SHEDDING LIGHT ON MEMORY RETRIEVAL: REACTIVATION OF RELATED INFORMATION AND ITS ASSOCIATION WITH THE HIPPOCAMPUS

BY

JOHN A. WALKER

DISSERTATION

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Doctoral Committee:

Professor Neal J. Cohen, Chair
Professor Monica Fabiani
Professor Gabriele Gratton
Professor Renee Baillargeon
Assistant Professor Joel L. Voss, Northwestern University

ABSTRACT

Memory retrieval is a multifaceted process that involves the coordination of multiple areas of the brain including the cortical memory stores and the hippocampus, an area of the brain shown to be necessary for creating and using flexible bindings between items in memory. One phenomenon that has been shown to be associated with the retrieval of information from those cortical memory stores is reactivation. Reactivation is the finding that when participants retrieve information the areas that were originally active while processing that information come back online and are reactivated. In a previous study I and others had shown that associative or relational bindings between items can be used to reactivate the cortical processors of one another (Walker, Low, Cohen, Fabiani, & Gratton, 2014). The current experiments examined this reactivation of sensory cortices by looking at its association with the hippocampus, both in terms of relating the reactivation activity to structural measures of the hippocampus but also to possible methods by which the hippocampus and sensory cortex communicate. Additionally, this reactivation phenomenon was studied across the lifespan by demonstrating the earliest known time at which infants show this pattern of reactivation as well as showing aging effects in the possible communication between the hippocampus and sensory cortices and subsequent reactivation.

The first experiment establishes an association between the hippocampus and reactivation of relationally bound stimuli in older adults aged 55-88 years old. In this study participants learned pairs of faces and scenes and were then shown one of the items (in this case the scene) in order to elicit reactivation of face processing regions. It was found that the magnitude of reactivation in these older adults is related to hippocampal volume.

Entrainment of oscillatory activity, particularly in the theta band, has been suggested as a possible route through which the hippocampus communicates with sensory cortices. The second

experiment combined data from two previous studies using the same face-scene pair study paradigm and examined whether oscillatory activity in the theta band was associated with memory ability and reactivation. Across all participants, the power of theta and oscillations (8-10 Hz) just above canonical theta (high theta) within the face processing regions was correlated with subsequent memory activity. When looking at the correlation between oscillatory power and reactivation, it was found that oscillatory power in that high theta band in the face processing region of interest was positively correlated with reactivation of that same region but only in young adults. Older adults showed no correlation between oscillatory power in the theta or high theta band and reactivation. These data indicate a possible route through which the hippocampus communicates with the cortex.

The third study shows the earliest time in the lifespan to show reactivation effects in the cortex to stimuli that were presented only once. 9-month-old infants studied pairs of movie clips and sounds as well as sounds only and movie clips only. Much like the older and younger adults, presentation of a sound that was previously paired with a movie elicited reactivation of processors for the missing item (in this case reactivation of extrastriate cortex that was originally active for the movie clips) in these infants.

The combination of these experiments show that this relational reactivation phenomenon takes place across the lifespan from 9 months old to 88 years old and is associated with the hippocampus. Oscillatory activity, which may represent the communication between the hippocampus and the sensory cortex, is associated with reactivation but this association is not present in old age.

To my mother and father for putting up with me for all these years and for giving me the love and support needed to achieve this document

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CHAPTER 1

INTRODUCTION

One of the most fundamental aspects the human experience is our ability to store and remember the events and experiences in our life. This ability to retrieve information that we have previously encountered is essential for operating during everyday life for knowing things as mundane as where one parked her car to remembering important information such as a due date or an anniversary. In the immortal words of Tennessee Williams "Life is all memory, except for the one present moment that goes by you so quickly you hardly catch it going." As the understanding of memory retrieval is so critical to how humans operate, it is not shocking that philosophers and scientists have argued about the nature of memory retrieval from the ancient Greeks all the way to present day. However, despite the centuries of enquiries on the subject it is still not entirely clear what processes take place to allow humans to retrieve information from the brain. While this dissertation cannot possibly hope to answer all of the questions that exist regarding what takes place when a person remembers a memory, this document hopes to shed light on some of the activity that takes place during memory retrieval and the interactions between different areas of the brain that support that retrieval.

Memories are Distributed throughout the Cortex

In order to understand how memory is retrieved, one must first understand how and where those memories are stored. From Descartes folds of the brain to L'Homme's idea of traces of memory left in the brain, by the 17th century many thought that every memory was stored within the brain. However, it was not until the 20th century that researchers started to understand that a memory for an event was not stored in a single place, but rather throughout the cortex. In one of the most well-known set of experiments Karl Lashley tried to understand

where memories for a maze running task were stored in the rat brain (Lashley, 1950). He tried making cuts and removing various parts of rats' brains but was unable to successfully damage what he termed the "maze-running habit". He thus concluded that memories for an event, or in this case a maze, are not stored in one single place but throughout the cortex.

Around the same time Friedrick von Hayek published a paper linking cortical memory stores with cortical sensory processors (Hayek, 1952). He argues that not only do perception and memory interact but that they are intricately tied such that perception is both the source of memory and the product of memory. It has been known for quite some time that different areas of the brain process different type of stimuli from physiologists studying head wounds. More recently these cortical processors have been better characterized showing that these they are organized hierarchically from initial input into primary sensory cortex for that type of stimuli (e.g. visual or somatosensory) and progressing along to more and more complex processors (Jones & Powell, 1970; Pandya & Yeterian, 1985; Van Essen & Maunsell, 1983). According to Hayek's proposal, this would mean that memories are stored throughout the cortical processors that were originally activated when initially processing that event (Hayek, 1952).

While Hayek's claim was only theoretical and with no real knowledge of the hierarchical nature of sensory processing in the brain, more recent neuroimaging results have provided evidence for his hypothesis. One excellent example comes from an experiment by O'Craven and Kanwisher (2000) in which they had participants look at pictures of novel faces and known locations from around the college campus on which they were located. While viewing those stimuli areas along the visual processing stream became active but in particular an area in the fusiform gyrus called the fusiform "face" area (Kanwisher, McDermott, & Chun, 1997) for the faces being shown and the parahippocampal "place" area (Epstein & Kanwisher, 1998) for the well known locations.

Following the presentation of these items, the participants were given audio cues describing either the person or the place and asked the participants to retrieve and visualize the cued item. During this visualization the same areas (i.e. the fusiform face area for faces and the parahippocampal place area for scenes) became active, indicating that activity in these processors is part of memory retrieval.

Retrieval of Memories Involves the Reactivation of Cortical Processors

With the establishment that memories are stored in the cortical processors in which the experience was initially processed, comes the question of what processes then take place in order for that memory to be retrieved. Cognitive psychologists have long argued that in order for a memory to be retrieved, the same operations that were present when the memory was encoded or stored must be recapitulated (Kolers, 1973; C Donald Morris, John D Bransford, & Jeffery J Franks, 1977). This idea of Transfer Appropriate Processing (C. Donald Morris, John D. Bransford, & Jefferey J. Franks, 1977) argues that the degree of similarity between the processing engaged during the initial encounter with the stimulus and the processing when attempting to recall that information will determine the degree of retrieval success. This has been demonstrated by showing that the amount of overlap between study and cue is related to the amount of successful memory retrieval (Blaxton, 1989; Roediger & Guynn, 1996).

The concept of Transfer Appropriate Processing can then be extended to the brain to argue that the degree to which activity in cortical processors overlaps between initial processing and retrieval will determine the success of memory retrieval. In other words, in order for stored information in the cortex to be retrieved, the cortical processors that were active when the information was encountered will need to be activated again, or reactivated. Multiple memory models posit the idea that memory retrieval involves reactivation of sensory processors in the

cortex (Davachi & Danker, 2013; Marr, 1971; McClelland, McNaughton, & O'Reilly, 1995; Moscovitch et al., 2005; Norman & O'Reilly, 2003). One aspect that many of these models have in common is that a structure called the hippocampus is responsible for storing and retrieving information stored in the cortex. The hippocampus does this via a process called pattern completion whereby it can take an incomplete pattern of information and then reactivate the missing part of the pattern within the hippocampus (Marr, 1971; Norman & O'Reilly, 2003). It is thought that this reactivation extends beyond the hippocampus itself to reactivate the initial pattern of activity for the stored information.

These theories are supported by functional magnetic resonance imaging (fMRI) evidence showing reactivation of sensory processors during memory retrieval. As mentioned earlier O'Craven and Kanwisher (2000) showed that when participants actively imagine a place or a person that the cortical processors that were active when initially viewing those items, in this case the parahippocampal gyrus and the fusiform gyrus respectively, become reactivated in the cortex. And this is not just the case just for faces and scenes. Reactivation of cortical processors has been shown in a variety of stimuli such as colors (Simmons et al., 2007), tools (Chao, Weisberg, & Martin, 2002), and words (Hofstetter, Achaibou, & Vuilleumier, 2012; Johnson & Rugg, 2007; Woodruff, Johnson, Uncapher, & Rugg, 2005).

It is important to note, however, that the reactivation studies described so far have only examined the reactivation of single items. Participants learn a list of items and then are cued to imagine those items by being given the name of the item. However, memory as people experience it is not just a list of single items but is highly associative. The structure in the brain that is thought to create and utilize such associations is the hippocampus.

The Hippocampus and Relational Memory

The hippocampus's importance to declarative memory became apparent following the surgery to a patient known as H.M., who had intractable epilepsy with a locus in his hippocampus (Scoville & Milner, 1957). To hopefully alleviate his epilepsy, H.M. received a lesion of the medial portion of the temporal lobe, including most of the hippocampus. While this did seem to cure his epilepsy, the surgery also left him with profound retrograde and anterograde amnesia. Prior to this point, doctors and scientists had thought that the hippocampus may have been involved with memory as unilateral resection of part of the hippocampus sometimes resulted in memory impairments (Milner & Penfield, 1955) but did not know the extent of the role that the hippocampus played in declarative memory.

More recent evidence has indicated that the role of the hippocampus is to create bindings between the various items in memory. This idea called the relational memory theory posits that the hippocampus's role in memory is to create flexible bindings between the items in an episode as well as between those items and the items currently stored in memory (N. J. Cohen & Eichenbaum, 1993; Eichenbaum, 2000; Eichenbaum & Cohen, 2001). The role for the hippocampus in the creation and usage of relational bindings comes from a number of studies showing that amnesic patients with damage to the hippocampus are especially impaired in relational memory ability as compared to single item memory (Duff, Gallegos, Cohen, & Tranel, 2013; D. E. Hannula, Ryan, Tranel, & Cohen, 2007a; Deborah E Hannula et al., 2015; D. E. Hannula, Tranel, & Cohen, 2006; Konkel, Warren, Duff, Tranel, & Cohen, 2008; Ryan, Althoff, Whitlow, & Cohen, 2000; Warren, Duff, Jensen, Tranel, & Cohen, 2012; Watson, Voss, Warren, Tranel, & Cohen, 2013) as well as numerous other studies relating hippocampal activity to relational memory in healthy populations (Giovanello, Schnyer, & Verfaellie, 2009; D. E. Hannula, Libby, Yonelinas, & Ranganath, 2013; D. E. Hannula & Ranganath, 2008, 2009; Monti

et al., 2015; Prince, Daselaar, & Cabeza, 2005; Suffczynski, Kalitzin, Pfurtscheller, & Da Silva, 2001; Sullivan Giovanello, Schnyer, & Verfaellie, 2004). In the context of memory retrieval and activation, this theory would hold that the hippocampus would be involved in the retrieval and reactivation of memory in the cortex. The relational memory theory would then predict that relational bindings can be used to reactivate items in the cortex.

Relations can be Used to Reactivate Associated Items

To test whether or not relational bindings could be used to reactivate sensory cortices, we used a paradigm developed in our lab (D. E. Hannula et al., 2007a) in which participants learned faces and scenes and then tested the participants' memory for those pairings by giving an old/new recognition test on the pairing of the items (Walker et al., 2014). Critically, prior to every test display, we displayed the scene from every pairing as a "scene preview." For some of the trials participants saw a scene that was previously studied with a face and for other trials, participants saw a completely novel scene that had not been associated with a face. If relational bindings can be used to reactivate sensory cortex, then the presentation of the old scene that was previously paired with a face prior to the test display should reactivate the missing face, resulting in an increase in activity in face processing regions in the cortex, and the novel scenes should show no increase in face processing regions. Indeed, this is what we found with increases in activity in a face processing region called the superior temporal sulcus (STS) to the old scenes, even though no faces were being presented on the screen.

Other studies have also shown this relational reactivation effect in the cortex (Staresina, Cooper, & Henson, 2013; Zeithamova, Dominick, & Preston, 2012).with Zeithamova et al. (2012) even demonstrating that the pattern of activity and not just the specific cortical areas can be reactivated, providing evidence for cortical reinstatement models. However, despite all of this

evidence that relational bindings can be used to reactivate the cortex, there is very little evidence linking the hippocampus to these cortical reactivations. A few studies have found a link between the hippocampus and reactivation of activity in other areas directly adjacent to the hippocampus in the medial temporal lobe (Staresina et al., 2013; Tompary, Duncan, & Davachi, 2016), however evidence linking the hippocampus to more remote reactivations has yet to be established. In Chapter 2 I address this issue by demonstrating that the hippocampus is, indeed, associated with cortical reactivation of sensory processors by showing that measures of hippocampal structure are related to the magnitude of observed reactivation.

Possible Routes of Communication Between the Hippocampus and Cortex

Another question that reactivation and retrieval of information in the cortex presents is: what processes take place that allow the hippocampus and the cortex to communicate with one another. As the long term stores for memory reside in the cortex and not in the hippocampus itself, the hippocampus must have a way of communicating with these various stores in order to allow memory retrieval. One possible method of communication across the brain is by synchronizing firing rates of neurons between the different areas in an oscillatory pattern.

The hippocampus has been shown to naturally have a theta rhythm to its firing patterns (Otto, Eichenbaum, Wiener, & Wible, 1991; Ranck, 1973). Multiple studies in rats have shown that when rats are navigating an environment, the power of the theta oscillations increases (O'Keefe & Recce, 1993; Otto et al., 1991). During sleep this theta power also increases and have been shown to entrain faster ripples of activity in the hippocampus oscillations (Chrobak & Buzsáki, 1994; Otto et al., 1991; Ranck, 1973). It is thought that this theta rhythm is entrained with other areas of the cortex and this allows the communication of information in the form of fast ripples. Sirota et al. (2008) found that the hippocampus will entrain with different parts of

the cortex and that this entrainment across structures temporally locked faster oscillatory activity in the gamma band (100-200 Hz).

In humans, higher theta power has been linked to better memory performance. It has been found that greater theta power in general (Cummins & Finnigan, 2007; Düzel et al., 2003) and over visual cortexes for visual tasks is linked with better recognition performance (Gruber, Tsivilis, Giabbiconi, & Müller, 2008; Osipova et al., 2006) and source recall in a recognition task (Guderian & Düzel, 2005). Hippocampal theta oscillations in humans have even been shown to be entrained with the cortex in humans during the retrieval of autobiographical memories with the amount of synchrony being related to amount of information recalled. But this entrainment was between the hippocampus and the prefrontal cortex and not sensory cortices (Fuentemilla, Barnes, Duzel, & Levine, 2014). Despite this evidence of theta oscillations being associated with memory processes and the hippocampus, demonstrating a possible route through which the hippocampus communicates with the cortex, there is no evidence of a link between oscillatory activity and reactivation in the cortex. In Chapter 3 I show that oscillatory power in the reactivated region is associated with the level of reactivation observed in that cortex in college-aged adults. However, we do not find such a link in older adults, indicating a possible memory component to the link between oscillations and reactivation.

Development and Aging

Another aspect of memory retrieval is that it is not uniform throughout the lifetime. As one develops from an infant to a child and then an adult, more and more memory systems come online and memory improves (Gathercole, 1998). However, as one ages past the college years, memory has been shown to decline (R. L. Buckner, 2004). By examining the development and decline in memory retrieval, one can get a better picture of the processes taking place by

examining what processes are impaired as well as what processes are online in the developing and aging brain.

In children it is generally thought that declarative memory does not come online until ages 3-5 (Dudycha & Dudycha, 1941). This is due to a phenomena called infantile amnesia. Infantile amnesia is the finding that people older than 3-5 years old cannot recall any episodic memories prior to 4-6 years of age. So infantile amnesia has been taken as evidence that episodic and relational learning do not come online until about 4 years and certainly not for infants. Evidence of this delay in relational learning ability comes from multiple studies that fail to show one trial learning of associative information any time before 12 months of age (Hayne, Boniface, & Barr, 2000; Herbert & Hayne, 2000) with Pears and Bryant (1990) demonstrating that children as old as 4 years old have difficulty learning rules between pairs of items. However, recent eye tracking studies from Jenny Richmond and colleagues show that 9-month-old and even 6-month-old infants show eye movement effects indicating relational memory (Cai et al., 2015; Chong, Richmond, Wong, Qiu, & Rifkin-Graboi, 2015; J. Richmond & Nelson, 2009; J. L. Richmond & Power, 2014). Additionally, physiological evidence shows that the hippocampus is already well developed by the time of 9-months, reaching a size upwards of around 50% of the size they will be when a person reaches adulthood (Utsunomiya, Takano, Okazaki, & Mitsudome, 1999). So if infants show eye movements at 9 months that suggest relational memory ability and the hippocampus may be developed enough to support relational memory, we wanted to see if 9-month-old infants show a relational reactivation effect similar to young adults. In Chapter 4 I demonstrate that 9 month old infants do, in fact, show this relational reactivation effect in the cortex.

On the other end of the spectrum, it is well known that as one ages, memory performance declines (R. L. Buckner, 2004). This deficit has been shown to be especially pronounced in associative learning (Baltes, Staudinger, & Lindenberger, 1999; Naveh-Benjamin, 2000; Naveh-Benjamin, Guez, Kilb, & Reedy, 2004), with this deficit linked to atrophy in the hippocampus (R. L. Buckner, 2004; Charlton et al., 2006; Duverne, Motamedinia, & Rugg, 2009; M. Fabiani, 2012; Morcom, Good, Frackowiak, & Rugg, 2003; N. Raz et al., 2005; Walhovd et al., 2005). However, the rate of atrophy is not uniform across individuals, creating greater variation in hippocampal size and this variability is associated with memory as it is thought that larger hippocampi are more intact and healthier (Carlesimo, Cherubini, Caltagirone, & Spalletta, 2010; Charlton et al., 2006; Naftali Raz, 2000; N. Raz et al., 2005). Furthermore, the possible route of communication between the hippocampus and the cortex, theta oscillations, has also been shown to be lessened in older adults (Cummins & Finnigan, 2007). With decreases in theta and hippocampal atrophy, it is not entirely clear how well older adults can demonstrate reactivation of sensory cortices during memory retrieval and how this reactivation is related to oscillatory power. In Chapter 2 I show that older adults do show reactivation and in Chapter 3 I explore age effects on the link between oscillatory activity and reactivation.

The Current Experiments

Chapters 2-4 detail 3 completed experiments studying the relationship between memory related reactivation in the cortex and the hippocampus, with a general discussion of these experiments and future directions in Chapter 6.

Chapter 2 establishes the link between memory related reactivation in the cortex and the hippocampus. In this study we had older adults learn pairs of faces and scenes and then presented the scenes prior to the test display. Much like the young adults (Walker et al., 2014),

we found that older adults show reactivation of face processing cortices to the presentation of the relationally bound scenes. This reactivation activity was found to be correlated with measures of hippocampal size as well as diffusion tensor imaging measures of hippocampal structure. These data establish a link between the hippocampus and cortical reactivation of sensory cortices that has long been theorized but not demonstrated. Additionally, we were able to show that older adults do show similar relational reactivation as that observed with younger adults.

Chapter 3 examines a possible method by which the hippocampus communicates with sensory cortices (i.e. oscillatory activity) and how this is related to the relational reactivation phenomena. To this end I combined two previous data sets, a set of young adults (aged 18-30) from (Walker et al., 2014) and the data set of older adults from Chapter 2 to study the association between theta oscillations, memory performance, and reactivation. The theta oscillatory power in the areas that show reactivation during the time period prior to those reactivations was found to be significantly correlated with subsequent memory performance at test across all participants. Similarly, oscillatory power in a band just above theta (8-10 Hz) in the areas that show reactivation also during the time period prior to the observed reactivation is correlated with subsequent memory performance across all participants as well. When testing the association between oscillatory activity and reactivation, I found a time period during which the higher oscillatory band activity (8-10 Hz) that was correlated with the amount of reactivation observed but only in younger adults. Older adults showed an overall reduction in theta power during the time window prior to reactivation as compared to younger adults and older adults showed no correlation between oscillatory activity and reactivation. This study provides a link between oscillatory activity and reactivation but also points to a possible decrement in the ability for the hippocampus to communicate and retrieve information from the cortex.

The final study demonstrates the youngest known demonstration of reactivation in the cortex for items learned in one trial. There has been considerable debate about what memory processes come online and when in infants. Here we show that 9-month-old infants show memory related reactivation in the cortex. For this study infants saw pairs of movie clips and sounds, movie clips alone, or sounds alone and then were re-presented with those items. Critically, only the sound was re-played from the movie sound pairing. If infants this young can create and utilize relational memories, then the presentation of the sound that was previously paired with the movie should elicit reactivation of visual areas. Indeed, these infants do show reactivation in the extrastriate cortex to the relationally bound sound but not to the sound that was originally presented alone. Infants also looked at the screen more for sounds that were previously paired with movies as compared to sounds that were not paired with movies, despite there being nothing on the screen for both conditions. These data demonstrate that infants as young as 9 months can create and utilize relational memories prior to the cessation of infantile amnesia.

CHAPTER 2

HIPPOCAMPAL STRUCTURE PREDICTS CORTICAL INDICES OF REACTIVATION OF RELATED ITEMS

Abstract

One of the key components of relational memory is the ability to bind together the constituent elements of a memory experience, and this ability is thought to be supported by the hippocampus. Previously we had shown that these relational bindings can be used to reactivate the cortical processors of an *absent* item in the presence of a relationally bound associate (Walker et al., 2014). Specifically, we recorded the event-related optical signal (EROS) when presenting the scene of a face-scene pair during a preview period immediately preceding a test display, and demonstrated reactivation of a face-processing cortical area (the superior temporal sulcus, STS) for scenes that had been previously paired with faces, relative to scenes that had not. Here we combined the EROS measures during the same preview paradigm with anatomical estimates of hippocampal integrity (structural MRI measures of hippocampal volume and diffusion tensor imaging measures of mean fractional anisotropy and diffusivity) to provide evidence that the hippocampus is mediating this reactivation phenomenon. The study was run in a sample of older adults aged 55-87, taking advantage of the high amount of hippocampal variability present in aging. We replicated the functional reactivation of STS during the preview period, specific to scenes previously paired with faces. Crucially, we also found that this phenomenon is correlated with structural hippocampus integrity. Both STS reactivation and hippocampal structure predicted subsequent recognition performance. These data support the theory that relational memory is sustained by an interaction between hippocampal and cortical sensory processing regions, and that these functions may be at the basis of episodic memory changes in normal aging.

