INDIVIDUAL DIFFERENCES IN MEMORY FUNCTIONS AND THEIR RELATION TO HIPPOCAMPAL CONNECTIVITY

by

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DISSERTATION ABSTRACT

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The hippocampus plays an important role in many aspects of learning and memory. It is most known for its role in episodic memory and spatial navigation, though it has also been shown to contribute to other processes like prioritizing memory for motivationally salient information and connecting related memories to form generalized knowledge. How can a single structure support different types of learning? As the hippocampus does not work in isolation to support memory, one proposal is that it may form connections with different brain regions to support different functions of memory. Recent work has shown how stable, trait-like connections can be leveraged to predict individual behavior. Thus, the present dissertation aims to explore 1) how different hippocampal connections relate to different memory processes, and 2) whether intrinsic hippocampal connections can be linked to individual memory performance. In three empirical chapters, I demonstrate how distinct hippocampal connections are associated with different functions of memory, including reward motivated learning, generalization and memory specificity. Moreover, I show how anterior and posterior hippocampus form distinct connections that may further support different aspects of memory. Finally, the dissertation demonstrates how stable, trait-like hippocampal connections can be linked to individual behavior. Together, these findings provide insight into the different functions of hippocampal connectivity and the utility

of intrinsic connections in understanding individual memory abilities.

This dissertation includes previously published and unpublished co-authored material.

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CHAPTER I

INTRODUCTION

Memories are traces of our experiences that can be stored and later recalled. They are critical to learning as they provide frameworks for interpreting new experiences and building knowledge structures. The hippocampus was first discovered as a structure critical for encoding memories of our personal experiences or episodes (episodic memory). In a well-known case study, Patient H.M. was unable to form new episodic memories or recall recent ones following complete resection of his medial temporal lobes. Researchers hypothesized the hippocampus and surrounding medial temporal lobe structures were essential to forming and storing new memories (Scovill & Milner, 1957). Additional evidence emerged from neuropsychological and lesion studies that showed similar impairments in learning following hippocampal damage (Filoteo, Todd Maddox, & Davis, 2001; Knowlton & Squire, 1993; McDonald & White, 1993; Packard & McGaugh, 1996). Theories of the hippocampus and its function in memory have since been refined. The hippocampus is thought to bind together features of an episode to form a single memory trace, consolidate the trace into long-term storage and coordinate later retrieval of the memory (Eichenbaum, Otto, & Cohen, 1992; Eichenbaum et al., 2012; Squire, 1992). Though this view of the hippocampus remains predominant, researchers have expanded on its function to include other aspects of learning and memory.

Memory can be influenced by other cognitive processes, such as emotion or motivation. Emotions are well-known to have a strong effect on memory (Kensinger, 2009; Phelps, 2004). Though they generally enhance memories, making them more vivid and easier to recall, they can sometimes have the opposite effect (Bisby et al., 2016; Kensinger, 2009; Phelps, 2004; Tyng et

al., 2017). For example, while negative emotions can improve memory for individual features of an episode, they can impair associations formed between the features, suggesting a direct influence of emotion on hippocampal binding processes (Bisby & Burgess, 2014; Bisby et al., 2016; Mather, 2007). There are multiple mechanisms through which emotion may modulate memory, such as drawing attention to an emotionally arousing stimulus or releasing hormones that can affect brain activity. These processes interact with hippocampal-based learning systems to enhance or impair memory (Anderson & Phelps, 2001; Cahill et al., 1994; Phelps, 2004; Wolf, 2008). Hippocampal-based learning can also interact with the brain's reward system. External rewards, such as money, can improve memory for high-valued over low-valued information (Adcock et al., 2006; Wittmann et al., 2005; Wolosin, Zeithamova, & Preston, 2012). Similar to emotions, rewards may act on memory by directing attention and prioritizing encoding of high-value information. This process is dependent on the brain's dopaminergic system (Anderson, 2013; Knowlton & Castel, 2022). Rewards signal the release of dopamine from the brain's reward system (midbrain and ventral striatum) to the hippocampus. Dopaminergic activity in the hippocampus facilitates encoding and consolidation of a memory into long-term storage (Lisman & Grace, 2005; Lisman, Grace, & Duzel, 2011; Shohamy & Adcock, 2010). Coordination between the hippocampus and reward system may then support adaptive learning by prioritizing memory for motivationally salient events.

While memory allows us to remember single episodes or experiences (memory specificity), it also allows us to form links across related ones (generalization). Generalization is critical to learning as it allows us to form concepts, build upon our existing knowledge, and make new decisions or inferences. The multiple memory systems view argues for a dissociation between the two types of learning, with a hippocampal-based system that supports the rapid

learning of new episodes and a cortical-striatal system that slowly learns regularities across experiences (McClelland, McNaughton, & O'Reilly, 1995; O'Reilly & Rudy, 2001). In line with this view, the hippocampus may only lend itself to generalization by retrieving specific memories. While reactivated, connections between the memories can be drawn to generate novel inferences or make new decisions (Carpenter & Schacter, 2017, 2018; Medin & Schaffer, 1978; Zeithamova, Schlichting, & Preston, 2012). Though this view has largely dominated the field of learning and memory, research is beginning to reveal how the hippocampus, in coordination with the VMPFC, may integrate related memories to build and update complex knowledge structures (Schlichting & Preston, 2016; van Kesteren et al., 2010; Zeithamova, Dominick, & Preston, 2012). At encoding, the hippocampus may be signaled to reactivate related memories, which are then updated to form a conjunctive or integrated representation (Schapiro et al., 2017; Schlichting & Preston, 2015; Zeithamova & Bowman, 2020). Thus, the hippocampus may also contribute to generalization through integrative encoding processes.

As discussed above, several functions can be ascribed to the hippocampus, including rapid encoding of individual experiences, prioritization of motivationally salient stimuli, integrating information across related events to generalize and infer new information. How can a single structure be implicated in these different types of learning? The hippocampus does not typically work in isolation to support memory. For example, the VMPFC is also recruited to reactivate and integrate related memories (Schlichting, Mumford, & Preston, 2015; Zeithamova, Dominick, & Preston, 2012). Reward regions, like the midbrain and striatum, increase activation when encoding high-value compared to low-value information (Adcock et al., 2006; Wittmann et al., 2005). As different brain regions are recruited for different processes, the hippocampus may work in coordination with them to support different types of learning. Thus, the first goal of the

Figure 1.1. Hypotheses for hippocampal contributions to different memory processes. Left Panel: The hippocampus may contribute to different memory processes through interactions with different brain regions. For example, to support specificity the hippocampus may interact with lateral parietal and lateral prefrontal cortex, which are regions known to maintain vivid and discriminable representations. On the other hand, generalization may rely on hippocampal interactions with lateral temporal cortex and VMPFC, which are known to support schematic, conceptual and semantic memory. Right Panel: Specialized functions of the anterior and posterior hippocampus may also explain its role in memory specificity and generalization. Fine-grained representations in the posterior hippocampus may lend themselves to maintaining detailed memory for single episodes, while coarse-grained representations may capture broader relationships between multiple episodes.

current dissertation is to understand how hippocampal interactions with different sets of brain regions contribute to different aspects of memory.

Anterior and posterior portions of the hippocampus have long been thought to serve specialized functions, such as encoding v. retrieval (Kim, 2015; Lepage, Habib, & Tulving, 1998), emotional v. cognitive processing (Fanselow & Dong, 2010), and vestibular v. visual processing (Hüfner et al., 2011). Recent theories suggest there is a representational gradient along the long axis of the hippocampus, with the anterior hippocampus supporting coarse-grained representations and the posterior hippocampus supporting fine-grained representations (Poppenk et al., 2013). Evidence for a representational gradient comes from both animal and human research. In rodents, the size of the receptive fields of place cells in the hippocampus increase from dorsal (posterior) to ventral (anterior) regions, suggesting a broader range of spatial information can be represented in the ventral compared to dorsal hippocampus (Kjelstrup et al., 2008). In humans, the anterior hippocampus similarly carries information on a broader

spatial and temporal scale (Brunec et al., 2018; Collin, Milivojevic, & Doeller, 2015), supports abstract representations of concepts (Bowman, Iwashita, & Zeithamova, 2020; Bowman & Zeithamova, 2018), and helps integrate overlapping experiences (Schlichting et al., 2015). Conversely, the posterior hippocampus separates representations for overlapping events (Schlichting et al., 2015) and carries information on a smaller spatial and temporal scale (Brunec et al., 2018; Collin et al., 2015). Thus, another way the hippocampus may contribute to multiple forms of memory is through a division of labor along its long axis. The present dissertation will further explore how anterior and posterior hippocampal connectivity support

Intrinsic Functional Connectivity

The development of functional MRI (fMRI) has allowed researchers to test the role of hippocampal interactions in memory in a healthy living brain. In addition to the standard task-based fMRI analyses that examine brain activity under different experimental conditions, another valuable tool for understanding how brain regions interact to support cognition is functional connectivity. Functional connectivity is used to measure the level of coordination between spatially distant brain regions over a given time (Friston, 1994). While functional connectivity measures can relate to underlying structural or synaptic connections (Honey et al., 2007; Passingham, Stephan, & Kötter, 2002; Rykhlevskaia, Gratton, & Fabiani, 2008), they are primarily used to determine how regions work in unison to support cognitive functions. In fMRI, functional connectivity is quantified as the correlation between the BOLD signals of two regions. Stronger correlations are thought to reflect greater functional relatedness (Friston, 1994). Functional connectivity is often used to examine how regions interact with one another in response to task demands (task-based functional connectivity). The strength of interactions is then linked to performance or compared between conditions to understand their functional

relevance (Friston et al., 1997; Rissman, Gazzaley, & D'Esposito, 2004). For example, increases in hippocampal connectivity following learning are associated with improved memory performance, suggesting the hippocampus works offline to consolidate recent experiences into long-term memory (Tambini, Ketz, & Davachi, 2010; Tompary, Duncan, & Davachi, 2015). While studies have examined how hippocampal connections support learning and memory, much of this research has focused on task-based interactions (Inman et al., 2018; McCormick et al., 2010; Ranganath et al., 2005).

Connectivity can also be measured independent of an external task (intrinsic connectivity). Resting-state connectivity, for example, measures the correlations in spontaneous fluctuations of brain activity during a period of rest. It is believed to capture the intrinsic or trait-like organization of functional networks distributed across the brain (Buckner, Krienen, & Yeo, 2013; Damoiseaux et al., 2006; Finn et al., 2015). Recent studies highlight the importance of intrinsic connections in predicting individual cognition (Finn et al., 2015; Gerraty et al., 2014; Poole et al., 2016). Finn and colleagues (2015) argue that intrinsic connections measured during rest can act as a connectivity "fingerprint" and may be useful for identifying individuals. Resting-state connectivity has been used to predict individual differences in personality traits (Liu, Kohn, & Fernández, 2019), fluid intelligence (Finn et al., 2015), attention (Fong et al., 2019; Rosenberg et al., 2015), and symptoms of mental health conditions (Kessler et al., 2016; Reinen et al., 2018). Moreover, resting-state connectivity and its relationship to behavior has been shown to be reliable over periods of time, suggesting these connections may capture stable, trait-like properties of the individual (Horien et al., 2019; Touroutoglou et al., 2015).

Intrinsic connectivity may also be indexed by background connectivity, that is, interactions that occur during a task after trial-related activity has been removed from the BOLD

signal. Removing trial-related activity prevents correlations driven by specific trial events, like stimulus onset (Cole et al., 2019). Background connectivity may capture brain states, like attention (Al-Aidroos, Said, & Turk-Browne, 2012), emotional arousal (Tambini et al., 2016), encoding vs retrieval (Cooper & Ritchey, 2019; Duncan, Tompary, & Davachi, 2014), and goal states (Norman-Haignere et al., 2012). It also may capture the same trait-like connections that are found at rest (Gess et al., 2014; Gratton et al., 2018; Horien et al., 2019; Smith et al., 2009). A study by Gratton and colleagues (2018) suggests background connectivity may be better explained by properties of the individual compared to those driven by the state of the individual or the task they are completing. They measured functional connectivity of nine individuals while completing rest or different tasks and repeated this protocol across 10 separate scanning sessions. They found the variability in functional networks was largely explained by the individual (trait-level) and commonalities between individuals (group-level). Functional networks also differed between scanning sessions (state-level) and between the different tasks (task-level), but these differences were much smaller than the differences between individuals. Thus, background connectivity measured during tasks may be largely capturing stable, trait-like connections that could be used to predict individual characteristics. In spite of the significant role intrinsic connections may play in individual cognition, there is surprisingly little research on how intrinsic hippocampal connections during rest and task can predict individual memory performance.

At rest, the hippocampus is part of a functional network which consists of regions of the prefrontal cortex, lateral temporal cortex, and medial and inferior parietal cortices (Figure 1.2) (Andrews-Hanna et al., 2010; Vincent et al., 2006). This network of regions is often described as the default mode network. The default mode network is characteristically activated during internal cognitive processing that occurs during rest, like mind-wandering, and deactivated in

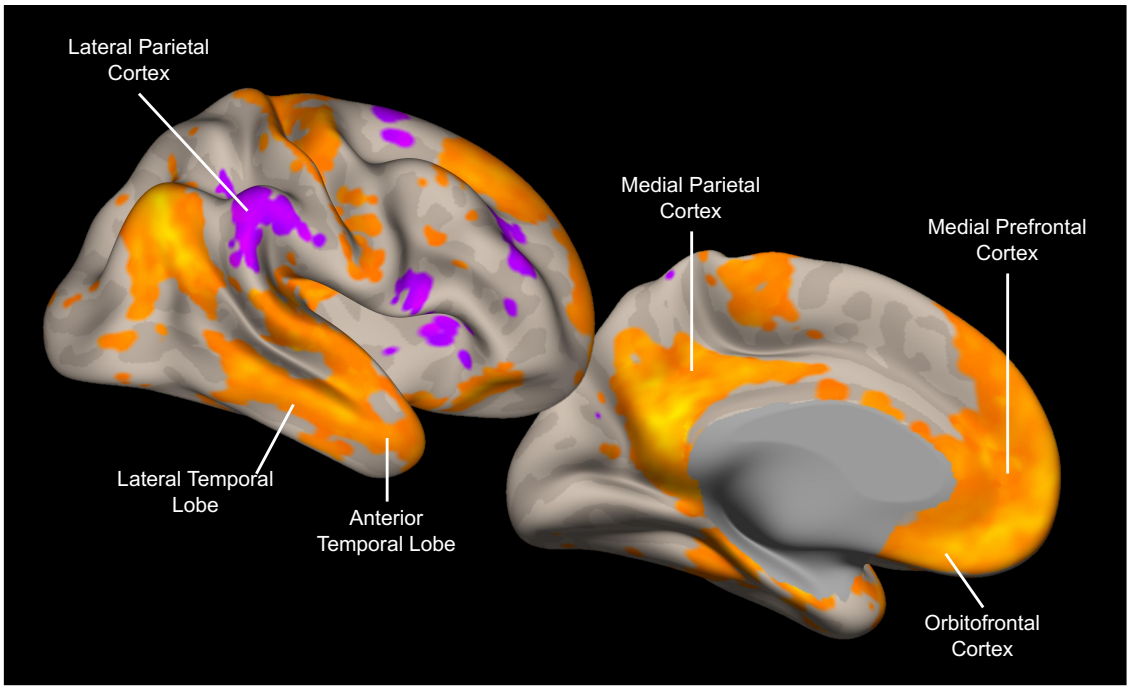

Figure 1.2. Functional connectivity of the hippocampus. Whole-brain resting-state functional connectivity of the hippocampus. At rest, the hippocampus is functionally connected with a network of regions, including the prefrontal cortex, lateral temporal lobe and medial and inferior parietal cortices. Data taken from Chapter 4 (n = 58).

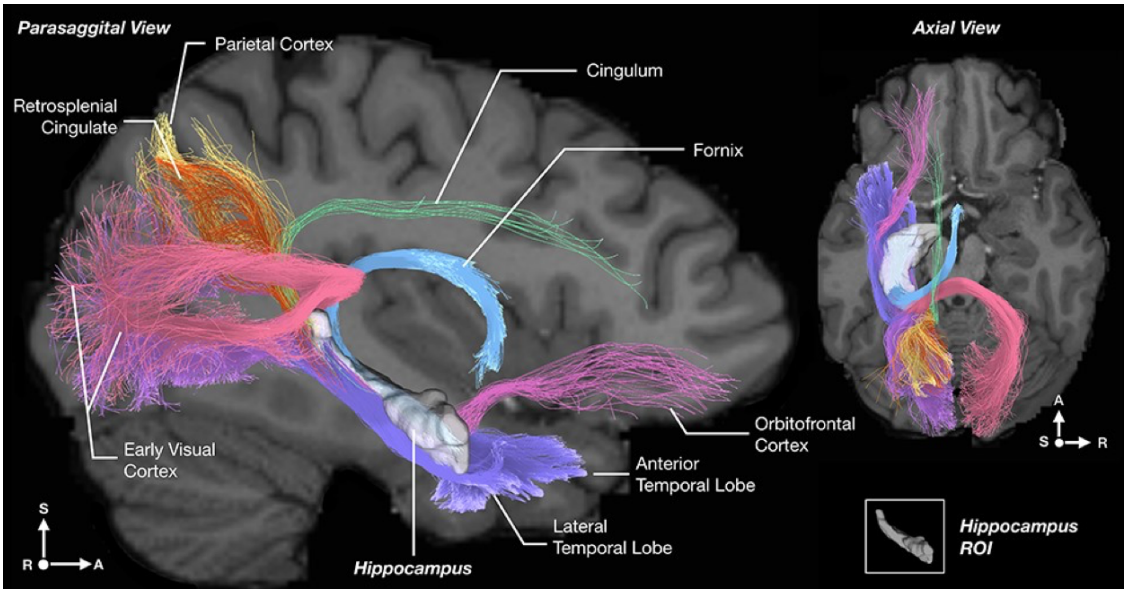

Figure 1.3. Structural connectivity of the hippocampus. Diffusion tractography of white-matter connections from the hippocampus for an example subject. Structural connectivity of the hippocampus largely reflects its functional connections, including parietal cortex, lateral temporal lobe and prefrontal cortex. Reprinted from "Extensive Cortical Connectivity of the Human Hippocampal Memory System: Beyond the "What" and "Where" Dual Stream Model," by C.C. Huang et al., 2021, *Cerebral Cortex, 31*, p. 4652. Copyright 2021 by Oxford University Press.

response to external task demands (Harrison et al., 2008; Mason et al., 2007; Raichle, 2015; Raichle et al., 2001; van Buuren et al., 2010). The hippocampus is also part of a subsystem of the default mode network that is recruited for memory recollection and mental imagery (Andrews-Hanna et al., 2010; Rugg & Vilberg, 2013). Importantly, hippocampal connections at rest are largely reflective of structural connections (Huang et al., 2021; Kier et al., 2004; Powell et al., 2004) (Figure 1.3), suggesting they may capture stable properties of the individual. Though some research has begun to explore how trait-like hippocampal connections predict episodic memory performance (Touroutoglou et al., 2015; Wang et al., 2010), less is known about how they contribute to other functions of memory.

Overview of the Dissertation

The goals of this dissertation are two-fold: 1) to understand how different hippocampal connections serve different functions of memory, and 2) to test whether intrinsic hippocampal connections contribute to individual memory abilities. In three empirical studies, I will show that trait-level hippocampal connections predict individual differences in reward motivated learning (Chapter 2), generalizing category knowledge (Chapter 3), and memory specificity and generalization abilities (Chapter 4). Importantly, these chapters will demonstrate how different sets of hippocampal connections contribute to different types of learning. Together, these studies add to a growing literature on the utility of intrinsic connectivity in identifying individual cognitive abilities and further our understanding of the role of the hippocampus in different forms of memory and cognition more broadly.

Chapter 2 will explore how interactions between the hippocampus and the brain's reward system underlie reward motivated learning. Theories suggest that rewards act on the dopaminergic connections between the hippocampus and the brain's reward system (midbrain,

ventral striatum) to facilitate learning, particularly for high-value information (Lisman & Grace, 2005; Lisman et al., 2011; Shohamy & Adcock, 2010). Consistent with these theories, hippocampal-midbrain connectivity during and following learning predict individual effects of reward on memory, with greater connectivity associated with greater effects of reward on learning (Gruber et al., 2016; Wolosin et al., 2012). These theories, however, have led to an emphasis on task-driven hippocampal-midbrain interactions. It is still unclear how the hippocampus forms intrinsic connections with the midbrain to support reward-motivated learning. Moreover, research often ignores the role hippocampal interactions with other reward-related regions might play. Chapter 2 of the present dissertation will address this gap in the literature. Importantly, it will show how individual differences in intrinsic hippocampal connectivity with a broader network of reward-related brain regions track individual effects of reward on memory. Moreover, it will show that patterns of connectivity and their relationship to behavior are relatively stable across task and rest, reflecting suggesting intrinsic or trait-like hippocampal connections contribute to reward motivated learning.

