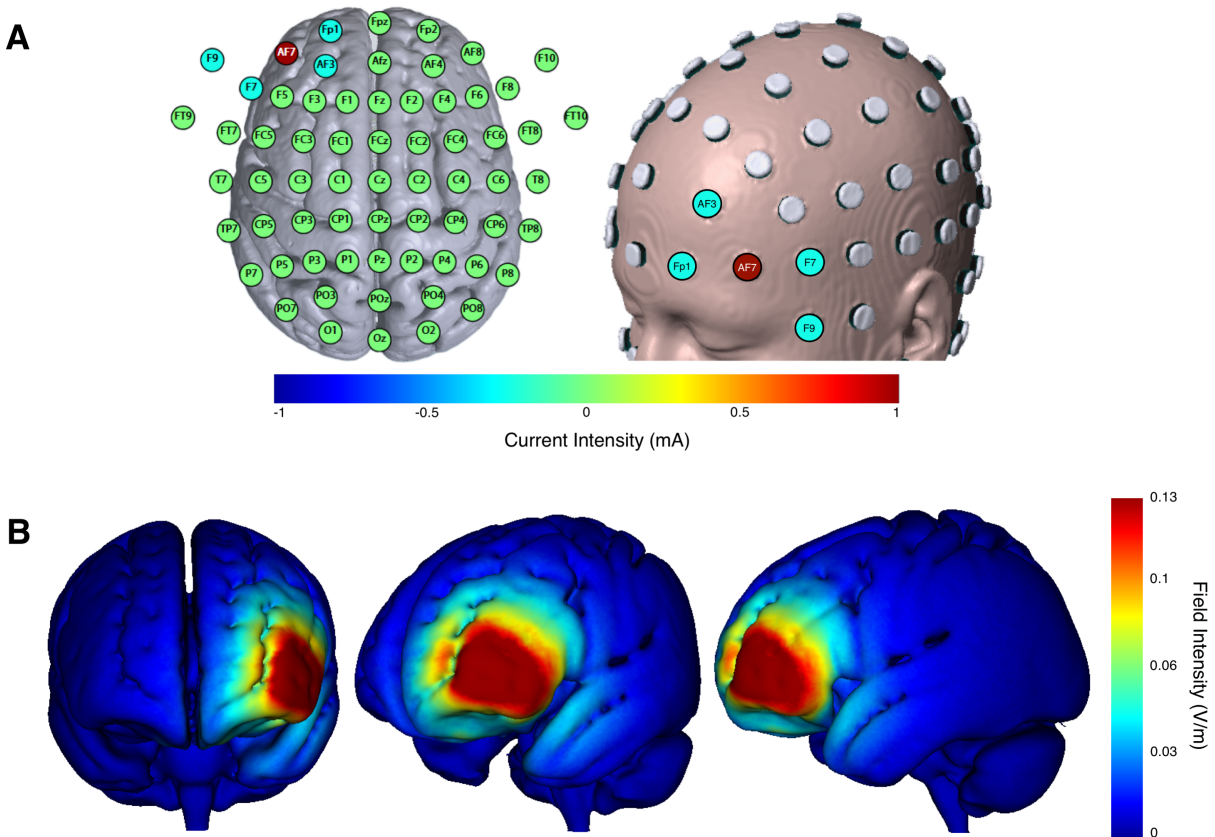
## FIGURES



**Figure 6.1**

The experimental design. (A) Progression and timing of an individual trial for the HD-tDCS session. Event sequences in each trial consisted of eight photographs derived from the lives of previous participants, and which captured a variety of experiences. In every trial, the eight photographs were presented such that each image was seen for 0.8 s followed by a 0.2-s fixation. Participants were given a 4-s response period to indicate their mnemonic judgments, with a subsequent 2.5 s inter-trial interval (ITI). During the presentation of each trial in the HD-tDCS session, event sequences could be displayed in either a (B) temporally intact fashion, which captured how events were originally photographed, or (C) temporally scrambled fashion, where