Introduction

It has long been known that, when a person recollects an event, s/he does not simply remember a recording of it but, rather, a reconstruction of multiple elements of that memory stored in various parts of the cortex (Norman & O'Reilly, 2003). During this reconstruction the same cortical processors that were active at the initial encounter are reactivated (Hofstetter et al., 2012; Johnson & Rugg, 2007; Marr, 1971; Norman & O'Reilly, 2003; Rugg, Johnson, Park, & Uncapher, 2008). For example it has been shown that the areas of cortex that were used to process a face or a location are again active when a person is asked to remember those items (O'Craven & Kanwisher, 2000). This phenomenon is not specific to faces or locations but has been demonstrated across a wide range of stimulus types such as colors (Simmons et al., 2007), tools (Chao et al., 2002), and words (Hofstetter et al., 2012; Johnson, McDuff, Rugg, & Norman, 2009), to name a few. Recently we and others were able to show that not only individual items can be reactivated in the cortex, but that items can reactivate other relationally-bound items from the same event (Hofstetter et al., 2012; Oudiette, Antony, Creery, & Paller, 2013; Staresina et al., 2013; Staresina, Henson, Kriegeskorte, & Alink, 2012; Walker et al., 2014; Zeithamova et al., 2012). It has been hypothesized that the hippocampus is a critical structure in the process of storing and retrieving the multiple pieces of information constituting a relational memory (N. J. Cohen & Eichenbaum, 1993; Eichenbaum, 2000; Eichenbaum & Cohen, 2001; Norman & O'Reilly, 2003). Although the importance of the hippocampus in relational memory is supported by a large amount of data (D. E. Hannula et al., 2006; Konkel et al., 2008; Watson et al., 2013), its critical role in reactivating relationally bound items has yet to be demonstrated. In this paper we demonstrate this link by showing that variability in hippocampal volume and connectivity in normally aging older adults is highly correlated with the extent of reactivation of cortical representations and with a person's ability to reactivate related information.

For the purposes of this paper we define reactivation as the activation, during retrieval, of the same cortical processor(s) used during the initial presentation of that item. Furthermore, we are interested in reactivation of relationally-bound information. Some studies investigating reactivation used some type of semantic cue that was known to participants prior to the experiment (e.g., the name of the object) in order to elicit reactivation. In such cases, however, reactivation could simply be the result of a semantic association established over a long period of time, and not specifically linked to a particular episode. In the case of relational memory, instead, we are interested in reactivation of an associated item after the presentation of another item arbitrarily paired with it during a *single study episode*. Evidence for relational memory in this case would therefore come from demonstrating the reactivation of cortical processors related to the processing of one item elicited by the presentation of the episodically-paired second item, even in the physical absence of the first item. In this case, evidence for relational memory reactivation would come from finding that a particular item elicits activation of a cortical region not normally involved in its processing, but involved instead in the processing of a stimulus type that was paired with it in a single previous episode.

There are strong theoretical bases for the involvement of the hippocampus in relational memory. It is generally accepted that the hippocampus is important in the formation and retrieval of declarative memories (N. Cohen & Squire, 1980). The hippocampus is believed to relationally bind together and store arbitrary associations (N. J. Cohen & Eichenbaum, 1993; Eichenbaum, 2000; Eichenbaum & Cohen, 2001). A considerable body of empirical evidence demonstrates the critical role of the hippocampus in creating and storing flexible associations after just one exposure (Duff et al., 2013; D. E. Hannula & Ranganath, 2009; D. E. Hannula, Ryan, Tranel, & Cohen, 2007b; D. E. Hannula et al., 2006; Konkel et al., 2008; Warren, Duff,

Tranel, & Cohen, 2010; Zeithamova & Preston, 2010). Furthermore, it is thought that the hippocampus can then use these relational bindings to reactivate an item in the presence of a relationally bound associate (N. J. Cohen & Eichenbaum, 1993; Eichenbaum, 2000; Eichenbaum & Cohen, 2001; Norman & O'Reilly, 2003).

We (Walker et al., 2014) were able to show evidence for reactivation in a study using a face-scene preview paradigm. In this paradigm, unique face and scene exemplars (novel and never repeated in the course of the study) are presented together at encoding. At test, for each trial, a scene is presented ahead of the test display (scene preview). We found that scene previews that were previously studied with a face showed reactivation of the same face processing regions found to be active when encoding those faces. Crucially, such reactivation was not found for novel scenes not previously paired with faces. We termed this type of reactivation "relational reactivation." Using a similar paradigm, D. E. Hannula and Ranganath (2009) had participants study pairs of faces and scenes and then tested the participants using a three-forced-choice recognition task to identify which face went with a scene, with a scene preview immediately prior to the test display. They found that hippocampal activity was related to later performance during the scene preview but not during the actual test display. Taken together these two studies lead to the prediction that hippocampal activity is associated with reactivating the face that was originally paired to the scene.

Others have reported similar evidence of hippocampal mediation of the relational reactivation process (Gordon, Rissman, Kiani, & Wagner, 2014; Hofstetter et al., 2012; Staresina et al., 2013; Staresina et al., 2012; Zeithamova et al., 2012). These studies show increased functional connectivity between the hippocampus and other parts of the medial temporal lobe (MTL) thought to be responsible for specific processing of stimuli during retrieval. Zeithamova

et al. (2012) were able to show a correlation between activity in the anterior MTL and an overall pattern of reactivation in the ventral visual stream when a participant was imagining a related item, indicating the possibility of an association between hippocampal activity and the overall pattern of reactivation. Similarly, Gordon et al. (2014) also found a correlation between hippocampal activity and reactivation of patterns of activity associated with people and places.

The current study extends previous research by examining whether structural hippocampal integrity is associated with the degree of reactivation of paired memory representations in the cortex. There is a strong link between hippocampal volume (controlling for intracranial volume) and overall relational memory performance (Chaddock et al., 2010; Erickson et al., 2009; Maguire et al., 2000). Furthermore, measures of water diffusion in the hippocampus such as fractional anisotropy (FA) and mean diffusivity (MD), both thought to index white matter integrity, have also been linked to overall and associative memory ability. Specifically, individuals with high mean FA and low MD in the hippocampus perform better across a range of memory tasks (Carlesimo et al., 2010; Charlton et al., 2006), although not everyone has found a link between mean FA and memory performance (Carlesimo et al., 2010). Here we examined whether hippocampal structure, as measured through hippocampal volume, mean FA, and MD, was associated with the ability to relationally-reactivate representations in the cortex. In order to maximize hippocampal variability we chose to use older adults in our study. As people age, their hippocampi starts to atrophy, and there is also evidence of white matter degradation (Charlton et al., 2006; N. Raz et al., 2005; Walhovd et al., 2005). These changes create greater variability in both hippocampal size as well as white matter measures among adults, especially older adults. Older adults are also known to show decline in episodic memory, albeit with a large variability across individuals (R. L. Buckner, 2004; Duverne et al.,

2009; M. Fabiani, 2012; Morcom et al., 2003). It is this greater variability that we harnessed to test whether hippocampal structure is associated with the ability to relationally reactivate items in the cortex.

To observe reactivation we employed a modified version of the paradigm used by Walker et al. (2014). In this paradigm participants study pairs of faces and scenes and then are tested on those pairs using a yes/no recognition task. As in the paradigm employed by Hannula and colleagues (2009; 2006), the critical aspect is that prior to every test display there is a scene preview. However, in our paradigm, instead of having only old scenes, some of the scenes are novel (i.e., never studied with a face before). By contrasting old scenes that were previously paired with a face and novel scenes that were never paired with a face, we can examine the extent to which participants are reactivating the face representation areas during the scene preview. In order to examine both the temporal and spatial dynamics of that reactivation we used the event related optical signal (EROS, (G. Gratton & Fabiani, 2010). This technique uses a combination of temporal and spatial resolution to determine not only "where" activity is taking place but also "when" the activity is taking place, allowing investigators to examine the order of activation of various areas of the brain, instead of just establishing that those areas were active during a particular trial type.

In this experiment participants studied pairs of faces and scenes, first viewing either a face or a scene individually followed by the pair together (see Figure 2.1). At test, participants were given an old/new recognition test for each of the face-scene pairs, each preceded by a scene preview. We found activity during scene previews in the posterior superior temporal sulcus (STS). The STS is an area known to be part of the network involved in processing faces, being shown to be active during both general face processing (Fairhall & Ishai, 2007; Grill-Spector,

Knouf, & Kanwisher, 2004; Puce, Allison, Bentin, Gore, & McCarthy, 1998; Puce et al., 2003) as well as in social judgments about a face (Hoffman & Haxby, 2000; Puce et al., 1998). It is also easily accessible by our imaging technique (which has limited penetration inside the head). The activity was greater for "old" scene previews compared to new or "novel" scene previews (which had no face associated with them), and was elicited in the *same region that was activated by faces presented alone* during the study phase (localizer) even though no faces were present. Critically, this reactivation was associated with hippocampal volume, FA, and MD such that those older adults with smaller hippocampi and less intact white matter tracts within the hippocampus were impaired at reactivating the faces. Further, all three measures were related to episodic memory performance.

Materials and Methods

Participants

Eighteen right-handed older adults participated in this study for a payment of $15 an hour. Three participants were excluded from the analysis due to withdrawal from the experiment prior to completion, leaving a total of 15 participants (8 women; mean age = 68.30 SD= 8.90; age range: 55-88 years old). Demographic information, including scores on the he Wechsler Memory Scale – Third Edition that was given one week prior to optical data collection, can be found in Table 2.1. All participants indicated that they had normal or corrected to normal vision and were not taking medications that would affect the central nervous system. Informed consent was obtained from each participant and all procedures were approved by the University of Illinois Institutional Review Board.

Stimuli

The stimuli consisted of 444 full-color face images (294 female faces) selected from a previously normed faces database (Althoff & Cohen, 1999) and 592 scenes from Brand X© photography. The faces were all sized to 384 x 384 pixels and the scenes were all sized to be 1024 x 768 pixels, filling the entirety of the screen.

Procedures

After signing an informed consent form, each participant was fit with an EROS recording helmet (see below) and were given a practice block of 12 study trials followed by 12 test trials so that s/he could get used to the timing of the trials. During the practice block, participants were given instructions to create a story linking the face and the scene together and to use that story to retrieve that same association during test. Following the practice block the participant completed six study/test blocks; they were allowed to take breaks in between blocks as necessary.

Study Block. Study blocks consisted of 72 study trials, divided into two sets of 36 trials. Each set of study trials started with a 1-s fixation cross. As can be seen in Figure 2.1b, the study trials started with a face and scene being shown individually for 750 ms each. Half the study trials had the face shown first ("face-first" trials) and half the trials had the scene shown first ("scene-first" trials). After the face and scene were shown individually, the face was superimposed on the center of the scene for 1500 ms. Participants were instructed to study each of the pairings as they were to be tested on those pairings later on. The blocks were divided by short breaks to minimize movement artifacts.

Test Block. Following each study block was a corresponding test block of 72 test trials, testing the pairs of items studied in the immediately preceding study block. These test trials were divided up into three sets of 24 test trials, with each set beginning with a 1-s fixation cross.

As can be seen in Figure 2.1b, a test trial consisted of a scene being presented for 1000 ms (the scene preview), followed by a fixation cross for 1000 ms, followed by the face superimposed on the center of the scene for 2500 ms. Participants were instructed to respond using a button box as to whether or not a specific face-scene pair was studied during the previous study block (old-new judgment). There were three types of test trials: match, re-pair, and novel. Match test trials were test trials in which the face and the scene being tested had been presented together during the study phase. The re-pair test trials were comprised of faces and scenes that had been presented in the study phase, but had not been paired together. The novel test trials were comprised of a novel scene with a previously studied face. The correct response for match trials was "old" as those pairs were previously studied together, whereas the correct response for re-pair and novel trials was "new" as the pairs in those trials were not studied together. Participants were asked to respond only once the face had appeared, and were explicitly told not to respond during the scene preview or fixation. Every test trial ended in a fixation screen presented for 1500 ms.

Counterbalancing for the study and test blocks consisted of four lists of 432 face-scene pairings created by randomly pairing 432 of the faces and 432 of the scenes and then randomly assigning each pair to each study and test type condition. Each pair was then randomly assigned to one of six blocks of 72 items each with the stipulation that each block contained 12 of each study-test type combination ([face first, scene first]x[match, re-pair, novel]). Of the remaining scenes, 144 were then randomly assigned to replace the scenes in the novel test trials. Four different lists were created to ensure that every scene was tested in one of the three categories. No scene and face were paired together more than once across these lists. The remaining 12 faces and 16 scenes were used to create a practice block of 12 study trials followed by 12 test

trials. These faces and scenes were not included in the four lists and the practice trials were the same for all participants.

Optical Recording

Optical data were recorded using six synchronized ISS model 96208 frequency domain oxymeters (Imagent®; ISS, Inc., Champaign, IL). The light sources were laser diodes emitting light at the wavelength of 830 nm (max amplitude: 10 mW, mean amplitude after multiplexing: 1 mW) modulated at 110 MHz. Optic fibers were used to channel each light to the surface of the scalp. The detectors were fiber optic bundles (diameter = 3 mm) connected to photomultiplier tubes (PMTs). The PMTs were fed with a current modulated at 110.0625 kHz, generating a heterodyning frequency of 6.25 kHz. The output current from the PMTs was digitized at 50 kHz, affording 8 points per heterodyning cycle. A time-multiplexing approach was used to record from sixteen sources for each detector. In this approach, each source was switched on for 1.6 ms, and off for 24 ms. This allowed to record for a total of 10 heterodyning cycles (80 points) for each multiplexing time unit. However, to avoid cross-talk, the first two cycles were discarded, and the remaining 64 points were subjected to a fast Fourier transform for computation of DC (average) intensity, AC (amplitude), and relative phase delay (in degrees and later converted to picoseconds). Only phase delay data are reported here.

Source and detector fibers were mounted on a modified motorcycle helmet. Our montage consisted of 24 detectors and 64 sources (see Figure 2.2), covering most of the cortical surface (darker grey areas in Figure 2.3). Source-detector distances ranged between 15 and 94 mm. To avoid cross talk, the sources were arranged such that during any given time division of the multiplexing cycle only one source was within 6 cm of any given detector. This allowed us to record from 384 channels (pairings of source and detector) at 39.0625 Hz.

The locations of the sources and detectors were digitized with a Polhemus "3Space" ® (Colchester, VT) 3D digitizer and co-registered with a volumetric T1-weighted MR image for each subject (Whalen, Maclin, Fabiani, & Gratton, 2008). The co-registered data were then Talairach-transformed to permit registration across subjects. The phase data were corrected off-line for phase wrapping, pulse artifacts were removed (Gabriele Gratton & Corballis, 1995), and the data were low-pass filtered to 5 Hz (Maclin, Gratton, & Fabiani, 2003). Channels with standard deviations of the phase greater than 150 ps were excluded from further analysis (for further details of these analytic steps, see (Gabriele Gratton & Fabiani, 2007).

Optical Statistical Analyses

The phase data were divided into epochs around stimulus events of interest with 204.8 ms pre-stimulus baseline and 768 ms post-stimulus recording for the study phase. The time locking event of interest was the onset of the first stimulus of a study trial (either the face in trials where the face was presented first or the scene in trials when the scene was presented first). For the test phase the phase data were also divided into epochs around the stimulus events of interest with a 204.8 ms baseline, but the post-stimulus recording consisted of 2022 ms so that it could include the scene preview and the fixation cross, both shown before the face is presented in the test trial.

In-house software "OPT-3D" (Gabriele Gratton, 2000) was used to reconstruct the optical path for each channel spatially , combine channels whose mean diffusion paths intersected for a given brain volume (voxel) and to compute group-level statistics. The resel size of the cortical projections were determined by the independence of the error terms at various voxel distances computed using the methods described by Worsley et al. (1999). An 8-mm Gaussian filter (based on a 2 cm kernel) was used to spatially filter the data. The group-level statistics were then converted to Z-scores and compared to critical Z-scores based on the number of resels

within an ROI and the subsequent correction for multiple comparisons. These Z scores are then orthogonally projected onto images of the sagittal surfaces of the brain in Talairach space (Talairach & Tournoux, 1988).

Due to its high spatial and temporal resolution (which may inflate the number of comparisons), statistical analysis of EROS during both the study and test phase was limited to ROIs selected a priori. Whole-brain analyses, as are often done in fMRI, which has only high spatial resolution, are not practical with EROS data as the number of data points (one for every resel at every time point) would make the correction for multiple comparisons too severe. Thus we focused on the STS and the DLPFC, the areas that were shown to be involved in reactivation in younger adults (Walker et al., 2014) and that have been shown to be important in the processing of faces (Fairhall & Ishai, 2007; Grill-Spector et al., 2004; Puce et al., 1998; Puce et al., 2003) and in the top-down control of memory retrieval (Miller & Cohen, 2001), respectively. These areas are also easily accessible with optical imaging, whereas other potential areas of interest such as the fusiform gyrus and the ventrolateral prefrontal cortex could not be accessed with the instrumentation used in the current study (For the spatial extent of areas covered see Figures 2.3-2.6). As in Walker et al. (2014), the boundaries for the STS ROI were defined in Talairach space (Talairach & Tournoux, 1988) as y = -65 to -43, and z = -8 to 20 and y = -72 to -45, and z = -3 to 24 for the left and right STS, respectively. These boundaries were based on the peak activation in the STS for faces in previous fMRI work (Bonda, Petrides, Ostry, & Evans, 1996; Fairhall & Ishai, 2007; Grill-Spector et al., 2004; James V. Haxby et al., 1999; Hoffman & Haxby, 2000; Ishai, Schmidt, & Boesiger, 2005; Ishai, Ungerleider, Martin, & Haxby, 2000; Kanwisher et al., 1997; Puce et al., 1998; Puce et al., 2003). The boundaries for the DLPFC ROI

were defined as y = 10 to 50, and z = 15 to 35 for both the left and right DLPFC. These boundaries were based on the spatial extent of Brodmann's areas 9 and 46.

Additionally, in order to control for multiple comparisons we also limited our analyses to temporal intervals of interest (IOIs) at both study and test. Previous work using intracranial event-related potentials and EROS has shown activity in the STS to the presentation of faces at around 170ms, between 200 and 650 ms and around 700 ms (Allison, Puce, Spencer, & McCarthy, 1999; Walker et al., 2014), therefore for our analyses at study we used an IOI of 150 to 750ms. As in Walker et al. (2014) we limited our scene preview (i.e., reactivation) analyses to the time range of 500-1500 ms. This is based on work that has shown that eyes disproportionately start to fixate on the matching face in the time range of 500-1500 ms in a similar paradigm if more than one face is present (D. E. Hannula et al., 2007b). However, for exploratory reasons we also report any activity that was found to be significant or marginally significant with a correction for multiple comparisons (see Table 2.3). Correction for multiple comparisons across voxels was applied based on the number of independent resolution elements (resels) within each ROI using random field theory (Friston et al., 1995; Gabriele Gratton, 2000; Maclin et al., 2003).

Structural Analyses

Images were collected on a Siemens Magnetom Trio 3T whole body MRI scanner. A standard 12-channel birdcage head coil was used and head motion was restricted with foam padding. High-resolution 3D MPRAGE (TI = 900ms; flip angle = 9°; .9 mm isotropic voxels) structural images were acquired parallel to the anterior commissure-posterior commissure (AC-PC) axis. Structural scans were acquired 3-11 months (average = 7.2 months) prior to optical data collection for the previous study of blood flow(Zimmerman et al., 2014).

Automatic segmentation of the hippocampus was performed using Freesurfer (v 5.3; details about the subcortical segmentation process have been described in Fischl et al. (2002) and Fischl et al. (2004). Intracranial volume (ICV), also calculated by Freesurfer, was used to correct for overall head size (see R. L. Buckner (2004). By regressing each ROI volume onto ICV, a slope (b) was obtained for the relationship between ROI and IVC. The resulting slope was used to normalize each volume for head size (normalized volume = raw brain volume – b(IVC- mean IVC);(Erickson et al., 2009; Head, Kennedy, Rodrigue, & Raz, 2009; N. Raz et al., 2005).

Diffusion-Weighted Analyses

Diffusion-weighted images were acquired during the same session as the structural scan. Due to technical difficulties data from one of the participants was lost. The diffusion-weighted images were acquired with a TR = 4,400 ms, TE = 98 ms, and 1.72 mm^2 in-plane resolution. Thirty-two 3 mm slices were obtained parallel to the anterior-posterior commissure plane with no inter-slice gap. The protocol consisted of four T2-weighted images (b-value = 0 s/mm^2) followed by two repetitions of 30-direction diffusion-weighted echo planar imaging scans (b-value = 1,000 s/mm^2).

Preprocessing and analyses were performed using tools from the FDT (Functional MRI of the Brain Diffusion Toolbox;(T. E. Behrens et al., 2003; T. E. J. Behrens et al., 2003) from FSL (Functional MRI of the Brain Software Library, v 5.0, (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Smith et al., 2004). Eddy-current distortions were corrected using affine registration of all volumes to a target volume with no diffusion weighting. The hippocampal ROI was used from the Free-Surfer segmentation of the structural MRI. Average FA and MD values were calculated by averaging across all of the voxels in the hippocampal ROI mask from the FA and MD maps, respectively, created using FDT.

Statistical Analysis

In order to control for the possible effects from demographic variables, all correlations reported are partial correlations, controlling for age, sex, and years of education.

Results

Behavioral Results at Test Display

Table 2.2 provides accuracy and reaction times for each condition. Overall participants made correct old-new judgments on 64% (M = .64, SD = .11) of the trials with an average response time of 1298.08 ms (SD = 121.59). There was an overall effect of test trial type on both accuracy [F (2, 42) = 4.52, p = .016], and response time [F (2, 42) = 47.69, p < .001]. Bonferroni-corrected pair-wise t tests showed that participants were marginally more accurate on novel trials (M = .75; SD =.16) than match/"old" trials (M = .64; SD = .19; t (14) = 2.19, p = .023), and were significantly more accurate on novel trials than re-pair trials (M = .55; SD = .19; t (14) = 2.69, p = .009). There was no difference between match or re-pair trials [t (14) = .0974, p = .103]. In terms of reaction time, participants were faster to respond during novel trials (M =1078 ms; SD = 249) than either match (M = 1404 ms; SD = 184; t (14) = -3.47, p = .002) or re-pair trials (M = 1411ms; SD = 236; t (14) = -4.0774, p = <.001). There was no difference in response time between match trials and re-pair trials, t (14) = -0.10, p = .46. The decrease in reaction time and the increase in accuracy for novel compared to either the match or re-pair trials could be due to the difference in item types at the test display. Both the match and re-pair trials required relational memory to detect whether or not the pair was old whereas novel trials only needed the participant to detect that the scene was novel.

Analysis of EROS Results

Activity at Study. The purpose of this analysis was to determine, before relational memory is established, that certain brain regions (and in particular the STS) only show activation after the presentation of faces and not of scenes (localizer task). This was achieved by examining the EROS data collected during the study phase, and contrasting the activity elicited by faces in the face-first trials with the activity elicited by scenes in the scene-first trials. Figure 2.3a shows the statistical maps of EROS data for the contrast *faces (first)* > *scenes (first)* at study. As expected this contrast revealed significant preferential activation for faces over scenes in the left STS. This preferential activation took place from 409-435 ms (peak Z = 2.651, Z_{crit} = 2.64; Talairach coordinates: y = -46, z = 1). Subsequent analyses revealed that these differential effects were due to activation (compared to a pre-stimulus baseline) in the face-first condition, and not to a significant negative deviation from baseline for the scene-first condition. At no point during study did the STS show activation levels for scenes that were significantly greater than baseline values. The statistical analyses are summarized in Table 2.3.

Activity at Test During Scene Preview. This analysis was run to determine whether participants are using the scene preview to reactivate the associated face in preparation for the upcoming test display. Specifically, this was accomplished by contrasting the EROS activity elicited by the preview of scenes that were previously paired with faces (i.e., those presented during the preview for match and re-pair trials) with that elicited by scenes that were not previously paired with faces (novel scenes). The focus was on face-specific areas (i.e., STS), which should show activation in the first condition, but not the second. Figure 2.3b shows the peak activations of this contrast in each significant time interval (see also Table 2.3 for the results of the statistical analyses). The data confirmed our predictions: there was significant activation in the left STS at around 767 ms after scene preview onset (peak Z = 2.692, Z_{crit} =

2.55; Talairach coordinates: y = -58, z = 9), and marginally significant activation in the left STS at around 742 ms (peak Z = 2.323, Z_{crit} = 2.64; Talairach coordinates: y = -58, z = 7) and again at 972 ms (peak Z = 2.415, Z_{crit} = 2.51; Talairach coordinates: y = -44, z = 3).