Chapter 3 will then examine how hippocampal-cortical connections contribute to generalization, specifically how we apply our category knowledge in new situations (category generalization). Previous studies show that hippocampal connectivity with the VMPFC supports the integration of new information with related memories (Schlichting & Preston, 2016; Zeithamova, Dominick, & Preston, 2012) and pre-existing knowledge structures (Bein, Reggev, & Maril, 2014; van Kesteren et al., 2010). The hippocampus and VMPFC are similarly recruited for representing category knowledge (Bowman et al., 2020; Bowman & Zeithamova, 2018), though it is unclear how these regions interact to support category generalization and whether other cortical regions are involved. To address these questions, Chapter 3 will test how intrinsic

hippocampal interactions with regions known for supporting generalized information, like concepts (Bowman & Zeithamova, 2018; Mummery et al., 2000) and schemas (van Kesteren et al., 2012; Webb, Turney, & Dennis, 2016), predict category generalization. To probe whether the hippocampus does not contribute to generalization beyond retrieving individual episodes, I will also inspect hippocampal connectivity with regions that support memory specificity, such as lateral prefrontal cortex (Badre et al., 2005; Bowman & Dennis, 2016; Kuhl et al., 2007). Finally, anterior and posterior hippocampal connectivity will be measured to compare their connectivity to putative specificity and generalization regions and their contribution to category generalization. Consistent with Chapter 2, I find that hippocampal-cortical connections are relatively stable across task and rest, suggesting they reflect intrinsic properties that can be linked to individual differences in memory. Indeed, I find that intrinsic hippocampal-VMPFC interactions predict individual differences in category generalization.

Building on Chapter 3, Chapter 4 will examine whether intrinsic hippocampal connections measured across the cortex predict generalization abilities and if they are separate from those that predict memory specificity. As features of an episode (who, what, where, when) are stored across the cortex, encoding and retrieving specific memories relies on communication between the hippocampus and a wide-spread network of cortical regions (Inman et al., 2018; McCormick et al., 2010; Ranganath et al., 2005). How then can we tease apart those connections that are relevant to generalization from those that support memory specificity? As posterior and anterior hippocampus represent information at different levels of granularity, one possibility is that they each form a distinct set of connections that are recruited for remembering specific or generalized information. Indeed, Chapter 3 demonstrates that anterior and posterior hippocampus have different intrinsic connectivity profiles that are consistent with their hypothesized roles.

Chapter 4 will build off this work by examining 1) whether distinct hippocampal connections at rest predict individual memory specificity and generalization abilities, and 2) whether anterior and posterior hippocampal connections serve specialized roles in the different types of learning. Similar to the previous chapters, I will show that individual differences in the strength of trait-like hippocampal connections at rest can predict individual memory abilities. I will further demonstrate that memory specificity and generalization abilities are linked to some distinct and some overlapping connections. There will be some evidence that anterior and posterior hippocampal connections differ in their relationship to memory specificity and generalization, though they are each associated with the different types of learning. This chapter will provide a more nuanced view of the role of trait-like anterior and posterior hippocampal connections in memory. Finally, Chapter 5 will synthesize findings across the studies and provide a general discussion that ties them to the broader literature.

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CHAPTER II

FUNCTIONAL CONNECTIVITY BETWEEN MEMORY AND REWARD CENTERS ACROSS TASK AND REST TRACK MEMORY SENSITIVITY TO REWARD

From Frank, L.E., Preston, A.R., & Zeithamova, D. (2019). Functional connectivity between memory and reward centers across task and rest track memory sensitivity to reward. *Cognitive, Affective, & Behavioral Neuroscience, 19*, 503-522. doi:https://doi.org/10.3758/s13415-019-00700-8

Why are some events remembered and others forgotten? Reward-based motivation is one factor that impacts which events are remembered. The modulation of memory by rewards is thought to result from reward-related activation of the dopaminergic midbrain and the projection of dopamine into the hippocampus, which facilitates long-term potentiation and memory formation (Lisman & Grace, 2005; Lisman et al., 2011; Shohamy & Adcock, 2010). Consistent with this model, several functional MRI studies have documented increased activation in the midbrain and ventral striatum, accompanied by univariate and multivariate signals reflecting reward in the hippocampus (HIP) and parahippocampal cortex (PHC) within the medial temporal lobe (Adcock et al., 2006; Gruber et al., 2016; Wittmann et al., 2005; Wolosin et al., 2012, 2013). A common finding in these studies is that individuals differ in the degree to which their memory is affected by extrinsic rewards (Adcock et al., 2006; Gruber et al., 2016; Wolosin et al., 2012, 2013).

Individual differences in memory sensitivity to reward have been related to both phasic and tonic interactions between the midbrain and medial temporal lobe (Shohamy & Adcock, 2010). Adcock et al. (2006) first found that task-related activation in the hippocampus, PHC, midbrain and ventral striatum were correlated participants. Wolosin et al. (2012) showed background hippocampal-midbrain interactions across both encoding and retrieval phases track

memory sensitivity to reward. Other studies focused on learning-induced connectivity increases, relating them to reward-motivated memory (Gruber et al., 2016; Murty et al., 2017), although hippocampal-midbrain interactions may relate to associative memory in general (Duncan et al., 2014; Tompary et al., 2015).

Across many memory studies, the emphasis has been on connectivity during task performance or connectivity changes after learning as primary predictors of behavior (Gruber et al., 2016; Murty et al., 2017; Tambini et al., 2010; Tompary et al., 2015). In contrast, other fields have focused on resting connectivity patterns, given that individual differences in intrinsic connectivity can remain relatively stable across time and tasks (Finn et al., 2015; Gratton et al., 2018), predicting individual differences in cognition (Finn et al., 2015; Gerraty et al., 2014; Poole et al., 2016; Wang et al., 2010). Therefore, we wanted to bridge these approaches and test whether there are stable interactions between memory and reward regions that track individual differences in memory sensitivity to reward, irrespective of when those interactions are measured. For example, even in the absence of a task, the strength of connectivity between hippocampus, midbrain, and ventral striatum varies across individuals (Kahn & Shohamy, 2013). Because these regions are involved in memory and reward processes, these task-independent interactions may relate to individual differences in memory sensitivity to reward. However, the idea of an individual's connectivity "fingerprint"—here used in a broad sense referring to connectivity patterns differentiating groups and tracking performance (Gratton et al., 2018; Wang et al, 2010) rather than identifying specific individuals (Finn et al., 2015)—has not yet been tested in the area of reward modulation of memory.

Theoretical perspectives, particularly the Lisman and Grace (2005) model, have emphasized the role of the dopaminergic midbrain in motivated learning. Influenced by this

model, neuroimaging studies on memory sensitivity to reward have typically focused on the midbrain as the primary reward region of interest (Adcock et al., 2006; Gruber et al., 2016; Wittmann et al., 2005; Wolosin et al., 2012). However, other reward-related regions are likely to contribute to motivational effects on memory. The ventral striatum is believed to play a central role integrating signals between the hippocampus and midbrain (Lisman & Grace, 2005; Miendlarzewska et al., 2016), is recruited during motivational encoding (Adcock et al., 2006; Wittmann et al., 2005), and has been shown to interact with the hippocampus both during rest (Kahn & Shohamy, 2013) and task performance (Adcock et al., 2006; Camara et al., 2009; Kafkas & Montaldi, 2015). Prefrontal regions, including the orbitofrontal cortex (OFC) and medial prefrontal cortex (MPFC), also interact with hippocampus and PHC (Blessing et al., 2016; Gerraty et al., 2014; Murty et al., 2016) and have been implicated in various reward-related processes (Amiez et al., 2006; Elliott et al., 2008; Kable & Glimcher, 2007). However, because of the theoretical emphasis on midbrain, and to a lesser degree striatum, it is unknown whether other reward-related regions also contribute to reward modulation of memory.

The current study had two main goals. First, we aimed to determine the role of a broader network of reward-related regions in mediating reward modulation of memory. Reward-related regions of interest were independently derived based on their involvement in reward processing using an automated meta-analysis tool Neurosynth (Yarkoni et al., 2011), irrespective of their prior implication in reward modulation of memory. Second, we aimed to determine to what extent individual differences in memory sensitivity to reward relate to individual differences in connectivity between memory and reward centers, and whether such a relationship may exist irrespective of when connectivity is measured. To evaluate the stability of connectivity patterns and their relationship to behavior, interactions between hippocampus and PHC with a network of

reward-related regions were measured using functional MRI during a monetary incentive encoding task (Adcock et al., 2006), as well as during rest scans before and after the task. The pattern of connectivity for each participant was related to their memory sensitivity to reward, defined as memory advantage for high-value trials, using analysis of variance and machine learning approaches. A separate report from this data set, focusing on hippocampal and PHC task-related activation patterns and how they represent reward, has been published previously (Zeithamova et al., in press).

Materials and Methods

Participants

Thirty-four healthy, English speaking volunteers enrolled in this study. Data from 9 participants were excluded for excessive head motion during task scans (framewise displacement > 1mm in at least 50 time points in more than 1 run; 4 participants), scanning interruptions (3 participants), or missing data (2 participants). An additional participant was excluded due to excessive head motion during a rest scan (>50% of time points removed during scrubbing). The remaining 24 subjects (18 females, ages 18-31, mean age = 22) were included in the connectivity analyses. Subjects received $40 for participation and up to $55.50 bonus for their memory performance. The study was approved by the Institutional Review Board of The University of Texas at Austin and all participants provided a written consent. A separate sample of 20 participants (5 females, ages 18-24, mean age 19) completed the same task but were not scanned.

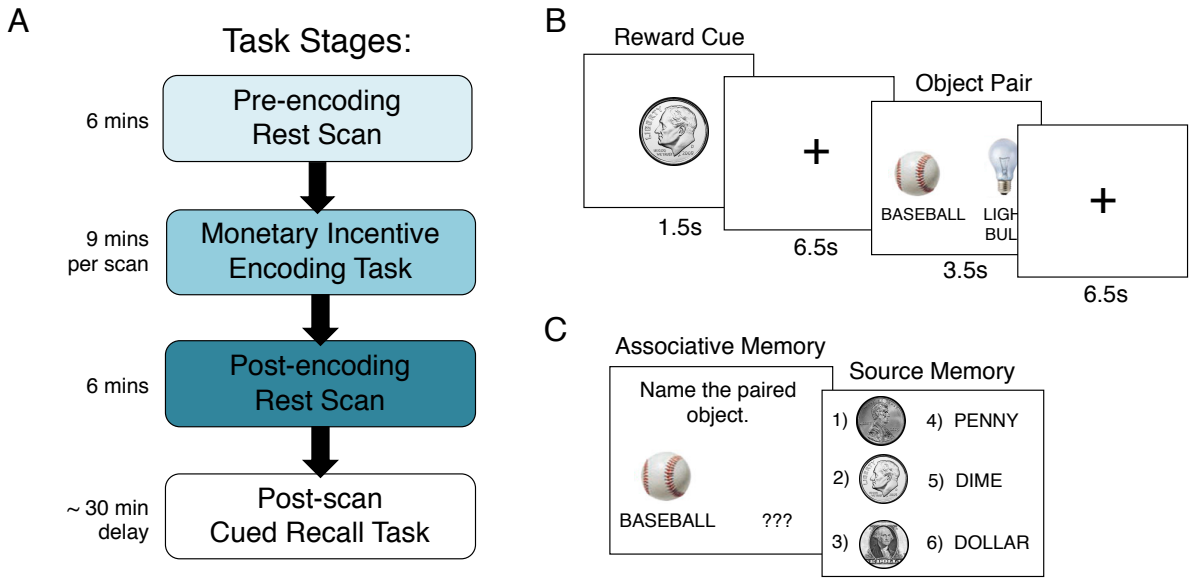

Figure 2.4. Behavioral procedures. **A.** The task consisted of three scanning stages: the pre-encoding rest scan, the monetary incentive encoding task, and the post-encoding rest scan. The final stage consisted of a cued recall task that was conducted outside of the scanner. **B.** Participants performed a modified monetary incentive task. They were asked to intentionally encode pairs of common objects. Preceding each object pair was a reward cue that indication how much money the participant would earn for correctly remembering the object pair. **C.** In a post-scan cued recall task, participants had to name the object previously paired with the one presented. A surprise source memory task for the associated reward cue followed each trial.

Behavioral Procedures

Following the consent procedure, participants were instructed on the task and completed five practice trials. Next, they were screened for MRI, changed into scrubs, and were positioned into an MRI magnet. The scanning session started with the acquisition of anatomical scans, followed by functional scans. Participants completed a pre-encoding rest scan (6 minutes), a motivated encoding task across five event-related runs (9 minutes each), and a post-encoding rest scan (6 mins), with 1-2 minutes between all scans (Figure 2.1A). During rest scans, participants were instructed to keep their eyes open, with a blank screen in front of them. During the motivated encoding task, participants were instructed to intentionally encode 150 pairs of common objects, each preceded by a cue (in pictorial or word form) indicating a reward value (penny, dime, or dollar) that they may earn if they remembered the object pair in a later memory

test (Figure 2.1B). The object pairs were drawn from a set of 300 color photographs of objects and randomly assigned to one of the six reward-cue conditions, resulting in 25 pairs per condition. Participants were informed that they would receive a cash bonus indicated by the reward cue for correctly recalling the associations in a cued-recall task that immediately followed the scanning session. Trials from all conditions were presented in a randomized order, with a balanced number of presentations in each of the five encoding runs. A self-paced cued recall test was completed following the scanning session, approximately 20-30 minutes after the post-encoding rest. During each test trial, participants were shown the left object of each pair and asked to name out-loud the associated object, followed by a source memory test during which participants selected the reward cue preceded that object (Figure 2.1C). Participants were not informed that they would be tested on the cue identity prior to the test. Source memory for cue identity was at chance in the fMRI sample (see Zeithamova et al., in press for details) and is not considered further in this report.

For each participant, the mean proportion of correctly recalled associations following each of the 6 possible cues was computed. A 2 (form: picture, word) x 3 (value: penny, dime, dollar) repeated measures ANOVA examined the within-subjects effect of reward value and form on memory. For significant effects, follow-up pairwise comparisons were conducted to determine the differences between the mean accuracies of each condition. The behavioral data were used to index individual differences in reward modulation of memory. Because the behavioral effect of reward was found to be U-shaped in the fMRI sample, we used the difference between dollar and dime trial accuracy as a measure of memory sensitivity to reward. We refer to this score as the *behavioral reward modulation* (BRM) score. Additionally, a median split of BRM scores sorted participants into two groups: modulators (those who demonstrated

memory sensitivity to reward) and non-modulators (those whose memory scores were insensitive to reward). A confirmatory analysis of the reward effect on memory was performed within each group to verify that "modulators" indeed showed a memory advantage for dollar trials while "non-modulators" did not. We refer to this dichotomized measure of memory sensitivity to reward as a *modulator status*.

fMRI Acquisition

Functional and structural MR images were collected at the Imaging Research Center at the University of Austin at Texas using a 3T Siemens Skyra MRI scanner. Functional images were collected in 72 oblique axial slices, approximately 20 degrees from the AC-PC line, using echo-planar imaging sequences with multiband acceleration factor = 3, GRAPPA factor = 2, TR = 2000 ms, TE = 31 ms, flip angle = 73°, 128 x 128 x 72 matrix resulting in 1.7 mm isotropic voxels. Using the same parameters, two 6-minute resting-state fMRI scans were conducted, one preceding and one following the encoding task. A T1weighted high-resolution MPRAGE image (256 x 256 x 192 matrix, 1 mm isotropic voxels) anatomical image was collected. An additional T2-weighted image was collected in an oblique coronal plane perpendicular to the hippocampal axis (TR = 13150 ms, TE = 82 ms, 512 x 60 x 512 matrix, 0.4 x 0.4 mm in-plane resolution with 1.5 mm slices, no gap).

Regions of Interest

As prior studies on motivated encoding have primarily focused on midbrain, little is known about how other reward-related regions may affect memory sensitivity to reward. Our goal was to include a wider reward-related network in the current investigation, irrespective of whether they have been previously implicated in reward modulation of memory. To obtain ROIs related to reward processing, a meta-analysis of 671 studies including the term "reward" was

collected from the Neurosynth database (http://neurosynth.org). We used the "reverse inference" map (currently referred to as the "association test"), which displays regions that preferentially activate in studies that include the term "reward" compared to studies that do not include the term "reward" and as such is considered diagnostic of the term in question (Yarkoni et al., 2011). Because the default Neurosynth threshold (FDR $p < .01$) yielded large clusters with multiple peaks in anatomically distinct regions, we further thresholded the maps with a voxel- wise threshold of $Z = 5.3$ to obtain clusters that did not extend across multiple anatomical regions. This meta-analysis resulted in five reward-related ROIs that centered on the anterior cingulate cortex (ACC), midbrain, medial prefrontal cortex (MPFC), orbitofrontal cortex (OFC), and ventral striatum (VS). Clusters centered on the midbrain and VS were disproportionately larger than the prefrontal ROIs and extended beyond the anatomical boundaries of their respective regions, thus these clusters were further reduced to the top 500 voxels. The localization of the resulting five reward-related ROIs in the standard space is presented in Figure 2.2A. The reward-related ROIs were reverse transformed from standard space to native space of each participant using FLIRT, a part of FSL (http://www.fmrib.ox.ac.uk/fsl). Finally, the reward ROIs were resampled to the functional space of the participant to serve as masks for extracting timeseries.

Given the number of reward-related regions, only hippocampus and PHC were selected as memory regions of interest to limit the total number of connections considered. Hippocampus and PHC were selected as our *a priori* memory ROIs as they have been consistently implicated in studies of reward effects on memory (Gruber et al., 2016; Wolosin et al., 2012, 2013). To obtain unbiased ROIs, we defined hippocampus and PHC anatomically in each participant's native space. We did not use a functional definition (e.g., Neurosynth) as it was not apparent

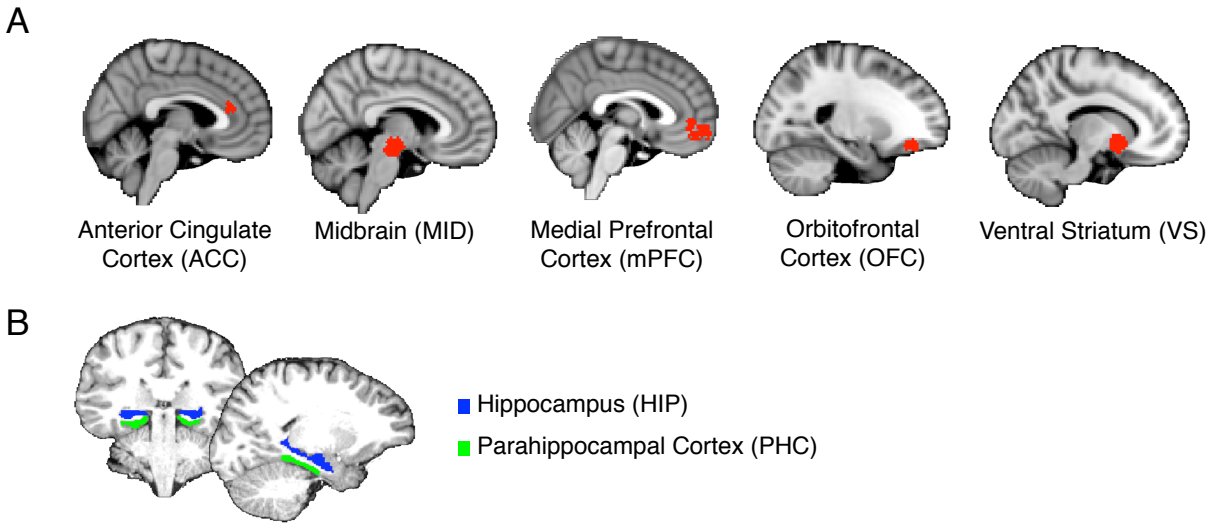

Figure 2.5. Regions of interest. **A.** Localization of five reward-related ROIs extracted from Neurosynth. **B.** Memory ROIs were anatomically-defined hippocampus and PHC, here shown on an example subject in native space.

whether standard memory voxels in these regions must be also most relevant for memory modulation by reward. However, the Neurosynth "memory" maps do cover essentially the whole anatomical hippocampus and PHC and would thus yield the same results. Anatomical ROIs were obtained by cortical parcellation and subcortical segmentation of the T1 anatomical scan via Freesurfer (https://surfer.nmr.mgh.harvard.edu). The T1 anatomical scan was then coregistered to the first functional scan using Advanced Normalisation Tools (ANTS, http://picsl.upenn.edu/software/ants/), and the coregistration parameters were applied to the Freesurfer segmentations. Finally, the participant-specific Freesurfer-defined hippocampus and PHC were transformed into the space of their functional scans, to be used as masks for extracting hippocampal and PHC timeseries. Hippocampus and PHC ROIs are presented for an example subject in Figure 2.2B.