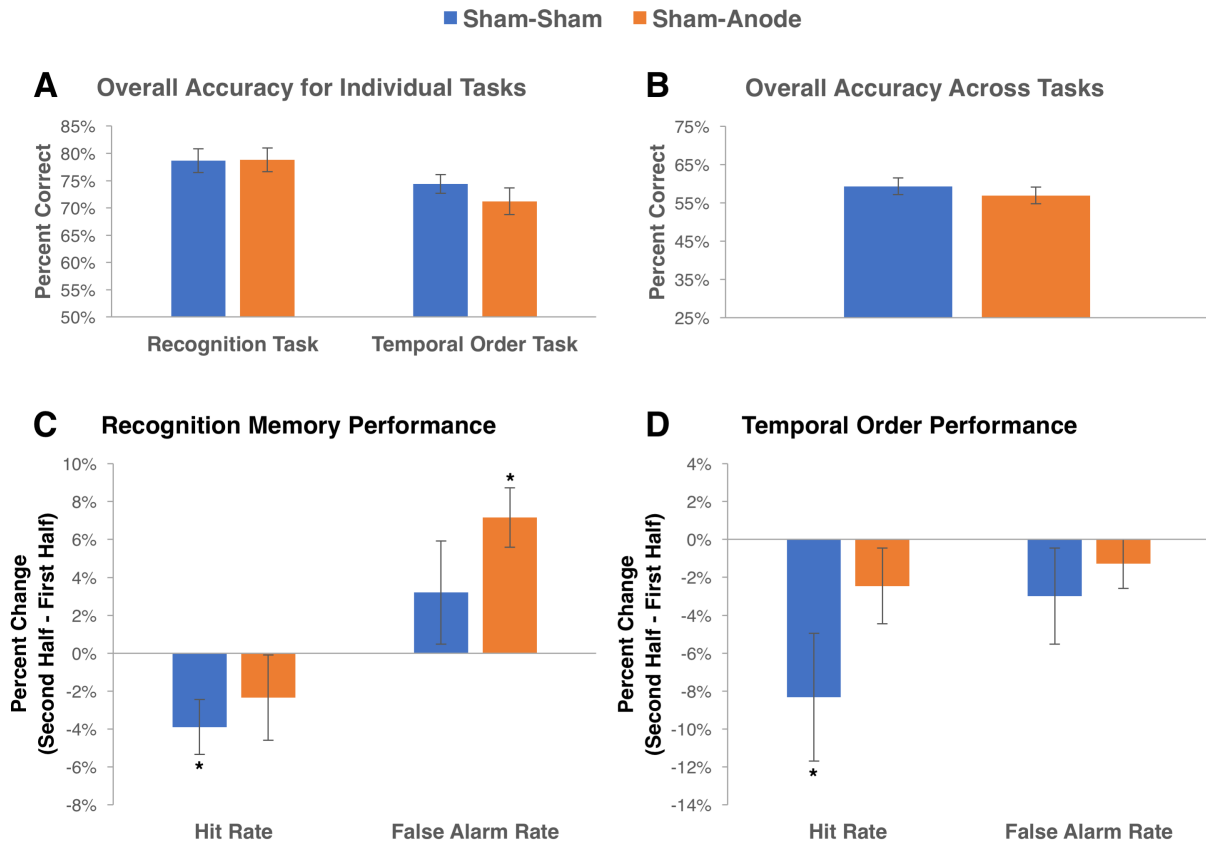
the last four images in a sequence were presented in an order that differed from the original event. (D) Timeline of the experiment, where participants first underwent the pre-exposure session followed immediately by the HD-tDCS session.



**Figure 6.2**

(A) Placement of the HD-tDCS electrode montage, along with the (B) resulting field intensities, both modeled on an MNI brain using 1 mA of current. Figures adapted from Soterix Medical's HD-Explore™ (Soterix Medical Inc., New York, NY; <http://soterixmedical.com/software/hd-explore>). The central electrode was placed at AF7 while the remaining electrodes were placed at a Fp1, AF3, F7, and F9 in the conventional 10/20