A conjunction analysis (Price & Friston, 1997) was performed to determine the amount of overlap between the left STS activity for faces during study and for old scene previews at test. As we predicted, we did find overlap between the study (409-435 ms) and scene preview (767 ms) activations at a combined threshold of $p < .04$. As can be seen in Figure 2.4, the overlap between the two activations takes place toward the center of the left STS region of interest (ROI).

Additionally, EROS activity in DLPFC (BA 9, 46) was also examined as this region has been shown to be active in this paradigm before (Walker et al., 2014) and is well known to be involved in top-down or controlled processing (Miller & Cohen, 2001). Significantly greater activation in the left DLPFC for new scenes greater than old scenes was found early on during the scene preview around 255 ms (peak Z = -2.777, Z_{crit} = -2.68; Talairach coordinates: y = 32, z = 33) and from 563-588 ms (peak Z = -3.011, Z_{crit} = -2.77; Talairach coordinates: y = 42, z = 29). A marginally significant effect in the opposite direction was observed around 742 ms (peak Z = -2.702, Z_{crit} = -2.85; Talairach coordinates: y = 12, z = 32). However, in the right DLPFC an opposite pattern (with greater activity for old scenes than new scenes) was observed around 255 ms (peak Z = 2.833, Z_{crit} = 2.8; Talairach coordinates: y = 17, z = 33) and 614 ms (peak Z = 2.871, Z_{crit} = 2.86; Talairach coordinates: y = 9, z = 32). A summary of the results of the statistical analyses of the EROS data is presented in Table 2.3.

Functional Connectivity (Cross-Correlational) Analyses. Forward- and backward-lagged cross-correlation analyses were performed to elucidate the possible connections between the

activity observed in the prefrontal cortex and that observed in the STS. For these analyses, the STS voxel showing the peak value in the old-new preview scene contrast at a latency 767 ms was selected as the seed point. The time course of the activity at this seed voxel was correlated with that in other voxels, using different lags (negative for backward cross-correlations, and positive for forward cross-correlations). The backward correlation analysis (in which activity in other regions predicted the seed voxel activity) revealed a significant correlation between activity in the seed voxel (left STS) and prior activity in the left DLPFC at a lag of -179 ms (peak Z = 4.328, Z_{crit} = 3.32); marginally significant correlations were observed at lags of -281 ms (peak Z = 2.829, Z_{crit} = 3.23) and -153 ms (peak Z = 3.160, Z_{crit} = 3.32). The forward correlation analysis (in which activity in the seed voxel predicted activity in other voxels) showed a significant correlation between activity in the seed voxel (left STS) and subsequent activity in the left DLPFC at a lag of 358 ms (peak Z = 3.528, Z_{crit} = 3.29) and the right DLPFC at a lag of 179 ms (peak Z = 3.432, Z_{crit} = 3.39), with a marginally significant correlation in the right DLPFC at a lag of 332 ms (peak Z = 2.464, Z_{crit} = 2.64). Thus, activity in the left STS was both predicted by and predictive of activity in DLPFC. Additionally activity in the left STS was correlated with activity in the right STS at lag of -25 ms (peak Z = 3.846, Z_{crit} = 3.34), lag 0 (peak Z = 4.640, Z_{crit} = 3.40), and lag 25 ms f (peak Z = 3.572, Z_{crit} = 3.30, indicating that the time courses of the difference between the activity elicited by old and new scenes during the preview period in STS was similar in the two hemispheres.

Structural Analyses

Structural images were also acquired to assess the extent to which the ability to reactivate the related item is associated with hippocampal volume. After normalization of the hippocampal volumes for overall ICV, we found that the average hippocampal volume for participants in our

study was 7949.12 mm^3 (SD = 1296.88 mm^3). If the hippocampus was involved in the process of relational reactivation, one would predict that those individuals with relatively intact hippocampi would be able to reactivate the related item; in contrast, those individuals whose hippocampi have atrophied to a greater extent (i.e. those with smaller hippocampal volumes) would show decreased or non-existent reactivation of the cortex. As predicted, we did find that hippocampal volume showed a positive correlation with overall reactivation in the left STS (r = .71, p = .007).

Additionally, as the behavioral task relies heavily on the ability to reactivate the related face to the presented screen to indicate whether or not the pair is new or old, we tested whether hippocampal volume was associated with overall performance on the task. Indeed, hippocampal volume was also significantly correlated with task performance (r = .72, p = .006), showing that those with smaller hippocampi did not perform as well on the task as those with larger hippocampi (see Figure 2.5).

To ensure that the correlations we are reporting are hippocampal specific we also looked at the volumes of the thalamus and the caudate nucleus as control areas. We found no significant correlation between normalized thalamus volume and reactivation nor between normalized thalamus volume and subsequent behavioral task performance (both p > .14). Similarly we did not find any correlation between normalized caudate volume and reactivation nor did we find any correlation between caudate volume and subsequent behavioral performance (both p > .10).

Diffusion-Weighted Analyses

Previous studies have linked higher mean FA and lower MD in the hippocampus to better behavioral performance in memory tasks. To assess how FA and MD in the hippocampus are

related to the ability to reactivate representations in the cortex, the correlations between these measures and the overall reactivation level in the left STS (measured by the amplitude of EROS difference between old and new scene at 767 ms from the onset of the preview period in each subject) were computed. The correlation between bilateral mean FA in the hippocampus and left STS re-activation did not reach significance (r = .36, p = .10). Analyses based on computing the correlations separately for mean FA values from each hemisphere showed a significant correlation for the right (r = .47, p =. 045) but not the hippocampus (r = .35, p = .11). It is important to note, however, that the correlations in the left and right hippocampi are not significantly different from each other (Z =.34, p = .367), and that the mean FA in both the left and right hippocampi are significantly correlated with subsequent behavior, r = .64, p = .009 and r = .56, p = .02, respectively (see Figure 2.6).

Similar analyses were conducted for MD. As can be seen in Figure 2.5, a robust correlation was found between bilateral hippocampal MD and the EROS reactivation measure (r= -.531, p= .031) indicating that individuals with higher MD in the hippocampus are also better able to reactivate representations in the cortex. The mean MD in the hippocampus also correlated with subsequent performance, r = -.743, p = .002.

Discussion

The goal of this experiment was to show a link between the integrity of the hippocampus and the observed phenomenon of relational reactivation. The data indicated a highly significant correlation between hippocampal volume and the extent to which a participant could reactivate an area of the cortex related to face processing (the left STS) in the absence of a face, but in the presence of a related scene, which would otherwise not reactivate this area. Furthermore, the data also showed that mean FA in the right hippocampus and MD within the hippocampus are

correlated with the extent to which a participant could reactivate the left STS, such that those with higher mean FA and lower MD within the hippocampus showed greater reactivation. All three of these measures were related to overall ability to perform the subsequent relational memory task. These results are consistent with the hypothesis that relational bindings can be used to reactivate stimuli-specific processing areas in the cortex even in the absence of that type of item, and that this process is mediated by the hippocampus.

In order to establish that the hippocampus was related to relational reactivation, it was necessary first to establish that relational reactivation took place. Even before this claim could be made, it was necessary to establish that activity elicited by a previously-paired scene in a face processing region (such as the STS) could be interpreted as "relational reactivation" of the associated face representation. To this end, it needs to be shown that, normally, scenes do not elicit activity in this region. This was accomplished by showing that, when each of the two items (face and scene) are presented alone during the study phase, STS responds to faces but not to scenes. Specifically we found that part of the left STS showed activity greater for faces than scenes from around 409 ms to around 435 ms. This left STS activity is consistent with past literature demonstrating that the STS is part of the face processing network (Allison et al., 1999; Fairhall & Ishai, 2007; C. Gratton, Sreenivasan, Silver, & D'Esposito, 2013; Grill-Spector et al., 2004; Puce et al., 1998; Puce et al., 2003). In addition, the EROS results were consistent with those observed in a previous study in younger adults (Walker et al., 2014), with only a slight delay (409-435 ms vs. 383-409 ms), which could be expected on the basis of the older age of the subjects in the current study. Unlike our previous findings we did not see any activity in the right STS for processing faces. This contrasts with data from the face processing literature, as most studies report that face processing either elicited bilateral STS activation or greater activity

in the right STS than the left (Fairhall & Ishai, 2007; Grill-Spector et al., 2004; Hoffman & Haxby, 2000; Ishai et al., 2000; Kanwisher et al., 1997; Puce et al., 1998; Puce et al., 2003). It is important to note, however, that the subjects on most of these studies were younger adults, and that they were asked to either passively view or answer simple questions about the faces. It is possible that the lack of significant right STS activity could be due to a difference in processing due to aging, the instructions in the present task to "try and create a story combining the faces and the scenes," or some interaction between the two.

These findings, however, indicated that the left STS is the most logical place to study for evidence of relational reactivation in the sample and paradigm used in the current study. Examining activity in this region after the presentation of old (i.e., previously-paired with faces) and new (i.e., not previously-paired with faces) scenes during the preview period, we observed evidence of relational reactivation (i.e., a difference between the brain response to old and new scenes) at approximately 767 ms (see Figures 2.2 and 2.3), as well as other latencies. As with the activity observed during study, the area and the timing of the activation are slightly delayed with respect to what we previously found with the younger adults (716-742 ms, (Walker et al., 2014). Again, this latency difference is consistent with age-related slowing in processing. We did not, however, find an earlier activation in the older adults as we did with the younger adults. This could be due to the difference between the populations, and to the greater heterogeneity of the older sample with respect to the younger sample. The activity observed in older adults for the contrast between old scenes and new scenes was in the right direction around the same time period as that found with younger adults but was never even marginally significant. It could be that older adults either do not have or have a smaller initial reactivation of the cortex; alternatively, the current experiment may have lower power than the previous one for this type of

comparison, due to greater variability across subjects linked to age-related processes, such as hippocampal atrophy.

It should not be assumed that the activity observed in STS during the scene preview constitutes the entirety of the reactivated face representation. Since there is a distributed network of processors that are active when viewing a face, it should be assumed that the reactivation must be distributed across the entire (or at least an extended portion) of this network – most of which is not accessible to EROS measurement because of its depth. The activity observed in the STS is only an indicator that relational reactivation is taking place. Importantly, however, there is evidence based on multi-voxel pattern analysis of fMRI data suggesting that the STS is one of the areas holding differential representations for faces (C. Gratton et al., 2013). Future experiments could look at how the entire system of processors is reactivated in concert with each other.

A potential alternative interpretation for the STS activity during scene preview is that it may reflect a response elicited by the repetition of scenes. In fact, as we contrasted scenes that were previously paired with faces with novel scenes, it is theoretically possible that any observed activity during the scene preview could be due to greater STS activity for repeated scenes as compared to novel scenes. However, the STS did not show increases in activity to the initial presentations of the scenes during either the initial study or during the presentation of novel scenes during test. It therefore appears unlikely that an area that is inactive during the initial presentation of a stimulus suddenly becomes activated upon the second presentation of that same stimulus. Whereas we cannot rule out this interpretation, it is far more likely that activity in the STS during the scene preview is due to face related activity, an interpretation corroborated by

research using other methods (Fairhall & Ishai, 2007; Grill-Spector et al., 2004; Hoffman & Haxby, 2000; Kanwisher et al., 1997; Puce et al., 1998; Puce et al., 2003).

With relational reactivation established we turned on the question of whether or not hippocampal anatomical integrity is associated with the ability to reactivate the cortex. Indeed, a strong correlation was observed between bilateral hippocampal volume and STS reactivation. Additionally, hippocampal volume was also found to be correlated with subsequent behavioral performance. These results are consistent with the predictions made by the relational memory theory (N. J. Cohen & Eichenbaum, 1993; Eichenbaum, 2000; Eichenbaum & Cohen, 2001), with previous studies showing positive correlations between hippocampal volume and relational memory performance (Chaddock et al., 2010; Erickson et al., 2009; Maguire et al., 2000), and substantial work demonstrating the critical nature of the hippocampus in the creation and use of relational memories (Duff et al., 2013; D. E. Hannula & Ranganath, 2009; D. E. Hannula et al., 2007b; D. E. Hannula et al., 2006; Konkel et al., 2008; Warren et al., 2010; Zeithamova et al., 2012; Zeithamova & Preston, 2010).

These correlations were present not only when volumetric measures of the hippocampus were considered, but also when other measure of structural integrity, more related to fiber tracts, were considered. Specifically, significant correlations emerged between individual variations in the reactivation process and both right hippocampal mean FA and bilateral hippocampal MD. This is consistent with previous work demonstrating that these diffusion measures, especially MD, are correlated with overall memory ability (Carlesimo et al., 2010; Charlton et al., 2006). It is not entirely clear why we only find the mean FA of the right hippocampus to be correlated with ability to reactivate in the cortex, especially since it is on the contralateral side from where reactivation is most evident. One possible explanation is that there is an association between

bilateral hippocampal mean FA and reactivation, but the statistical power was insufficient to fully capture the association. This is supported by the observation that correlations between mean FA and memory performance tend to be more elusive than those obtained using MD as the predictor (Carlesimo et al., 2010). Regardless, our findings not only demonstrate the role of the hippocampus in memory, but they take the relational memory theory outside of its traditional domain within the MTL and emphasize the importance of hippocampal-cortical interactions in this phenomenon. These results support the idea that one of the hippocampus's roles is to use relational bindings to reactivate and bring online memories stored in the cortex and that possible degradation to this system (e.g. atrophy) results in a disruption in the ability to reactivate and perform a relational memory task.

Although we are here tentatively attributing the individual differences in the reactivation process to hippocampus atrophy, another explanation is possible: Namely, some individuals may have had smaller (or less well myelinated) hippocampi to begin with. Previous longitudinal research has shown that in fact hippocampus size does reduce with age, and that white matter within the hippocampus tends to lose some of its myelin (Charlton et al., 2006; N. Raz et al., 2005; Walhovd et al., 2005). However, since we did not have a longitudinal component in our study (i.e., subjects were only evaluated at one point in time) we cannot distinguish between these two hypotheses. Future research could examine how the rate of change in hippocampal size (and integrity) could be associated with changes in relational memory ability and relational reactivation over time.

It is also important to note that the correlations between STS reactivation and the hippocampal measures seem to be driven primarily by four participants with higher activation in the STS. While it is concerning that the effects are driven by just a few participants, those

participants constitute more than 25% of our sample. Furthermore, they are not outliers from the data set, and are 4 of the 5 subjects with behavior performance exceeding .6. It could be postulated that the hippocampus must have a sufficient amount of integrity in order to trigger reactivation in the STS, and generate a good performance level in the task. Further studies could attempt to model this pattern of activity and examine whether other cortical sensory processing regions show similar patterns of activity.

Another caveat is that we cannot speak to the specificity of the reactivation activity for each particular face-scene pair, as we examined average activity across trials rather than in individual trials. There is a possibility that the observed activity indexes a general relational reactivation of face-related regions rather than the reactivation of specific face representations. This reactivation of a face processing region is correlated with subsequent accuracy at test. As such, whether general or specific, this relational reactivation does subserve the retrieval of the specific face representation at some point. Future studies using a multi-voxel pattern analysis approach could be used to determine whether hippocampal size and integrity are related to the specificity of reactivation activity.

The data also indicated greater activity in the right DLPFC for scenes that were previously paired with a face versus those that were not. These activations were in line with previous research demonstrating DLPFC activity in this type of task (D. E. Hannula & Ranganath, 2009; Walker et al., 2014) as well as other studies investigating brain activity associated with the encoding and recall of relational items (Cabeza, Locantore, & Anderson, 2003; Dobbins, Foley, Schacter, & Wagner, 2002; Duzel, Habib, Guderian, & Heinze, 2004; Lepage, Brodeur, & Bourgouin, 2003; Murray & Ranganath, 2007). Conversely, greater activation for novel scenes as compared to scenes previously paired with a face was observed in

the left DLPFC at several time points. This result runs counter to previously published imaging data with these types of tasks (Cabeza et al., 2003; Dobbins et al., 2002; Duzel et al., 2004; D. E. Hannula & Ranganath, 2009; Lepage et al., 2003; Murray & Ranganath, 2007; Walker et al., 2014) and the current theories that would expect that older adults generally over-recruit prefrontal areas when retrieving items from memory (Cabeza, Anderson, Houle, Mangels, & Nyberg, 2000; Rajah, Languay, & Valiquette, 2010). This difference could be due to older participants paying specific attention to the patterns of novel versus old scenes. Previous research has shown that concentrating on switching between different types of pairings such as novel-old to old-old is associated with greater DLPFC activity (Dolan & Fletcher, 1997). As novel scenes only constitute 1/3 of the scene previews, there is a far greater likelihood that the novel scene previews were immediately preceded by old scene previews, constituting a switch, than novel scene previews immediately preceding old scene previews. It is possible that the older adults were paying attention to these changes, resulting in greater DLPFC activity for novel scenes than old scenes.

The functional connectivity analyses indicated that DLPFC activity is related to the observed relational reactivation in STS. The cross-correlation analysis used the voxel from the left STS showing the largest reactivation effect as seed. Reactivation activity in this seed voxel could be predicted by activity in the left DLPFC activity (as indicated by the backward cross-correlation analysis), and predicted activity in both left and right DLPFC (as indicated by the forward cross-correlation analysis). These findings are consistent with the idea that the DLPFC is important in these types of relational memory tasks for top-down control and the ability to maintain information over a delay (D'Esposito & Postle, 1999; Fuster & Alexander, 1971; Rowe & Passingham, 2001; Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000).

Conclusions

The current study sought to investigate the link between the hippocampus and the ability to use relational bindings to reactivate associated items. Its main goals were to establish that relational reactivation took place and that this reactivation was associated with hippocampal integrity. In both cases, the results confirmed the predictions: reactivation of the same cortex used for initially processing faces at study was found to follow the presentation of scenes (in the absence of any face) that were paired with a face but not of scenes that were never paired with a face. This reactivation took place at around 767 ms following the presentation of the scene and was systematically preceded and followed by DLPFC activity. Critically, the data indicated that this reactivation was highly correlated with hippocampal volume such that the larger the hippocampal volume, the more reactivation was observed in the cortex. This reactivation was also correlated with mean FA within the right hippocampus and MD within the hippocampus bilaterally, such that the higher mean FA in the right hippocampus and the lower mean MD across both hippocampi, the greater the reactivation observed in the cortex. This study provides direct evidence of an association between the hippocampus and the ability to relationally reactivate items in the cortex. These findings support the idea that the hippocampus is critical for the use of relational bindings, a main tenet of the relational memory theory (N. J. Cohen & Eichenbaum, 1993; Eichenbaum, 2000; Eichenbaum & Cohen, 2001). Furthermore, these results demonstrate the interaction between the hippocampus and cortical processors to reactivate relationally-bound information stored throughout the cortex.

Chapter 2 Figures

Figure 2.1. Schematic representation of the experimental paradigm, illustrating the sequence of stimuli during study (a), where the top row represents a face-first trial and the second row represent a scene-first trial, and test (b). Note that during test scenes were always presented first, generating a scene preview period.

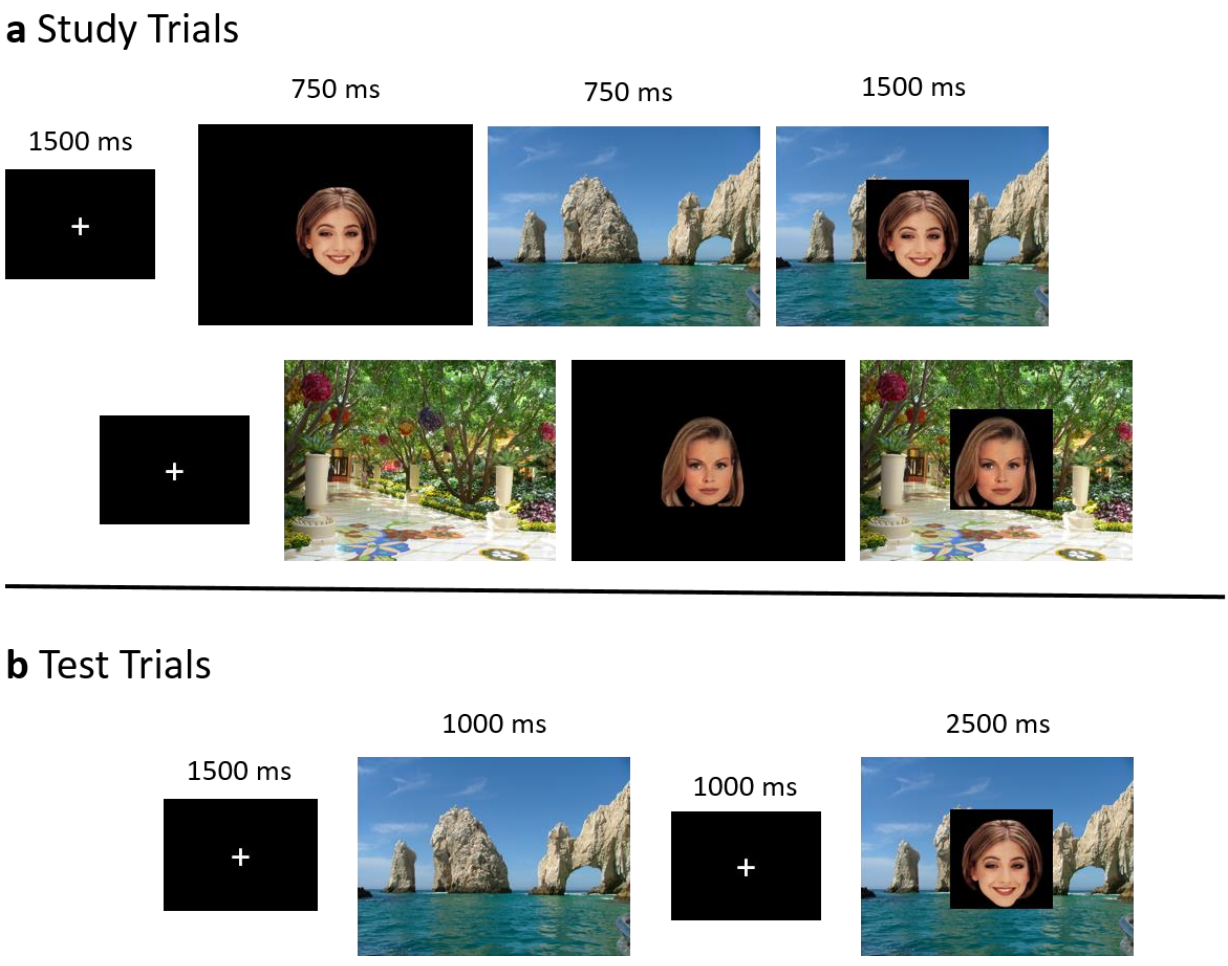


Figure 2.2. Locations of the optical sources (red) and detectors (orange) used for recording the event-related optical signal (EROS) in a representative subject.