Deriving Functional Connectivity Measures

Preprocessing was conducted using tools from FSL version 5.0 and ANTS. The functional and anatomical images were brain extracted using BET. Functional images were

motion corrected within each run using FLIRT from FSL, realigned across runs to the first functional image using ANTS, and high-pass filtered (128 s cutoff). Functional connectivity was measured during the pre-encoding rest scan, the five encoding scans, and the post-encoding rest scan using similar processing procedures. As connectivity measures may be affected by noise in the BOLD signal evoked by motion and physiological processes (Murphy et al., 2013; Power et al., 2012), we followed the preprocessing procedures outlined by Power et al. (2012) to remove noise-related signal fluctuations. First, timecourses were extracted for cerebrospinal fluid (CSF), white matter (WM), and the whole brain, as signal changes in these regions provide a good proxy to signal changes driven by motion and other confounds. The six realignment motion parameters, framewise displacement (FD), and global signal change (DVARS) were also extracted. We then created a "scrubbing" mask using the time series for FD and DVARS. Time points that exceeded either threshold (FD > 0.5 mm or DVARS > 0.5%) were marked for removal, as was one time point before and two time points after (Power et al., 2012). Additionally, the first two time points in each scan were removed. The scrubbing masks were applied to the timecourses for each subject, removing on average approximately 6% of the time points from the pre-encoding scan, 9.5% from the post-encoding scan, and an average of 8% of time points across all five encoding scans.

To extract the background connectivity during the encoding scans, we low-pass filtered the encoding time series, removing signal at or above the task frequency (task frequency = .056 Hz, filter threshold = .045 Hz). The low-pass filter removed task-related fluctuations while keeping the low-frequency (background) signals that are more reflective of intrinsic activity (Newton et al., 2011; Tambini et al., 2016). As low-pass filtering also removes high-frequency noise, leading to higher connectivity estimates (Van Dijk et al., 2010), we additionally low-pass

filtered the rest timeseries at the same frequency when comparing connectivity across task and rest. Low-pass filtering was performed after computing FD and DVARS but before scrubbing of problematic timepoints.

Connectivity measures were obtained by partial correlations of the pre-processed, scrubbed timeseries between each of the memory ROIs and each of the five reward-related ROIs, controlling for WM, CSF, whole brain signal, motion parameters, and their derivatives. The resulting Pearson's *r* coefficients from the partial correlation analysis were Fisher z transformed to conform to the assumptions of normality before being submitted to further analyses. For the encoding scans, connectivity was measured and Fisher z transformed within each run. The normalized connectivity values were then averaged across the five encoding scans to produce a single measure of background connectivity during encoding.

Analysis of Variance Approach

To test whether connectivity patterns related to memory sensitivity to reward and whether this relationship is stable across task stages, the connectivity values were submitted to two repeated-measures ANOVAs. The first ANOVA only included rest data (pre-encoding, post-encoding), akin to prior work on resting state connectivity (Gruber et al., 2016). The second ANOVA included all three task stages (pre-encoding rest, encoding task, post-encoding rest), with low-pass filtered rest timeseries for comparison with task timeseries. In addition to task stage as a within-subject factor, both ANOVAs also included memory structure (hippocampus, PHC) and reward structure (ACC, midbrain, MPFC, OFC, VS) as within-subject factors and modulator status (modulator, non-modulator) as a between-subjects factor.

The following effects were relevant to our questions of interest: (1) the main effect and interactions of modulator status, testing whether connectivity patterns relate to individual

differences in memory sensitivity to reward; (2) the main effect and interactions of the task stage factor, testing the idea that connectivity patterns may be relatively stable across task and rest as well as track individual differences in memory sensitivity to reward; (3) the interactions of the reward region factor with the modulator status, testing whether all reward regions contribute similarly or differentially. Of note, the main effect of reward region was not of interest as the overall functional connectivity value may depend on physical distance between regions and a size of a region, and may not be easily interpretable (Honey et al., 2009; Salvador et al., 2005). When an interaction was found, we followed up with an investigation of the locus of the interaction. While the report focuses on the effects of interest, full ANOVA results are reported in tables. Greenhouse Geisser corrections were used when appropriate, reported in the tables as "GG." To validate that our findings were not driven by treating memory sensitivity to reward as a binary variable, we re-tested significant effects of interest from both ANOVAs using ANCOVA, with the continuous measure of behavioral reward modulation as a covariate.

Functional Relationships Among Connections

Observing comparable or differential modulator effects across multiple reward ROIs in the ANOVAs provides one indication for unique or uniform contributions of reward regions to reward modulation of memory. To more directly test whether the reward regions are a part of the same functional network, we additionally examined their cross-correlational structure. We performed two principal component analyses: one on rest-only connectivity values (no low-pass filter to maintain information on high-frequency fluctuations) and one that included all of the connectivity values across task and rest (using low-pass filtered timeseries for comparable task and rest pre-processing). Components were considered for further analysis when they explained at least 10% of variance. For each considered component, we further tested the likelihood of

obtaining such component by chance, using a comparison to a null distribution of components. To obtain the null distribution, we performed 10,000 simulated principal components analyses on data obtained by randomly shuffling connectivity values across participants, separately for each connection. The percent of variance explained by each component (first most informative, second most informative, etc.) was then compared to the null distribution's percent explained. The same results would be obtained by testing eigenvalues.

Loadings on each component were compared for the five reward ROIs using one-way ANOVA, and component scores were then related to behavioral reward modulation using multiple regression. Using dimensionality reduction prior to the multiple regression allowed us to test how underlying components, or potential networks of regions, contributed to the connectivity-behavior relationship while taking into account the collinearity between connectivity values and limiting in a data-driven manner the number of predictors considered.

Connectivity Pattern Classification

While traditional inference tests, such as analysis of variance, test the probability that observed differences between groups arose by chance alone, machine learning classification approaches allow us to more directly quantify how well the participants can be distinguished from one another based on their connectivity pattern. We used Support Vector Classification (SVC), to test the degree to which participants can be classified as either modulators or non-modulators based on their pattern of connectivity across the ten ROI connections (2 memory ROIs x 5 reward ROIs).

SVC was implemented using the "e1071" (Meyer et al., 2017) statistical analysis package of R (https://www.r-project.org/) and conducted separately within each task stage. The default parameters for nu-classification were used ($C = 1$, $\varepsilon = .1$, $\gamma = .1$, no tuning) with a radial basis

function kernel. We used a leave-one-subject-out cross-validation approach, training the model on N-1 subjects and then applying the trained classifier to predict the withheld subject's modulator status. The process was repeated as each subject in turn was withheld from the training set and used to test the model. The accuracy for the model was recorded as the percentage of correct classifications. A permutation test was used to test for significance. We conducted 5000 simulations, each time randomly shuffling the modulator status labels across participants and then computing the same leave-one-subject-out cross-validated classification accuracy as with the real data. The true classifier accuracy was compared to the distribution of the simulated classification accuracies to derive the probability of obtaining such accuracy by chance alone. Accuracy that occurred with probability less than $p = .017$ was considered significant, reflecting Bonferroni correction across three task stages for an overall alpha = .05.

To verify the results were not driven by the median split approach, Support Vector Regression (SVR) was used to predict the continuous measures of behavioral reward modulation (BRM score) for each participant from connectivity measured at each task stage. The same statistical package, default parameters, and leave-one-subject out cross-validation approach were used for SVR as were used for SVC. The predicted BRM values for each subject were then correlated with the observed BRM values to assess whether the individual differences in connectivity patterns contain information about individual differences in behavioral reward modulation of memory. We employed Bonferroni corrections for the three correlations (alpha = .05/3 = .017).

Complementary Connectivity Analyses

In addition to the main questions of interests, the current study provides data suitable to address questions from prior studies on reward modulation of memory. We conducted two sets

of exploratory analyses that maintain the focus on connectivity and may be informative for the readers, even though they do not directly address the main goals of the study.

Correlations between connectivity changes and behavior. The ANOVA, PCA, and machine learning approaches are well suited for testing the role of a broad set of reward regions and the connectivity fingerprint hypothesis, especially for the larger set of related connections considered here. In contrast, prior studies on reward modulation of memory have typically focused on single connections and learning-related effects, reporting first-order correlations relating pre-to-post encoding connectivity increases. While a disproportionate role of post-encoding rest could be indicated by a significant modulator by task stage interaction in our ANOVA, we also wanted to generate data directly comparable to prior studies. We thus additionally computed pre-to-post connectivity changes for each connection and correlated it with BRM. Because increased dopamine availability in the medial temporal lobe may enhance encoding in general (Duncan et al. 2014; Lisman et al., 2011), we also correlated the connectivity values with overall recall rates for each participant.

Anterior and posterior differences within hippocampus. Previous work suggests there are functional differences between the anterior and posterior portions of the hippocampus (Brunec et al., 2018; McKenzie et al., 2014; Poppenk et al., 2013). In the context of reward motivated learning, however, evidence for differential contributions of anterior and posterior hippocampus is lacking or conflicting (e.g., Murty et al., 2017; Wolosin et al., 2013). We have performed exploratory analyses of anterior/posterior hippocampal connectivity patterns to test whether their connectivity patterns or connectivity changes are differentially related to behavior in our paradigm.

The middle slice of each participant's hippocampus ROI was used as a boundary for the anterior and posterior divisions. For participants that had an odd number of slices in their hippocampus ROI, the middle slice was assigned to the posterior portion. The ROIs were then used to extract the timeseries during each rest and task scan. Connectivity between anterior and posterior hippocampus with each reward region was measured using the procedures outlined above. Functional differences between anterior and posterior hippocampus were tested using repeated measures ANOVA with hippocampal ROI (anterior, posterior) x task stage (pre-encoding, encoding, post-encoding) x reward ROI (ACC, midbrain, MPFC, OFC, VS) as within-subject factors and modulator status as a between-subjects factor. Of main interest was the interaction between hippocampal ROI and modulator status, testing whether anterior and posterior hippocampus differentially related to reward modulation of memory.

Results

Behavioral Results

Mean overall cued recall performance was .48 (*SD* = .19). A 2 (reward cue visual form) x 3 (reward cue value) repeated measures ANOVA revealed a marginally significant effect of reward value ($F(1.18,27.03) = 3.86$, $p = .054$, $\eta^2_p = .14$, GG), with a significant quadratic ($F(1,23) = 9.93$, $p = .004$, $\eta^2_p = .30$) rather than a linear effect ($F(1,23) = 1.97$, $p = .174$). Follow-

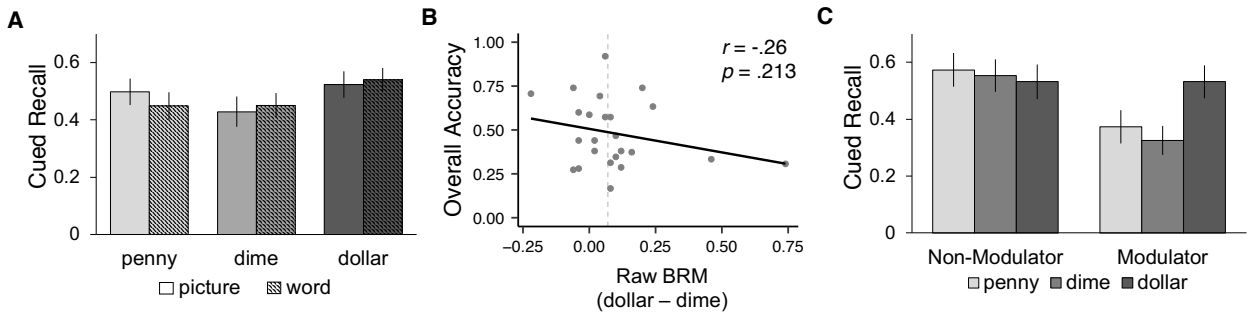

Figure 2.6. Behavioral results. **A.** Mean cued recall rates in each reward cue condition. **B.** Correlation between overall accuracy and raw behavioral reward modulation (dollar minus dime) scores. **C.** Mean cued recall rates for each reward value condition, separately for modulators and non-modulators.

up pairwise comparisons revealed that the quadratic effect was driven by greater recall on dollar trials (M = .53, SD = .20; $t(23) = 2.41$, p = .024), and unexpectedly, penny trials (M = .47, SD = .22; $t(23) = 2.45$, p = .022), compared to dime trials (M = .44, SD = .22). The difference between dollar and penny trials did not reach significance ($t(23) = 1.40$, p = .174). There was no main effect of visual form ($F(1,23) = .04$, p = .840, η^2_p = .002) nor an interaction between form and value ($F(2,46) = 1.66$, p = .202, η^2_p = .07). Thus, accuracies were collapsed across visual form and used for all subsequent analyses. Cued recall rates for each reward value and form condition are presented in Figure 2.3A.

A separate behavioral sample (n = 20) revealed a significant main effect of value ($F(1.23, 27.6) = 14.1$, p = .001, GG), comparably described as linear ($F(1,19) = 15.5$, p = .001) or quadratic ($F(1,19) = 10.8$, p = .004). Similar to the fMRI sample, cued recall accuracy was greater for dollar trials (M = .61, SD = .19) than for dime trials (M = .44, SD = .21; $t(19) = 3.83$, p = .001). Unlike the fMRI sample, the behavioral sample showed a memory advantage for dollar trials compared to penny trials (M = .44, SD = .19; $t(19) = 3.94$, p = .001) and no differences between penny and dime trials ($t(19) = .17$, p = .87).

While the U-shaped pattern of recall accuracies in the fMRI sample was unexpected and did not replicate in the separate behavioral sample, non-linear reward effects are plausible (e.g.,

Elliott et al., 2003). For example, penny trials may have been perceived as a loss relative to the (neutral) dime trials, making them more salient for encoding (Bartra et al., 2013; Seymour & McClure, 2008; Shigemune et al., 2014; Tversky & Kahneman, 1981). Because the difference between dollar and penny trials was not significant and because both penny and dollar may have increased salience for individuals sensitive to reward, we instead used the memory advantage of dollar over dime trials (replicated across both behavioral and fMRI samples) as a measure of individual differences in memory sensitivity to reward. The raw dollar minus dime difference scores ranged from -.25 to .75 (median of .07) and were not significantly correlated with the overall accuracy (Figure 2.3B), suggesting that reward modulation of memory affected which events are preferentially remembered rather than providing an overall memory advantage. Because the raw difference scores were skewed by an outlier (>3 SD from the mean), we used a rank order of these scores in all subsequent analyses when correlating memory sensitivity to reward with connectivity measures. We refer to the dollar-dime difference score as *a raw behavioral reward modulation* (raw BRM) score and the rank-order measure used for all subsequent analyses as a *behavioral reward modulation* (BRM) score.

For visualization and analysis purposes, we also constructed a dichotomized measure of reward modulation of memory using a median split of BRM scores. This approach created two groups of participants that we refer to as modulators (sensitive to reward) and non-modulators (insensitive to reward). We performed confirmatory analyses to validate that the median split of participants yielded sensible groupings. Figure 2.3C shows cued recall accuracy per value, separately for each group. There was no effect of reward value in non-modulators (one-way ANOVA $F(1.15,12.7) = 1.36$, $p = .273$), with raw BRM scores (dollar-dime difference) not different from zero ($M = -.02$, $t(11) = -.98$, $p = .348$), confirming that memory performance in

this group was not significantly affected by reward value. In contrast, modulators showed an effect of reward value (one-way ANOVA $F(1.18,13.01) = 8.69$, $p = .009$, $\eta^2_p = .44$), with greater accuracy for dollar trials than for dime trials (i.e., significant raw BRM scores; $M = .21$; $t(11) = 3.59$, $p = .004$), and greater accuracy for dollar trials than for penny trials ($t(11) = 2.43$, $p = .033$). Thus, the median split generated two sensible groups of participants that differ in their memory sensitivity to reward.

ANOVA Results

Rest-only ANOVA. We first addressed the relationship between rest connectivity and memory sensitivity to reward in a repeated-measures ANOVA with rest period (pre-encoding, post-encoding), memory ROI (hippocampus, PHC) and reward ROI (ACC, midbrain, MPFC, OFC, VS) as within-subjects factors and modulator status as a between-subjects factor. The rest timeseries were not low-pass filtered for this analysis, as such a preprocessing step is not ordinarily applied during rest timeseries analyses as it may remove meaningful high-frequency fluctuations. All connections are depicted in Figure 2.4A, and the complete ANOVA results are reported in Table 2.1A.

Modulator status was marginally significant ($p = .051$), with modulators ($M = .36$, $SD = .10$) demonstrating numerically greater hippocampus/PHC-reward network connectivity than non-modulators ($M = .29$, $SD = .06$). Modulator status significantly interacted with reward structure. This interaction was driven by greater hippocampus/PHC connectivity with ACC, OFC, and VS in modulators than non-modulators (all $t > 2.15$, all $p < .045$), with no effect of modulator status in hippocampus/PHC-midbrain and hippocampus/PHC-MPFC connectivity (both $t < 1.4$, $p > .18$). When reward modulation of memory was treated as a continuous measure using ANCOVA, the results were similar but weaker. The main effect of BRM ($r(22) = .35$;

$F(1,22) = 3.12$, $p = .091$, $\eta^2_P = .12$) remained marginally significant, but the interaction between reward structure and BRM did not ($F(2.83,62.22) = 1.99$, $p = .128$).

The ANOVA additionally revealed a main effect of rest period, with connectivity increasing from the pre-encoding ($M = .30$, $SD = .10$) to post-encoding rest scan ($M = .36$, $SD = .11$). Rest period did not interact with modulator status ($p > .6$), or BRM in the ANCOVA ($p > .3$), indicating that although the overall connectivity increased from pre-encoding to post-encoding, its relationship to behavior did not change significantly.

Omnibus ANOVA across rest and encoding task. To compare rest connectivity with background task connectivity, we used connectivity measures from low-passed timeseries to match task and rest preprocessing. Connectivity measures were submitting to the same ANOVA as reported above, with task stage factor having three values (pre-encoding, encoding, post-encoding). This analysis allows us to directly test the hypothesis that patterns of connectivity and their relationship to behavior across task and rest. The results of the ANOVA are reported in Table 2.1B, and all connectivity values are depicted in Figure 2.4B. From the effects of interest, we found a main effect of modulator status, with greater connectivity in modulators ($M = .52$, $SD = .14$) than non-modulators ($M = .32$, $SD = .21$). We also found a significant interaction between modulator status and reward structure. Follow-up two-sample t-tests showed that the interaction was driven by significant differences between modulators and non-modulators in hippocampus/PHC connectivity with ACC, MPFC, OFC and VS (all $t(22) > 2.1$, $p < .05$), but not with midbrain ($t(22) = .90$, $p = .377$). The effect of modulator status and the interaction between modulator status and reward structure were not driven by a median split of participants and were replicated when memory sensitivity to reward was treated as a continuous measure using ANCOVA (main effect of BRM: $F(1,22) = 7.13$, $p = .014$, $\eta^2_P = .25$; BRM*reward structure

interaction: $F(2.80,61.58) = 3.25$, $p = .031$). We found no effect of task stage and no interaction between task stage and modulator status in this analysis (both $p > .2$), suggesting connectivity between memory and reward networks and its relationship to behavior remained relatively stable across the pre-encoding, encoding, and post-encoding scans.

Summary of the ANOVA findings. Both omnibus and rest-only ANOVAs showed an effect of modulator status on memory-reward region connectivity and revealed that the modulator effect was not driven by all connections equally. A set of reward regions disproportionately drove the overall effect: ACC, OFC and VS connectivity with hippocampus/PHC consistently differed between modulators and non-modulators, while midbrain connections consistently did not. While we found an overall increase in connectivity between reward and memory regions from pre-encoding to post-encoding in the rest-only ANOVA, there were no interactions between modulator status and task stage in either analysis. These results are consistent with the idea that there are stable individual differences in brain connectivity patterns that relate to behavior.