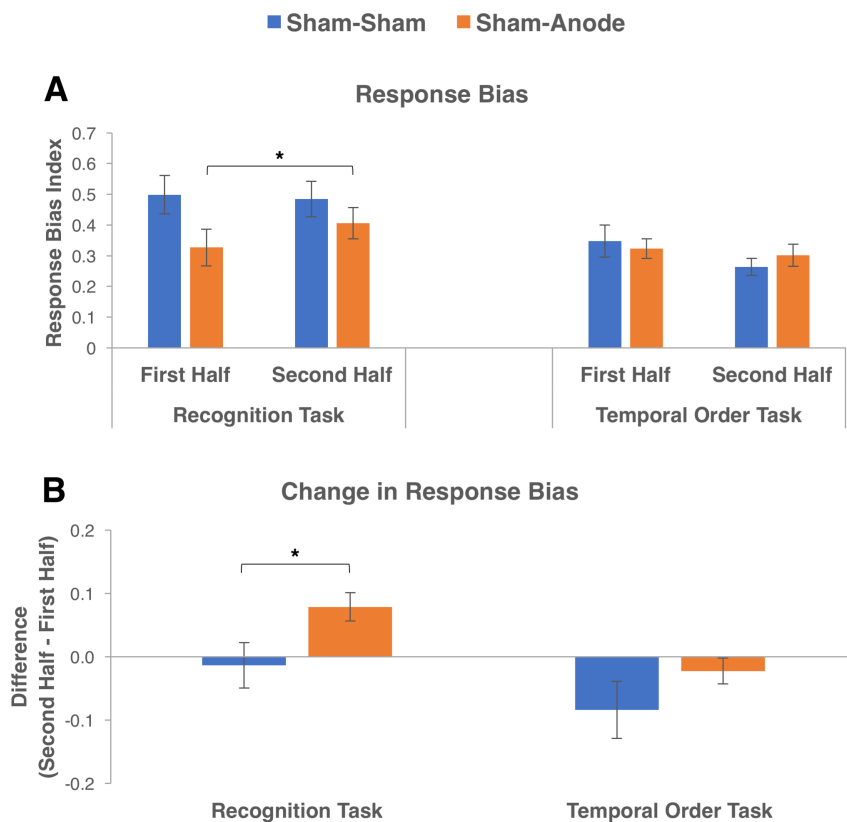
placement system. Electrodes were secured using Soterix Medical’s HD Cap (Soterix Medical Inc., New York, NY).



**Figure 6.3**

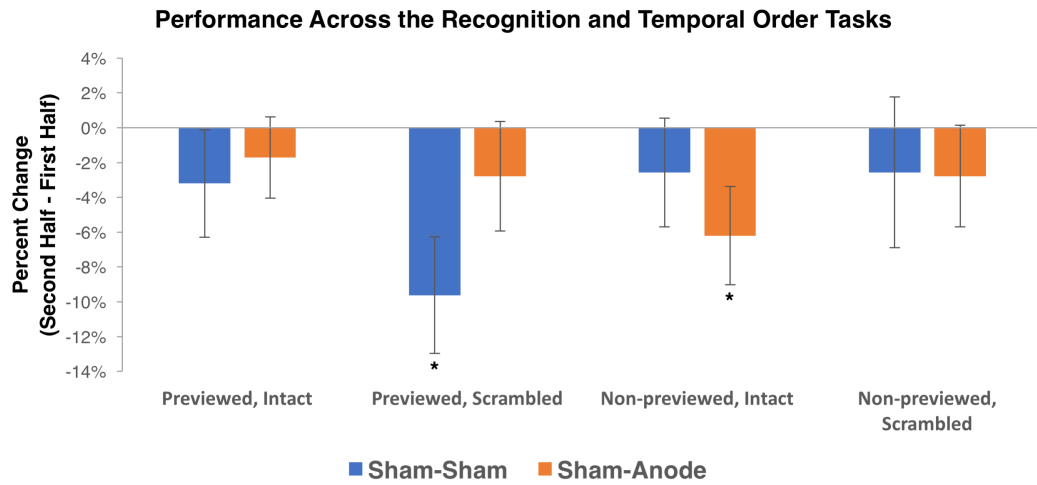
Behavioral performance as a function of task. The hit rate, false alarm rate, and correct rejection rate were calculated separately for the recognition memory task and the temporal order task. For the recognition task, the hit rate included the proportion of Previewed event sequences correctly identified, the false alarm rate consisted of the proportion of Non-previewed event sequences incorrectly indicated as Previewed ones, and the correct rejection rate consisted of the proportion of correctly-identified Non-previewed event sequences. For the temporal order task, the hit rate entailed the proportion of correctly-identified Scrambled event sequences, the false alarm rate

included the proportion of Intact event sequences incorrectly judged as Scrambled ones, and the correct rejection rate involved the proportion of correctly-identified Intact event sequences. The overall mean accuracy is shown for (A) each task individually and (B) combined across both tasks where only trials in which correct responses to both tasks were included. Changes in the mean hit rate and mean false alarm rate across the HD-tDCS session are depicted for (C) the recognition memory task and (D) the temporal order task. The error bars show the standard error.



**Figure 6.4**

(A) Participants' mean response bias (Br) for each task in each of the two halves of the HD-tDCS session and (B) the difference in mean response bias between the first and second halves. The error bars represent the standard error.