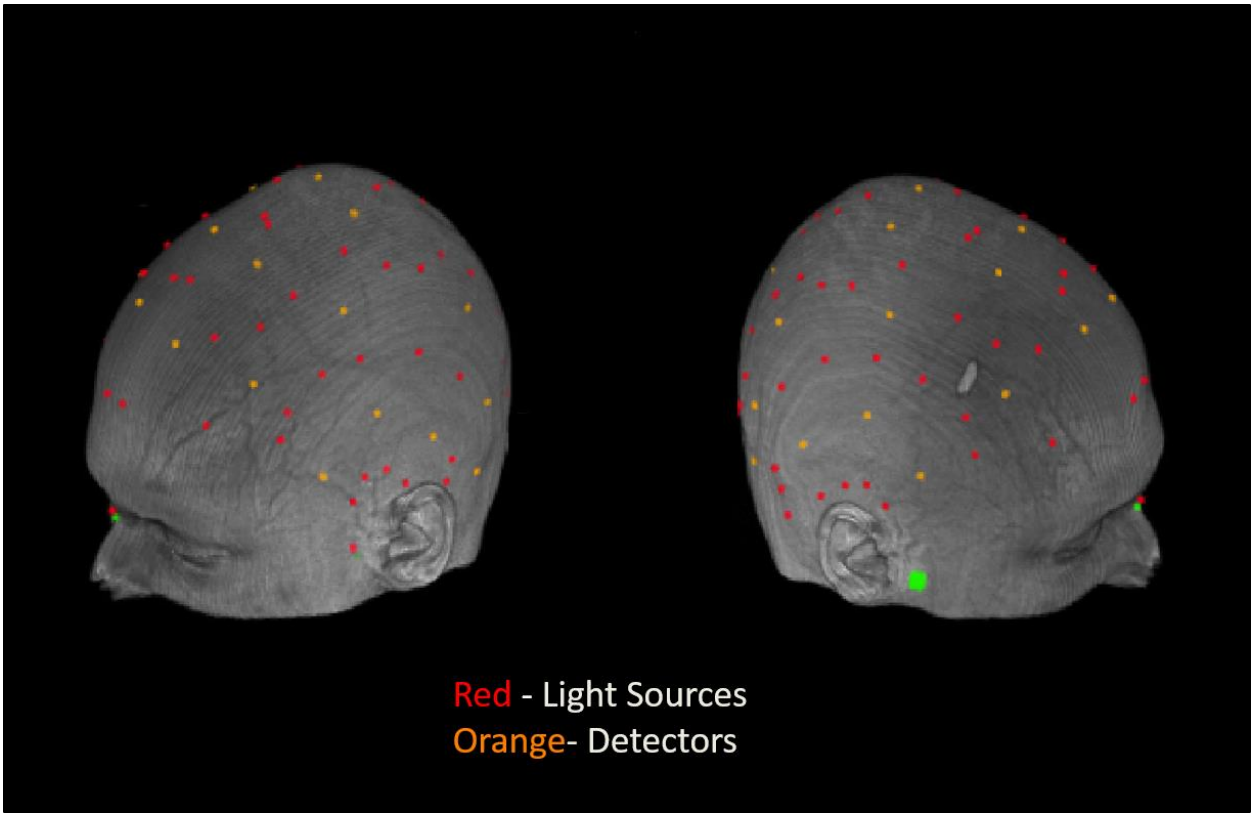


Figure 2.3. Spatial maps based on group level *Z*-statistics of the EROS data projected on sagittal brain surfaces (left hemisphere view). Dark gray shading represents the brain area sampled by the recording montage. The light green rectangle indicates the STS ROI. (a) Activity during study trials for face-first trials versus scene-first trials in the left STS at 409 ms and 435 ms. (b) Activity during the scene preview for previously studied scenes versus completely novel scenes in the left STS at 742 ms and 767 ms.

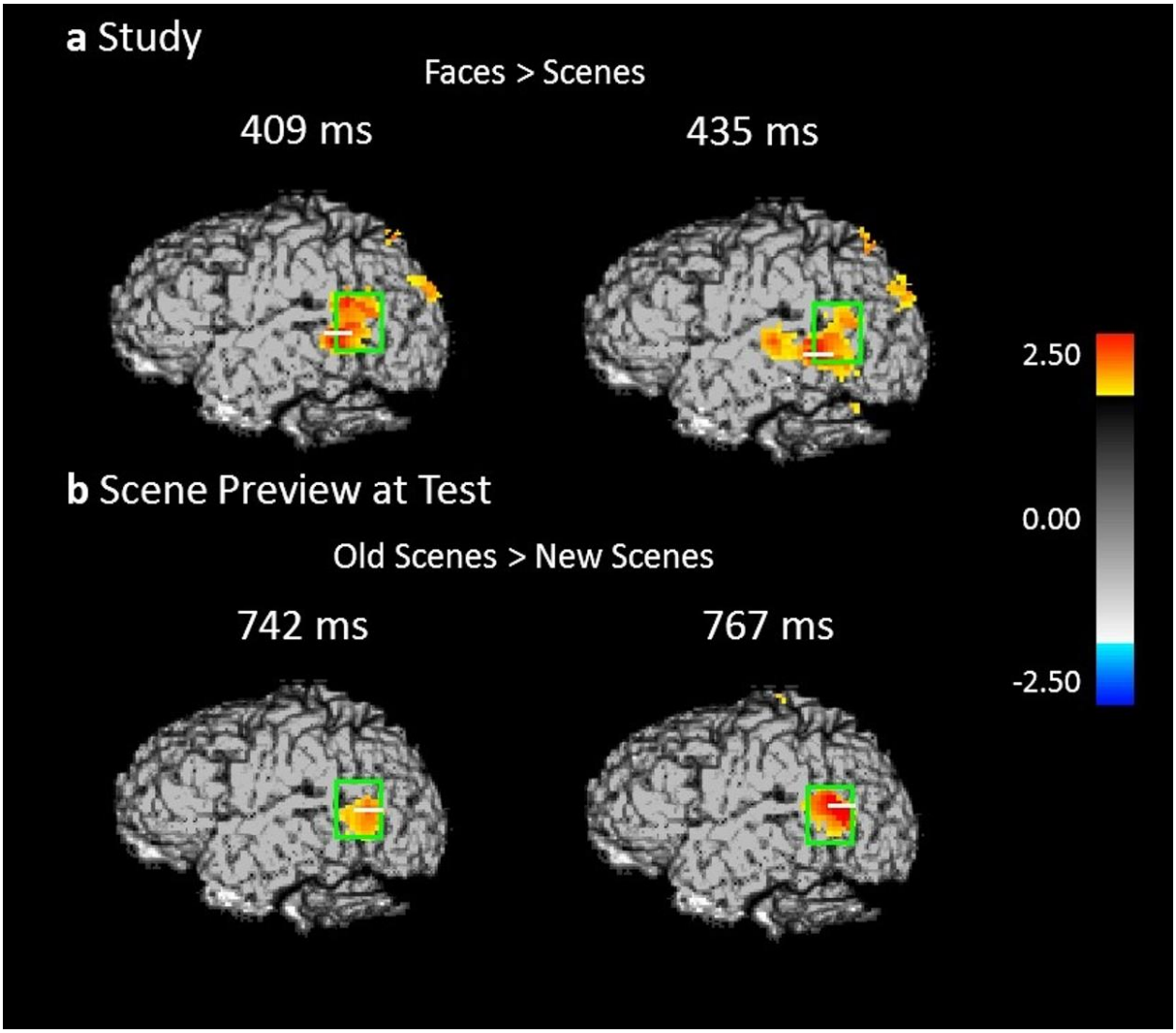


Figure 2.4. Spatial map of the conjunction analysis projected onto the left sagittal surface at a threshold of $p < .04$ for the conjunction ($p < .2$ for each condition separately). Blue represents the activity for faces > scenes from 409-435 ms during study, green represents the activity for old scenes > new scenes from 742 – 767 ms during the scene preview, and red represents the overlap between those two activations.

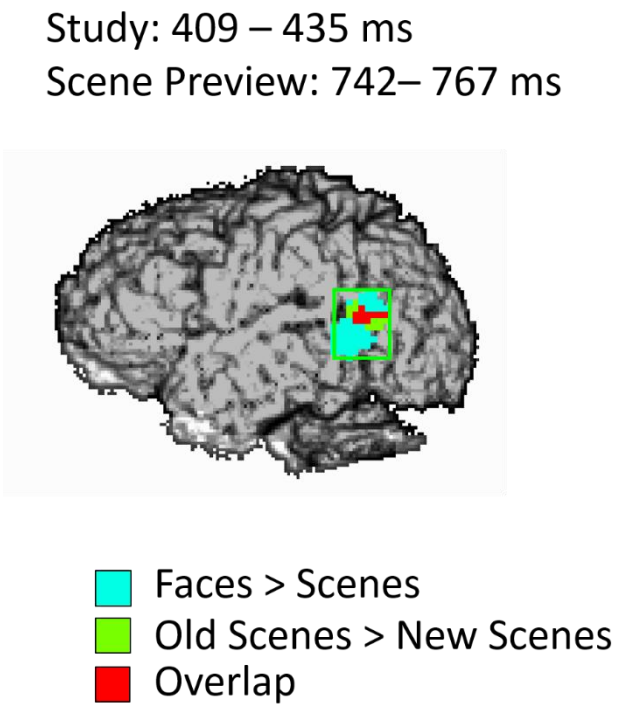


Figure 2.5. Bilateral hippocampal volume normalized by head size is significantly correlated with (a) ability to reactivate face representations represented by the average difference between the EROS activity elicited by old (previously-paired) and new (not-previously paired) in STS at 767 ms after the onset of the preview period, in z scores and (b) behavioral accuracy on the subsequent recognition task.

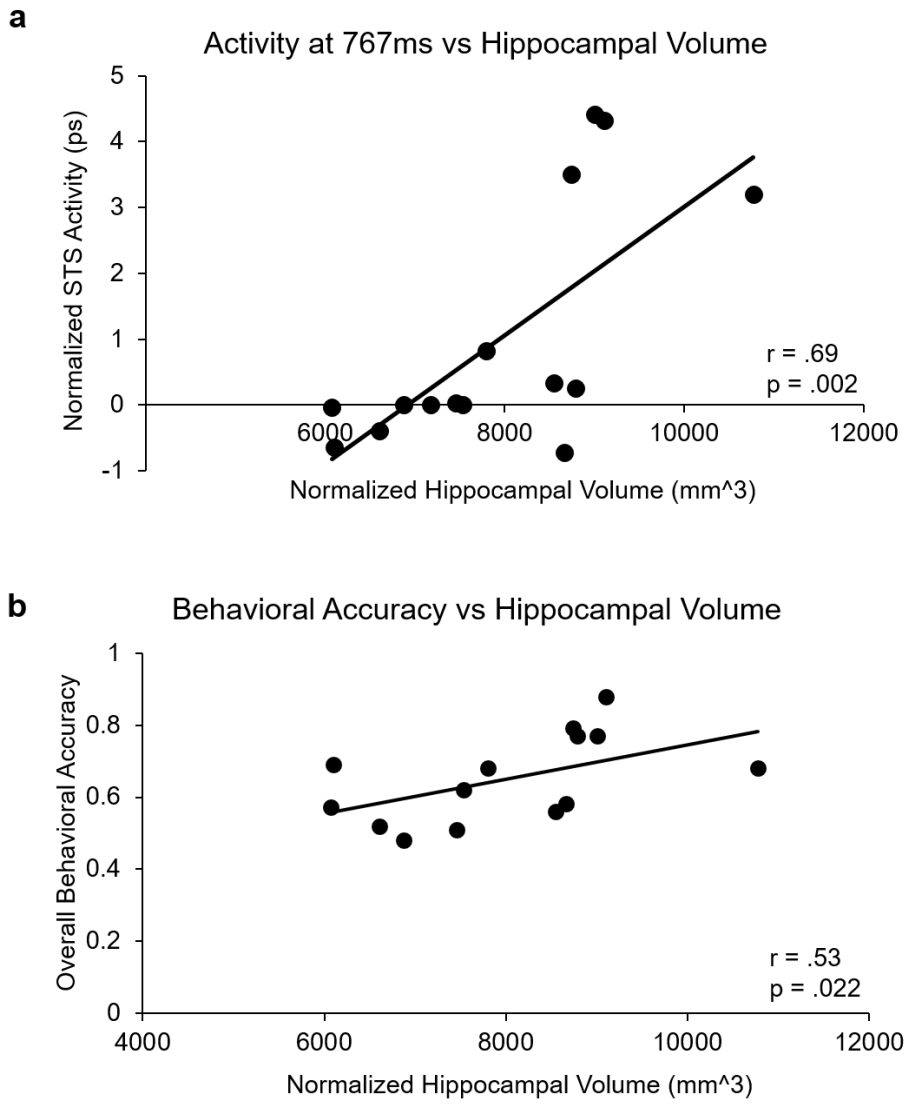
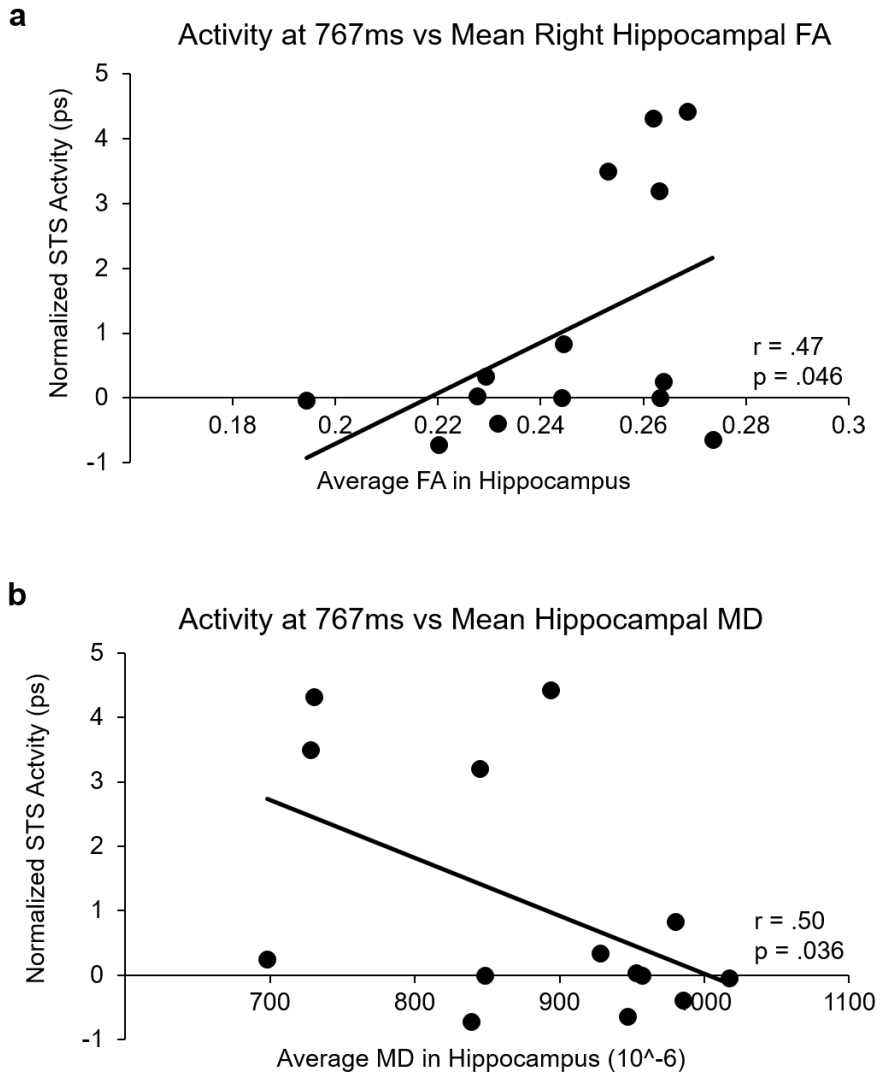


Figure 2.6. (a) Mean right hippocampal FA and (b) mean hippocampal MD are significantly correlated with the average relational-reactivation EROS activity in STS.



Chapter 2 Tables

Table 2.1

Mean (with Standard Deviation in Parentheses) Demographic Characteristics

Measure	*M*	*SD*
Age (years)	68.30	8.90
Education (years)	15.45	3.66
Wechsler Memory Scale	117.33	13.02

Table 2.2

Proportion of Correct Recognition Responses and Response Times for Each Trial Type

	Response Accuracy		Response Time (ms)	
Test Trial Type	*M*	*SD*	*M*	*SD*
Match	.64	.19	1404	184
Re-Pair	.55	.19	1411	236
Novel	.75	.16	1078	249

Table 2.3

Locations and Statistical Analyses for Areas Found to be Active During Study (Faces > Scenes) and Scene Preview (Old Scenes >New Scenes)

Study				
Location	Time Period	Location (y,z)	Z_{obs}	Z_{crit}
Left STS	409-435 ms	(-46, 1)	2.651	2.64
Scene Preview				
Location	Time Period	Location	Z_{obs}	Z_{crit}
Left STS	742 ms	(-58, 7)	2.323	2.64
	767 ms	(-58, 9)	2.692	2.55
	972 ms	(-44, -3)	2.415	2.51
	1561 ms	(-44, -3)	2.572	2.60
	1843 ms	(-44, 7)	3.711	2.84
Left DLPFC	255 ms	(32, 33)	-2.777	-2.68
	563-588 ms	(42, 29)	-3.011	-2.77
	742 ms	(12, 32)	-2.702	-2.85
	1612 ms	(48, 24)	-2.593	-2.90
Right DLPFC	255 ms	(17, 33)	2.833	2.83
	614 ms	(9, 32)	2.871	2.86

CHAPTER 3

THETA OSCILLATORY ACTIVITY IN THE CORTEX IS ASSOCIATED WITH REACTIVATION AND SUBSEQUENT BEHAVIOR

Abstract

As memories are distributed throughout the cortex, there must be a mechanism by which the hippocampus, a structure that has been shown to be necessary in the creation and utilization of relational bindings, can retrieve that information. Multiple theories have suggested that the hippocampus may use oscillations to communicate with the sensory cortices in order to retrieve information stored in that cortex. Likewise, others have shown that when a memory is retrieved, the same cortical processors come back online and are reactivated. Using a dataset from Walker et al. (2014) with college-aged participants and another data set from Chapter 2 with older adults that both show reactivation of face processing cortices (the left superior temporal sulcus; STS) to the presence of related scenes, we sought to find if these two phenomena that have been associated with memory retrieval are associated with one another. Here we show that power in the oscillatory band just above theta (8-10 Hz) in the STS, immediately prior to the later reactivation, is associated with the magnitude of that reactivation in college-aged adults. Furthermore, we show that the oscillatory power in the theta band (4-8 Hz) and in the 8-10 Hz band in the STS is associated with later memory performance across all participants. These findings provide evidence that theta and oscillations just above theta are associated with memory retrieval and reactivation in the cortex and are a possible source through which information from the cortex can be retrieved. We also show that there is a difference in this pattern due to aging in that older adults show lower oscillatory power in the theta band in the STS and also do not show this link between oscillatory power and reactivation.

Introduction

It has long been known that memories are not stored in one place in the brain but rather, it is thought that memory is stored throughout the cortex in the same cortical regions that initially processed that information (Lashley, 1950; Norman & O'Reilly, 2003). This means that if the original event involves the use of multiple cortical processors, that the memory for that event will be distributed across those processors. When a person goes to remember the memory for that event, the information must then be retrieved from those cortical processors and be reconstituted back together. The general consensus is that the structure that creates the original bindings between the various pieces of information from an event and then uses those bindings to reconstitute the memory is the hippocampus (N. J. Cohen & Eichenbaum, 1993; Eichenbaum, 2000, 2004; Eichenbaum & Cohen, 2001). How the hippocampus communicates between the various sensory cortices is not entirely known. Multiple theories have postulated that in order to retrieve information from the cortex, the hippocampus and the sensory cortices will coordinate their neural firings (Kumaran & McClelland, 2012; Marr, 1971; McClelland et al., 1995). This synchronization allows the hippocampus to activate these cortical processors and bring online the stored information. In this study we looked at the possible role of oscillatory activity in the reactivation of sensory cortex as a marker of this synchronicity between the hippocampus and sensory cortex and how oscillatory power is related to reactivation in the cortex as well as subsequent behavior in a memory task.

Reactivation, as defined in this experiment, is the activation due to memory of cortical processors that were previously activated when initially experiencing a stimulus. Previously it has been shown that when asked to remember an item, that the same cortical processors that were active when first experiencing the item are activated again, or reactivated (Johnson et al.,

2009; Johnson & Rugg, 2007; O'Craven & Kanwisher, 2000). It is thought that this reactivation is when the information from the cortical stores is being retrieved and, indeed, many find an association between amount of reactivation and behavioral performance (Hofstetter et al., 2012; Johnson et al., 2009; Johnson & Rugg, 2007; Staresina et al., 2013; Walker et al., 2014; Woodruff et al., 2005). We and others have shown that reactivation can also take place utilizing relational bindings in that presentation of one item of a pair will elicit reactivation of cortical processors for the other, relationally bound item of that pair (Schlichting, Zeithamova, & Preston, 2014; Walker et al., 2014; Zeithamova et al., 2012). Furthermore we have shown that the strength of this relational reactivation is related to measures of hippocampal structure (See Chapter 2). So if oscillatory processes are how the hippocampus communicates and retrieves information from the cortex and reactivation is the retrieval of information from the cortex, then there is good reason to believe that these two phenomena are related and may interact.

There is evidence that reactivation may be modulated by oscillatory processes as there is quite a bit of evidence of oscillatory activity related to memory in the animal literature. Some of the best known work regarding oscillations and memory retrieval come from a phenomena called "replay" whereby the place cells within the hippocampus can become reactivated in the same order they were experienced as the recently performed task (Wilson & McNaughton, 1994). These reactivations of place cells are activated in fast ripples (approximately 200 Hz) and have predominantly been found during sleep. However more recent evidence has shown that these fast wave ripples reactivate place cells in advance of a decision or task in an awake rat as well (Chrobak & Buzsáki, 1994; Foster & Wilson, 2006). It is thought that these reactivations are the rat replaying the maze running in the brain and that these ripples, especially during sleep, are to help consolidate the memory for the task into the cortex (Chrobak & Buzsáki, 1994). In addition

to these fast ripples, theta oscillations (4-8 Hz) have also been found during exploration of spaces and that these high-frequency bursts seem to be phase locked to the theta oscillations (Chrobak & Buzsáki, 1994; Otto et al., 1991; Ranck, 1973). It has been proposed that these slower theta oscillations are actually the carrier waves on which the fast ripples are communicated between the hippocampus and the cortex (Chrobak & Buzsáki, 1994). Evidence of the possibility for theta oscillatory communication between the hippocampus and neocortex comes from Sirota et al. (2008) in which they were able to show that different areas of the cortex, namely the medial prefrontal cortex and somatosensory cortex, become entrained with the hippocampus during a maze task, and that this phase locking served as a timing for local high frequency activity, suggesting that theta activity served as a way for the cortex and the hippocampus to synchronize and communicate. Furthermore, theta activity in the extrastriate cortex in monkeys has been shown to be positively associated with stimulus specificity of single units during a recognition task, indicating theta activations may play a role in memory tasks (Lee, Simpson, Logothetis, & Rainer, 2005), demonstrating a possible mechanism with which to reactivate sensory cortex.

In humans, the primary evidence for oscillatory modulation of reactivation comes from the literature of using electroencephalography (EEG) and magnetoencephalography (MEG) to study recognition memory. A few studies have found a link between increased oscillatory power in the theta band and just above the theta band (10-12 Hz) and recognition memory (Düzel et al., 2003; Gruber et al., 2008; Osipova et al., 2006) For instance Osipova et al. (2006) found greater theta power over visual cortexes for pictures of buildings or landscapes that were correctly recognized as old versus those landscapes that were incorrectly identified as new. In another study, theta power was shown to increase in a network of areas including the frontal, temporal, and visual cortices when participants claim to have recalled the type of scene associated with a

recognized face (Guderian & Düzel, 2005). More recently Fuentemilla et al. (2014) looked at retrieval of autobiographical memories and found that oscillatory entrainment between the hippocampus and the medial frontal cortex during autobiographical memory retrieval was tied with overall activity in the medial frontal cortex, an area known to be associated with autobiographical memory ability (Spreng & Grady, 2009). However, to the best of our knowledge, no one has ever shown a link between reactivation of the cortex and an increase in theta oscillatory power.