Functional Relationships Among Connections

Rest-only PCA. To investigate which reward regions may be a part of the same functional network, we investigated the cross-correlation structure of connectivity values across participants. Pairwise correlations of all rest-based connectivity values are presented in Figure 2.5A. After separating them into principal components, we found four components that explained at least 10% of variance in the connectivity values and were retained for further analyses (Figure 2.5B). Monte Carlo simulations (Figure 2.6A) indicated that all components explained more

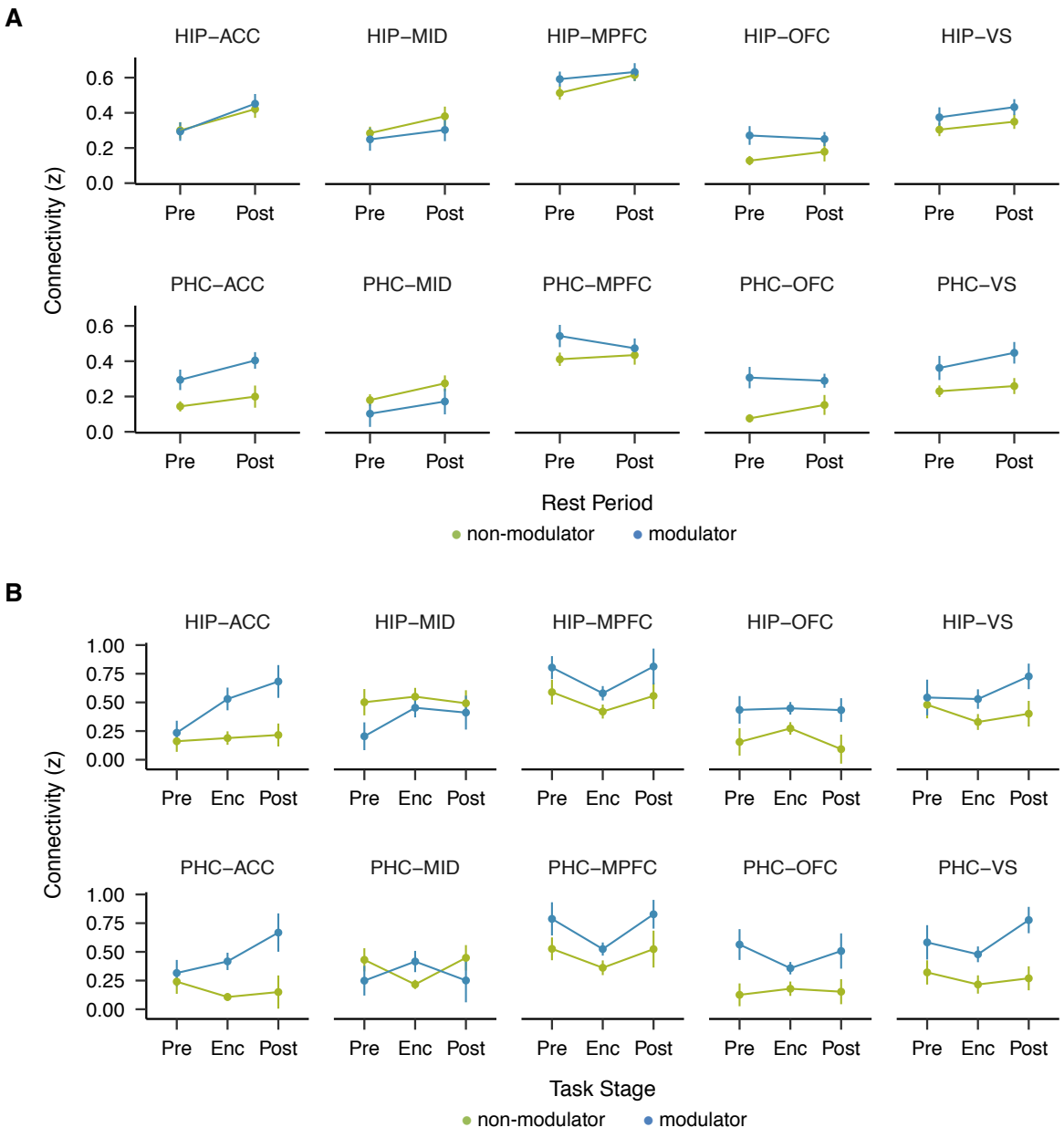

Figure 2.7. ANOVA results. **A.** Pre-encoding and post-encoding connectivity between memory (hippocampus, PHC) and reward (ACC, midbrain, OFC, VS, MPFC) ROIS are shown separately for modulators and non-modulators. **B.** Low-frequency background connectivity between memory and reward ROIs are plotted across the three task stages (pre-encoding, encoding, post-encoding) separately for modulators and non-modulators. HIP = hippocampus; MID = midbrain.

Table 2.1. ANOVA results

A. Rest-only ANOVA Table

Source	df_{effect}	df_{error}	F	p	η_p^2
Modulator	1	22	4.26	0.051	0.16
Task stage*	1	22	6.33	0.020	0.22
Task stage x Modulator	1	22	0.24	0.630	0.01
Memory ROI***	1	22	18.16	0.000	0.45
Memory ROI x Modulator	1	22	3.21	0.087	0.13
Reward ROI *** (GG)	3.03	66.72	31.93	0.000	0.59
Reward ROI x Modulator* (GG)	3.03	66.72	3.78	0.014	0.15
Task stage x Memory ROI	1	22	0.95	0.340	0.04
Task stage x Memory ROI x Modulator	1	22	0.01	0.932	0.00
Task stage x Reward ROI	4	88	1.78	0.140	0.08
Task stage x Reward ROI x Modulator	4	88	1.15	0.339	0.05
Memory ROI x Reward ROI** (GG)	2.84	62.46	4.36	0.008	0.17
Memory ROI x Reward ROI x Modulator (GG)	2.84	62.46	1.91	0.141	0.08
Task stage x Memory ROI x Reward ROI (GG)	2.50	55.05	2.17	0.112	0.09
Task x Memory x Reward x Modulator (GG)	2.50	55.05	0.23	0.842	0.01

B. Omnibus ANOVA Table

Source	df_{effect}	df_{error}	F	p	η_p^2
Modulator*	1	22	7.15	.014	.25
Task stage	2	44	1.44	.248	.06
Task stage x Modulator	2	44	1.10	.343	.05
Memory ROI	1	22	3.75	.066	.15
Memory ROI x Modulator	1	22	2.59	.122	.11
Reward ROI *** (GG)	2.87	63.24	9.69	.000	.31
Reward ROI x Modulator** (GG)	2.87	63.24	4.78	.005	.18
Task stage x Memory ROI (GG)	1.53	33.67	2.00	.159	.08
Task stage x Memory ROI x Modulator (GG)	1.53	33.67	.19	.765	.01
Task stage x Reward ROI	8	176	1.92	.060	.08
Task stage x Reward ROI x Modulator	8	176	1.53	.150	.07
Memory ROI x Reward ROI	4	88	1.35	.256	.06
Memory ROI x Reward ROI x Modulator	4	88	.61	.656	.03
Task stage x Memory ROI x Reward ROI (GG)	4.84	106.4	.69	.631	.03
Task x Memory x Reward x Modulator (GG)	4.84	106.4	.97	.436	.04

Note: A. The omnibus ANOVA examined the effects of memory structure (HIP, PHC), reward structure (ACC, MID, MPFC, OFC, VS), task stage (pre-encoding, encoding, post-encoding), and modulator status (non-modulator, modulator). B. The rest ANOVA examined memory structure (HIP, PHC), reward structure (ACC, MID, OFC, VS, MPFC), rest period (pre-encoding, post-encoding) and modulator status (modulator, non-modulator). * $p < .05$, ** $p < .01$, *** $p < .001$

variance than expected by chance (all $p < 0.01$), except for component 3 which was marginal ($p = 0.083$). Preferential loading of each reward region on different components was tested using one-way ANOVA (Figure 2.6B).

The first component explained 28.2% of variance in connectivity scores and loaded preferentially on ACC, OFC and VS connections, and to a lesser extent, MPFC and midbrain (one-way ANOVA, $F(4,15) = 3.91$, $p = .023$). The second component explained 16.6% of variance and was loading preferentially on midbrain connections, and to a lesser extent, negatively on OFC and MPFC connections (one-way ANOVA, $F(4,15) = 38.2$, $p < .001$). The third component explained 12.5% of variance and loaded comparably across all reward regions (one-way ANOVA $F(4,15) = .74$, $p = .580$). The fourth component explained 11.6% of variance and was loading preferentially on MPFC connections (one-way ANOVA $F(4,15) = 5.26$, $p = .008$). Multiple regression then tested the relationship between the component scores and behavioral reward modulation across participants. The first component score significantly tracked behavioral reward modulation (beta = 7.09, $SE = 3.13$, $p = .03$) while the remaining components did not (all $p > .18$). These results indicate ACC, OFC and VS connectivity with hippocampus/PHC co-vary, and jointly track memory sensitivity to reward. Midbrain and MPFC connectivity co-varied to a lesser degree with the other reward-related regions and with each other. Furthermore, the components that midbrain and MPFC most strongly loaded on did not track memory sensitivity to reward, opening the possibility that they may each be a part of functionally different systems.

The lack of differentiation between modulators and non-modulators based on hippocampus/PHC-midbrain was unexpected, especially given that significant effects of connectivity were observed for other reward-related regions in both ANOVA and PCA. While

reward modulatory effects on midbrain interactions with memory regions have been documented previously (Gruber et al., 2016; Wolosin et al., 2012), the effect may not result in increased sensitivity to reward per se. Instead, overall greater interactions – irrespective of external rewards – may lead to greater dopamine availability in the hippocampus and greater memory overall (Duncan et al., 2014; Lisman et al., 2011; Tompary et al., 2015).

To test this idea, we performed a second multiple regression with component scores as predictors, but this time using overall accuracy as an outcome. The second component significantly predicted the overall accuracy across participants (beta = .28, SE = .11, p = .02), while the other three components did not (all $p > .5$). Thus, a distinct pattern of resting state connectivity, captured by the second component loading preferentially on the hippocampus/PHC-midbrain connectivity, was also relevant to behavior, but tracked overall memory rather than memory sensitivity to reward.

Omnibus PCA across task and rest. To test the degree to which cross-correlations may remain stable across task and rest, a second PCA was performed on the whole set of 30 connectivity values per subject (10 connections for each pre-encoding, encoding, and post-encoding periods). Connectivity values derived from low-pass filtered timeseries were used to match pre-processing across task and rest. Three components explained more than 10% of variance. Monte Carlo simulations (Figure 2.6A) indicated that only components 1 and 2 explained more variance than expected by chance (both $p < 0.001$). Component 3 did not (p = 0.8) and was thus not considered further. The loadings of each reward regions on the two retained components are presented in Figure 2.6C.

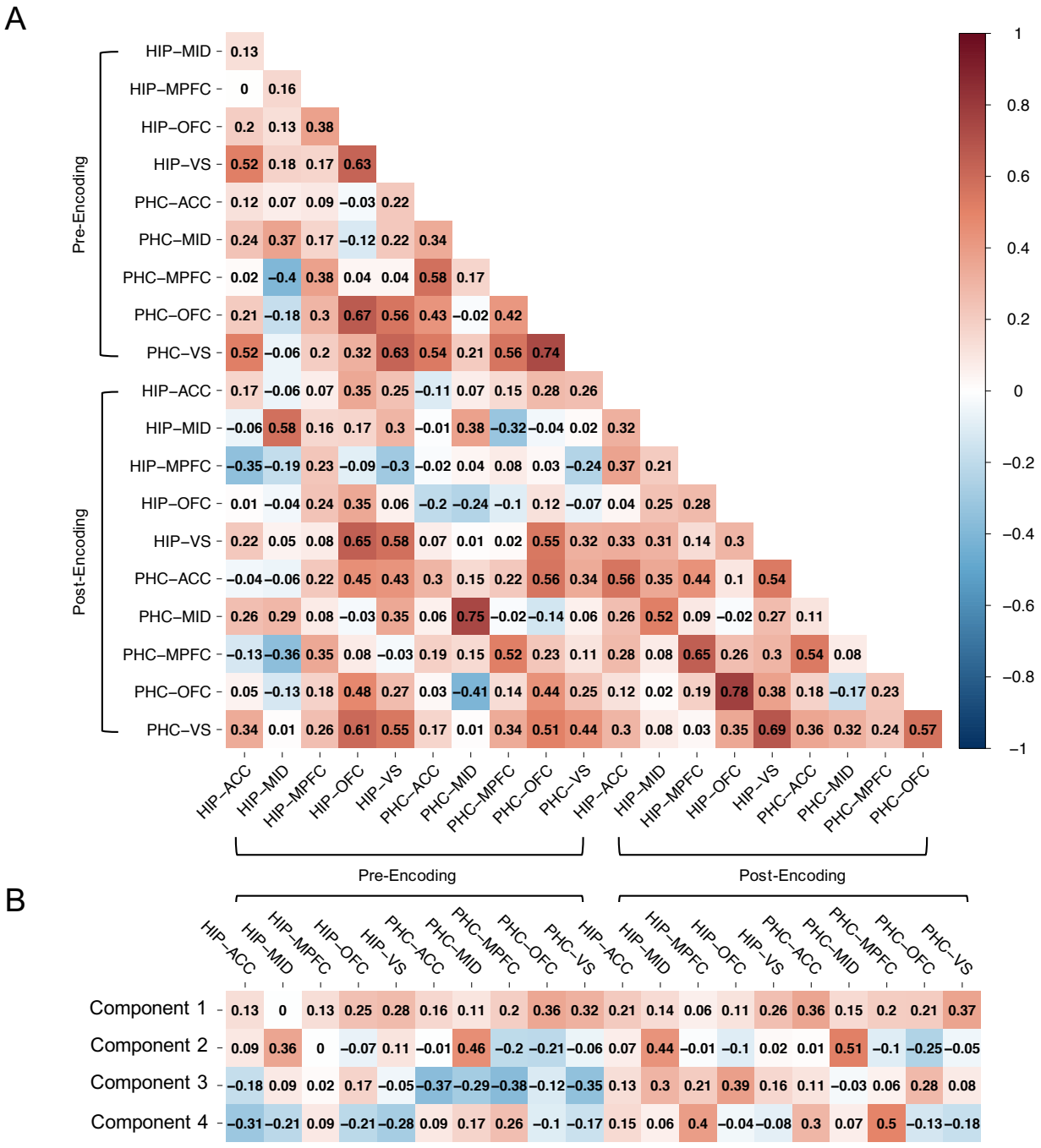

Figure 2.8. Relationships among connections. **A.** Pairwise, cross-participant correlations of all rest-based connectivity measures. **B.** Loadings of each pre-encoding and post-encoding connection on the four components that were generated by PCA.

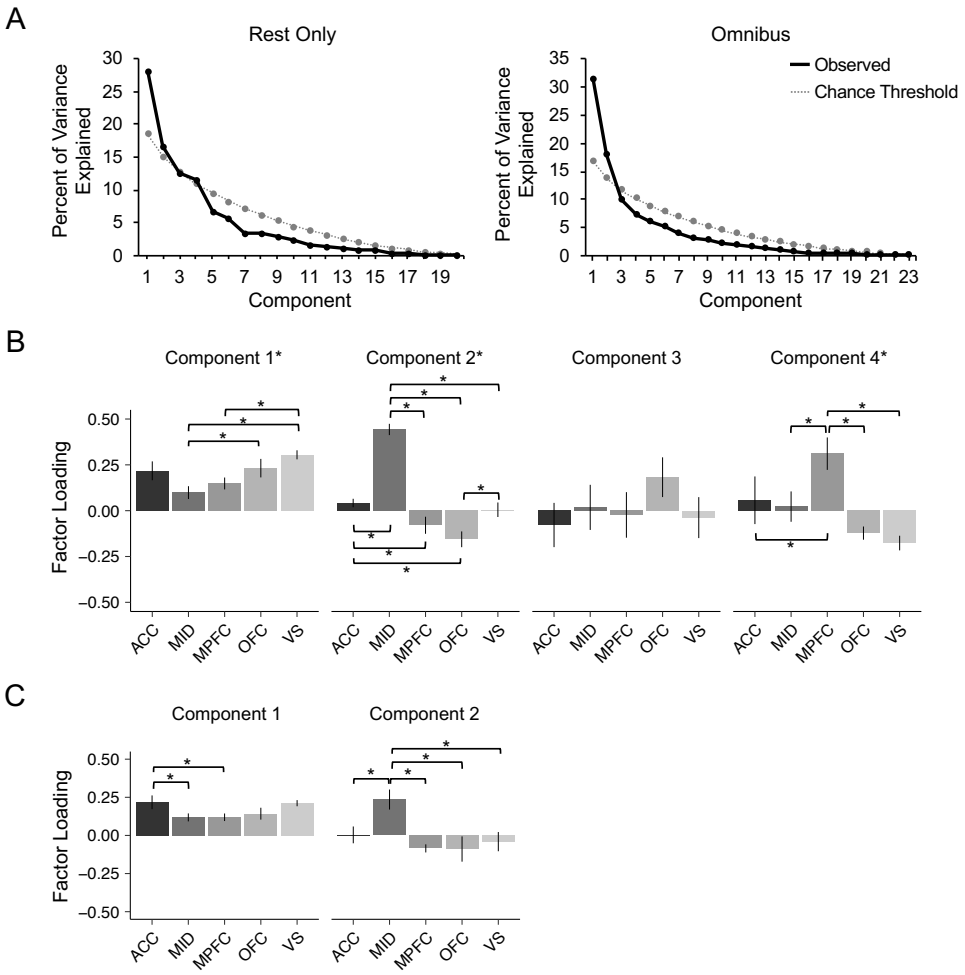

Figure 2.9. The loadings of each reward ROI's connections on PCA generated components. **A.** The percent of variance explained by each component in both the rest only PCA (left) and omnibus PCA (right). The gray dotted line denotes the upper threshold for chance ($p < .05$) of percent explained by each component. **B.** The relative contribution of each reward ROI (ACC, MID, MPFC, OFC, VS) on each of the four retained PCA-derived components on pre-encoding and post-encoding resting state connectivity between memory and reward ROIs. **C.** The relative contribution of each reward ROI on the two retained components derived from the omnibus PCA across task and rest. In both B & C, bars with stars denote significant pair-wise differences in loadings.

The first component explained 31.4% of variance and showed marginal differences between loadings among reward regions (one-way ANOVA $F(4,25) = 2.30$, $p = .086$), with numerically greatest loadings of ACC and VS. The second component explained 18.0% variance and most strongly loaded on midbrain connections ($F(4,25) = 4.78$, $p = .005$). Multiple regression with component scores as predictors and BRM as an outcome showed that the first component was a significant predictor of BRM (beta = 2.99, $SE = 1.00$, $p = .007$), while the other

was not ($p > .09$). A second multiple regression with the overall accuracy as an outcome did not reveal any significant effects (all $p > .2$). Thus, the omnibus PCA partially replicated the rest-only PCA. Taken together, the PCA findings indicate that: (1) connectivity patterns of ACC, VS and potentially OFC are functionally coupled, with a composite connectivity score that most strongly loaded on these regions tracking memory sensitivity to reward, (2) midbrain and potentially MPFC connectivity patterns co-vary to a lesser degree with the other reward regions and each other, and (3) resting state hippocampus/PHC-midbrain connectivity may be more predictive of overall memory performance than memory sensitivity to reward.

Predicting Memory Sensitivity to Reward from Connectivity Patterns Using Machine Learning

The ANOVA and PCA findings reported above showed that connectivity between memory and reward-related regions tracked individuals' memory sensitivity to reward, and that this relationship may be relatively preserved irrespective of task stage. To more directly quantify how well patterns of connectivity may differentiate between modulators and non-modulators, we applied SVC to predict modulator status from connectivity patterns in each task stage (inputs = 10 connectivity values, outputs = modulator status). Classification accuracy that occurred with a probability of less than .017 (.05/3 to correct for multiple comparisons) was considered significant. Using cross-validation, we found that classification of modulator status from connectivity patterns was reliably above chance in the pre-encoding scan (accuracy = 79.2%, $p = .010$) and the encoding scan (accuracy = 75%, $p = .006$). Classification based on the post-encoding scan was lower and not reliably different from chance (accuracy = 58.3%, $p = .157$) (Figure 2.7A). Although the classification accuracy based on post-encoding connectivity did not reach significance, we did not find evidence that the probability of mis-classification would be

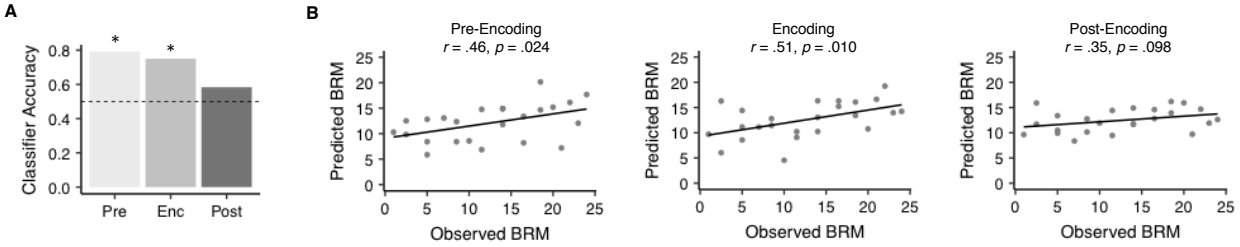

Figure 2.10. Predicting memory sensitivity to reward from connectivity patterns. **A.** Support vector classification accuracy of connectivity predicting modulator status at each of the task stages. The classifier accuracy for both pre-encoding and encoding connectivity were reliably above chance (indicated by the dashed line), as determined by a permutation test. **B.** Comparison of observed BRM and predicted BRM by support vector regression at each task stage.

reliably greater at post-encoding compared to pre-encoding or encoding task stages (both $\chi^2 <$ 2.1, $p > 1.5$).