**Figure 6.5**

Change in mean performance across individual conditions when only trials in which responses to both the recognition task and the temporal order task were correct. The error bars depict the standard error.



## CHAPTER SEVEN

### Conclusion

The studies presented in the previous chapters have incorporated the use of wearable camera technology to examine the retrieval of real-world event memories through neuroimaging and brain stimulation experimental methodologies. The resultant findings have provided further understanding of the neural correlates supporting real-world episodic memory. This includes how such regions may facilitate the recall of specific event dimensions associated with an event's original experiential source, recognition of an event based on associated photographs, and an event's temporal order.

While laboratory-based stimuli have long been utilized to study the behavioral and neural underpinnings of episodic memory retrieval, recent studies have indicated that recall of such memories may result in differential engagement of brain regions than autobiographical memories (Cabeza & St. Jacques, 2007; Gilboa, 2004; McDermott et al., 2009). Further research is necessary to understand the neural correlates of episodic and autobiographical memory retrieval, particularly those from the real world, and such an endeavor may benefit from incorporating methodological approaches that allow the use of stimuli drawn directly from participants' own lives. With the increasing accessibility and portability of wearable digital camera devices, this technology may assist in the study of autobiographical memory through capturing daily life events, without participants' explicit input, for use as mnemonic probes. Chapter 2 included a detailed review of the behavioral and neural findings resulting from such incorporation of wearable digital camera devices into autobiographical memory retrieval research, and how these types of studies can broaden current knowledge to include experiences from individuals' lives. To take advantage of the benefits offered by wearable camera devices, a series of neuroimaging

and brain stimulation investigations incorporating this technology was conducted to assess the neural substrates mediating the retrieval of events drawn from the real world.

A functional magnetic resonance imaging (fMRI) experiment was first conducted to examine real-world autobiographical memory retrieval and how different event features may be represented in the brain. This study employed wearable camera devices to photograph events from participants' lives over the course of three weeks. One week after participants wore the camera devices, they were exposed to a subset of photographic sequences, which allowed for manipulation of recognition based on previously encountering photographs. The following day, participants underwent fMRI scanning while viewing the entire set of photographic sequences and made judgments about the original source of depicted events – which assessed whether experiences were derived from their own life or another individual's life – and temporal order, which examined whether images were presented in the order in which they were originally captured. Overall, this fMRI experiment investigated the neural correlates supporting memory processes related to the original source of events, recognition based on previously encountering photographs of events, and events' temporal order. Three fMRI studies were derived from this experiment and were presented in Chapters 3-5.

Chapter 3 described the first fMRI study, which examined how the patterns of neural activation differ during the retrieval of real-world events depending on whether such experiences were personally experienced and whether the presented photographs of these experiences were encountered previously. This study used multi-voxel pattern analysis and found dissociable neural activity patterns corresponding to these different dimensions of retrieval. Moreover, these patterns of neural activation were associated with regions previously implicated in either autobiographical memory or laboratory-based memory, as identified by a prior meta-analysis

(McDermott et al., 2009). Regions associated with autobiographical memory – such as medial temporal lobe areas, including the hippocampus/parahippocampal gyri – contained diagnostic information related to events’ original experiential source and were superior at differentiating neural activity patterns related to this event dimension. This network was capable of distinguishing between the original source of experiences to determine whether the events were derived from participants’ own lives or other individuals’ lives. In comparison, the network of areas implicated in laboratory-based memory – such as regions in the inferior and middle frontal gyrus, including the left rostrolateral prefrontal cortex (RLPFC) – contained diagnostic information regarding the novelty of events, based on photograph recognition, and were superior at differentiating between neural signatures of this characteristic. Patterns of activity within this network could be used to reliably determine whether or not photographs of the events had been previously encountered. Moreover, both networks were able to distinguish between events that had been personally experienced from those that had only been previously encountered as photographic sequences, which represents the distinction between personal experience and secondhand event knowledge. Overall, the networks of regions associated with autobiographical and laboratory-based memory retrieval were differentially sensitive to events’ original experiential source and event recognition, and could even distinguish between more specific dimensions.