In this study we used two previously collected datasets of event-related optical signal (EROS) data to examine the association between oscillations as measured by oscillatory power in the theta band and reactivation in sensory cortices as well as its influence on a subsequent memory experiment. One data set consists of college-aged adults from Walker et al. (2014) and the other data set consists of older adults (aged 55+) from Chapter 2. Participants from both data sets performed the same task in which they studied pairs of faces and scenes and then were tested on those pairings by being given a two alternative forced choice test on whether or not a presented face was previously pared with a presented scene. Critically, prior to the test display, the scene was presented as a "scene preview". We have shown that the presentation of a scene that was previously studied with a face during this scene preview will elicit a reactivation of the related face processing areas (in this case the left posterior STS) even though no face was present (Walker et al., 2014). This reactivation took place during two time periods for the college-aged adults (486 ms and 716 ms) but only during one time period for the older adults (742-767 ms). It is important to note that the latter reactivation in the college-aged adults and the reactivation in older adults were both correlated with subsequent performance at test whereas the earlier reactivation in college-aged adults was not. Here we show that theta oscillatory power is

associated with subsequent memory performance and is also associated with the reactivation of sensory cortexes in the college-aged population but not in the older population.

Materials and Methods

Participants

College Aged Adults Twenty-one right-handed college-aged adults (10 women; mean age = 23.38 SD= 4.19) participated in this study for a payment of $15 an hour. Three participants were excluded from the analysis due to withdrawal from the experiment prior to completion.

Older Adults. Eighteen right-handed older adults participated in this study for a payment of $15 an hour. Three participants were excluded from the analysis due to withdrawal from the experiment prior to completion leaving a total of 15 participants (8 women; mean age = 68.29 SD= 8.89; age range: 55-88 years old).

All participants indicated that they had normal or corrected to normal vision and were not taking medications that would affect the central nervous system. Informed consent was obtained from each participant and all procedures were approved by the University of Illinois Institutional Review Board.

Stimuli

The stimuli consisted of 588 full-color face images (294 female faces) selected from a previously normed faces database (Althoff & Cohen, 1999) and 882 scenes from Brand X© photography. The faces were all sized to 300 x 300 pixels and the scenes were all sized to be 800 x 600 pixels, filling the entirety of the screen.

Procedures

Following signing an informed consent form, each participant was fit with an EROS recording helmet (see below) and were given a practice block of 12 study trials followed by 12

test trials so that s/he could get used to the timing of the trials. During the practice block, older adults were given instructions to create a story linking the face and the scene together and to use that story to retrieve that same association during test whereas the college-aged participants were not given these instructions. This was done because piloting found that whereas younger participants naturally used this strategy, older adults could not perform the task above chance without explicitly being given the strategy. Following the practice block the college-aged participants completed eight study/test blocks over two days (4 blocks per day) and the older participants completed one day of six study/test blocks. All participants were allowed to take breaks in between each block as necessary.

Study Block. Study blocks consisted of 72 study trials divided into two sets of 36 trials. Each set of study trials started with a 1s fixation cross. As can be seen in Figure 3.1a, the study trials started with a face and scene being shown individually for 750ms each. Half the study trials had the face shown first ("face-first" trials) and half the trials had the scene shown first ("scene-first" trials). After the face and scene were shown individually, the face was superimposed on the center of the scene for 1500 ms. Participants were instructed to study each of the pairings as they were to be tested on those pairings later on. The blocks were divided by short breaks to minimize movement artifacts.

Test Block. Following each study block was a corresponding test block of 72 test trials, testing the pairs of items studied in the immediately preceding study block. These test trials were divided up into three sets of 24 test trials, with each set beginning with a 1 s fixation cross. As can be seen in Figure 3.1b, a test trial consisted of a scene being presented for 1000 ms (the scene preview), followed by a fixation cross for 1000 ms. followed by the face superimposed on the center of the scene. Participants were instructed to respond during when the face-scene pair

was shown using a button box as to whether or not a face-scene pair was studied together during the previous study block (old-new judgment). College-aged participants were given 2000 ms for the face-scene pair whereas older adults were given 2500 ms to account for their slower responses. There were three types of test trials: match, re-pair, and novel. Match test trials were test trials in which the face and the scene being tested had been presented together during the study phase. The re-pair test trials were comprised of faces and scenes that had been presented in the study phase, but had not been paired together. The novel test trials were comprised of a novel scene with a previously studied face. The correct response for match trials was "old" as those pairs were previously studied together, whereas the correct response for re-pair and novel trials was "new" as the pairs in those trials were not studied together. Participants were asked to respond only once the face had appeared, and were explicitly told not to respond during the scene preview or fixation. Every test trial ended in a fixation for 1500 ms.

Counterbalancing for each of the experiments can be found in Walker et al. (2014) for the college-aged adults and Chapter 2 for the older adults.

Optical Recording

Optical data were recorded using six synchronized ISS model 96208 frequency domain oxymeters (Imagent®; ISS, Inc., Champaign, IL). The light sources were laser diodes emitting light at the wavelength of 830 nm (max amplitude: 10 mW, mean amplitude after multiplexing: 1 mW) modulated at 110 MHz. Optic fibers were used to channel each light to the surface of the scalp. The detectors were fiber optic bundles (diameter = 3 mm) connected to photomultiplier tubes (PMTs). The PMTs were fed with a current modulated at 110.0625 kHz, generating a heterodyning frequency of 6.25 kHz. The output current from the PMTs was digitized at 50 kHz, affording 8 points per heterodyning cycle. A time-multiplexing approach was used to

record from sixteen sources for each detector. In this approach, each source was switched on for 1.6 ms, and off for 24 ms. This allowed to record for a total of 10 heterodyning cycles (80 points) for each multiplexing time unit. However, to avoid cross-talk, the first two cycles were discarded, and the remaining 64 points were subjected to a fast Fourier transform for computation of DC (average) intensity, AC (amplitude), and relative phase delay (in degrees and later converted to picoseconds). Only phase delay data are reported here.

Source and detector fibers were mounted on a modified motorcycle helmet. The area covered by our montage covers the entirety of the top of the head. The coverage of the montage can be seen in Figure 3.2, represented by the darker grey shading on the brain. Our montage consisted of 24 detectors and 64 sources. Source-detector distances ranged between 15 and 94 mm. To avoid cross talk, the sources were arranged such that during any given time division of the multiplexing cycle only one source was within 6 cm of any given detector. This allowed us to record from 384 channels (pairings of source and detector) at 39.0625 Hz on each session.

The locations of the sources and detectors were digitized with a Polhemus "3Space" ® (Colchester, VT) 3D digitizer and co-registered with a volumetric T1-weighted MR image for each subject (Whalen, Maclin, Fabiani, & Gratton, 2008). The co-registered data were then Talairach-transformed to permit registration across subjects. The phase data were corrected off-line for phase wrapping, pulse artifacts were removed (Gabriele Gratton & Corballis, 1995), and the data were low-pass filtered to 5 Hz (Maclin et al., 2003). Channels with standard deviations of the phase greater than 150 ps were excluded from further analysis (for further details of these analytic steps, see (Gabriele Gratton & Fabiani, 2007).

Optical Statistical Analyses

For this experiment we only analyzed the activity during the scene preview at test. To calculate the event related spectral perturbation (ERSP) of the data we performed a wavelet analysis using the newtimef.m function from EEGLab (Lopez-Calderon & Luck, 2014) on the AC, DC, and phase delay separately. The oscillatory power data were divided into epochs around the stimulus events of interest with a 492.56 ms baseline but the post-stimulus recording consisted of 2022 ms so that it could include the scene preview and the fixation cross, both shown before the face is presented in the test trial. As part of the wavelet analysis, the data were downsampled from 39.0625 Hz to 38.5742 Hz.

In-house software "OPT-3D" (Gabriele Gratton, 2000) was used to reconstruct the optical path for each channel spatially , combine channels whose mean diffusion paths intersected for a given brain volume (voxel) and to compute group-level statistics. The resel size of the cortical projections were determined by the independence of the error terms at various voxel distances computed by using the methods described by Worsley et al. (1999). An 8 mm Gaussian filter (based on a 2 cm kernel) was used to spatially filter the data. The group-level statistics were then converted to Z-scores and compared to critical Z scores based on the number of resels within an ROI and the subsequent correction for multiple comparisons. These Z scores are then orthogonally projected onto images of the sagittal surfaces of the brain in Talairach space (Talairach & Tournoux, 1988).

Due to its high spatial and temporal resolution (which may inflate the number of comparisons), statistical analysis of EROS was limited to a priori ROIs. Whole-brain analyses, as are often done in fMRI, which has only high spatial resolution, are not practical with EROS data as the number of data points (one for every resel at every time point) would make the correction for multiple comparisons too severe. Thus we focused on the STS and the DLPFC, the

areas that were shown to be involved in reactivation in college aged adults (Walker et al., 2014) and that have been shown to be important in the processing of faces (Fairhall & Ishai, 2007; Grill-Spector et al., 2004; Puce et al., 1998; Puce et al., 2003) and in the top-down control of memory retrieval (Miller & Cohen, 2001), respectively. These areas are also easily accessible with optical imaging, whereas other potential areas of interest such as the fusiform gyrus and the ventrolateral prefrontal cortex could not be accessed with the instrumentation used in the current study (For the spatial extent of areas covered see Figures 2.3-2.6 from Chapter 2). As in Walker et al. (2014), the boundaries for the STS ROI were defined in Talairach space (Talairach & Tournoux, 1988) as y = -65 to -43, and z = -8 to 20 and y = -72 to -45, and z = -3 to 24 for the left and right STS, respectively. These boundaries were based on the peak activation in the STS for faces in previous fMRI work (Bonda et al., 1996; Fairhall & Ishai, 2007; Grill-Spector et al., 2004; James V. Haxby et al., 1999; Hoffman & Haxby, 2000; Ishai et al., 2005; Ishai et al., 2000; Kanwisher et al., 1997; Puce et al., 1998; Puce et al., 2003). The boundaries for the DLPFC ROI were defined as y = 10 to 50, and z = 15 to 35 for both the left and right DLPFC. These boundaries were based on the spatial extent of Brodmann's areas 9 and 46.

Additionally, in order to control for multiple comparisons we also limited our analyses to temporal intervals of interest (IOIs) at both study and test. As reactivation activity found in Walker et al. (2014) and Chapter 2 was in the first 1000 ms, we limited our analyses to that time window. However, for exploratory reasons we also report any activity that was found to be significant with a spatial correction in Table 3.1. Correction for multiple comparisons across voxels was applied based on the number of independent resolution elements (resels) within each ROI using random field theory (Friston et al., 1995; Gabriele Gratton, 2000; Maclin et al., 2003).

Structural Analyses

Images were collected on a Siemens Magnetom Trio 3T whole body MRI scanner. A standard 12-channel birdcage head coil was used and head motion was restricted with foam padding. High-resolution 3D MPRAGE (TI = 900ms; flip angle = 9°; .9 mm isotropic voxels) structural images were acquired parallel to the anterior commissure-posterior commissure (AC-PC) axis. Structural scans were acquired 3-11 months (average = 7.2 months) prior to behavioral data collection.

Automatic segmentation of the hippocampus was performed using Freesurfer (v 5.3; details about the subcortical segmentation process have been described in Fischl et al. (2002) and Fischl et al. (2004)). Intracranial volume (ICV), also calculated by Freesurfer, was used to correct for overall head size (see R. L. Buckner (2004) for detailed method). By regressing each ROI volume onto ICV, a slope (b) was obtained for the relationship between ROI and IVC. The resulting slope was used to normalize each volume for head size (normalized volume = raw brain volume – b(IVC- mean IVC)) (Erickson et al., 2009; Head et al., 2009; N. Raz et al., 2005).

Results

Behavioral Results

Overall participants performed above chance when asked to indicate whether or not the pair was old or new (M = .69, SD = .11), $t(32) = 34.93$, $p < .001$. Despite having less time to respond, college-aged adults (M = .74, SD = .09) were more accurate at identifying old pairs than the older adults (M = .64, SD = .11), $t(32) = 2.81$, $p < .05$. For a full analysis of each groups behavioral results see Walker et al. (2014) for the college-aged adults and Ch 2 for the older adults.

Analysis of Time Frequency Results

First we looked to see what periods of time during the scene preview period showed greater amounts of theta power related to memory. In order to do this we contrasted the ERSPs from old scenes that were previously studied with faces to new scenes that were not studied with a face. We looked at two bands of oscillatory activity, theta (4-8 Hz) and what we are calling high theta (8-10 Hz), as both have been implicated in recognition memory in humans and animals (Chrobak & Buzsáki, 1994; Düzel et al., 2003; Fuentemilla et al., 2014; Gruber et al., 2008; Guderian & Düzel, 2005; Osipova et al., 2006; Otto et al., 1991; Ranck, 1973; Sirota et al., 2008). Specifically, we looked at the oscillatory power in the left STS, the area that showed relational reactivation in these data sets, during the time period prior to the reactivations found to be associated with memory, the reactivation at 716 ms in college-aged adults and 742 ms for older adults. Looking at the oscillatory activity for old scenes minus new scenes for the entire time period prior (104-700 ms) to these found reactivations, we found that overall there was an increase in theta power in the left STS for all participants combined (peak Z = 3.816, Z_{crit} = 2.53; Talairach coordinates: y = -66, z = 2). This same pattern is present in both the college-aged adults (peak Z = 2.991, Z_{crit} = 2.63; Talairach coordinates: y = -56, z = -1) and in older adults (peak Z = 2.517, Z_{crit} = 2.42; Talairach coordinates: y = -66, z = 12) (See Figure 3.2) with younger adults showing greater theta oscillatory power in the STS during this time period (peak Z = 2.529, Z_{crit} = 2.42; Talairach coordinates: y = -66, z = 12) (See Figure 3.3). Within this time period we also found individual periods of increased theta power in both the young and older adults. In younger adults there was increased theta power for 155-207 ms (peak Z = 3.240, Z_{crit} = 2.72; Talairach coordinates: y = -58, z = 4), 311-518 ms (peak Z = 2.939, Z_{crit} = 2.58; Talairach coordinates: y = -66, z = 2), and 596-622 ms (peak Z = 3.064, Z_{crit} = 2.72; Talairach coordinates: y = -46, z = 1). In older adults there was increased theta power over 129-285 ms

(peak Z = 2.529, Z_{crit} = 2.44; Talairach coordinates: y = -48, z = 26) and over 466-544 ms (peak Z = 2.789, Z_{crit} = 2.58; Talairach coordinates: y = -66, z = 12). Outside of the period from 104-700 ms we found no increases in theta oscillatory power in college-aged nor older adults.

For high theta we did not find this same increase in oscillatory power over the entire window of 104-700 ms (peak Z = 2.121, Z_{crit} = 2.50; Talairach coordinates: y = -66, z = 7). However, when we split up the groups into college-aged and older adults we find that college aged participants do show an increase in high theta power over this time window (peak Z = 3.782, Z_{crit} = 2.54; Talairach coordinates: y = -44, z = -3) whereas the older adults did not (peak Z = 1.556, Z_{crit} = 2.46; Talairach coordinates: y = -66, z = 12) (See Figure 3.2). However, college-aged adults only showed a marginally higher amount of high theta power as compared to the older adults during this time window (Z = 2.386, Z_{crit} = 2.50; Talairach coordinates: y = -44, z = 7)(See Figure 3.3). Within this time window we find a very similar pattern of activity to that of theta with increases in high theta activity from 181-285ms (peak Z = 2.690, Z_{crit} = 2.35; Talairach coordinates: y = -46, z = -6), 414-440 ms (peak Z = 2.668, Z_{crit} = 2.63; Talairach coordinates: y = -53, z = -8), and 570-648 ms ((peak Z = 3.376, Z_{crit} = 2.71; Talairach coordinates: y = -44, z = 2). No time period from 100-700 ms showed significant oscillatory high theta power in older adults. Similar to theta, we found no increases in high theta oscillatory power in college-aged nor older adults outside of the period from 104-700 ms. For a full listing of areas that we found to show greater theta and high theta oscillatory power see Table 3.1.

As these increases in oscillatory power were in an area that is related to face processing but are elicited by the presentation of a relationally-bound scene, in the absence of any face, this pattern of activity strongly suggests that these increases in oscillatory power are memory related. To test whether or not these increases in theta oscillatory power are related to memory we looked

at the correlations between amount of increase in oscillatory power with an ROI and subsequent behavioral performance at test. As can be seen in Figure 3.4 we found that accuracy at the later test was significantly correlated with the increase in theta and high theta oscillatory activity during the scene preview from 104-700 ms, $r = .409$, $p < .05$ and $r = .489$, $p < .01$, respectively. When we looked at college-aged adults and the older adults separately, we found that neither were significant in their own right with only the older adults showing a marginal correlation between theta oscillatory power and subsequent accuracy, $r = .46$, $p = .08$. However, when we looked at high theta we found a marginally significant correlation between high theta oscillatory power for 104-700 ms and accuracy in college-aged adults, $r = .471$, $p = .065$. And despite the high oscillatory activity during 104-700 ms not showing a significant increase between old scenes and new scenes, the level of oscillatory power during this time period is correlated with subsequent behavior in older adults, $r = .536$, $p < .05$. We also looked at the time periods within 104-700 ms that showed greater oscillatory power for old scenes as compared to new and found that for older adults, theta oscillatory power from 129-285 ms was significantly correlated with subsequent accuracy and from 466-544 ms was marginally correlated with subsequent accuracy, $r = .524$, $p < .05$, and $r = .508$. $p = .053$, respectively. For college aged adults we found no individual time period within the window of 104-700 ms to be significantly correlated with subsequent accuracy, all $p > .1$.

Next we looked to see whether or not these increases in theta and high theta oscillatory power are correlated with the found reactivations in college-aged and older adults. The younger adults had two different reactivations in the STS during the scene preview, one at 486 ms and one at 716 ms, with only the latter being correlated with subsequent accuracy at test, whereas the older adults only showed one significant reactivation in the STS at 742 ms, which was also

correlated with subsequent accuracy at test. We found that none of the significant increases in the traditional theta band correlated with amount of reactivation observed in the STS in college-aged or older adults. Similarly, no significant increases in high theta correlated with either the early reactivation in young adults nor the reactivation in older adults. Conversely, when we looked at the correlation between high theta and the different reactivations, we found that in young adults it was not the entire period prior of 104-700 ms that correlated with the latter reactivation in college-aged adults ($r = .297$, $p=.26$) but rather a significant increase in high theta power right before the reactivation from 570-648 ms that was correlated with reactivation in the cortex at 716 ms, $r = .508$, $p < .05$ (See Figure 3.5).

We also wanted to look at the relationship between the hippocampus and theta oscillations by looking at the correlations between theta and high theta oscillatory power and hippocampal volume. In Chapter 2 we found that hippocampal volume among other measures of hippocampal structure were correlated with the amount of observed reactivation and subsequent accuracy. When we combine the college-aged and older adults we find that there is a correlation between accuracy and hippocampal volume, $r = .522$, $p < .01$. When looking at the volumes in our college-aged adults, though, we found that those volumes do not correlate with either subsequent behavior ($r = .288$, $p = .28$) and only marginally correlate with the reactivation at 486 ms ($r = .459$, $p = .074$) and is not correlated with the reactivation at 716 ms, $r=.308$, $p = .245$. We looked to see if hippocampal volume is correlated with any of the found increases in theta oscillatory power and found no significant correlations, all $p > .1$.

Discussion

The goal of this experiment was to examine the association between two phenomena that have been linked to memory retrieval from the cortex, theta oscillations and reactivation. We

found that in college-aged adults there is a correlation between reactivation and oscillatory power in the reactivated region in a frequency band just above theta that has been termed high theta (10-12 Hz) but not theta (4-8 Hz). This provides evidence for many theories that suggest that the way that information is retrieved from the cortex is through oscillatory entrainment and reactivation of the sensory cortices (Kumaran & McClelland, 2012; Marr, 1971; McClelland et al., 1995). Conversely, in older adults we did not find any such correlations between either theta or high theta and reactivation of sensory cortices. This indicates that while we did find that oscillatory power is associated with reactivation, there may be an aging component to this relationship.

For both college-aged and older adults we did find that the strength of the oscillatory power in the area that shows reactivation, the left STS, is associated with subsequent performance for an old/new recognition test of face-scene pairings. This is in line with previous results showing an increase in theta power over sensory cortices during recognition tests (Düzel et al., 2003; Gruber et al., 2008; Guderian & Düzel, 2005; Osipova et al., 2006) as well as memory retrieval (Fuentemilla et al., 2014). It is important to note, though, that during the time period we examined, we did not require the participant to make any overt response during the scene preview. Participants were just looking at the scene in preparation for the upcoming test display. Most experiments mentioned have looked at theta only at the time of response (Düzel et al., 2003; Fuentemilla et al., 2014; Gruber et al., 2008; Guderian & Düzel, 2005; Osipova et al., 2006) so there was a possibility that this association between theta and memory performance was linked to an overt response. These data indicate that the link between theta and memory performance does not require the participant to be actively responding in that moment but can be done passively.

For high theta we found significant increases in oscillatory power in college-aged adults but not in older adults. Coupled with the finding that older adults show less theta power and marginally less high theta power in the STS, this may indicate an aging component to the strength of oscillations in sensory cortex. It is well known that older adults have deficits in the ability to recall associative information as they get older (Baltes et al., 1999; Naveh-Benjamin, 2000; Naveh-Benjamin et al., 2004) and this may be one of the possible mechanisms. These findings are in line with a previous study showing that older adults have lower theta power over the entire head during a recognition task (Cummins & Finnigan, 2007). We extend these results and show that one of the places that demonstrate this reduction in theta is the sensory cortex that is associated with the reactivation of relational information critical to task performance. Despite the fact that we do not find any significant increase in high theta over the period prior to the found reactivations in older adults, this pattern of oscillatory power is associated with subsequent memory performance. So it could be that one of the reasons why the older adults perform worse than the college-aged adults in this task is their reduction in power in this high theta band.

Furthermore, the lack of a found correlation between oscillatory power and reactivation in older adults may be due to the lessened theta and high theta oscillatory power. In college-aged participants we did not show any correlation between theta power and subsequent reactivation of the cortex so it is not surprising to find the same in older adults. However, we did find the correlation between high theta power immediately prior to the latter reactivation in college-aged adults. In older adults we found no such correlation because there was no time period during which older adults showed greater high theta power for old scenes versus new scenes. It could be that, much like the activity in the overall window prior to the reactivation did not show

significantly higher high theta power but still correlated with behavior in older adults, activity sometime prior to the reactivation could correlate with the reactivation.

Another aspect of interest is the timing of the oscillatory activity. In both the theta and high theta bands, the time periods that showed significant increases in oscillatory activity took place prior to the last observed reactivation in both the college-aged and older adults but not during or after. This may indicate a role for the oscillations to communicate with sensory cortex and entrain that cortex to allow for subsequent reactivation and retrieval of memory (Fuentemilla et al., 2014; Sirota et al., 2008). If the increase in theta activity represents entrainment of the sensory cortex by the hippocampus then it may be that once the sensory cortex is entrained, higher oscillatory power is no longer necessary for the cortex to reactivate and retrieve the information from the cortex. Another possibility is that this increased theta power represents communication to and from the cortex as many animal researchers have shown with high frequency waves using theta as a carrier frequency (Chrobak & Buzsáki, 1994; Otto et al., 1991; Ranck, 1973). Theta may indicate communication to and from the cortex, selecting the right pattern of activity to reactivate, which may mean the reactivation is just the culmination of the retrieval of memory and not the point at which the retrieval of memory takes place. Further research is needed to examine what information is exchanged and when during memory retrieval and how this relates to the phenomena of oscillatory activity and reactivation.