To verify that successful classification did not depend on treating reward modulation as a dichotomized variable, ε-SVR was conducted to predict behavioral reward modulation as a continuous measure. Consistent with the SVC findings,

cross-validated SVR revealed that connectivity between memory and reward regions reliably predicted BRM during the encoding scan ($r = .51$, $p = .010$), and marginally predicted during the pre-encoding rest scan ($r = .46$, $p = .024$). The SVR on post-encoding connectivity did not reach significance ($r = .35$, $p = .098$) (Figure 2.7B).

Complementary Connectivity Analyses

Correlations between connectivity changes and behavior. Though we did not find interactions between task stage and reward modulation of memory in the rest-only ANOVA, a changing relationship between connectivity and behavior may be

Table 2.2. Correlations of post–pre resting connectivity changes with behavior

Connection	BRM (*r*)	Accuracy (*r*)
HIP-ACC	.07	.15
HIP-MID	-.05	.13
HIP-MPFC	-.24	.24
HIP-OFC	-.16	.11
HIP-VS	-.26	-.28
PHC-ACC	.08	.07
PHC-MID	-.14	.40
PHC-MPFC	-.34	.02
PHC-OFC	-.23	.30
PHC-VS	-.13	.12

better characterized by a correlation of task-induced increases in connectivity with behavior (Gruber et al., 2016; Murty et al., 2017; Tambini et al., 2010). To test the effect of connectivity increases on behavior, we ran exploratory correlations between pre-to-post connectivity increases and both BRM and overall accuracy (Table 2.2). None of the memory-reward ROI connections predicted BRM (all $p > .15$, uncorrected for multiple comparisons) nor overall cued recall rates (all uncorrected $p > .05$). There was a marginal correlation between PHC-midbrain connectivity and overall accuracy ($r = 0.40$, $p = .052$), providing a partial replication of prior reports on midbrain connectivity changes tracking behavior (Duncan et al., 2014; Gruber et al., 2016).

Anterior and posterior differences within hippocampus. Functional differences between anterior and posterior hippocampus were tested in a 3 (task stage) x 2 (hippocampus ROI: anterior, posterior) x 5 (reward ROI) repeated measures ANOVA with modulator status as a between-subjects factor. The results for the ANOVA are reported in Table 2.3, and all connections are displayed in Figure 2.8. We found a main effect of modulator status, indicating that hippocampal connectivity with reward regions tracked memory sensitivity to reward. We also found a significant interaction between reward ROI and hippocampal division, indicating that anterior and posterior hippocampus are preferentially connected to distinct reward regions. Of main interest were interactions between hippocampal division and modulator status that would indicate that anterior and posterior portions of the hippocampus differentially predict reward modulation of memory. However, all interactions that included modulator status and hippocampal ROI as factors were non-significant (all $F < 1.5$, $p > .3$), providing no evidence for such dissociation.

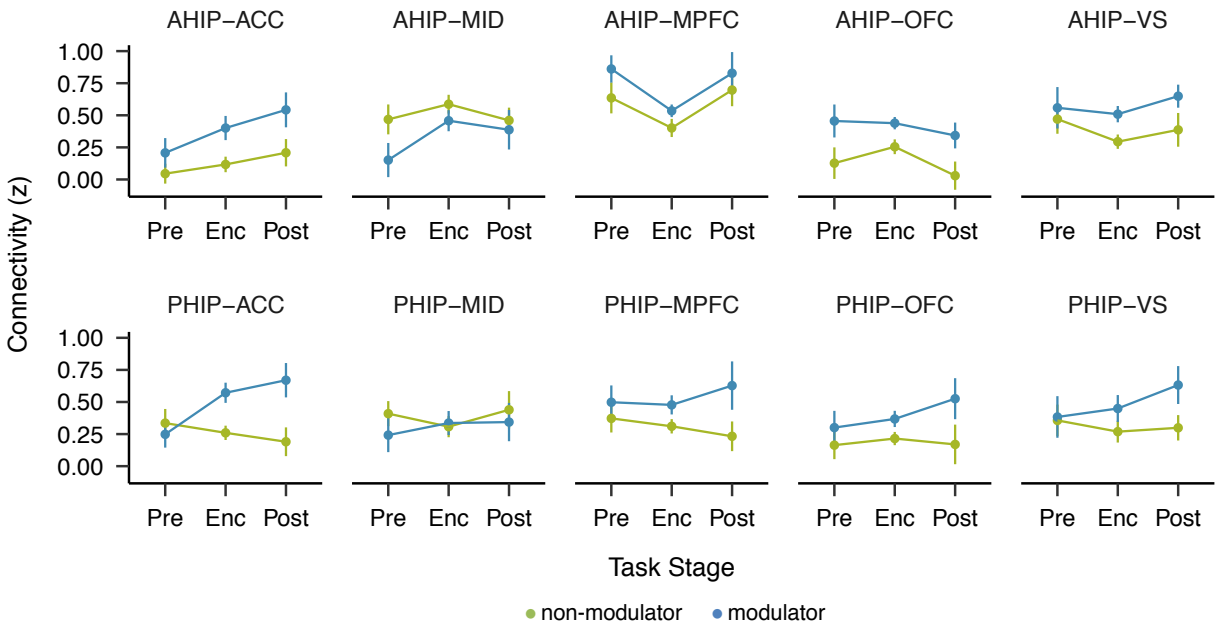

Figure 2.11. Connectivity of anterior and posterior hippocampus with reward ROIs. Background connectivity between reward ROIs and anterior/posterior hippocampus across the three task stages are presented separately for modulators and non-modulators.

Table 2.3. Anterior v. posterior hippocampus ANOVA table

Source	df_{effect}	df_{error}	F	p	η_p^2
Modulator*	1	22	4.96	.037	.18
Task stage	2	44	.86	.431	.04
Task stage x Modulator	2	44	1.49	.237	.06
Hippocampus ROI	1	22	1.89	.183	.08
Hippocampus ROI x Modulator	1	22	.03	.856	.00
Reward ROI***	4	88	6.07	.000	.22
Reward ROI x Modulator*	4	88	3.56	.010	.14
Task stage x Hippocampus ROI	2	44	.12	.892	.01
Task stage x Hippocampus ROI x Modulator	2	44	1.23	.302	.05
Task stage x Reward ROI	8	176	1.93	.058	.08
Task stage x Reward ROI x Modulator	8	176	.65	.738	.03
Hippocampus ROI x Reward ROI (GG)***	2.91	63.97	10.53	.000	.32
Hippocampus x Reward ROI x Modulator (GG)	2.91	63.97	.61	.609	.03
Task stage x Hippocampus x Reward ROI (GG)**	4.04	88.93	4.04	.005	.16
Task x Hippocampus x Reward x Modulator (GG)	4.04	88.93	1.06	.382	.05

Note: ANOVA included within-subject effects of task stage (pre-encoding, encoding, post-encoding), hippocampus ROI (anterior, posterior), and reward ROI (ACC, midbrain, MPFC, OFC, VS), with modulator status (non-modulator, modulator) as a between-subjects factor. * $p < .05$, ** $p < .01$, *** $p < .001$

As a last analysis, we tested whether connectivity increases from pre- to post-encoding rest may be differentially related to behavior for anterior and posterior hippocampus. Thus, we correlated BRM with post-pre connectivity changes in each connection, separately for anterior and posterior hippocampus. No significant correlations were found (all $|r| < .32$, all $p > .05$).

Discussion

The current study measured functional connectivity between memory and reward regions before, during, and after a monetary incentive encoding task. Using both standard and machine learning approaches, we observed that connectivity of hippocampus and PHC with reward-related regions tracked individual differences in memory sensitivity to reward. This effect was differentially driven by a subset of reward regions: ACC, OFC, and VS connectivity patterns co-varied together across participants and were consistently predictive of individual differences in reward modulation of memory. Midbrain connectivity with hippocampus and PHC was not related to memory sensitivity to reward, and the MPFC connectivity with memory regions varied across analyses. The relationship between connectivity and reward modulation of memory was present prior to encoding and during encoding, with weaker but not reliably different effects during post-encoding rest. Overall connectivity between memory and reward regions increased from pre- to post-encoding rest, but connectivity changes were not significantly related to behavior. These results demonstrate stable individual differences in intrinsic communication between memory and reward-related regions that track individual differences in reward modulation of memory. Furthermore, the results implicate a wider set of reward-related regions in memory modulation by reward than previously considered.

Theoretical perspectives have emphasized the role of midbrain, and to some degree VS, in memory modulation by reward (Lisman & Grace, 2005). A central finding of the current study

is that connectivity of reward regions VS, ACC, and OFC with hippocampus and PHC was related to the degree to which individuals' memory was impacted by reward. The role of VS in reward modulation of memory is predicted by current models, which postulate that VS integrates and relays dopamine signals from the hippocampus to the midbrain (Lisman & Grace, 2005). A prior study on reward-motivated encoding found univariate activation in VS covaried with hippocampus and PHC, further tracking the impact of reward on memory (Adcock et al., 2006). Our study, however, is the first to show connectivity between VS, jointly with OFC and ACC, and memory centers in hippocampus and PHC predicted individual differences in reward modulation of memory, irrespective of when connectivity was measured. Interestingly, background VS-hippocampal connectivity is also observed in procedural learning when procedural learning is rewarded (Hamann et al., 2014). Thus, while the traditional multiple memory systems view postulates a division of labor between hippocampus, supporting declarative memory, and striatum, supporting procedural memory (Squire, 1992), there may be a strong degree of interactions between these systems supporting both episodic memory and procedural learning (Doll et al., 2015; Hamann et al., 2014; Kafkas & Montaldi, 2015; Wimmer et al., 2012).

Our study also implicated two reward regions previously not considered in the context of reward motivated learning – the OFC and ACC – which showed similar profiles to VS. While novel in the area of reward modulation of memory, prior work has reported hippocampal connectivity with ventromedial/orbitofrontal regions across various contexts of learning (Gluth et al., 2015; Ranganath et al., 2005; Tsukiura & Cabeza, 2008; Zeithamova et al., 2012). For instance, background hippocampal-OFC connectivity inversely tracks transfer of learned reward to related experiences (Gerraty et al., 2014). In a sensory preconditioning paradigm, participants

encoded face-face pairs and then were trained to associate a gain, loss, or no value with one of the faces. Hippocampal-OFC connectivity was negatively correlated with transfer, meaning that participants with stronger connectivity showed lesser tendency to extend the learned face value to related faces. Thus, although the role of interactions between memory regions and OFC may vary depending on the specific task, our study converges with prior work to show that participants with greater hippocampal-OFC connectivity are more likely to differentiate events based on their explicitly assigned values.

The functional relevance of ACC in memory in humans is currently less understood. During rest, ACC demonstrates functional connectivity with both hippocampus and PHC (Cao et al., 2014; Margulies et al., 2007). In rodents, the ACC has been implicated in consolidation of learned associations into long-term memory, showing coordinated cellular changes with the hippocampus (Wang et al., 2012; Weible et al., 2012). Here, ACC, OFC, and VS connectivity with hippocampus and PHC co-varied across participants. While intrinsic, coordinated activity between the hippocampus, ventral striatum, and OFC has been reported previously (Gerraty et al., 2014; Kahn & Shohamy, 2013), our data implicate that ACC may comprise a functional network with VS and OFC.

Although ACC and OFC may show distinct functions in some tasks (Luk & Wallis, 2013), the ACC, OFC, and VS all share similar functions during reward processing, such as tracking anticipated reward values and outcomes (Amiez et al., 2006; Bialleck et al., 2011; Knutson et al., 2005; Yan et al., 2016) and signaling the value of choices (Boorman et al., 2009; Rogers et al., 2004; Strait et al., 2014). Together, these regions may serve to promote motivationally-salient behaviors or suppress motivationally-irrelevant behaviors (Hare et al., 2008; Kaping et al., 2011; Nieuwenhuis & Takashima, 2011; O'Doherty, 2011; Walton et al.,

2015). Greater background hippocampal and PHC interactions with ACC, OFC, and VS may reflect greater availability of reward signals to memory structures, resulting in enhanced modulation of memory by reward in our paradigm. While the unique contribution of each region will require further inquiries into their individual roles in motivated learning, our data provide several new insights into their functional interactions.

An unexpected aspect of the current data was the U-shaped relationship between reward value and memory found in the fMRI sample. While this finding was unexpected and not replicated in the accompanying behavioral sample, it is neurobiologically plausible. U-shaped responses to reward have been identified in the medial frontal and medial orbitofrontal cortices (Elliott et al., 2003). Notably, regions like ACC and VS signal the reward prediction error, or the discrepancy between expected and experienced rewards (Abler et al., 2006; Fiorillo et al., 2003; Montague et al., 1996; Silvetti et al., 2011). These signals do not reflect the absolute value of losses and gains but rather the relative value, flexibly scaling around an expected reference point (Seymour & McClure, 2008; Tobler et al., 2005). In the current task, the dime trials may have served as a reference condition, with dollar trials being perceived as rewards and penny trials as relative losses. The salience of both losses and gains can impact performance (Bartra et al., 2013; Shigemune et al., 2014), manifesting as the U-shape in cued recall accuracy across the reward conditions. Taken together, reward effects on memory may reflect the influence of reward prediction error signals on encoding, which may be non-linear in nature.

Contrary to prior studies, we did not find a relationship between hippocampal-midbrain connectivity and reward modulation of memory, even when the hippocampus was separated into anterior and posterior sections (Adcock et al., 2006; Gruber et al., 2016; Murty et al., 2017; Wolosin et al., 2012). Rather, we found a correlation between a component score from PCA that

loaded preferentially on midbrain-hippocampus/PHC connections and overall accuracy. While this finding was not expected *a priori*, it is consistent with the proposal that interactions between midbrain and medial temporal regions are not unique to externally motivated rewards but support encoding and consolidation in general (Lisman et al., 2011). Consistent with this view, midbrain has been shown to interact with hippocampus in encoding tasks that do not involve reward (Duncan et al., 2014; Zeithamova et al., 2016), with both background connectivity during encoding (Duncan et al., 2014) and rest connectivity after encoding (Tompary et al., 2015) tracking associative memory. Our findings suggest that midbrain connectivity during reward motivated encoding may be more relevant to overall associative memory than reward modulation of memory and potentially plays a distinct functional role in memory from other reward-related regions.

Of note is the relatively short delay between encoding and test in our paradigm that may also affect the pattern of midbrain effects observed. Reward-related memory effects have been documented during immediate tests of memory (Gruber, 2016; Wolosin, 2012; 2013), but appear stronger after overnight consolidation (Patil et al., 2017; Tompary et al., 2015; Wittmann et al., 2005). The delayed impact of reward on memory performance is thought to reflect enhancement of dopamine-dependent consolidation processes by rewards (Lisman et al., 2011). Thus, while midbrain interactions with hippocampus and PHC predicted overall memory in our paradigm, it is possible that an additional midbrain contribution to reward-enhanced consolidation would be observed if recall had been performed after a 24-hour interval had elapsed.

One reward region that did not show a consistent relationship to behavior in our paradigm was MPFC. Connectivity with MPFC was predictive of memory sensitivity to reward in the omnibus ANOVA across rest and task, but the relationship to behavior did not replicate in other

analyses. Although prefrontal reward regions like OFC and MPFC are spatially proximal and often considered together, the PCA results indicate that they may participate in partially distinct networks. A more conclusive characterization of the role of MPFC in motivated encoding and memory in general awaits future studies.

In addition to implicating a broader set of reward regions in motivated encoding than previously considered, a second key contribution of our study is novel evidence for the connectivity fingerprint hypothesis (Finn et al., 2015; Gratton et al., 2018). Measuring patterns of connectivity before, during, and after motivated encoding, we found that individual differences in reward modulation of memory were predicted by connectivity between memory and reward regions, irrespective of when connectivity was measured. Though post-encoding connectivity was less consistently related to behavior, we found no reliable differences in predictability of behavior between the task stages. These results are in line with the recent findings of stable connectivity patterns and their relationship to individual differences in cognition (Finn et al., 2015; Gratton et al., 2018; Poole et al., 2016; Touroutoglou et al., 2015; Wang et al., 2010), newly extending them to the area of motivated encoding.

Our focus on stable, individual differences in connectivity complement other approaches to linking connectivity to behavior, including memory. Resting state functional connectivity can change on a short time-scale in response to a task (Tambini et al., 2010; Urner et al., 2013), with learning-related connectivity changes relating to memory performance (Gruber et al., 2016; Murty et al., 2017; Tambini et al., 2010; Urner et al., 2013). During task performance, across-region coupling may change even more rapidly, differentiating between memory task conditions at the order of minutes or even from individual trial to individual trial (Kafkas & Montaldi, 2015; Rissman et al., 2004; Zeithamova et al., 2012; Zeithamova et al., 2016). For example, Kafkas &

Montaldi (2015) showed that hippocampal-VS connectivity was greater during encoding of unexpected versus expected stimuli. Thus, both the stable and variable aspects of connectivity provide information relevant to cognition.

Which aspects of connectivity (stable or task-induced) are more pronounced or most relevant to behavior is an open question (Gratton et al., 2018), but may depend on the task and the specific region. For example, Gruber et al. (2016) found reward modulation of memory related to task-induced connectivity changes, whereas we found that stable connectivity patterns predicted behavior. Regarding task differences, the Gruber et al. (2016) study tested incidentally encoded scene-object associations, with four possible scenes repeated many times across encoding. Two scenes were always low-value and two high-value. Performance on a forced-choice test asking which of the four scenes was previously associated with a given object (with "unsure or new" as a fifth option) could thus partially rely on remembering the object's value, which is plausible given that object-scene memory was relatively close to chance. In contrast, the present study required intentional encoding of trial-unique object pairs, with trial value being unrelated to the memoranda. Regarding regional differences, Gruber et al. (2016) found midbrain connectivity changes that tracked behavior, which was partially replicated in our data. In contrast, we found stable connectivity patterns of other reward-related regions with memory regions to relate to behavior. Although speculative at this time, these commonalities and differences across findings open up a new avenue for inquiry regarding the factors that determine how stable vs. dynamic aspects of connectivity may relate to different aspects of cognition.

Complementary to our main questions of interest, we further conducted an exploratory analysis of potential functional differences between the anterior and posterior hippocampus. While anterior/posterior differences have been previously documented in various memory

paradigms (Bowman & Zeithamova, 2018; Brunec et al., 2018; McKenzie et al., 2014; Poppenk et al., 2013), the evidence within the domain of motivated encoding is sparse and varying. For example, Murty et al., (2017) reported a stronger link between anterior hippocampal connectivity and behavior while Wolosin et al. (2013) found reward modulation effect in posterior hippocampus. We found anterior/posterior differences with respect to connectivity with distinct reward regions, however, the relationship to memory sensitivity to reward was comparable for anterior and posterior hippocampus. Taken together, these studies indicate that reward modulation of memory may not be strongly dissociated along the anterior/posterior axis.

In summary, the current study significantly expands our understanding of motivational influences on memory, newly demonstrating the role of stable, individual differences in connectivity in predicting how individual's memory is impacted by reward. The results also demonstrate a role for several reward-related regions in motivated encoding that have not been previously considered, highlighting the importance of both theoretically and empirically-driven approaches in understanding brain-behavior relationships. More broadly, the work informs current theories on functional differentiations within the reward processing network and brings new evidence for the fruitfulness of utilizing individuals' connectivity patterns in the study of cognition (Finn et al., 2015; Gratton et al., 2018).

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CHAPTER III

DIFFERENTIAL FUNCTIONAL CONNECTIVITY ALONG THE LONG AXIS OF THE HIPPOCAMPUS ALIGNS WITH DIFFERENTIAL ROLE IN MEMORY SPECIFICITY AND GENERALIZATION

From Frank, L.E., Bowman, C.R., & Zeithamova, D. (2019). Differential functional connectivity along the long axis of the hippocampus aligns with differential role in memory specificity and generalization. *Journal of Cognitive Neuroscience, 31*(12), 1958-1975. doi: https://doi.org/10.1162/jocn_a_01457

Healthy memory function involves both the ability to remember details of individual events (specificity) and the ability to link related experiences to form new knowledge (generalization). It is well established that the hippocampus supports rapid learning of specific events (Bunsey & Eichenbaum, 1996; Scoville & Milner, 1957; Vargha-Khadem, 1997). More recent work has also demonstrated a role for the hippocampus in integrating related events to form generalized memories (Bowman & Zeithamova, 2018; Shohamy & Wagner, 2008; Zeithamova, Dominick, & Preston, 2012). How the hippocampus can simultaneously support memory for individual experiences and knowledge generalization is an area of active investigation (Berens & Bird, 2017; Poppenk, Evensmoen, Moscovitch, & Nadel, 2013; Schapiro, Turk-Browne, Botvinick, & Norman, 2017).