In addition to assessing broad networks of regions to determine the neural activity patterns underlying event features during recall, including those related to the original source of events and recognition based on prior encounters with photographs, specific brain regions can be evaluated to assess how they may support such characteristics. The hippocampus is critical for episodic and autobiographical memory retrieval (Cabeza & St. Jacques, 2007; Kim, 2012;

Maguire & Mummery, 1999; McDermott et al., 2009; Svoboda et al., 2006). The second fMRI study, reported in Chapter 4, investigated changes in neural activation along the long axis of the hippocampus with regards to events' original experiential source, event recognition based on photographic encounters, and events' temporal order. Each hippocampus was split into six regions of equal length, with the estimated parameter values extracted from the resulting areas to determine condition-specific activity. Activity in response to the three mnemonic features were localized to different hippocampal regions. While intermediate and posterior hippocampal areas were more sensitive to events from participants' own lives – relative to those from other individuals' lives – anterior areas were more sensitive to novel events, in comparison to those that had been previously encountered. Additionally, anterior and intermediate regions were more sensitive to temporally intact events, compared to temporally scrambled ones. Altogether, engagement of the hippocampal long axis during retrieval differed in terms of the recalled events' attributes.

Another region crucial for episodic memory, particularly retrieval processes, is the prefrontal cortex (Cabeza & St. Jacques, 2007; Gilboa, 2004; Lepage et al., 2000; Ranganath et al., 2000; Svoboda et al., 2006). The RLPFC is a prefrontal area that has been implicated in episodic retrieval processes – such as memory monitoring – as well as higher cognitive processes more generally, including relational integration (Dobbins & Wagner, 2005; Gilbert et al., 2006; Ranganath et al., 2000; Reynolds et al., 2006; Simons et al., 2008; Wendelken et al., 2008; Westphal et al., 2016). The third fMRI study, detailed in Chapter 5, examined the left and right RLPFC for hemispheric differences in sensitivity to recognition based on prior encounters with event photographs as well as the temporal order of events. Analyses identified RLPFC regions through two sets of univariate contrasts that were based on events' novelty and temporal order:

both sets of contrasts identified areas based on a temporal order mismatch detection effect where there was greater activity for temporally scrambled events, in comparison with temporally intact ones, but required this effect for different conditions of recognition. The left RLPFC exhibited this mismatch detection effect for new events while the right RLPFC demonstrated this mismatch effect for previously encountered events. Not only was the RLPFC the only cortical area that demonstrated this distinction across hemispheres, but task-related functional connectivity also revealed differences in coupling with other regions. Although the two RLPFC areas coupled with each other, they primarily coupled with ipsilateral frontal and parietal regions that represented two separate networks. While the left RLPFC demonstrated connectivity with the left frontoparietal control network associated with decision-making and cognitive control (Dosenbach et al., 2007; Power et al., 2011; Vincent et al., 2008), the right RLPFC exhibited connectivity with the right ventral attention network associated with stimulus-driven attention (Corbetta & Shulman, 2002; Fox et al., 2006). As such, the RLPFC's activation and connectivity during recall differed as a function of events' novelty and temporal order across the hemispheres.

While fMRI is a powerful technique for understanding how activation changes across the brain during specific conditions, other experimental techniques allow the assessment of specific regions' contributions to cognitive functions in a more causal manner. Such techniques include brain stimulation methodology, including non-invasive transcranial direct current stimulation (tDCS), which can modulate targeted areas to determine their impact on behavioral and cognitive processes. Based on the differential RLPFC sensitivity found in the fMRI study described in Chapter 5, a follow-up experiment using high-definition tDCS (HD-tDCS) was conducted in order to focally modulate the left RLPFC. The study paradigm of this experiment was based on the previous fMRI experiment – and utilized prior photographic sequences – but combined into a

one-day experimental session. Participants were first shown a subset of photographic sequences to allow for later recognition testing. During the subsequent session, HD-tDCS was applied while participants viewed photographic sequences and indicated judgments based on events' temporal order and recognition of whether images had been previously encountered. This HD-tDCS experiment assessed the left RLPFC to determine its causal involvement in recognition and temporal order processes during episodic memory retrieval.

The results of this HD-tDCS experiment were described in Chapter 6. Anodal stimulation of the left RLPFC heightened false alarm rates, where participants increased the frequency with which they mistakenly endorsed novel events as familiar ones. The application of left RLPFC stimulation induced a significant shift in response bias, which was not found when only sham stimulation was employed. This may be due to the modulation of memory monitoring processes, which is consistent with previous findings from studies involving lesions (Parkin et al., 1996; Schacter et al., 1996; Verfaellie et al., 2004), neuroimaging (Cruse & Wilding, 2009; Dobbins & Wagner, 2005; Gilbert et al., 2006; Miller et al., 2001; Ranganath et al., 2000; Reynolds et al., 2006; Simons et al., 2008; Westphal et al., 2016), and other tDCS methods (Pergolizzi & Chua, 2017; Zwissler et al., 2014). These findings indicate that anodal stimulation of left RLPFC is capable of altering participants' recognition memory judgments.