One of the drawbacks of these data is that we failed to link the oscillatory activity to the hippocampus. One of the main lines of thought is that this increase in theta activity in the cortex is due to hippocampal activity and that theta in the cortex represents communication with the hippocampus (Chrobak & Buzsáki, 1994; Fuentemilla et al., 2014; Sirota et al., 2008). However, we did not show any correlation between theta or high theta activity and hippocampus. One of

the possibilities for this is that hippocampal volume may not be the ideal measure to link the hippocampus with oscillatory activity. In our college-aged adults that show greater oscillatory power, it is unclear what differences in hippocampal measures mean. In older adults, differences in hippocampal volumes are linked to differences in hippocampal atrophy and has been shown to be linked to memory performance (R. L. Buckner, 2004; Charlton et al., 2006; Duverne et al., 2009; M. Fabiani, 2012; Morcom et al., 2003; N. Raz et al., 2005; Walhovd et al., 2005) but that link between hippocampal atrophy and size is not present in healthy college-aged participants. So any variance between hippocampal volumes in college-aged adults may not be memory related so one would not expect a correlation between hippocampal volumes and memory related oscillatory activity. With older adults there is this established link between hippocampal volume and memory processes (See Chapter 2) but this population shows lower overall oscillatory activity. As such other measures of the hippocampus might be necessary to demonstrate the link to oscillations in the cortex.

Additionally, it is important to note that the band that is referred to in this paper as high theta could just as easily be called low alpha as 8-10 Hz is part of the alpha band (8-12 Hz). As such, one could possibly interpret the activity in the high theta band as being due to attention, which is often linked to alpha oscillations. Whereas high theta is definitely part of the alpha band, the effects observed here differ in many ways from the established literature on attention and awareness effects (Fries, Reynolds, Rorie, & Desimone, 2001; Mathewson et al., 2014; Mathewson, Fabiani, Gratton, Beck, & Lleras, 2010; Mathewson, Gratton, Fabiani, Beck, & Ro, 2009). Notably, our contrast is between old scenes and new scenes and we show increased high theta activity for old scenes and not new scenes, which is contrary to the attention literature on alpha. Generally alpha increases over task irrelevant areas(Suffczynski et al., 2001), but in this

study, not only does high theta increase over the STS, an area relevant to the task, but this activity is related to subsequent memory performance. Whereas memory and attention often interact, these effects observed for high theta are more in line the memory related oscillatory activity attributed to theta and not the attentional activity attributed to alpha.

Conclusion

The current study sought to examine the link between two different phenomena that have been related to memory retrieval, cortical reactivation and theta oscillations. Using datasets from two previous studies that showed reactivation of face processing regions in the left STS to the presentation of a relationally bound scene, we found that oscillations in the STS in a band just above theta (8-10 Hz) prior to the observed reactivation are positively associated with the magnitude of reactivation in the cortex. Conversely, in older adults we did not find any such correlation. Furthermore, we found that theta oscillatory power during the period prior to the reactivation are correlated with subsequent memory performance across participants with college-aged adults demonstrating greater theta power than older adults during this time period. This demonstrates that there is an association between the oscillations and cortical reactivation in the service of memory and that this association may be affected by aging.

Chapter 3 Figures

Figure 3.1. Schematic representation of the experimental paradigm, illustrating the sequence of stimuli during study (a), where the top row represents a face-first trial and the second row represent a scene-first trial, and test (b). Note that during test scenes were always presented first, generating a scene preview period.

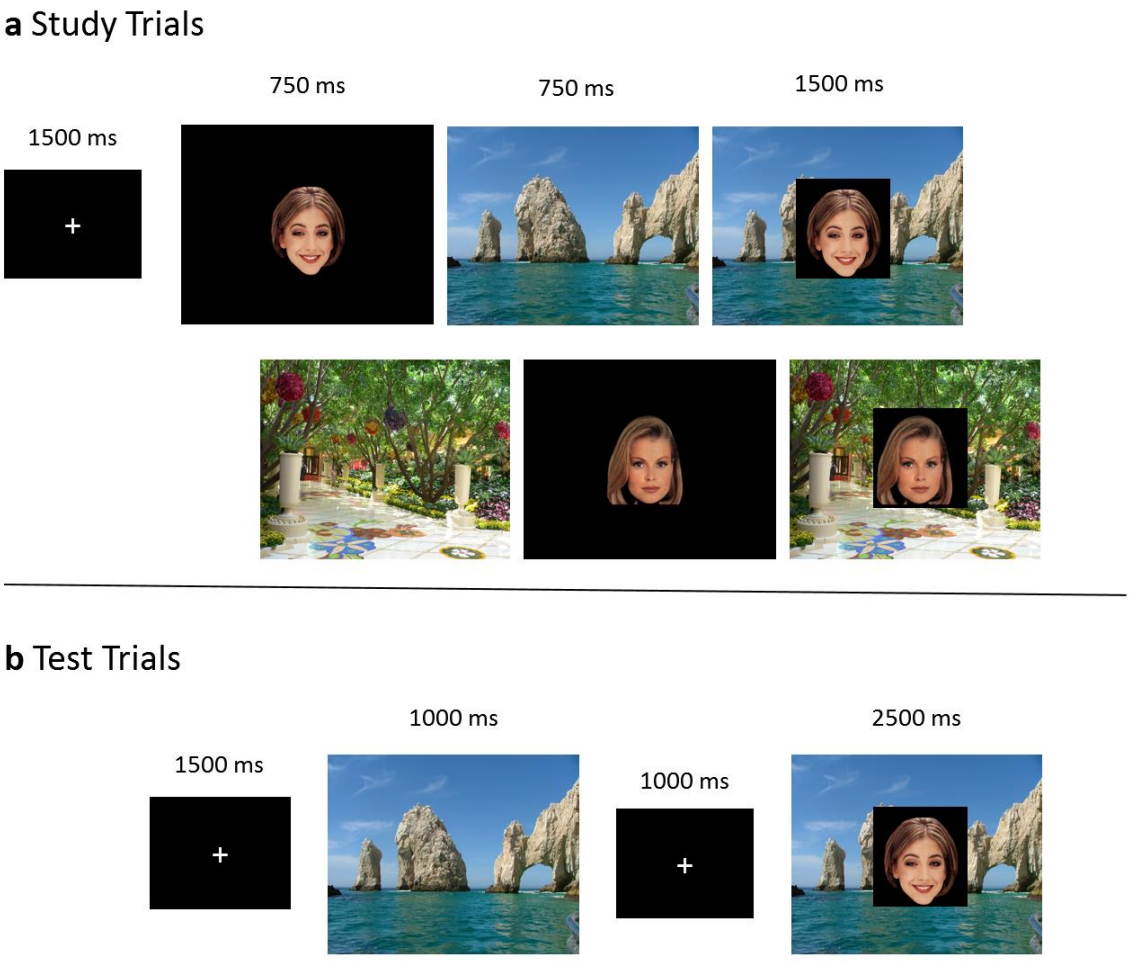


Figure 3.2 Spatial maps based on group level *Z*-statistics of the ERSP data projected on sagittal brain surfaces (left hemisphere view). Dark gray shading represents the brain area sampled by the recording montage. The light green rectangle indicates the STS ROI. Oscillatory power during the scene preview for previously studied scenes versus completely novel scenes in the left STS from 104 -700 ms for college-aged and older adults in both the theta and high theta bands.

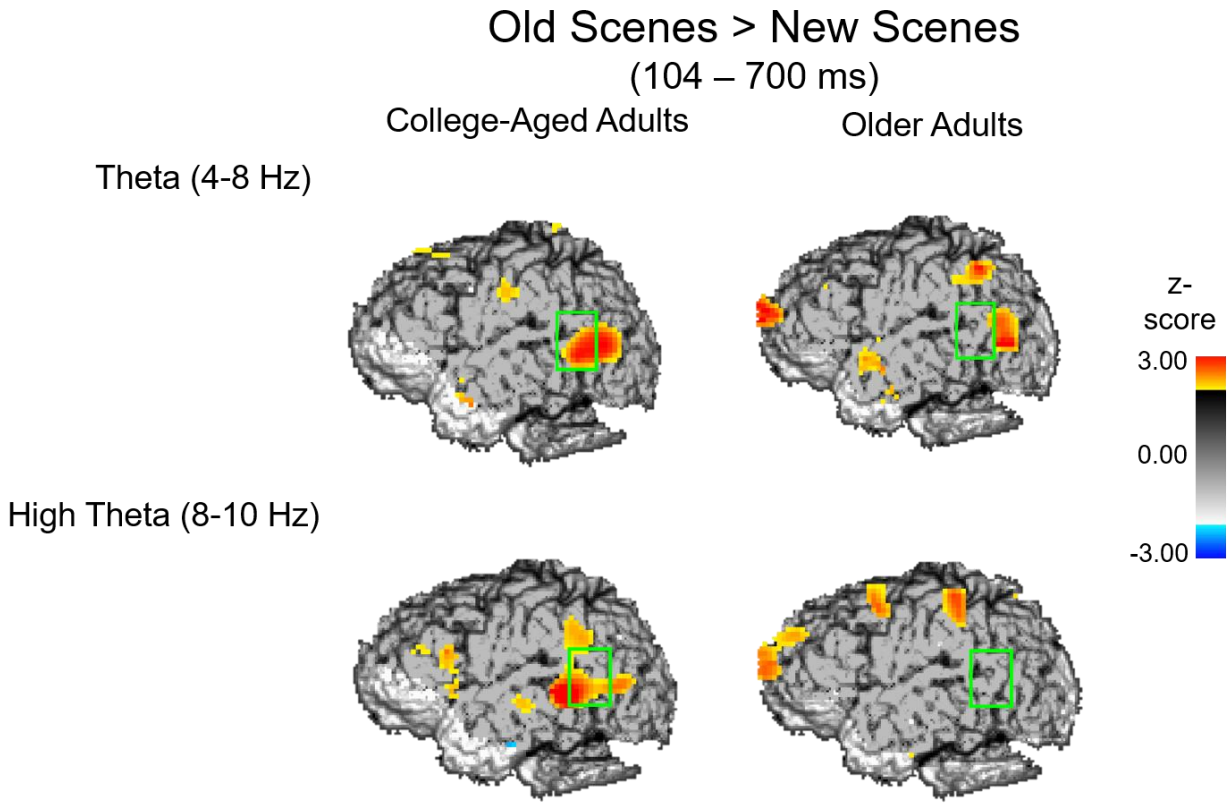


Figure 3.3 Spatial maps based on group level *Z*-statistics of the ERSP data projected on sagittal brain surfaces (left hemisphere view) displaying the contrast between college-aged adults and older adults for old scenes versus completely novel scenes from 100-700 ms across both the theta and high theta bands.

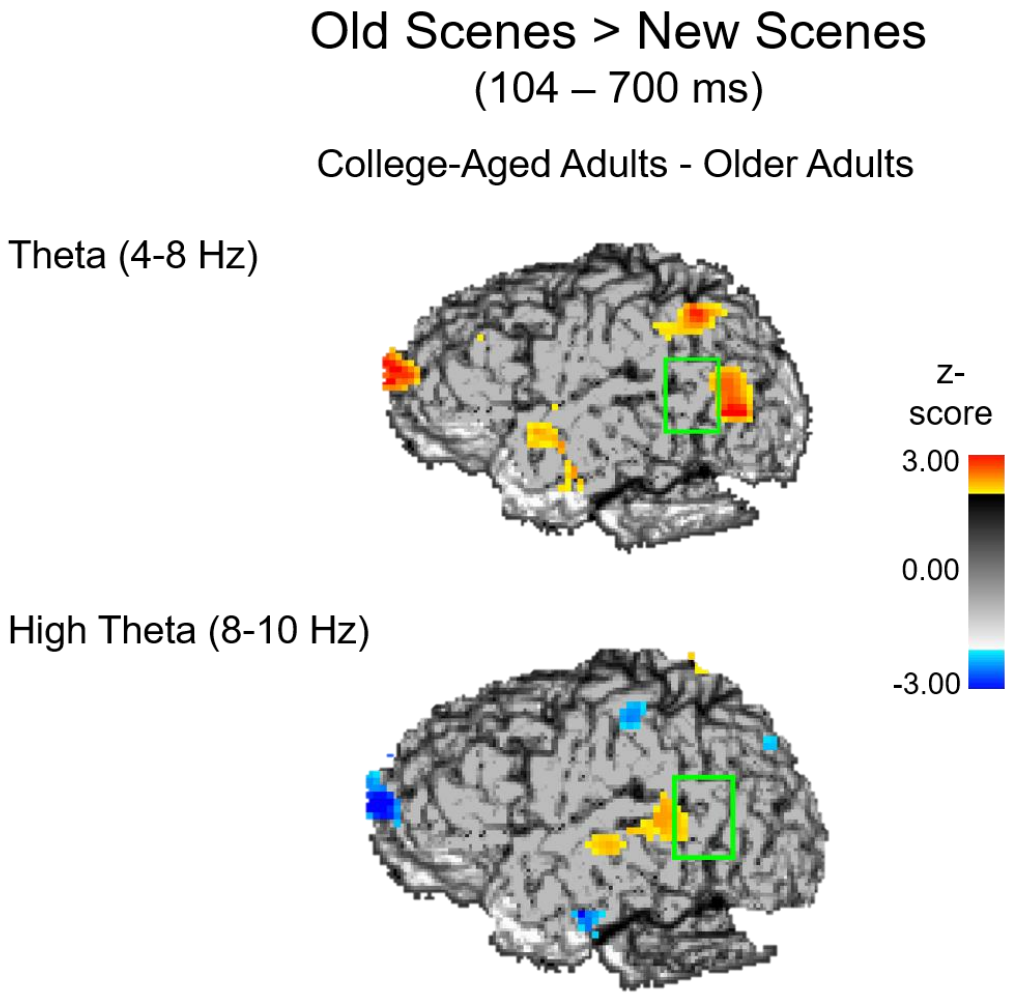
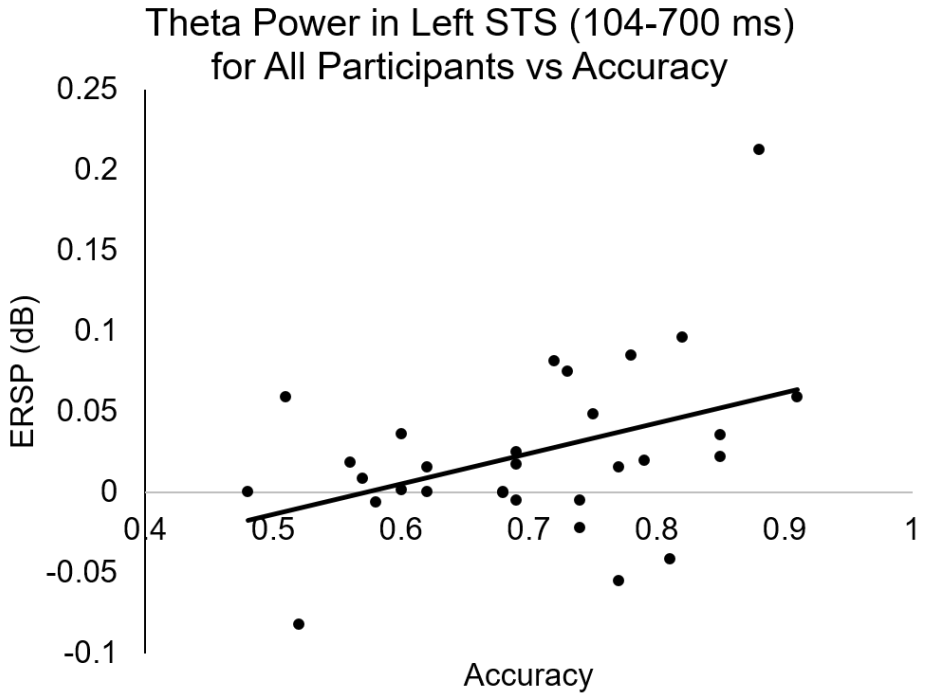


Figure 3.4 Correlations between (a)theta power and (b) high theta power from 104-700 ms in the left STS for all participants vs accuracy on a subsequent old/new pair recognition test.



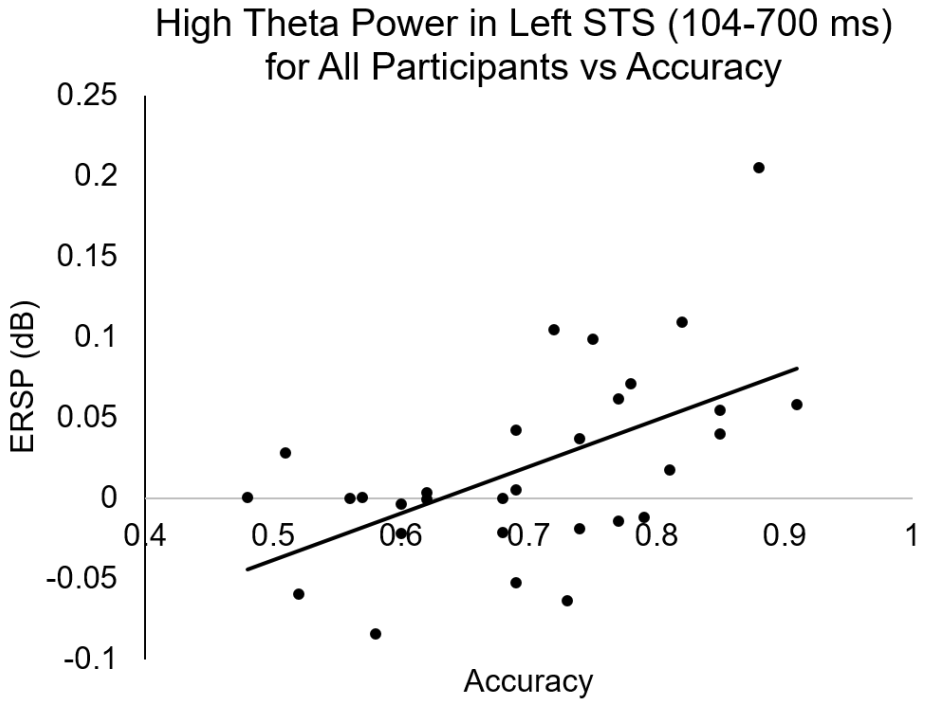
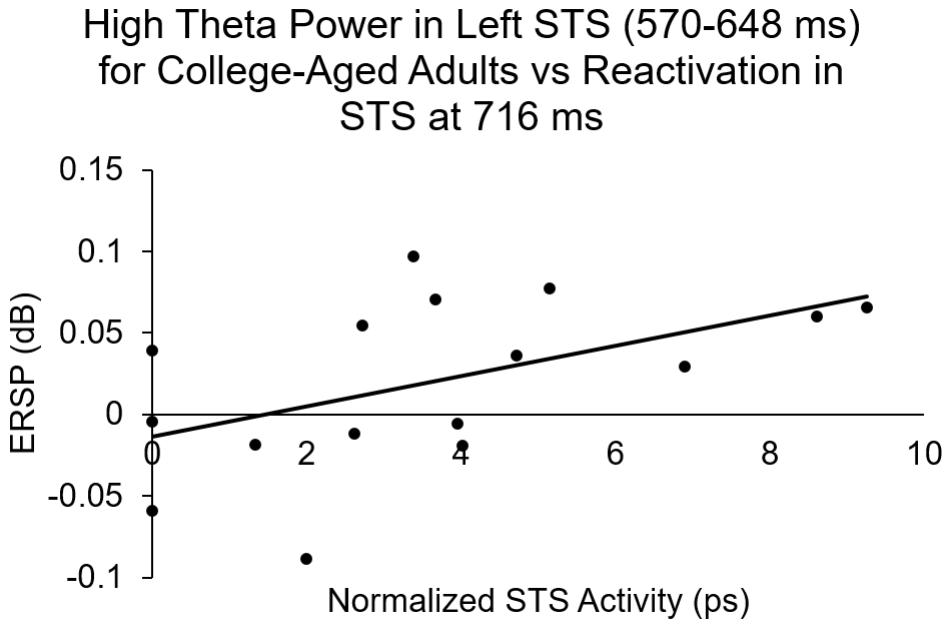


Figure 3.5 Correlation between high theta power in the left STS for old scenes greater than new scenes from 570-648 ms for college-aged adults vs the reactivation activity in the left STS at 716 ms.



Chapter 3 Tables

Table 3.1

Locations and Statistical Analyses for Areas Found to have Greater Oscillatory Power During the Scene Preview (Old Scenes >New Scenes)

Theta (4-8 Hz)				
Location	Time Period	Location (y,z)	Z_{obs}	Z_{crit}
All Participants				
Left STS	104-699 ms	(-66, 2)	3.816	2.53
Right STS	518-544 ms	(-51, 7)	3.138	2.89
	648-725 ms	(-51, -3)	3.147	2.74
Left DLPFC	259-311 ms	(22, 32)	2.998	2.72
	907-1036 ms	(17,34)	3.162	2.89
Right DLPFC	285-674 ms	(32, 34)	3.379	2.64
College-Aged Adults				
Left STS	104-700 ms	(-56, -1)	2.991	2.63
	155-207 ms	(-58, 4)	3.240	2.72
	311-518 ms	(-66, 2)	2.939	2.58
	596-622 ms	(-51,19)	3.064	2.72
Right STS	648-699 ms	(-48, -1)	3.009	2.74
	803-1062 ms	(-58,23)	3.947	2.78
Right DLPFC	129-233 ms	(9, 17)	3.044	2.71
	362-440 ms	(34, 34)	3.115	2.86
	544-699 ms	(39, 24)	3.244	2.82
Older Adults				
Left STS	104-700 ms	(-66, 12)	2.517	2.42
	129-285 ms	(-48, 26)	2.529	2.44
	466-544 ms	(-66, 12)	2.789	2.58
Right STS	518-544 ms	(-51, 7)	3.138	2.89

Table 3.1 (cont.)

High Theta (8-10 Hz)				
Location	Time Period	Location (y,z)	Z_{obs}	Z_{crit}
All Participants				
Left STS	181-388 ms	(-66 ,7)	2.595	2.38
Left DLPFC	51-207 ms	(32, 24)	3.386	2.77
	933-1088 ms	(9, 34)	3.448	2.86
College-Aged Adults				
Left STS	107-700 ms	(-44, -3)	3.782	2.54
	181-285 ms	(-44, -6)	2.690	2.35
	414-440 ms	(-53, -8)	2.668	2.63
	570-648 ms	(-44, 2)	3.376	2.71
Left DLPFC	181-207 ms	(34, 22)	3.158	2.87
	985-1088 ms	(9, 34)	3.100	2.84

CHAPTER 4

RELATIONAL MEMORY IN INFANTS: 9-MONTH-OLDS CAN REACTIVATE ASSOCIATED PROCESSING AREAS TO ONCE PRESENTED STIMULI

Abstract

The point at which infants can start to create and utilize relational memories from single episodes has yet to be established. Some studies have been able to show that associations can be created as early as three months (e.g. Rovee-Collier et al., 1980), but it typically takes multiple trials for infants to learn these associations. Memory for associations formed after a single episode is typically attributed to after the first year of life however there is eye tracking evidence that 9-month-old infants may demonstrate this type of memory (Nelson & Richmond, 2009). Here we tested the ability for 9-month-old infants to demonstrate relational memory in the brain using the Event-Related Optical Signal (EROS) technique. This optical imaging technique allows us to get cm precision on a ms level timescale to examine whether infants can show the same type of relational activation to the presentation of one item in an episodically learned pair as is present in young adults (Walker et al., 2014). We had infants listen to nonsense sounds by themselves or with a short audio-less movie clip and then re-presented those sounds by themselves. We found that those sounds that were previously paired with movies reactivated visual cortices whereas the sounds that were not paired with movies showed no such activity, demonstrating that infants as young as 9 months old can create and use relational memory. Furthermore we found that infants look at the screen more for those sounds that were paired with movies, demonstrating that relational memory can also manifest in behavior at this age.

Introduction

During the first year of life infants are constantly experiencing new items and events and must learn from their environment to develop critical skills. Despite this being such an important time in a person's life, how infants are learning and what ability they have to create memories is still under debate. This can be attributed in part to the fact that infants are unable to verbally respond and perform many of the memory tasks that are performed with young adults or even children. While infants appear to be learning associations between different items in their environment (e.g. the vocalization "mama" goes with his or her mother), it is unclear the mechanism through which they learned those associations. Recent eye tracking evidence has shown that infants as young as 6 months old demonstrate the ability to create associations between different items in as little as one trial (Cai et al., 2015; Chong et al., 2015; J. Richmond & Nelson, 2009; J. L. Richmond & Power, 2014), very similar to that shown in young adults (D. E. Hannula et al., 2007a). Here we tested whether infants (aged 9 months) also demonstrate a similar pattern of brain activity to young adults while being tested on these associations, namely reactivation of cortical processors, demonstrating evidence of relational memory in the brain.