A recent proposal suggests that information is represented at varying levels of specificity along the long axis of the hippocampus: representations in the posterior hippocampus are thought to be detailed and fined grained, while those in the anterior hippocampus are more coarse and global (Poppenk et al., 2013). This hypothesis stems from animal research showing that receptive fields of hippocampal place cells increase in size from the dorsal (analogue of human posterior) to ventral (analogue of human anterior) hippocampus (Kjelstrup et al., 2008), representing

information at increasingly larger spatial scales. Recent work has extended this representational gradient to humans, finding that functional MRI signals within the anterior hippocampus were more correlated across voxels and self-correlated across time than signals in the posterior hippocampus (Brunec et al., 2018), consistent with the idea that posterior hippocampus represents events on a fine-grain temporal and spatial scale to capture detailed variations while anterior hippocampal representations span a larger temporal and spatial scale to enable generalization across events. Two recent functional MRI findings further corroborate this idea. In an associative inference task where participants encoded overlapping pairs of items that shared a common element (A-B, B-C), Schlichting and colleagues (2015) found that the anterior hippocampus formed integrated representations of the overlapping events (A-B-C representation), whereas overlapping event representations remained separated in the posterior hippocampus. Collin and colleagues (2015) found hierarchical representations of narratives along the hippocampal long axis, from individual events to multi-event narratives, suggesting that this functional organization may be a consistent property of the hippocampus that spans multiple domains.

In addition to functional differences within the hippocampus, regions outside the hippocampus also differentially contribute to memory specificity and generalization. Lateral prefrontal cortex, particularly the inferior frontal gyrus (IFG), supports memory specificity by resolving interference between related items (Badre & Wagner, 2005; Bowman & Dennis, 2016; Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998; Kuhl, Dudukovic, Kahn, & Wagner, 2007). Additionally, portions of posterior parietal cortex such as the angular gyrus (ANG) support memory specificity by representing individual items with high fidelity during retrieval (Kuhl & Chun, 2014; Xiao et al., 2017). Distinct regions have been implicated in

memory generalization. The ventromedial prefrontal cortex (VMPFC) contributes to generalization by integrating related memories during encoding (Schlichting et al., 2015; Zeithamova et al., 2012), encoding new information in light of prior knowledge (van Kesteren et al., 2013), and transferring conceptual knowledge to new examples (Bowman & Zeithamova, 2018; Kumaran, Summerfield, Hassabis, & Maguire, 2009). Lateral temporal cortices, especially the middle temporal gyrus (MTG), also support generalized memories, such as semantic memory (Mummery et al., 2000), conceptual knowledge (Bowman & Zeithamova, 2018; Davis & Poldrack, 2014), and 'gist' representations (Dennis, Kim, & Cabeza, 2008; Turney & Dennis, 2017).

Despite evidence that generalized and specific memory representations exist both within the hippocampus and in cortex, we know relatively little about how regions supporting these distinct functions interact with one another. Studies have shown strong functional connections during rest between the hippocampus (as a whole) and cortical regions indicated above, including the medial prefrontal cortex, lateral temporal cortices, and portions of parietal cortex (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Vincent et al., 2006). However, evidence is mixed regarding functional connectivity differences along the long axis of the hippocampus (Blessing, Beissner, Schumann, Brünner, & Bär, 2016; Robinson, Salibi, & Deshpande, 2016; S. F. Wang, Ritchey, Libby, & Ranganath, 2016). Recent studies have also started to investigate the functional relevance of hippocampal-cortical connectivity for memory specificity and generalization. Regarding specificity, hippocampal-IFG connectivity supports subtle memory discriminations during retrieval (Bowman & Dennis, 2016; Manelis, Paynter, Wheeler, & Reder, 2013), and neural stimulation manipulating the strength of hippocampal-parietal connectivity can lead to enhancement of associative memory (Tambini, Nee, &

D'Esposito, 2017; J. X. Wang et al., 2014). Regarding generalization, studies have focused on hippocampal-VMPFC connectivity, which has been shown to track the demands on memory integration during encoding (van Kesteren et al., 2010; Zeithamova et al., 2012). Furthermore, individual differences in hippocampal-VMPFC connectivity track individual differences in generalization performance (Gerraty, Davidow, Wimmer, Kahn, & Shohamy, 2014; van Kesteren et al., 2010), with *smaller* connectivity values associated with better performance. Recent work has also linked portions of lateral temporal cortices to this hippocampal-VMPFC circuit (Liu, Grady, & Moscovitch, 2017, 2018), but not in a memory generalization task, leaving the role of this region in generalization unclear.

In the present study, we sought to characterize differences in hippocampal-cortical connectivity along the long-axis of the hippocampus during rest and in the context of a generalization task. Participants first trained outside the scanner to classify cartoon animals into two novel categories, then completed three types of tasks while undergoing fMRI: rest, passive viewing of training and generalization items, and active classification of training and generalization items. We hypothesized that putative memory specificity regions (IFG, ANG) would show stronger connectivity with posterior compared to anterior hippocampus, while putative generalization regions (VMPFC, MTG) would show stronger connectivity with anterior compared to posterior hippocampus. We further hypothesized that the strength of these functional connections, especially the connectivity between anterior hippocampus and cortical generalization regions, would be related to generalization performance.

In order to measure connectivity across all task stages, we focused primarily on background connectivity, a functional connectivity measure of low-frequency signal coupling between regions after trial-by-trial signal fluctuations are removed. One view of background

connectivity emphasizes its dynamic nature, where background connectivity is interpreted to be reflective of temporary brain states associated with cognitive processes, such as levels of attention (Al-Aidroos, Said, & Turk-Browne, 2012), emotional arousal (Tambini, Rimmele, Phelps, & Davachi, 2017), encoding versus retrieval (Duncan, Tompary, & Davachi, 2014), and goal states (Norman-Haignere, McCarthy, Chun, & Turk-Browne, 2012). In contrast, other research has underscored that patterns of connectivity are relatively stable across levels of external task engagement (Frank, Preston, & Zeithamova, 2019; Gratton et al., 2018; Horien, Shen, Scheinost, & Constable, 2019; Touroutoglou, Andreano, Barrett, & Dickerson, 2015), with measures of background connectivity providing principally the same information as measures of resting state connectivity. Thus, we computed both background connectivity across levels of task engagement and traditional resting state connectivity to test whether any observed differences in anterior and posterior hippocampal connectivity with cortical memory regions are dynamic characteristics driven by task engagement or whether they reflect stable characteristics of hippocampal memory networks. If the anticipated anterior and posterior connectivity differences are driven by generalization demands, we might expect them to emerge only when participants are actively categorizing items. If connectivity patterns are relatively stable, we can principally obtain the same information from whichever phase of the experiment (including rest alone), but including all phases provides us with the best estimates of connectivity values for each connection based on all available data.

Method

Participants

The sample size was determined based on an a priori power analysis conducted for the task-based analyses presented in Bowman and Zeithamova (2018), which determined a sample

size of n=32 to be adequate to detect category representations in hippocampus and VMPFC with 80% power. Based on the expected 15-20% exclusion rate due to motion or poor task performance, we decided to collect 40 full datasets. Two participants did not complete the full scan and were immediately replaced. Thus, a total of forty-two volunteers were recruited from the University of Oregon and the surrounding community and received financial compensation for their participation. Sixteen participants were excluded from analyses for failing to complete the task (2 participants), below-chance performance at the end of training and/or in the categorization test (5 participants), structural abnormality (1 participant), and excessive movement (movement > 2 mm within a run or insufficient data remaining following scrubbing as described in fMRI preprocessing, 8 participants), leaving data from 26 participants reported in all analyses (17 females; age, 18-28 years; mean age, 20.8 years; SD age, 3.0 years). All participants provided written informed consent, were right handed, had learned English before 7 years of age, and were screened for MRI contraindications, neurological conditions and medications known to affect brain function. All experimental procedures were approved by Research Compliance Services and the University of Oregon.

Procedure

Participants completed four experimental phases: category training (outside the scanner), a resting-state scan, passive viewing of category examples, and a categorization phase that required generalization of category knowledge to new stimuli (Figure 3.1). Results of a task-based activation analysis of the categorization fMRI data have been reported previously (Bowman & Zeithamova, 2018), including detailed descriptions of the stimuli, category structure, training and generalization task procedures. Briefly, participants first performed five blocks of feedback-based category training outside the scanner. Shortly thereafter, participants

entered the scanner and completed a single run of rest, lasting five minutes, during which participants viewed a fixation cross and kept their eyes open. During two runs of passive viewing, participants viewed training items as well as new items of the same typicality without making overt responses. Participants were told to pay attention to each stimulus because they might be tested on them later. During categorization runs, participants viewed training items as well as novel items at all levels of typicality and classified them into the two categories using button presses. In both passive viewing and categorization, each stimulus was presented for 5 seconds followed by a 7-second ITI. Anatomical images were collected following categorization runs. After the scan, participants completed a brief questionnaire and were verbally debriefed. Connectivity was measured during rest, passive viewing, and categorization.

fMRI Data Acquisition

Scanning was completed on a 3T Siemens MAGNETOM Skyra scanner equipped with a 32-channel head coil at the University of Oregon Lewis Center for Neuroimaging. Head motion was minimized using foam padding. The scanning session started with a localizer scan followed

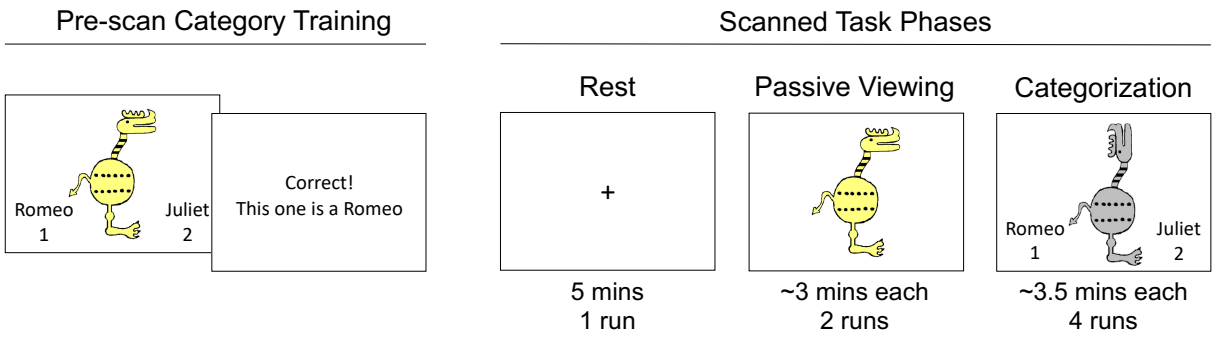

Figure 3.12. Behavioral procedures. Prior to the fMRI scan, participants were trained on the category structures of cartoon animals. The scanned portion of the task consisted of three phases that demanded varying levels of engagement. During rest, participants did not perform any task and were not required to give responses. During passive viewing, participants viewed old and new stimuli without giving any response. During categorization, participants viewed old and new stimuli while responding to which category each one belonged.

by seven functional runs using a multiband gradient echo pulse sequence [TR = 2000 ms; TE =26 ms; flip angle = 90˚; matrix size = 100 x 100; 72 contiguous slices oriented 15˚ off the anterior commissure – posterior commissure line to reduce prefrontal signal dropout; interleaved acquisition; FOV = 200 mm; voxel size = 2.0 x 2.0 x 2.0 mm; generalized autocalibrating partially parallel acquisitions (GRAPPA) factor = 2]. One hundred fifty volumes were collected for the rest scan, 100 volumes for each passive viewing run, and 106 volumes for each categorization run. A standard high-resolution T1-weighted MPRAGE anatomical image (TR = 2500 ms; TE = 3.43 ms; TI = 1100 ms; flip angle = 7˚; matrix size = 256 x 256; 176 contiguous slices; FOV = 256 mm; slice thickness = 1 mm; voxel size = 1.0 x 1.0 x 1.0 mm; GRAPPA factor = 2) was collected following all functional runs. Scanning concluded with a custom anatomical T2 coronal image (TR = 13,520 ms; TE = 88 ms; flip angle = 150˚; matrix size = 512 x 512; 65 contiguous slices oriented perpendicularly to the main axis of the hippocampus; interleaved acquisition; FOV = 220 mm; voxel size = 0.4 x 0.4 x 2 mm; GRAPPA factor = 2).

Regions of Interest

Regions of interest were defined anatomically in individual participants' native space based on the cortical parcellations and subcortical segmentation from Freesurfer version 6 (https://sufer.nmr.mgh.harvard.edu/) and collapsed across hemispheres (Figure 3.2). We defined anterior and posterior hippocampal ROIs separately for each participant by dividing the Freesurfer hippocampal ROI at the middle slice. If there were an odd number of slices, the middle slice was assigned to the posterior hippocampus. We chose the IFG, ANG, VMPFC and MTG for our cortical ROIs based on their differential involvement in memory generalization and specificity. The IFG ROI was obtained by combining the three IFG subregions (labeled as pars opercularis, pars orbitalis, and pars triangularis) provided by Freesurfer. The ANG ROI was

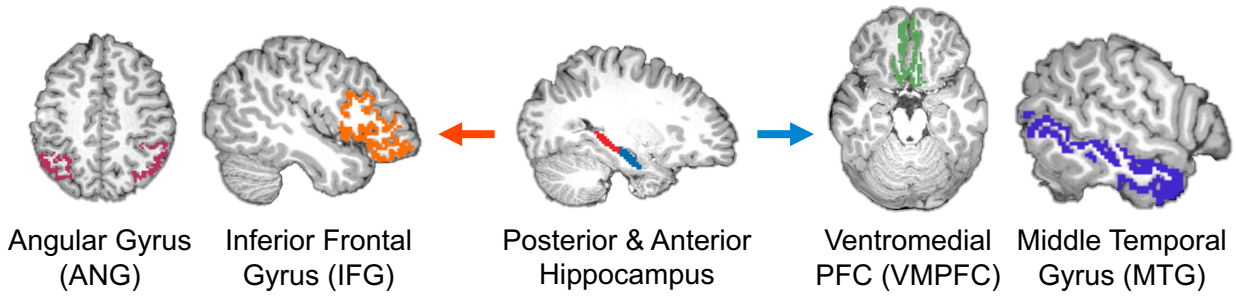

Figure 3.13. Regions of interest. Functional connectivity was measured between posterior (red) and anterior (blue) hippocampus with each of the four cortical ROIs. We predicted that posterior hippocampus would be preferentially connected to ANG and IFG, while anterior hippocampus would show greater connectivity with VMPFC and MTG.

defined using the 2009 Freesurfer parcellations angular gyrus label (Destrieux, Fischl, Dale, & Halgren, 2010). The VMPFC ROI consisted of Freesurfer-defined medial orbitofrontal cortex. The MTG ROI was defined using the Freesurfer middle temporal gyrus label. All individual-participant anatomical ROIs were resampled to functional space using ANTs (Advanced Normalization Tools; http://stnava.github.io/ANTs/) and applied as masks to extract the mean timeseries from each region.

fMRI Preprocessing

Raw dicom images were converted to Nifti format using the dcm2nii function from MRIcron (https://www.nitrc.org/projects/mricron). Functional images were skull stripped using BET (brain extraction tool), which is part of FSL version 5.0.9 (www.fmrib.ox.ac.uk/fsl). Motion correction was computed within each functional run using MCFLIRT in FSL to realign all volumes to the middle volume. Across-run realignment was computed using ANTs with the first functional volume serving as the reference volume. The first volumes of all other runs were registered to the reference volume, and the transformation computed was applied to all other images in the run. Brain-extracted and motion corrected images from each rest, passive viewing

and categorization run were entered into the FEAT (fMRI Expert Analysis Tool) in FSL for high-pass temporal filtering (100 s) and spatial smoothing using a 2 mm FWHM kernel.

As connectivity measures can be inflated by motion and physiological noise, additional steps are required to control for these confounds when calculating connectivity (Murphy, Birn, & Bandettini, 2013; Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). First, we extracted the timeseries for cerebrospinal fluid, white matter, and whole brain signal, and calculated framewise displacement (FD) and global signal change (DVARS) for each functional scan. These values were used as nuisance regressors when calculating connectivity (see below) and used to determine individual volumes for exclusion. Individual volumes were flagged for exclusion if either FD exceeded 0.5 mm or DVARS exceeded 0.5%, as well as one volume before and two volumes after each flagged volume (Power et al., 2012). The first two volumes of each run were also excluded. This scrubbing procedure flagged for removal an average of 6.9% of volumes from rest, an average of 5.3% from passive viewing runs, and an average of 6.8% from categorization runs. Individual runs were excluded from analyses if over 30% of volumes were flagged for removal. All participants included in the final analyses had the rest run and both passive-viewing runs. For three participants, one or two categorization runs were excluded from the final analysis. Participants were excluded entirely if they had more than two individual runs excluded across all functional runs (2 participants).

Measuring Connectivity

When measuring background connectivity, the aim is to remove the effect of co-activation driven by external stimuli prior to calculating connectivity. For example, if two regions respond to the same stimulus, their signal will increase synchronously whenever a stimulus is presented, irrespective of whether these regions communicate with each other. One

method for removing task-related signal from the timeseries is to first model task-related activation and compute connectivity on the residuals. However, as the actual hemodynamic response to each stimulus likely differs somewhat from the model, some residual task-related activation likely remains. A more recent approach for removing task-related signals is to use a low-pass filter set below the task frequency (e.g. Norman-Haignere et al., 2012; Tambini et al., 2017). While it is impossible to rule out that some low frequency task-related features remain, this method can successfully remove trial-by-trial signal fluctuations that may otherwise drive connectivity measures.

Adopting this approach here, all functional scans, including rest, were filtered with a Gaussian linear low-pass filter (16 s) to remove activity cycling faster than task frequency (12 s during both passive viewing and categorization). To determine the appropriate threshold for the low-pass filter, we examined the power spectrum of the BOLD signal from the lateral occipital cortex during a single categorization run (see Figure 3.3 for an example participant). A conservative threshold of 16 s was chosen to adequately remove task-related frequencies. While low-pass filtering is not commonly applied to rest scans, it was necessary to apply it here for analyses that compare connectivity during rest scans with background connectivity measured during task-based scans (Frank, Preston, & Zeithamova, 2019; Van Dijk et al., 2010). We also recalculated all main analyses on rest connectivity only, using resting state connectivity measures from non low-pass filtered timeseries, to validate our findings were not driven by additional preprocessing.

Following low-pass filtering (or no filtering), we excluded all the volumes previously flagged for exclusion prior to calculating connectivity. Connectivity was measured as the partial correlation between each hippocampal ROI (anterior and posterior hippocampus) and each

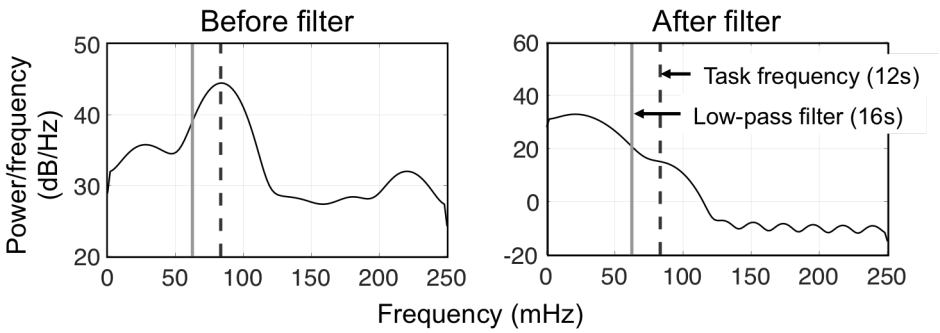

Figure 3.14. Low-pass filter for measuring background connectivity. Left: Power spectrum of a lateral occipital cortex signal during the first run of categorization for an example participant before filtering shows a peak at task frequency (dashed line, 83 mHz = 12 s). A conservative threshold of 62.5 mHz = 16 s (solid line) was chosen for the low-pass filter to assure the removal of all task-related frequencies, as demonstrated by a disappearance of the peak at task frequency on the right panel.

cortical ROI (ANG, IFG, VMPFC, MTG) while controlling for motion and physiological noise. We included the standard six realignment motion parameters, the above-described physiological noise parameters (cerebrospinal fluid, white matter, whole brain signal), and all their derivatives as nuisance regressors. Excluded volumes were removed from all regressors. The resulting correlation coefficients were Fisher z transformed for subsequent analysis.