It should be noted that neither the fMRI experiment nor the HD-tDCS experiment instructed participants to memorize any photographic sequences. Despite this, participants were highly accurate in determining mnemonic judgments related to photographic source and novelty, even when participants' original events may have originally occurred up to three weeks prior in the fMRI study or when photographic sequences had been seen immediately preceding the testing session in the HD-tDCS study. This indicates that the photographs resulting from the

wearable digital cameras employed in the presented studies were useful in capturing events from participants' lives and also provided enough detail and information that allowed accurate determination of event features.

The assessment of events' original experiential source, novelty, and temporal order across the presented studies allowed for more in-depth understanding of episodic memory retrieval processes as well as the regions that support them. The Chapter 3 fMRI study included an examination of regions implicated in autobiographical memory, including the hippocampus, and how the patterns of activation within these areas contained diagnostic information regarding the experiential source of previous events. That is, this network of regions was capable of determining whether the source of an event was originally from participants' own lives or from other individuals' lives. It is fitting that the Chapter 4 fMRI study found experiential source-related activation in the hippocampus. Moreover, such activity was specifically localized to posterior and intermediate regions of the hippocampal long axis, which demonstrated more activation for events from participants' own lives than other individuals' lives. Such findings are consistent with other studies of autobiographical memory that have found hippocampal involvement during recall, including more recent studies that have also employed wearable camera technology to capture participants' lives for use as mnemonic cues (e.g., Milton, Muhlert, Butler, Benattayallah, et al., 2011; Rissman et al., 2016). Overall, these results help clarify what regions – and which specific areas within those structures – may contain information pertaining to the recall of an event's features, such as their original source.

In addition to the experiential source of events, the hippocampus demonstrated effects related to events' novelty and temporal order. The hippocampus exhibited greater activity for novel events, relative to familiar ones, along anterior portions of the long axis. In contrast, the

hippocampus also showed increased activity for temporally intact events, relative to temporally scrambled ones, along both anterior and intermediate long-axis regions. Not only does the hippocampus support effects related to the determination of an event's original source, but it also facilitates judgments of events' novelty and temporal order. Accordingly, the hippocampus supports multiple facets of episodic and autobiographical memory retrieval.

The Chapter 3 fMRI study also examined the neural signatures of areas associated with laboratory-based memory – including the left RLPFC – and determined that information within these regions pertained to whether event photographs had been previously seen. As such, these regions as a whole were capable of successfully recognizing events' novelty. Consistent with the left RLPFC's involvement in this laboratory-based memory network, it has been implicated in assessments of event novelty in the current studies. The third and fourth studies – Chapter 5 and Chapter 6, respectively – both included examinations of the left RLPFC to further understand its involvement in recognition and temporal order processes during event retrieval. Although the Chapter 5 fMRI study suggests that the left RLPFC may be capable of comparing novel events with previous representations, potentially through the use of reasoning processes, the Chapter 6 HD-tDCS study suggests that this region might perform memory monitoring mechanisms as well. When these results are considered separately, they are consistent with the broader literature assessing the RLPFC, which has been implicated in a variety of higher order cognitive functions, including both reasoning and memory processes (Dobbins & Wagner, 2005; Gilbert et al., 2006; Ranganath et al., 2000; Reynolds et al., 2006; Simons et al., 2008; Wendelken et al., 2008; Westphal et al., 2016). Taken together, these findings may indicate two facets of the same general mnemonic function: the left RLPFC supports the recognition of whether photographs of events had been previously encountered.



The presented experiments have employed a variety of methodological and analytical techniques in order to examine the neural correlates of episodic memory retrieval in terms of recalled events' original experiential source, novelty, and temporal order in which they unfolded. The resultant findings add to extant knowledge of both specific regions and broader networks as well as how they may mediate episodic recall for events drawn from participants' own experiences. Moreover, these studies illustrate how wearable camera devices can be harnessed to photograph events from participants' lives and produce images that can then be incorporated as mnemonic probes in both neuroimaging and brain stimulation experiments. As such, the present experimental paradigms have combined wearable camera technology with fMRI and HD-tDCS methodology to investigate the neural substrates of episodic memory retrieval and extend such findings to events from the real world.

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