One of the hallmarks of the human memory system is its ability to create rich and flexible associations between items after only one experience, an ability called relational memory. Broadly defined, relational memory is the ability to flexibly bind two or more otherwise unassociated items together in memory (N. J. Cohen & Eichenbaum, 1993; Eichenbaum, 2000; Eichenbaum & Cohen, 2001). This ability can bind together items in as little as one episode and is what allows the ability to remember single events from one's life. Whether or not infants as young as 9 months old are capable of creating these relations is not entirely clear. Some theories point to the phenomena of "infantile amnesia", or the inability for older children and adults to

remember episodes from infancy, as evidence that children cannot create episodic memories until around 3-5 years old (Dudycha & Dudycha, 1941; Schacter & Moscovitch, 1984). And indeed, other studies looking at the use of relational memory with transitive inference have shown that children younger than 4 years old cannot seem to create the types of associations between pairs of items to allow higher level inference between pairs of items (i.e. that A > C if they learn that A >B and B > C) (Pears & Bryant, 1990). However, more recent studies have demonstrated that infants as young as 18 months old can learn pairs of actions with a cue (Herbert & Hayne, 2000). Furthermore these infants can remember up to 4 weeks later the pair of actions if given the verbal cue. Hayne et al. (2000) found that 12 months old may have the ability to create at least rudimentary relational memories in that 12 month old infants can create associations between pairs of actions and demonstrate those actions across different contexts, demonstrating contextual flexibility (a hallmark of relational memory). However, in that same study Hayne et al. (2000) found that infants as old as 10 months cannot show the same contextual flexibility.

Perhaps the best evidence that infants possess the ability to create relations between items comes from Jenny Richmond and colleagues using eye tracking. One of the benefits of using eye tracking is that it can be an implicit measure of memory, not requiring any sort of response, which is ideal for populations such as infants who cannot respond (D. E. Hannula et al., 2010). Using an eye tracking task first developed in our lab (D. E. Hannula et al., 2007a), J. Richmond and Nelson (2009) had 9-month-old infants lean pairs of faces and scenes and then tested them on those associations by re-presenting the scene along with three previously studied faces and measured which one of the faces the infant looked to most. If one of the three faces presented at test matched the face that was originally viewed with that scene, infants looked disproportionally

at the matching face as compared to the others. This same effect has since been replicated in a different population of 9-month-olds (Cai et al., 2015) and has even been shown in 6-month-old infants (Chong et al., 2015; J. L. Richmond & Power, 2014), strongly suggesting that infants possess relational memory ability.

There is also good reason to suspect that 9 month olds possess relational memory ability based on the development of brain areas that are critical to relational memory, specifically the hippocampus. The hippocampus is a structure in the medial temporal lobe that has been shown to be necessary for the creation and utilization of relational memories (N. J. Cohen & Eichenbaum, 1993; N. J. Cohen et al., 1999; Eichenbaum & Cohen, 2001; D. E. Hannula et al., 2007a; D. E. Hannula et al., 2006; Konkel et al., 2008; Warren et al., 2012; Watson et al., 2013). Although the hippocampus does not grow as quickly as the rest of the cortex during the first year of life (Gilmore et al., 2012), it is still an area that shows rapid development in the first year of life with some estimates putting the size of the hippocampus at around 50% of the size it will be in adulthood at around 9-10 months (Utsunomiya et al., 1999). This points to the possibility that infants as young as 9 months may possess the physiological capability to create relational memories.

If infants have a relatively developed hippocampus, especially in comparison to other parts of their brain, and they show eye movement effects suggesting the possibility for relational memory, why do some experiments fail to show relational memory in infants younger than 12 months? One possibility is that younger infants may be able to create and utilize relational memories, but they cannot express them in these experiments. Many of the experiments that test some sort of associative or relational memory require infants to perform some sort of action (e.g. Hayne et al., 2000) whereas the experiments that provides evidence for relational memory only

requires infants to look at the associated item (Cai et al., 2015; Chong et al., 2015; J. Richmond & Nelson, 2009; J. L. Richmond & Power, 2014). So to test whether or not 9 month-old infants possess the ability to create relational memories we also wanted to look at a phenomena that could identify the use of relational memories without requiring an explicit response. This phenomena is relational reactivation.

Reactivation takes advantage of the knowledge that different areas of the brain process different types of stimuli when a person first experiences that stimuli. Then when a person goes to remember an item, those same cortical areas that were active during initial processing come back online (or reactivated) (Johnson et al., 2009; Norman & O'Reilly, 2003; O'Craven & Kanwisher, 2000). Furthermore, we and others have found that the presentation of an item will reactivate the relationally bound item that was studied with it, even though the relationally bound item nor any item of its type was present on the screen (Schlichting et al., 2014; Walker et al., 2014; Zeithamova et al., 2012). The important aspect of this type of paradigm is that the participant was not required to respond to the presentation of the item, indicating that this brain response can be elicited without requiring any overt behavioral action.

In this study we had infants look at movie clips and listen to sounds with half of the movies and sounds being presented together and half of the movies and sounds being presented alone. We then re-presented the items with one notable exception: if a movie was previously paired with a sound, then only that sound was re-presented. This allowed us to test if these infants can create relational memories. If 9 month-old infants are able to create and utilize relational memories as the eye tracking literature has shown, then the presentation of the sound that was previously paired with the movie should reactivate the same cortical processors that were active when the infant watches movie clips. Indeed, we found that activity in the

extrastriate visual processors came back online to the presentation of the sound even though no visual stimuli were being presented, demonstrating relational reactivation and that infants as young as 9 months old can create relational memories.

Materials and Methods

Participants

Twenty-one 9-10 month-old infants were recruited for this study for a payment of $15 an hour. Of the 21 infants that were recruited, 5 were excluded for failing to watch enough of the video clips. The final sample consisted of 16 infants (8 female; mean age = 9.58 months; SD = .30). Infants were selected to have been born no more than 2 weeks prior to due date and have had no major health problems and no known hearing or vision difficulties. Infants who have viewed Baby Einstein videos before were also excluded to keep all stimuli novel to the infant. Informed consent was obtained from the caregivers of each of the infants and all procedures were approved by the University of Illinois Institutional Review Board.

Stimuli

Stimuli consisted of 60 movie clips and 60 audio sounds. The movie clips were 3 second long movies taken from Baby Einstein videos. The video clips consisted of moving inanimate objects or outdoor scenes but no human faces were shown. The audio clips were 250 ms audio clips played 4 times to create a 1000ms sound. The audio clips were taken from Monica Fabiani, Kazmerski, Cycowicz, and Friedman (1996) and from the internet and were selected to be only nonsense sounds that should have been novel to the infant.

Procedures

Following informed consent, measurements of the infants head were taken while the mother filled out demographic forms. The infant was then sat in his/her mother's lap approx.

100 cm from a computer monitor and was fit with an EROS recording helmet (see below). The infant was then shown as much of three study/test blocks as the infant would allow.

The study/test blocks consisted of 30 trials of study and 30 trials re-presentation of those or some of those items that we called "test." All trials were preceded by a 1000ms fixation cross. There were three different study trials: movie only (MO), sound only (SO), and movie and sound (MS). The MO condition consisted of a 3000 ms movie clip being played on the computer screen without sound and the SO condition consisted of a black screen being presented for 3000 ms and a 1000 ms sound being played 1000 ms after the black screen appeared. The MS condition consisted of a 3000ms presentation of a movie and the presentation of a 1000 ms sound 1000 ms after the start of the movie clip. The delay for the sound was introduced so that, there would be a chance either before or after the presentation of the sounds to see the movie by itself to avoid the possibility of unitization between the movie and sound.

Test trials consisted of a re-presentation of the stimuli from the study trials with one exception: for the MS test trials only the sound was played and while the screen remained black. The order of the study trials was counterbalanced such that every possible ordering of MO, SO, and MS trials was present during the study of each block. The lag between each study trial and its corresponding test trial was fixed to 2 (see Figure 4.1) as was done by Richmond and colleagues (Cai et al., 2015; Chong et al., 2015; J. Richmond & Nelson, 2009; J. L. Richmond & Power, 2014). This made it so the ordering of the test was always the same as the ordering of the study of each block. Additionally movies and sounds were counterbalanced so that each item was presented alone or with an item of the opposite category across participants to avoid the possibility that some movie clips may combine better with audio clips and vice versa.

Video Recording

In order to ensure that infants were watching the movies during study so they could reactivate them at test, we recorded the infants looking behavior using a Logitech® c920 webcam set to record at 60 frames per second at a resolution of 640 x 480 pixels. The camera was situated immediately in front of the screen but slightly below it so as not to block any part of the screen. Two naïve raters viewed the videos and rated for every frame whether or not the infant was looking at the screen. If the two raters disagreed a third rater would make the decision. Only those MO or MS trials in which infants were looking at the screen a minimum of 1 s were counted for the analyses.

Optical Recording

Optical data were recorded using three synchronized ISS frequency domain oxymeters (Imagent®; ISS, Inc., Champaign, IL). The light sources were laser diodes emitting light at the wavelength of 830 nm (max amplitude: 10 mW, mean amplitude after multiplexing: 1 mW) modulated at 110 MHz. Optic fibers were used to channel each light to the surface of the scalp. The detectors were fiber optic bundles (diameter = 3 mm) connected to photomultiplier tubes (PMTs). The PMTs were fed with a current modulated at 110.0625 kHz, generating a heterodyning frequency of 6.25 kHz. The output current from the PMTs was digitized at 50 kHz, affording 8 points per heterodyning cycle. A time-multiplexing approach was used to record from sixteen sources for each detector. In this approach, each source was switched on for 1.6 ms, and off for 24 ms. This allowed to record for a total of 10 heterodyning cycles (80 points) for each multiplexing time unit. However, to avoid cross-talk, the first two cycles were discarded, and the remaining 64 points were subjected to a fast Fourier transform for computation of DC (average) intensity, AC (amplitude), and relative phase delay (in degrees and later converted to picoseconds). Only phase delay data are reported here.

Source and detector fibers were mounted on a modified motorcycle helmet. The area covered by our montage covers the entirety of the top of the head. The coverage of the montage can be seen in Figure 4.3, represented by the darker grey shading on the brain. Our montage consisted of 16 detectors and 44 sources. Source-detector distances ranged between 15 and 90 mm. To avoid cross talk, the sources were arranged such that during any given time division of the multiplexing cycle only one source was within 6 cm of any given detector. This allowed us to record from 384 channels (pairings of source and detector) at 44.6429 Hz.

To characterize the positioning on the helmet, pictures were taken of the infant with the helmet on and the locations of the sources and detectors were digitized with a Polhemus "3Space" ® (Colchester, VT) 3D digitizer using a 3D printed reference head of a 9 month old and co-registered with a volumetric T1-weighted MR image for that 9 month-old. The co-registered data were then Talairach-transformed to permit registration across subjects. The phase data were corrected off-line for phase wrapping, pulse artifacts were removed (Gabriele Gratton & Corballis, 1995), and the data were low-pass filtered to 10 Hz (Maclin et al., 2003). Channels with standard deviations of the phase greater than 150 ps were excluded from further analysis (for further details of these analytic steps, see (Gabriele Gratton & Fabiani, 2007).

Optical Statistical Analyses

The phase data were divided into epochs around stimulus events of interest with 179 ms pre-stimulus baseline and 3002 ms post-stimulus recording for the study phase. The time locking event of interest was the onset of the sound for SO trials and the first time the infants start to look at the screen for MO and MS trails.

In-house software "OPT-3D" (Gabriele Gratton, 2000) was used to reconstruct the optical path for each channel spatially , combine channels whose mean diffusion paths intersected for a

given brain volume (voxel) and to compute group-level statistics. The resel size of the cortical projections were determined by the independence of the error terms at various voxel distances computed by using the methods described by Feng, Zeng, and Chance (1995). An 8 mm Gaussian filter (based on a 2 cm kernel) was used to spatially filter the data. The group-level statistics were then converted to Z-scores and compared to critical Z scores based on the number of resels within an ROI and the subsequent correction for multiple comparisons. These Z scores are then orthogonally projected onto images of the sagittal surfaces of the brain in Talairach space (Talairach & Tournoux, 1988).

Due to its high spatial and temporal resolution (which may inflate the number of comparisons), statistical analysis of EROS during both the study and test phase was limited to a priori ROIs. We focused on the extrastraite cortex as well as the ventral visual stream as these are the areas in which we would expect to see reactivation of visual areas to the audio cue.

Results

Viewing Behavior

In order to ensure that infants were viewing the movie clips we examined viewing behavior using a video recording of the infants' faces. The infants looked at the screen for a minimum of 1 s for 74.1% of the movie clips previously paired with sound (SD = .16) and 69.89% of the movie clips shown alone (SD = .13). Overall the infants contributed and average of 17.4 (SD = 5.1) number of trials to the movies previously paired with sound and 16.5 (SD = 5.8) number of trials to the movies that were not pared with sound. We also looked at viewing behavior for the presentation of the sound at test in the MS condition to see if there was an expectancy effect for the video to appear on the screen when the associated sound was played. As can be seen in Figure 4.2, we found that there is an expectancy viewing effect such that

infants will look toward the scenes for sounds at test that were previously paired with a movie for a higher proportion of time (MS condition; M = .67; SD = .23) than when a sound that was never paired with a movie is re-presented (SO condition; M = .48; SD = .13), $t(15) = 2.59$, p = .021. This indicates that behaviorally infants are expressing the ability to create and use relational memories as they show a greater expectancy to see a movie on the screen to the presentation of the related sound as compared to an equally familiar sound but ones that were not presented with a movie.

Analysis of EROS Results

Activity at Study. In order to establish that reactivation of visual processing areas to the associated sound took place, we first had to establish what activity took place when the infants originally viewed a movie. To do this we looked at activity for the MO condition as compared to baseline in the visual cortices in the infants. As can be seen in Figure 4.3a, we found robust activity in the extrastriate cortex during the first 1000 ms of viewing, bilaterally (peak in left extrastriate: $Z = 3.484$, $Z_{crit} = 2.87$; peak in right extrastriate: : $Z = 3.155$, $Z_{crit} = 2.98$). We also found activity along the ventral visual pathway in the left ventral temporal cortex from 268 ms to 313 ms ($Z = 2.938$, $Z_{crit} = 2.37$) and at 851 ms ($Z = 3.201$, $Z_{crit} = 2.44$) and in the right lateral occipital cortex at 492 ms ($Z = 3.248$, $Z_{crit} = 2.83$) and marginally significant activity in the right ventral temporal cortex at 447 ms ($Z = 2.402$, $Z_{crit} = 2.55$).

Activity at Test. To test whether or not 9 month-old infants can demonstrate the capability for relational memory, we looked at activity in the visual cortices to the second presentation of the associated sound in the MS condition as compared to the second presentation of the sound in the SO condition. If 9 month-old infants can create and utilize relational memories, then they should reactivate some of the same cortical processors that were active

when initially viewing the movie to the relationally-bound sound, even though nothing is being presented visually, much like what adults have shown (Walker et al., 2014). Consistent with our hypothesis, we found significant activity in left extrastriate cortex to the presentation of a sound previously presented with a movie (MS) but not to the equally familiar SO condition. This activity starts at 223 ms (Z = 3.836, Z_{crit} = 3.12) and is present again at 313 ms (Z = 4.220, Z_{crit} = 3.19) and 671 ms (Z = 3.002, Z_{crit} = 2.84). We also found marginally significant activity in the right extrastriate cortex as well (Z = 2.817, Z_{crit} = 2.90). Along the ventral visual pathway we also found activity in the left lateral occipital cortex at 134 ms (Z = 3.613, Z_{crit} = 3.01), at 223 ms (Z = 2.773, Z_{crit} = 2.75) and at 671 ms (Z = 4.134, Z_{crit} = 2.73). We did not find any significant activity at test along the right ventral visual pathway.

In order to establish whether or not the observed activations during test were, indeed, reactivations, we did a conjunction analysis with the observed reactivations and the activations during study. As the observed activity during study was longer than those observed during test, we used a time window for study activations of the same length as the test phenomena found, centered around the peak activation found for a study activation (268 ms in the left extrastriate cortex and 403 ms in the right extrastriate cortex). We found that the test activity at 671 ms in the left extrastriate cortex and the marginally significant activity in the right extrastriate cortex reactivated the same areas of the extrastriate cortex that were originally activated to the presentation of the movie clips, demonstrating that the infants are showing relational reactivation of visual processors to associated sounds (see Figure 4.4). The earlier activations in the left extrastriate cortex (223 ms and 313 ms) did not reactivate the same areas that were present during study.

Discussion

In one of the first experiments to ever test relational memory ability in infants by looking at brain activity, we were able to find that infants as young as 9 months old are able to create and utilize relational memories. We were able to find that infants show relational reactivation of visual processing regions (the extrastriate cortex) to the presence of a relationally-bound sound even though nothing was ever being presented on the screen. Importantly, this was achieved after only one presentation of the sound-movie clip pairing, indicating relational memory. Furthermore, this reactivation manifested in behavior with infants showing expectancy behavior by looking at the screen more when a sound that was previously paired with a movie was played as compared to a sound that was also previously played, but not with a movie, in line with what previous studies using eye tracking found (Cai et al., 2015; Chong et al., 2015; J. Richmond & Nelson, 2009; J. L. Richmond & Power, 2014). These data provide strong evidence that infants do, in fact, possess the ability to create and use relational memories.

In order to establish that reactivation took place, we first had to see what areas of the brain was activated to the presentation of a movie clip. We found bilateral activity in the extrastriate cortex throughout the first second of viewing a movie. Then we looked at activity elicited by sounds that were previously paired with movies and we found that the extrastriate cortex is activated again despite no video being presented. This activity came online at 223 ms, 313 ms, and 617 ms, all in the left extrastriate cortex with only a marginally significant activation in the right extrastriate cortex at 940 ms. The activations at 617 ms in the left extrastriate cortex and at 940 ms in the right extrastriate cortex overlapped demonstrating reactivation of the same cortex that was active for movies to the presentation of the relationally bound sound. This relational reactivation is similar to that observed in both younger (Schlichting et al., 2014; Walker et al., 2014; Zeithamova et al., 2012) and older adults (Chapter 2),

demonstrating that infants have the ability to create and utilize at least rudimentary relational memories.

We also found activity during study in both the left and right ventral visual pathway and activity in the left ventral visual pathway for test. We found significant activity in the left ventral temporal cortex and in the right lateral occipital cortex for study and in the left lateral occipital cortex for test. Both the lateral occipital cortex and the ventral temporal cortex have been shown to be active as part of visual processing (Bar & Aminoff, 2003; Denys et al., 2004; Grill-Spector et al., 1999; J. V. Haxby et al., 2001; Ishai et al., 2005; Ishai et al., 2000). Unlike the activity found in the extrastriate cortex that showed increased activity for the entire first second, this activity was only found at select time points during study. Furthermore, there was no overlap between activations found in the ventral visual stream at study and activity found at test. One possible reason for this is the possible difference in development in the infants. As the observed activations are further along the visual processing stream than the extrastriate cortex, the differences in development between the infants may affect timing and location of the higher order processors more than the extrastriate cortex. Another possibility is that the ventral visual stream is situated at the very edge of what optical imaging can measure. As the skull curves more along the more ventral parts of the brain, there is more variability in the EROS signal and so it is harder to find significant effects in the ventral visual pathway than in the extrastriate cortex. Perhaps a study with more infants could overcome the lower signal to noise and find reactivation effects along the ventral visual pathway.

One thing of note in this data, is the pattern of left laterality in terms of the activities found during test. This pattern of left lateralization is also present in our previous studies looking at relational reactivation in young adults (Walker et al., 2014) and in older adults (Chapter 2).

One possibility for the left lateralization is that these reactivations are serving as a prediction of the future. Once the infant hears the associated sound he or she predicts there to be a movie clip on the screen and reactivates the related movie in anticipation. This hypothesis is supported by the expectant viewing behavior and is supported by theories suggesting that prediction for the future is left lateralized (Kutas, Federmeier, & Urbach, 2014).

It is important to state, however, that it is difficult to compare the reactivation pattern of activity to reactivation seen in younger and older adults. As we cannot ask the infants what they experienced, it is difficult to know the specificity of these reactivations nor the quality of the memory. We do know that it informs future behavior through eye movements but studies with adults have shown that there may be a dissociation between eye movement behavior and what a person consciously remembers (D. E. Hannula & Ranganath, 2009; D. E. Hannula et al., 2007a; Ryan et al., 2000). These data only show that infants have the capability to use relational memories, but future studies are needed to understand how their use differs from that of healthy adults or even children.

One possible problem with the study is that we fixed the amount of items between a studied item and its test to a lag of 2. This was originally done to keep in line with the maximum lag to show relational memory effects in the previous eye tracking papers (Cai et al., 2015; Chong et al., 2015; J. Richmond & Nelson, 2009; J. L. Richmond & Power, 2014). One drawback of this design is that it could possibly mean that infants could learn that 3 trials after the presentation of a movie and sound, the sound for that movie would take place and that this learned rule could explain the data. However, any rule learning that took place would only go against our observed effects. If infants did learn this rule, one would expect that infants would learn that the re-presentation of the sound that was originally paired with a movie should not be

accompanied by a movie. This would decrease looking behavior and, if these reactivations are due to predictions, then rule learning would also dampen the reactivation effect. One possible way to dissociate whether or not the observed reactivations are due to retrieving the related movie or just a general activation of visual cortices due to rule learning would be to examine how specific theses reactivations are to the stimulus being retrieved. As our experiment used all movie clips for the items to be reactivated, it was not possible to perform these analyses. Future studies may want to vary the item type or category in order to observe the specificity of the reactivation.

Conclusion

In this study we examined the ability for 9-month-old infants to show reactivation of cortical processors in the cortex to relationally bound items, demonstrating that 9-month-old infants have the ability to create and utilize relational memories. We found that infants do reactivate the left extrastriate cortex and marginally reactivate the right extrastriate cortex to sounds that were previously paired with moves but not sounds that were previously played by themselves. This pattern of activation was found after the infants studied each movie-sound pairing only once. These activations, which are in cortex that is well established to be part of the visual processing stream, in the absence of any visual stimuli demonstrate that infants can create and use relational bindings between items. This is in line with previous research showing that infants show relational eye movements upon being tested with pairs of items (Cai et al., 2015; Chong et al., 2015; J. Richmond & Nelson, 2009; J. L. Richmond & Power, 2014) and extends that research to show that infants also demonstrate relational memory in terms of patterns of brain activity. This could mean that the failure to demonstrate at least rudimentary relational memory in 9-month-old infants or older in previous studies could be due to the infants' inability

to perform a given task, as both eye tracking and the optical imaging task her do not require any explicit actions.

Chapter 4 Figures

Figure 4.1. Schematic representation of the experimental paradigm, illustrating one of the sequences of stimuli during study and test. The test trail always followed the corresponding study trial by three trials but all orders of MS, SO, and MO were equally presented to the infant.