Comparing Hippocampal Connectivity

To test whether functional connectivity differed between anterior and posterior hippocampus and if these differences depended on the task phase, we conducted a 2 (hippocampal ROI: anterior, posterior) x 4 (cortical ROI: ANG, IFG, VMPFC, MTG) x 3 (phase: rest, passive viewing, categorization) repeated-measures ANOVA. Of particular interest was the interaction between hippocampal ROI and cortical ROI. Follow-up t-tests were conducted to compare connectivity between anterior and posterior hippocampus with each cortical ROI. We predicted that memory specificity regions (ANG, IFG) would show greater connectivity with posterior than anterior hippocampus, while generalization regions (VMPFC, MTG) would be more connected to anterior than posterior hippocampus. The three-way interaction between

hippocampal ROI, cortical ROI, and task phase was also examined to determine if anterior and posterior hippocampal connectivity differences depended on the level of task engagement. The main effects of hippocampal and cortical ROIs were not interpreted as they were not of interest. The full results are reported in an ANOVA summary table.

Connectivity-Behavior Correlations

Although our sample size was chosen for task-based analyses and was small for an individual differences analysis, we wanted to replicate prior reports (Gerraty et al., 2014; van Kesteren et al., 2010) and test whether connectivity measures tracked behavioral generalization performance. We conducted a multiple regression with hippocampal-cortical connections as predictors and generalization (categorization accuracy for new stimuli) as the outcome. As these analyses were underpowered, the likelihood of Type II error was quite high and the results should be interpreted with caution. In order to limit the number of predictors in a single model, separate regressions were conducted for anterior hippocampus connections and posterior hippocampus connections. We hypothesized that anterior hippocampus connectivity with generalization regions would be correlated with generalization success. In addition to average connectivity values, we also related behavior to connectivity within each phase separately to test the stability of connectivity-behavior relationships across phases. When a connection was a significant predictor of behavior in at least one phase, we then compared connection-behavior relationships across phases by computing a z-test for equality of two dependent correlations (Steiger, 1980).

Continuous Hippocampal Connectivity

In addition to the dichotomous anterior versus posterior analysis, we were interested in whether connectivity differences along the hippocampal long-axis were graded in nature. To test

for a functional connectivity gradient, we measured connectivity continuously (i.e., in each slice) from the posterior to anterior hippocampus. The timeseries were extracted from each slice along the longitudinal axis of the hippocampal ROI in functional space individually for the right and left hippocampus in each participant. Peripheral slices that contained fewer than 15 voxels were excluded from the analysis. The number of voxels in slices retained for analyses ranged between 16 and 71 voxels, with a mean number of voxels = 32.49. Following the same procedures outlined above, connectivity was measured between each hippocampal slice in an individual participant and each ipsilateral cortical ROI. Because the length of the hippocampus differs between hemispheres and between individuals, the connectivity values from individual slices were interpolated using a weighted average into six bins (Brunec et al., 2018), resulting in six connectivity values for each hippocampal ROI, which were then averaged across hemispheres. Since task phase did not interact with anterior and posterior hippocampal connectivity differences in the prior ANOVA (see Results below), connectivity was averaged across the task phases and submitted to a 4 (cortical ROI: ANG, IFG, VMPFC, and MTG) x 6 (connectivity bin: posterior to anterior) repeated-measures ANOVA. Of particular interest was the interaction between cortical ROI and connectivity bin. Following a significant interaction (see Results), one-way ANOVA's were conducted to investigate the linear and quadratic effects of connectivity bin for each cortical ROI. Since hippocampal bins were numbered from posterior to anterior, a linear increase in connectivity across the six bins indicated increasing connectivity strength from posterior to anterior, while a linear decrease indicated increasing connectivity strength from anterior to posterior. We also examined quadratic effects of hippocampal bin to determine if connectivity was non-linear along the posterior to anterior axis. For all ANOVAs reported in the

manuscript, Greenhouse Geisser corrections for sphericity were used when appropriate, indicated by "GG" in the resulting ANOVA reports.

Whole-brain Connectivity

While our cortical ROIs were selected based on their contributions to different memory functions, we wanted to further characterize anterior and posterior hippocampus connectivity networks and their overlap across the whole brain. A general linear model was used to identify whole-brain correlations with two seed regions, the bilateral anterior hippocampus and bilateral posterior hippocampus, during each scanning phase. The mean timeseries for each anterior and posterior hippocampus ROI were entered as regressors into FSL FEAT, along with nuisance regressors (cerebrospinal fluid, white matter, whole brain signals, six motion parameters) and their derivatives. We first computed whole-brain connectivity separately for each participant and for each functional scan (one rest scan, two passive viewing scans, four categorization scans) using first-level analyses in FEAT. We then averaged the resulting connectivity maps across separate runs of the same task (passive viewing or categorization) in individual participants using fixed-effects higher-level analyses in FEAT. We then generated a single whole-brain connectivity map per participant by averaging across the three scanning phases. These maps were normalized to MNI space and submitted to group-level analyses using one-sample t-tests to identify regions showing connectivity with anterior and posterior hippocampus across the group. The resulting maps were thresholded using a voxel-wise threshold of $Z = 3.1$, and cluster-extent threshold of $p = .05$. As the whole-brain connectivity maps for both anterior and posterior hippocampus yielded among others a large cluster that spanned across many regions and three or four lobes, we further masked the statistical maps with anatomical masks for each lobe generated using the MNI Structural Atlas and reported significant clusters within each lobe. Multiple local

maxima are reported when the resulting clusters spanned across multiple regions within a lobe. The masking procedure was only done in order to generate meaningful activation tables; the original activation maps are displayed in figures. Finally, we computed an overlap map using a conjunction of the anterior and posterior hippocampal connectivity maps, obtaining regions that were significantly connected with both anterior and posterior hippocampus.

Results

Anterior v. Posterior Connectivity with Cortical Memory ROIs

To test whether cortical memory ROIs were differentially connected to anterior and posterior hippocampus and whether their connection strengths were modulated by task demands, we conducted a 2 (hippocampal ROI: anterior, posterior) x 4 (cortical ROI: ANG, IFG, VMPFC, MTG) x 3 (phase: rest, passive viewing, categorization) repeated-measures ANOVA. The complete results of the ANOVA are reported in Table 3.1. Consistent with our prediction of differential connectivity patterns between anterior and posterior hippocampus, we found a significant interaction between hippocampal ROI and cortical ROI (Figure 3.4A). Follow-up t-tests revealed that ANG ($t(25) = 3.82$, $p = .001$, $\eta_p^2 = .37$) and IFG ($t(25) = 2.07$, $p = .049$, $\eta_p^2 = .15$) showed greater connectivity with the posterior relative to anterior hippocampus, while VMPFC ($t(25) = 5.34$, $p < .001$, $\eta_p^2 = .53$) showed greater connectivity with anterior than posterior hippocampus. The MTG showed no significant difference in connectivity with anterior and posterior hippocampus ($t(25) = .66$, $p = .517$, $\eta_p^2 = .02$).

The overall pattern of connectivity was similar when measured using rest-only data without low-pass filtering. There was a significant interaction between hippocampal and cortical ROIs ($F(2.22,55.39) = 25.37$, $p < .001$, $\eta_p^2 = .50$, GG), driven by greater VMPFC connectivity with anterior hippocampus ($t(25) = 6.99$, $p < .001$, $\eta_p^2 = .66$), and marginally greater ANG connectivity with posterior hippocampus ($t(25) = 1.93$, $p = .066$, $\eta_p^2 = .13$). IFG and MTG connectivity differences were numerically in the predicted direction but were not significant (IFG: $t(25) = 1.37$, $p = .184$, $\eta_p^2 = .07$; MTG: $t(25) = .30$, $p = .766$, $\eta_p^2 = .004$).

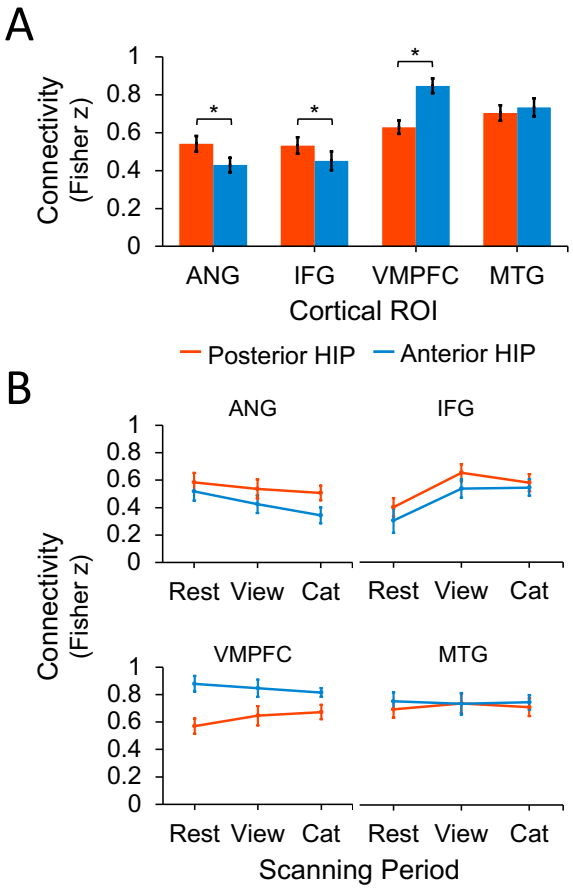

Figure 3.15. Anterior v. posterior hippocampal connectivity. **A.** Low-frequency connectivity between anterior/posterior hippocampus and each cortical region, collapsed across phases. **B.** Results of omnibus ANOVA examining connectivity between each hippocampal section (anterior, posterior) and each cortical ROI (ANG, IFG, VMPFC, MTG) in each task phase (rest, passive viewing, categorization).

The three-way interaction between hippocampal ROI, cortical ROI and task phase was not significant, suggesting that the anterior v. posterior differences in hippocampal connectivity were relatively stable across the task (Figure 3.4B). While there was no significant three-way interaction, we did find a two-way interaction between cortical ROI and task phase. Follow-up one-way ANOVAs examined connectivity of each cortical ROI with the entire hippocampus (averaged across anterior and posterior) across the three task phases. The IFG was the only cortical region that demonstrated a significant effect of phase ($F(2,50) = 4.90$, $p = .011$,

Table 3.4. Omnibus connectivity ANOVA

Source	df_{effect}	df_{error}	F	p	η_p^2
Hippocampal ROI	1.00	25.00	0.27	0.605	0.01
Cortical ROI	3.00	75.00	22.95	0.000	0.48
Phase (GG)	1.58	39.57	0.41	0.620	0.02
Hippocampal ROI x Cortical ROI (GG)	2.20	54.98	24.95	0.000	0.50
Hippocampal ROI x Phase (GG)	1.99	49.69	0.90	0.413	0.04
Cortical ROI x Phase (GG)	3.93	98.12	2.96	0.024	0.11
Hippocampal ROI x Cortical ROI x Phase (GG)	4.28	106.93	1.53	0.196	0.06

$\eta_p^2 = .16$; all others $F < 1$, $p > .4$). The effect of task phase in IFG was driven by significantly smaller IFG connectivity with the hippocampus during rest compared to passive viewing ($t(25) = 2.53$, $p = .018$) and categorization ($t(25) = 2.36$, $p = .026$), with no difference between passive viewing and categorization ($t(25) = .24$, $p = .813$). This finding suggests that low-frequency interactions between the IFG and hippocampus may be driven by task engagement, while interactions between the hippocampus and other cortical regions (ANG, VMPFC, MTG) are more stable.

Connectivity-Behavior Relationships

We tested whether the strength of hippocampal-cortical connectivity, averaged across phases, was related to participants' generalization performance using multiple regressions. Within the anterior hippocampal connections, we found VMPFC-anterior hippocampus connectivity to significantly predict categorization (beta = -.625, $t(21) = -2.64$, $p = 0.015$). No other anterior hippocampal connection tracked performance (all |beta| < .37, $|t(21)| < 1$, $p > .3$). However, given the small sample size for individual differences and the possibility of Type II error, the lack of a relationship to behavior in other ROIs should not be over interpreted. Within the posterior hippocampal connections, we found no connection to be a significant predictor of performance, but VMPFC-posterior hippocampus connectivity was a marginal predictor (beta = -

.472, $t(21) = -2.05$, $p = 0.053$; all other connections |beta| < .32, $|t(21)| < 1$, $p > .3$). Contrary to our prediction, the strength of the VMPFC connectivity-behavior relationship did not differ significantly between anterior and posterior hippocampus ($z = .17$, $p = .865$).

Given the negative direction of the connectivity-behavior relationship, we wanted to ensure that it was not driven by non-compliant participants performing poorly and having high connectivity values due to motion. We first tested whether motion (indexed by mean FD for each participant) can be predicted from connectivity values, computing the same regression as above but replacing generalization with mean FD as the dependent variable. No connection was found to significantly predict motion. Second, we recomputed the above regression with generalization as the outcome variable but included mean FD for each participant as a covariate.

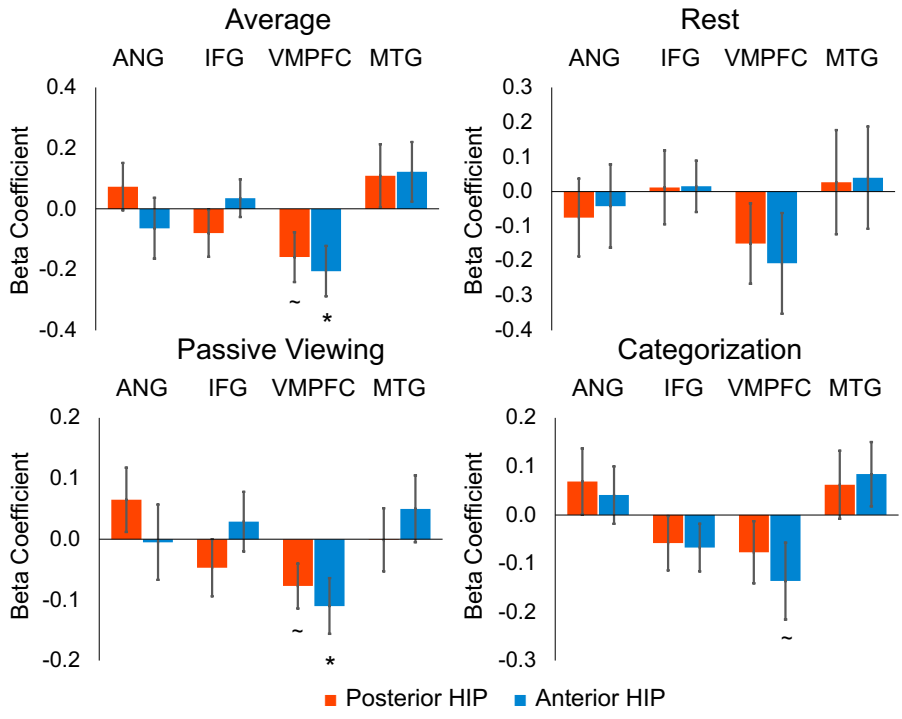

Figure 3.16. Connectivity-generalization relationships. Regressions were conducted on generalization performance using anterior hippocampal connections and posterior hippocampal connections as predictors. Separate models were then run at each task phase to test the relative stability of connectivity-behavior relationships. The rest phase connectivity values were derived from non low-pass filtered timeseries for this figure for a more direct comparison to prior rest-based connectivity work, but analyses of low-pass filtered data also did not reveal any significant predictors.

VMPFC-hippocampal connectivity remained a significant (anterior) and marginal (posterior) predictor of performance even after controlling for participants' motion.

While the anterior v. posterior connectivity differences were relatively stable across task phases, we wanted to evaluate whether the connectivity-behavior relationship was relatively stable as well. We thus conducted the same regression analyses within each phase (rest, passive viewing, categorization; Figure 3.5). The connectivity-behavior relationship did not reach significance during the rest phase (all |beta| < .41, $|t(21)| < 1.6$, $p > .14$), both anterior and posterior hippocampal-VMPFC connectivity was reliably related to performance during the passive viewing phase (anterior hippocampus: beta = -.59, $t(21) = -2.78$, $p = .011$; posterior hippocampus: beta = -.44, $t(21) = -2.12$, $p = .046$), and only anterior hippocampus-VMPFC connectivity reliably tracked performance during the categorization phase (anterior hippocampus: beta = -.43, $t(21) = -2.31$, $p = .031$; posterior hippocampus: beta = -.31, $t(21) = -1.23$, $p = .232$) (Figure 3.5). However, although the relationship between VMPFC-hippocampus connectivity and performance was not significant in all phases, we did not find evidence that the strength of the relationship differed significantly across phases (all pairwise $|z| < 1.1$, all $p > .3$). No other cortical region beyond VMPFC was implicated in the analyses of individual phases.

Continuous Hippocampal Connectivity

To test whether the observed differences in connectivity changed along the hippocampal long axis gradually or in a more step-wise fashion, we examined connectivity of each cortical region with individual cross-sectional hippocampal slices, and then interpolated the connectivity values into six distinct bins. A 4 (cortical ROI: ANG, IFG, VMPFC, MTG) x 6 (hippocampal bin: labeled from posterior to anterior) repeated measures ANOVA was conducted (Figure 3.6). Given there was no three-way interaction between hippocampal ROI, cortical ROI, and task

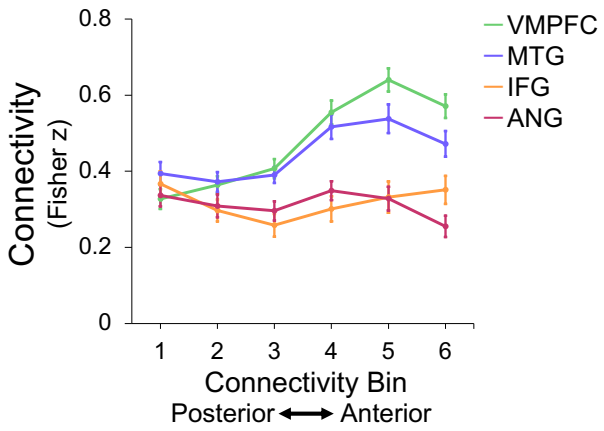

Figure 3.17. Continuous hippocampal connectivity. Hippocampal connectivity with each cortical region along a posterior to anterior gradient. Connectivity with VMPFC and MTG increased linearly from the posterior hippocampus to the anterior hippocampus. Each cortical region also revealed non-linear trends.

phase in the ANOVA reported above, connectivity was averaged across the three tasks for this analysis. There was a main effect of cortical ROI ($F(3,75) = 22.83$, $p < .001$, $\eta_p^2 = .48$) and a main effect of connectivity bin ($F(2.74,68.55) = 15.37$, $p < .001$, $\eta_p^2 = .38$, GG), which were not of interest and not considered further. Of main interest, there was a significant interaction between cortical ROI and hippocampal bin ($F(5.26,131.37) = 20.76$, $p < .001$, $\eta_p^2 = .45$, GG). To follow up on this interaction, we tested the effects of hippocampal bin using separate one-way, repeated measures ANOVAs for each cortical ROI. In addition to the main effect of hippocampal bin, linear and quadratic trends were of interest. We found main effects of hippocampal bin for all cortical ROIs: ANG ($F(3.07,76.69) = 3.90$, $p = .011$, $\eta_p^2 = .14$, GG), IFG ($F(2.68,66.91) = 4.19$, $p = .011$, $\eta_p^2 = .14$, GG), VMPFC ($F(2.82,70.54) = 43.97$, $p < .001$, $\eta_p^2 = .64$, GG), and MTG ($F(2.33,58.25) = 15.40$, $p < .001$, $\eta_p^2 = .38$, GG). There was a significant linear effect for both the VMPFC ($F(1,25) = 76.54$, $p < .001$. $\eta_p^2 = .75$) and MTG ($F(1,25) = 17.30$, $p < .001$, $\eta_p^2 = .41$), showing a gradient of increasing connectivity from posterior to anterior hippocampus. There was no linear effect of hippocampal bin in ANG ($F(1,25) = 1.51$, $p = .230$, $\eta_p^2 = .06$) or IFG ($F(1,25) = .19$, $p = .664$, $\eta_p^2 = .008$). Contrasts also revealed quadratic effects of hippocampal bin for IFG ($F(1,25) = 16.22$, $p < .001$, $\eta_p^2 = .39$), and a marginal quadratic effect for angular gyrus ($F(1,25) = 3.70$, $p = .066$), but not for MTG or VMPFC (both $F < 3$, $p > .1$). The effects of connectivity bin partially replicated when we tested rest connectivity prior to low-

pass filtering. Both MTG and VMPFC showed significant main effects of bin (both $F > 5$, both $p < .005$), while ANG and IFG showed no effect of bin (both $F < 2.5$, both $p > .1$).