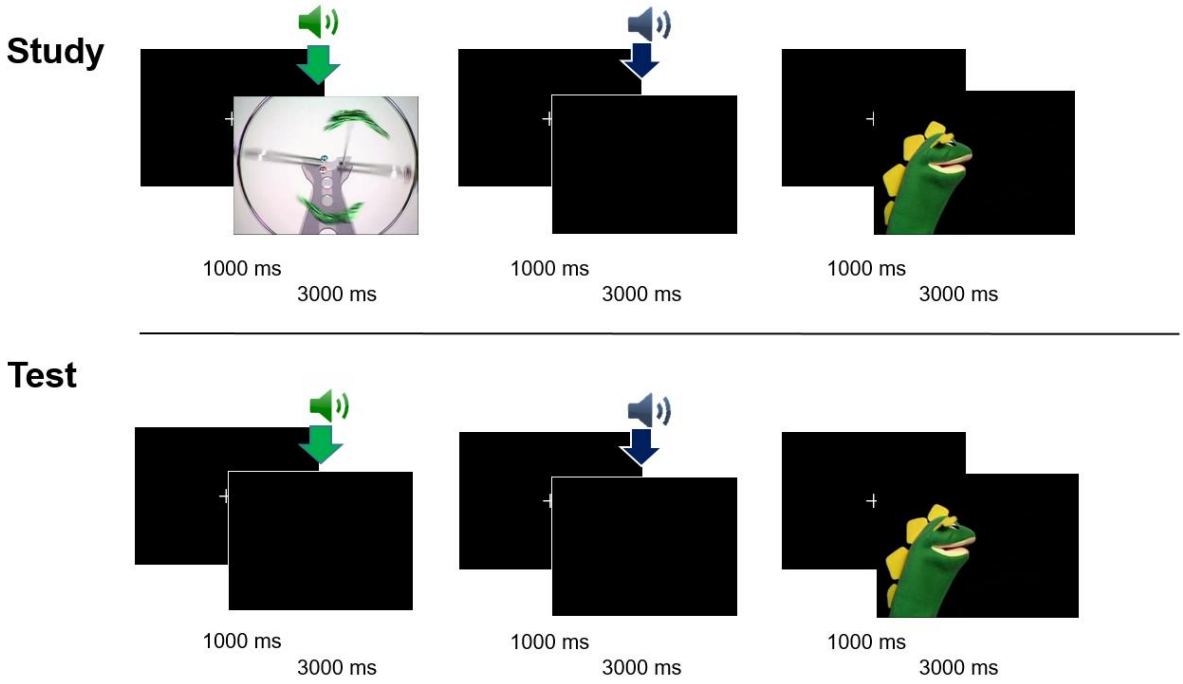


Figure 4.2. Proportion of looking at the screen for the 2 seconds during and after the presentation of the sound that was previously played with a movie and the presentation of a sound that was not previously played with a movie. Infants look more at the screen for sounds that were previously played with a movie, demonstrating an expectancy effect.

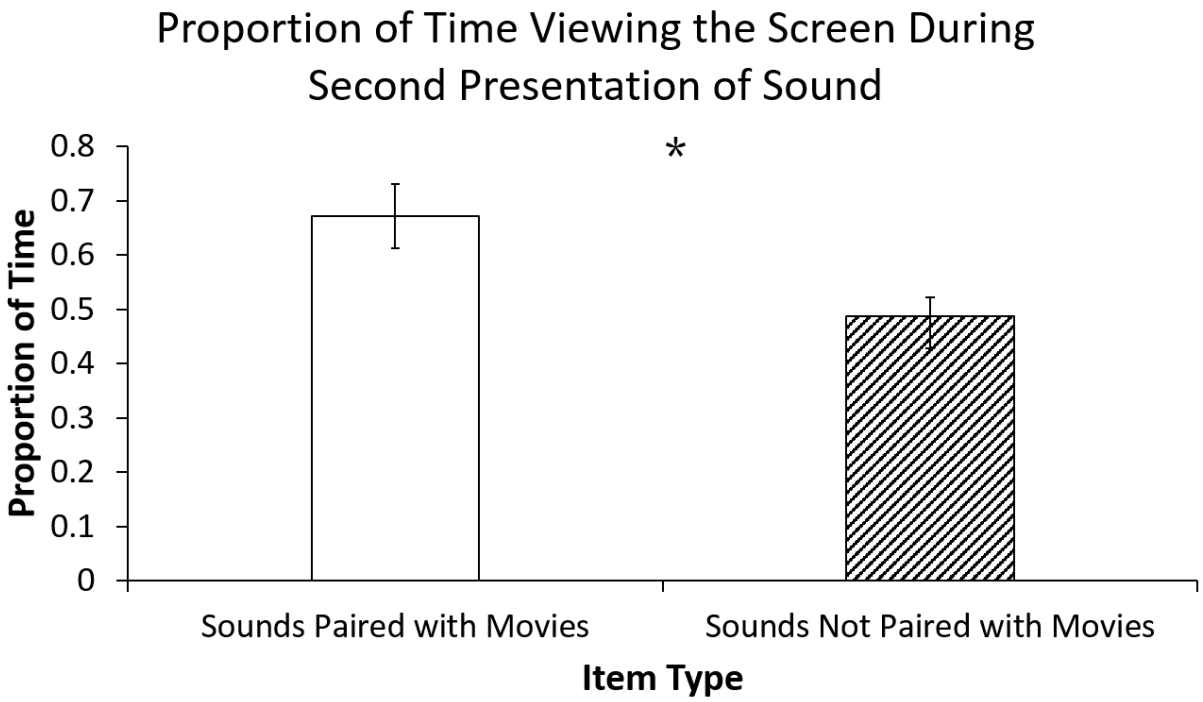


Figure 4.3. Spatial maps based on group level *Z*-statistics of the EROS data projected on sagittal brain surfaces. Dark gray shading represents the brain area sampled by the recording montage. The light green rectangle indicates the extrastriate ROI. (a) activity during the initial presentation of movies as compared to baseline in the left extrastriate cortex during the first 1000 ms. (b) activity time locked to the presentation of a sound that was previously paired with a movie as compared to a sound that was previously played alone in the left extrastriate cortex at 223 ms, 313 ms, and 671 ms and in the right extrastriate cortex at 940 ms.

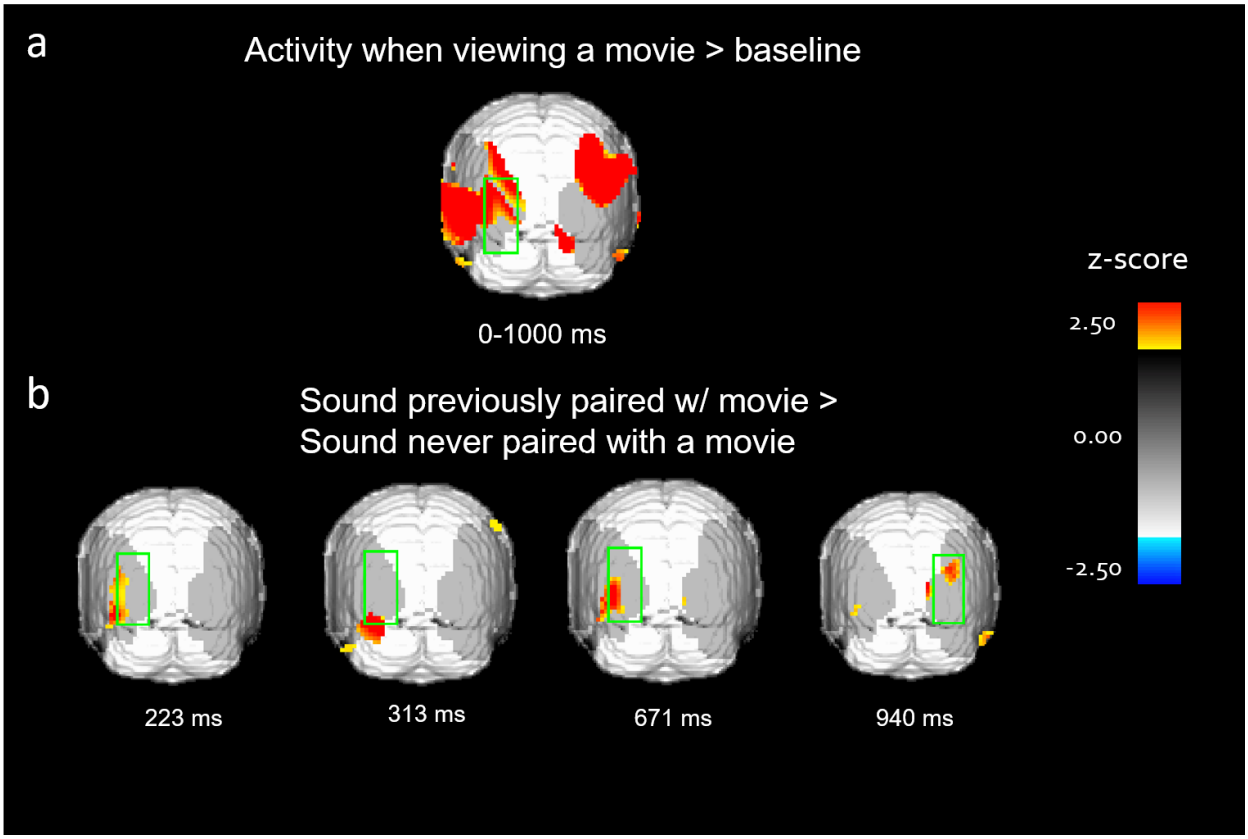
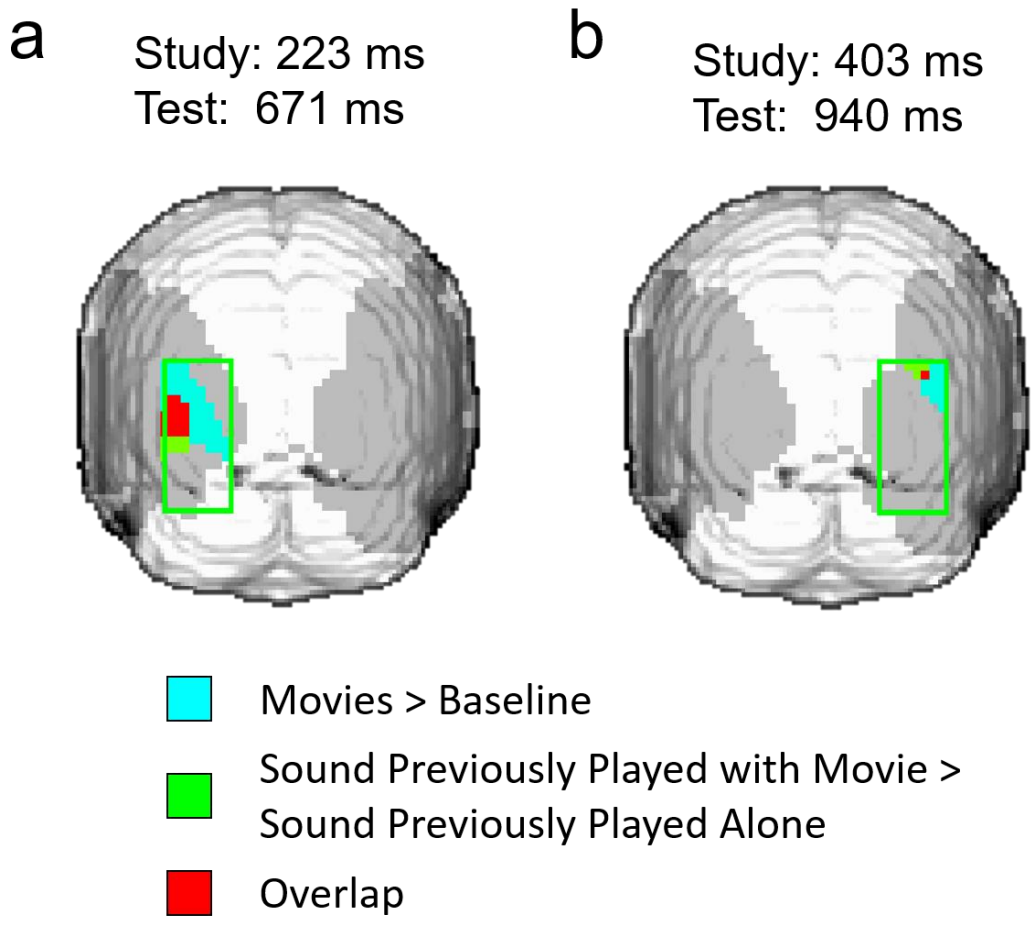


Figure 4.4. Spatial map of the conjunction analysis projected onto the back of the head at a threshold of $p < .04$ for the conjunction ($p < .2$ for each condition separately). (a) Blue represents the activity for movies > baseline at (a) 223 ms during study and (b) 403 ms during study, green represents the activity for sounds previously paired with movies > sounds previously played alone at (a) 671 ms during test and (b) 940 ms during test, and red represents the overlap between the activations at study and at test.



CHAPTER 5

GENERAL CONCLUSIONS AND FUTURE DIRECTIONS

The set of experiments presented here sought to examine the association between the hippocampus and cortical reactivation. It has been known for quite some time that the hippocampus is involved in the creation and utilization of episodic memories (Scoville & Milner, 1957). Similarly, it has long been theorized that memories are stored out in the cortex (Hayek, 1952; Lashley, 1950). Despite these decades-long lines of research, the interactions between the hippocampus and cortex during memory retrieval are not well characterized.

The prevailing theories would suggest that the hippocampus communicates with the cortex, bringing online the memory representations stored in the cortex so they can be utilized (N. J. Cohen & Eichenbaum, 1993; Davachi & Danker, 2013; Eichenbaum, 2000; Eichenbaum & Cohen, 2001; Marr, 1971; McClelland et al., 1995; Moscovitch et al., 2005; Norman & O'Reilly, 2003). It is thought that the observed reactivation of these cortical processors during memory retrieval represents or is the very least indicative of retrieval of information from that store by the hippocampus (Davachi & Danker, 2013; Marr, 1971; McClelland et al., 1995; Moscovitch et al., 2005; Norman & O'Reilly, 2003; Rugg et al., 2008; Rugg & Vilberg, 2013). The data reported in Chapter 2 demonstrate this link between cortical reactivation and the hippocampus. Those individuals who had higher hippocampal volumes showed greater reactivation of related cortical processors. Furthermore, diffusion measures of the hippocampal also show this correlation with reactivation. These data provide the oft theorized but missing link between the hippocampus and the reactivation of cortical processors, at least in terms of relational reactivation.

How the hippocampus communicates with the cortex to achieve this memory retrieval is also not entirely known. One of the main theories is that the hippocampus and cortex synchronize their neural firing patterns in order to facilitate the retrieval of information (Chrobak

& Buzsáki, 1994; Fuentemilla et al., 2014; Sirota et al., 2008). The main candidate for the frequency of this synchrony is the theta band (4-8 Hz) as the hippocampus has a natural theta rhythm (Otto et al., 1991; Ranck, 1973) and multiple studies have found a link between theta power and recognition performance (Cummins & Finnigan, 2007; Düzel et al., 2003; Gruber et al., 2008; Guderian & Düzel, 2005; Osipova et al., 2006). The data presented in Chapter 3 demonstrates that oscillatory power is related to reactivation in the cortex but only in a band (8-10 Hz) slightly higher than traditional theta and only in younger adults. Across all participants, the power in the theta and high theta (8-10 Hz) bands in the to-be-reactivated region is also correlated with subsequent memory performance. These findings provide evidence of oscillatory activity's link, especially in the high theta band, to memory retrieval and reactivation in young adults, supporting the theory that oscillatory power represents memory related activity and a possible route by which the hippocampus communicates with the cortex.

In older adults, there is less theta power overall and there are no time periods during which the oscillatory power within the to-be-reactivated region correlate with subsequent reactivation. Furthermore, there are no time periods in which high theta power in the reactivated region is found to be significant in older adults. The lack of any statistically significant increased high theta power could explain why there is no correlation between oscillatory activity and reactivation in older adults as that was the band that showed the correlation with reactivation in younger adults. However, despite this lack of oscillatory activity, older adults still show reactivation of the related sensory cortex. This would suggest that while increases in theta and high theta oscillatory activity within a task relevant region may be correlated with subsequent performance, significant increases in oscillatory power in these bands are not needed to elicit reactivation. It would seem that when there is a sufficient increase in oscillatory power in the

high theta band, that this increase will be correlated with reactivation, but when oscillatory power does not show an increase, then reactivation can still take place.

Examining the results across both Chapter 2 and Chapter 3, there does not seem to be any evidence of an association between the hippocampus and these oscillatory activities. None of the observed increases in oscillatory power are correlated with hippocampal volume in neither the young adults nor the older adults. As this theta activity is supposedly supposed to reflect communication between the hippocampus and the cortex. However, in looking at the associations between hippocampal volume and reactivation, it is not surprising that there were no significant correlations between oscillatory power and the hippocampus. Young adults showed no correlation between the hippocampus and reactivation, yet found a correlation between oscillatory power and reactivation. Conversely, reactivation activity in older adults was significantly correlated with hippocampal volume but not with oscillatory activity. It may be that hippocampal volume is not the correct choice for finding the association between oscillatory activity, reactivation, and the hippocampus. Older adults have greater variability in hippocampal measures such as volume due to individual differences in atrophy of the structure (Charlton et al., 2006; N. Raz et al., 2005; Walhovd et al., 2005), yet older adults also show a lower amount of theta power over the whole head as compared to young adults (Cummins & Finnigan, 2007) and the data from Chapter 3 show that this decrease is also in task related areas (i.e the area that shows relational reactivation). Younger adults have less variability in hippocampal measures yet have greater theta power over the head and in the subsequently reactivated region. So there is not an ideal group that has high variability in hippocampal volume without a reduction in overall theta power. Future studies could examine the association between the hippocampus and

oscillatory and reactivation by choosing another measure of the hippocampus that are more variable in young adults.

Another goal of these experiments is to look at reactivation and memory retrieval across the lifespan. The data from Chapter 4 show that infants demonstrate a pattern of relational reactivation very similar to the younger adults from Walker et al. (2014) and Chapter 3 and the older adults from Chapters 2 and 3. This demonstrates that this type of memory related reactivation takes place across the lifespan and starts prior to the cessation of infantile amnesia. While there is no data for the hippocampal sizes of these infants when they performed this task, it is estimated that the hippocampus of a 9-month-old infant can be upwards of 50% of the size of what it will be when the person is an adult (Utsunomiya et al., 1999). While a structure being 50% of its adult size shows a great deal of development for a 9-month-old, it is still only 50% of the volume of an adult. The presence of reactivation activity this early in life indicates that relational reactivation of a missing item from a pair may be one of the more basic memory retrieval processes that take place.

Furthermore, the presence of the reactivation in infants speaks to the automaticity of this memory reactivation and retrieval process. In both the young and the older adults, reactivation was found to by presenting relationally-bound scenes immediately prior to a test display. One could argue that reactivation of the related face processing areas was due to explicit memory retrieval in preparation for the upcoming test display. However, these infants did not have to perform any task, the stimuli were simply presented in front of them. Merely listening to the relationally bound sound elicited reactivation in visual processing regions to the presence of an associated sound. This idea of memory reactivation and retrieval being automatic is in line with theories suggesting the role for memory in prediction and that the brain is constantly retrieving

information to form predictions based on the incoming set of information (Bar, 2007, 2009; Randy L Buckner, 2010). In this case the infants heard the sound that was previously paired with a movie clip and retrieved the representation of the movie clip, this created the expectancy that the movie clip would be playing alongside the sound as it had been when the infant first saw the pairing. And infants do look at the screen more for sounds that were previously paired with movie clips versus those sounds that were previously played alone, demonstrating this expectancy effect.

One of the lingering questions left regarding reactivation and retrieval of information from the cortex, is what do these reactivations of sensory cortex indicate? While answering these questions is beyond the scope of this dissertation, some of the findings do speak to these questions and lead to possible future directions. The correlations found in these studies between magnitude of reactivation and subsequent memory accuracy make it clear that relational reactivation serves memory in some way. Some have argued that these reactivations indicate that memory retrieval has taken place and that this reactivation demonstrates that information becoming active (Johnson & Rugg, 2007; Rugg et al., 2008; Rugg & Vilberg, 2013). In order to remember or retrieve information from the cortex, those cortical stores must be brought online and that this reactivation is the brining online of these stores.

However, the timing of the found theta and high theta oscillations in Chapter 3 may bring into doubt that the timing of the reactivation is when the information is retrieved. One of the theories of how theta oscillations allow for communication between different areas of the brain is that the theta oscillations work as a timing mechanism, entraining the activity for faster oscillations in the gamma band that then use the theta oscillations as a carrier frequency to relay information to different parts of the cortex (Buzsaki & Draguhn, 2004; Chrobak & Buzsáki,

1994; Duzel, Penny, & Burgess, 2010; Nyhus & Curran, 2010; Osipova et al., 2006). The data from Chapter 3, though, indicate that the increase in oscillatory power in both the theta and high theta bands always preceded but was never found to overlap with either of the reactivations that are correlated with subsequent memory. If the reactivation represents when information from that memory store is coming online and these increases in oscillatory power represent communication between the hippocampus and the cortex, then there should be some overlap between these two phenomena to allow for the hippocampus to reactivate and retrieve the representations. One possible explanation for this temporal discrepancy is that communication is going on between the hippocampus and the cortex during this increase in theta or high theta power to select the representation to reactivate, setting in motion the reactivation of that information without needing to communicate with the area during the actual time of reactivation.

Another possible explanation of the temporal discrepancy between the increase in oscillatory power and the reactivation is that information is being retrieved using these theta and high theta oscillations and the reactivation is just the culmination of that memory retrieval. This is supported by the data in that the increase in theta power was positively correlated with subsequent memory accuracy but not associated with any found reactivation. This means that there may be some process taking place during the increases in theta power, when the hippocampus is presumably communicating with the cortex, that facilitates later recognition of associated pairs of items. This communication may represent a kind of retrieval separate from the observed reactivation. Future studies may want to use techniques with high temporal resolution to measure behavior such as eye tracking in addition to the high resolution techniques used to measure oscillatory activity in the brain to possibly track what information is available

and when to see how memory related responses line up temporally with patterns of increased oscillatory power and reactivation.

One of the main shortcomings of this set of experiments is the lack of measurement of activity from the hippocampus. All three of these experiments were done using the event related optical signal (EROS) and while this allowed for recordings with higher temporal and higher spatial resolution of the cortex than functional magnetic resonance imaging (fMRI) or electroencephalography (EEG), respectively, it also means that recording hippocampal activity was not possible. This meant that the only way to relate the observed phenomena to the hippocampus within these experiments was to look at structural measurements of the hippocampus. While this makes sense for populations such as older adults where differences in structural measures can serve as a proxy for phenomena like atrophy (Charlton et al., 2006; N. Raz et al., 2005; Walhovd et al., 2005), in other populations such as young adults, it is not as clear what differences in hippocampal volumes mean. This may be one of the reasons why there was a failure to see any correlation between hippocampal volumes and both the increases in oscillatory power and reactivation. Future studies could either measure hippocampal activity in addition to cortical oscillations using techniques such as magnetoencephalography (MEG) or demonstrate the role of the hippocampus by manipulating its activity through stimulation of the networks that include the hippocampus.

Conclusion

Memory retrieval is a multifaceted process that involves the coordination of multiple areas of the brain including the hippocampus and the sensory memory stores. The current series of studies examined the association between cortical reactivation of relational information and the hippocampus, looking at connections between reactivation and both the structure of the

hippocampus as well as the possible communication between the sensory cortex and the hippocampus as measured by oscillatory activity in the theta band. The first study showed that the magnitude of relational reactivation was associated with larger hippocampi. The second study showed that young adults show a correlation between oscillatory activity in the high theta band (8-10 Hz) in the face processing region of interest and reactivation of that same area. Conversely older adults showed no such correlation, showing differential age-related associations with oscillatory activity. Additionally, these studies looked at reactivation across the lifespan by looking at reactivation in infants, young adults, and older adults. The third study showed that 9-month-old infants also show this relational reactivation effect, demonstrating that relational reactivation is present as early as 9 months and is present across the lifespan. Taken together, these three studies demonstrate that relational reactivation represents retrieval of relational information from the cortex in the service of memory. This retrieval is associated with the hippocampus, possibly through oscillatory activity in young adults, and is present for nearly the entire lifespan (participants here ranged from 9 months old to 88 years old). Further research will be needed to better describe the relationship between reactivation and oscillatory activity as well as what each represents in terms of memory retrieval from the cortex.

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