Visual inspection of Figure 3.6 suggested that increases for MTG and VMPFC connectivity were not gradual, but rather increased step-wise from the posterior half of the hippocampus (bins 1-3) to the anterior half (bins 4-6). In addition, there was a drop in connectivity for most regions with the most anterior bin. This observation was confirmed in MTG with post-hoc pairwise comparisons between hippocampal bins, where bins 1-3 showed equivalent connectivity (all pairwise $p > .3$) while bins 4-6 showed greater connectivity with MTG than bins 1-3 (all $p < .02$). The changes between bins 3 and 4 were the largest increases in connectivity between neighboring bins (Fisher z increase = .128, $SE = .024$, $p < .001$). In VMPFC, connectivity values differed significantly across all pairs of bins (all $p < 0.015$) except for most posterior bins 1 and 2 ($p = .135$) and bins 4 and 6 ($p = .383$). The greatest change of connectivity between neighboring bins was again between bins 3 and 4 (Fisher z increase = 0.146, $SE = 0.022$, $p < 0.001$). Bin to bin connectivity changes in the IFG were reliably quadratic, with significant decreases from bins 1-3 (all $p < .05$) and marginal increases from bins 3-5 (all $p < .07$). Connectivity changes in ANG were less pronounced from bin to bin, though there was a significant change from bin 3 to bin 4 and from bin 5 to bin 6 (both $p < .03$).

Whole-Brain Connectivity of Anterior and Posterior Hippocampus

We next examined whole-brain connectivity maps for the anterior and posterior hippocampus and the degree of their overlap. As anterior v. posterior hippocampal connectivity differences did not significantly vary across task phases in the prior analyses, our report is limited to connectivity averaged across the three phases. The anterior and posterior hippocampus showed widespread cortical connectivity (Figure 3.7). Anterior hippocampus was correlated with

Table 3.5. Anterior hippocampal connectivity

				Peak coordinate		
	Hemisphere	Voxels	z-statistic	X	Y	Z
Frontal lobe cluster	L	6643				
Ventromedial prefrontal cortex			6.97	49	84	29
Inferior frontal gyrus			6.27	64	78	27
Anterior cingulate gyrus	R	112	4.43	41	80	41
Superior frontal gyrus	L	57	4.17	48	69	68
Precentral gyrus	R	34	4.54	42	48	65
Postcentral/precentral gyrus	R	3506	5.83	17	60	53
	R	99	5.83	17	60	53
Postcentral gyrus	L	310	5.72	63	48	68
	R	279	5.40	30	48	71
Central opercular cortex	R	230	4.85	21	58	42
	R	190	4.83	17	62	39
	L	69	4.86	71	58	42
Parietal operculum cortex	L	49	4.08	69	47	43
Posterior cingulate gyrus	R	1916	6.12	44	39	51
Supramarginal gyrus	L	71	4.30	76	39	42
Temporal lobe cluster	L	6639				
Amygdala			6.61	58	61	25
Anterior middle temporal gyrus			6.41	74	64	28
Anterior parahippocapal gyrus			6.35	54	55	24
Temporal lobe cluster	R	5793				
Amygdala			8.09	36	59	28
Posterior temporal fusiform cortex			6.57	26	57	24
Temporal pole			6.48	21	71	24
Superior lateral Occipital Cortex	L	592	5.71	66	27	52
	R	360	5.00	21	30	52
	R	595	4.92	32	20	43
	L	389	4.58	60	19	44
	L	75	4.93	67	25	53
Inferior lateral Occipital Cortex	L	127	4.59	67	22	36
Occipital fusiform gyrus	R	270	4.68	33	32	30
Temporal occipital fusiform cortex	L	66	4.34	60	32	28
Lingual gyrus	L	76	4.29	49	24	35
	L	45	4.44	52	25	31
	L	34	4.38	52	18	35

Regions with significant functional connectivity with anterior hippocampus across task phases (voxel threshold Z = 3.1, cluster extent threshold p = 0.05). Clusters that spanned more than one lobe were further broken down by lobe (see Methods). Representative subpeaks are reported when clusters spanned multiple regions in a lobe.

Table 3.6. Posterior hippocampal connectivity

				Peak coordinate		
	Hemisphere	Voxels	z-statistic	X	Y	Z
Frontal lobe cluster		25244	6.89	43	80	48
Anterior cingulate gyrus	R		6.89	43	80	48
Paracingulate gyrus	L		6.35	47	79	49
Middle frontal gyrus	R		6.31	26	90	38
Paracingulate gyrus	R		6.22	42	86	35
Lateral orbitofrontal cortex		51	3.95	55	78	27
Temporal lobe cluster	R	3374				
Inferior lateral occipital cortex	R		6.12	18	28	30
Posterior middle temporal gyrus	R		5.66	16	46	30
Temporooccipital middle temporal gyrus	R		5.61	14	43	30
Temporal lobe cluster	L	2954				
Posterior temporal fusiform cortex	L		5.48	62	49	27
Posterior middle temporal gyrus	L		5.42	74	48	33
Temporal occipital fusiform cortex	L		5.41	64	31	28
Occipital fusiform gyrus	L		5.26	63	29	27
Temporal pole	L	98	5.3	71	72	31
	L	32	3.91	71	71	22
Heschl's gyrus	R	40	3.97	19	54	41
Parietal lobe cluster		19329	6.62	51	45	36
Thalamus	L		6.62	51	45	36
Precuneus	L		6.24	49	24	61
Superior lateral occipital cortex	L		6.21	59	24	58
Precuneus	R		6.18	41	32	45
Postcentral gyrus		31	4.18	60	48	65
Occipital lobe cluster		15167	6.40	59	17	42
Occipital pole	L		6.40	59	17	42
Lingual gyrus	R		6.30	35	33	29
Superior lateral occipital cortex	L		6.28	59	23	58

Regions with significant functional connectivity with posterior hippocampus across task phases (voxel threshold $Z = 3.1$, cluster extent threshold $p = 0.05$). Clusters that spanned more than one lobe were further broken down by lobe (see Methods). Representative subpeaks are reported when clusters spanned multiple regions in a lobe.

Table 3.7. Anterior and posterior hippocampus connectivity overlap

Region	Hemisphere	Cluster size
Paracingulate gyrus / Superior frontal gyrus	M	1153
Frontal orbital cortex	L	10
	R	23
Frontal orbital cortex / Inferior frontal gyrus	L	13
Rostral anterior cingulate cortex	M	24
	M	89
Dorsal anterior cingulate cortex	M	44
Caudate	R	11
	L	89
Thalamus	M	32
Precuneus / Posterior cingulate gyrus	M	1381
Superior frontal / Middle frontal gyrus	R	75
	L	298
Superior frontal gyrus	L/M	18
Precentral gyrus	M	52
Precentral / postcentral gyrus	R	111
	L	905
	R	444
Insular cortex	R	14
	R	20
Parietal operculum cortex	R	10
Planum temporale	L	20
Superior temporal / Middle temporal gyrus	R	265
Middle temporal gyrus	R	19
Middle temporal / Inferior temporal gyrus	L	686
Temporal fusiform cortex / Parahippocampal cortex	R	17
Parahippocampal cortex	L	85
Temporal occipital fusiform cortex	R	52
	L	28
Temporal occipital fusiform cortex / Occipital fusiform gyrus	L	28
	L	16
Occipital fusiform gyrus	R	358
Lingual gyrus	L	14
	L	35
	L	16
Lateral occipital cortex	R	696
	L	88
	L	681

Regions of overlap were defined in a conjunction analysis of anterior and posterior whole-brain connectivity maps.

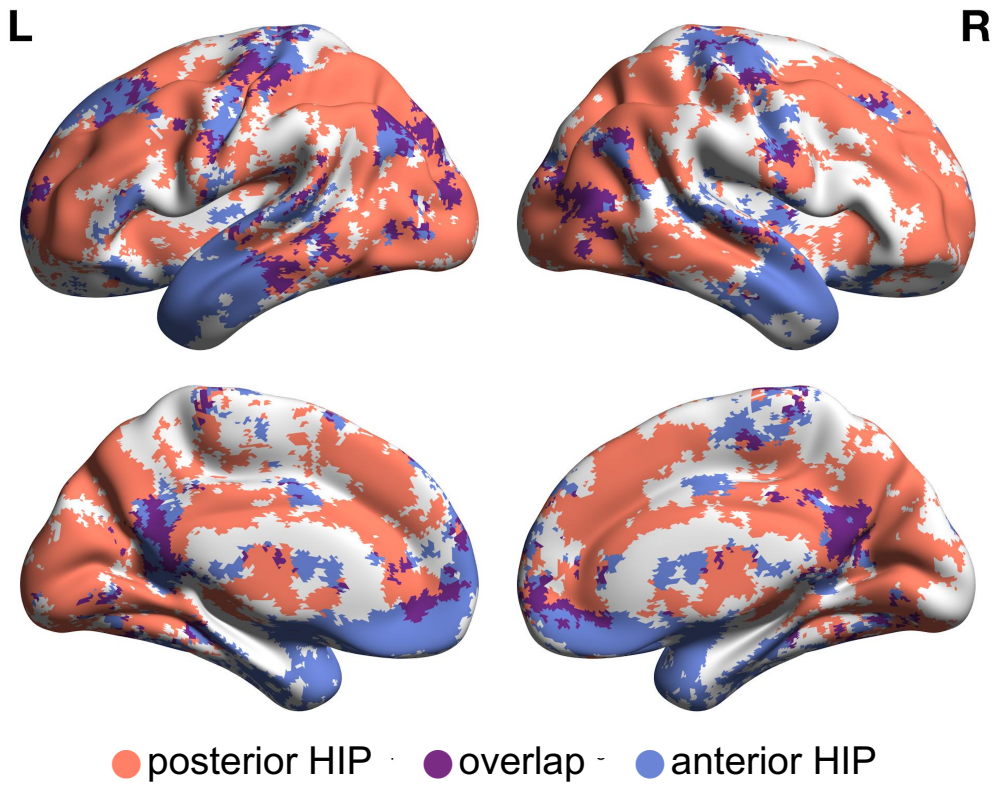

Figure 3.18. Whole-brain connectivity of the anterior and posterior hippocampus. Relative to the widely distributed hippocampal-cortical connectivity, there was little overlap in regions interacting with both anterior and posterior hippocampus.

portions of the VMPFC, anterior lateral temporal cortices and lateral orbitofrontal cortices (Table 3.2). Posterior hippocampus formed a larger network of regions that included lateral prefrontal cortex, dorsomedial prefrontal cortex, lateral parietal cortices, and posterior temporal and occipital visual cortices (Table 3.3). Though anterior and posterior hippocampal connectivity maps jointly spanned much of the cortex, there was relatively little overlap (Figure 3.7). Regions that interacted with both anterior and posterior hippocampus included medial prefrontal cortex, anterior and posterior cingulate cortex, precuneus, portions of lateral temporal cortex, and portions of lateral occipital cortex (Table 3.4, Figure 3.7).

Discussion

How does the hippocampus support memory for individual events *and* generalization across experiences? We tested whether distinct portions of the hippocampus (posterior v. anterior) differentially interacted with portions of cortex that have been previously linked to memory specificity (ANG, IFG) versus those implicated in memory generalization (VMPFC, MTG). Consistent with their putative roles in memory specificity, we found that ANG and IFG were preferentially connected to the posterior hippocampus. Consistent with their putative role in generalization, we found that the VMPFC and MTG were preferentially connected to the anterior hippocampus, although the effect in MTG was only apparent in when connectivity was measured continuously along the long axis of the hippocampus. Individual differences in hippocampal-VMPFC connectivity tracked individual differences in concept generalization performance, but this relationship was not unique to the anterior portion of the hippocampus. Whole-brain connectivity analyses revealed widespread connectivity networks for anterior and posterior hippocampus, with relatively little overlap between them. Lastly, anterior and posterior hippocampal connectivity differences persisted across the three scanning phases and were apparent even at rest. This finding suggests that the anterior and posterior hippocampus may form distinct intrinsic functional networks that are relatively independent of task engagement.

A key finding of the current study is that anterior and posterior hippocampus have distinct connectivity profiles that persist across different levels of task engagement. The notion of long-axis specialization within hippocampus is not new. Several models have posited functional differences between anterior and posterior portions of the hippocampus in terms of vestibular versus visual processing (Hüfner, Strupp, Smith, Brandt, & Jahn, 2011), encoding versus retrieval (Kim, 2015; Lepage, Habib, & Tulving, 1998), and emotional versus cognitive

processing (Fanselow & Dong, 2010). Anatomically, cellular and genetic differences exist between the two hippocampal divisions (Thompson et al., 2008), as do structural connectivity differences in humans (Adnan et al., 2016) and rodents (Fanselow & Dong, 2010; Moser & Moser, 1998). Human fMRI studies have also noted differences in the functional connectivity between the anterior and posterior hippocampus (Adnan et al., 2016; Blessing et al., 2016; Blum, Habeck, Steffener, Razlighi, & Stern, 2014; Kahn, Andrews-Hanna, Vincent, Snyder, & Buckner, 2008; Poppenk & Moscovitch, 2011; see also Poppenk et al., 2013, for a review). Here, we highlight a novel aspect of the anterior v. posterior dissociations within the hippocampus, demonstrating greater anterior hippocampal connectivity with putative memory generalization regions and greater posterior hippocampal connectivity with putative memory specificity regions. These findings align well with a recent model of representational gradient along the long axis of the hippocampus proposed by Poppenk and colleagues (2013), postulating fine-grained representations in the posterior hippocampus and coarse-grained representations in the anterior hippocampus. As such, the posterior hippocampus may be especially suited for retaining differentiating details of individual experiences on fine spatial and temporal scale while anterior hippocampus may be especially suited for aggregating information across events to support generalization (Bowman & Zeithamova, 2018; Brunec et al., 2018; Schlichting et al., 2015). The novel evidence that the anterior and posterior hippocampus form distinct functional connections with cortical regions differentially supporting memory specificity and generalization provides one mechanism for how these complementary memory functions may both be served by the hippocampus.

A large body of past research has implicated the ANG and IFG in maintaining specific memory representations, with the IFG resolving interference between related items (Achim &

Lepage, 2005; Badre, Poldrack, Paré-Blagoev, Insler, & Wagner, 2005; Bowman & Dennis, 2015, 2016; Jonides et al., 1998; Kuhl et al., 2007), and ANG supporting detailed retrieval of past events (Johnson, Suzuki, & Rugg, 2013; Kuhl & Chun, 2014; Lee, Samide, Richter, & Kuhl, 2018; Richter, Cooper, Bays, & Simons, 2016; Vilberg & Rugg, 2007; Xiao et al., 2017). As such, we predicted that if the critical difference in anterior v. posterior hippocampal function were one of representational granularity, the posterior hippocampus would show stronger functional connectivity with these regions than would the anterior hippocampus. The results were consistent with this prediction, indicating that the posterior hippocampus may be more strongly geared towards fine-grain representations both because of the computational properties of its cells (Kjelstrup et al., 2008) and its functional interactions with cortical regions that support differentiation between overlapping memories.

Prior studies have shown that the VMPFC and MTG support multiple forms of memory generalization, including concept generalization (Bowman & Zeithamova, 2018; Davis, Goldwater, & Giron, 2017), false memories (Garoff-Eaton, Slotnick, & Schacter, 2006; Turney & Dennis, 2017), and schema-based memories (Brod, Lindenberger, Werkle-Bergner, & Shing, 2015; van Kesteren et al., 2013). Based on the notion that representations in the anterior hippocampus are broad and well suited to integrating across experiences (Brunec et al., 2018; Collin et al., 2015), we expected—and found—greater functional connectivity of VMPFC and MTG with the anterior than posterior hippocampus. The VMPFC findings are consistent with work showing that hippocampal-VMPFC interactions support linking of related information in memory (Gerraty et al., 2014; van Kesteren et al., 2010; Zeithamova et al., 2012), and provide novel evidence that the VMPFC interactions are particularly strong with the anterior portion of the hippocampus. The MTG showed numerically stronger connectivity with anterior compared to

posterior hippocampus, although this relationship was only significant when connectivity was measured continuously. While the role of lateral temporal cortices in semantic memory has long been known (Mummery et al., 2000, 1999), they have only recently been linked to a VMPFC-hippocampal network that supports learning based on prior knowledge (Liu et al., 2017). The present findings add to this work by demonstrating that both VMPFC and MTG are more strongly connected to the anterior hippocampus, both in the context of a concept generalization task and during rest.

Linking connectivity strength with concept generalization performance, individual differences in hippocampal-VMPFC connectivity tracked categorization success. These results corroborate prior reports linking VMPFC *activation* to the formation of conceptual knowledge (Kumaran et al., 2009; Zeithamova, Maddox, & Schnyer, 2008), including generalized concept representations (Bowman & Zeithamova, 2018). Prior work that has also implicated VMPFC-hippocampal *interactions* in some forms of memory generalization, such as narrative schema formation (van Kesteren et al., 2010), associative inference (Zeithamova et al., 2012) and transfer of reward valence across related stimuli (Gerraty et al., 2014). The current work extends the work on VMPFC-hippocampal interactions to the new domain of concept generalization, indicating that they may serve to link information across experiences to serve many forms of memory generalization. Additionally, we also show the relative stability of the connectivity-behavior relationship that did not significantly differ across phases, although it was most prominent during task performance specifically.

An interesting observation is the *negative* direction of the relationship between generalization success and VMPFC-hippocampus connectivity strength observed here, as well as in two prior reports (Gerraty et al., 2014; van Kesteren et al., 2010), with stronger connectivity

being associated with poorer generalization. These connectivity findings contrast with findings that involve task-based *activations* and show its *positive* relationship to generalization performance (Kumaran et al., 2009; Zeithamova et al., 2008). The mechanisms of this negative connectivity-behavior relationship remain unclear. VMPFC-hippocampal connectivity seems to be increasing when a schema linking previously separate events needs to be formed (van Kesteren et al., 2010; see also Zeithamova et al., 2012). Thus, one possibility is that low baseline or post-encoding connectivity reflects that information has been already successfully linked. Gerraty and colleagues (2014) measured connectivity based on a rest scan conducted on a separate day from when participants underwent an associative learning and transfer task. Thus, lower resting/baseline VMPFC-hippocampal connectivity could also reflect a trait-like property of this network that makes it open to on-demand engagement in new schema learning. Pending further investigation and better insights into the mechanisms reflected in VMPFC-hippocampal functional connectivity, the reasons behind the negative correlation-behavior relationship remain speculative.

Although VMPFC-anterior hippocampus connectivity was the strongest predictor of concept generalization success, the data did not indicate the connectivity-behavior relationship to be unique to the anterior hippocampus. Posterior hippocampus-VMPFC connectivity, although not reaching significance overall, showed a similar trend. Prior work has demonstrated that related events may be encoded as integrated or separated representations (Chanales, Oza, Favila, & Kuhl, 2017; Schlichting et al., 2015; Zeithamova & Preston, 2010, 2017). Thus, within the framework of representational granularity along the long hippocampal axis, one may speculate that these connections reflect different process. For example, information represented in both portions of the hippocampus may be relevant to generalization decisions, but differentially

reflect reliance on specific versus generalized representations. Alternatively, the posterior hippocampus-VMPFC interactions may reflect post-encoding linking of previously separated representations that are then encoded in the anterior hippocampus. However, whether the posterior and anterior hippocampal connectivity with VMPFC reflect the same or distinct processes cannot be answered based on the current data. As noted above, the sample size was not optimized for an individual difference analysis and thus the findings linking connectivity to behavior should be replicated in a larger study.

Finding anterior v. posterior differences, we further asked whether hippocampal-cortical functional connectivity was graded along the long axis or if instead there was a step-wise increase at an anterior/posterior boundary. The results did not show a clear pattern of graded changes along the hippocampal long axis and instead pointed to more complex patterns. In particular, both the VMFPC and MTG showed a stepwise increase from the posterior half to the anterior half of the hippocampus. The IFG showed a quadratic effect, which may represent differences in hippocampal anatomy, such as the relative distribution of hippocampal subfields (Malykhin, Lebel, Coupland, Wilman, & Carter, 2010) or the relative density of structural connections to other brain regions (Dolorfo & Amaral, 1998; Shepherd, Özarslan, King, Mareci, & Blackband, 2006). For the most anterior bin, the weaker connectivity detected here across multiple ROIs likely reflects differences in shape, reduced number of voxels, and/or differences in signal to noise in this portion of the hippocampus (Brunec et al., 2018). Nonlinearities may have also arisen from functional heterogeneity within the cortical regions themselves. For example, the IFG has anatomical subregions that may perform distinct computations that are differentially relevant for memory specificity and generalization (Badre et al., 2005; Badre & Wagner, 2007; Gold et al., 2006), possibly leading to differences in connectivity with the

hippocampus. Thus, it remains an open question whether these nonlinear effects are driven by differences within the hippocampus, the cortical ROIs, or by some other factor.

Across most analyses, we found little evidence that hippocampal connectivity patterns were modulated by task engagement. Rather, anterior and posterior hippocampal connectivity differences were present across all phases, including unfiltered rest data. Thus, it seems that differences in anterior and posterior connectivity are not driven by task demands, but are instead relatively stable characteristics of hippocampal networks. These results extend prior findings on resting-state connectivity differences between anterior and posterior hippocampus (Adnan et al., 2016; Blessing et al., 2016; Blum et al., 2014; Kahn et al., 2008; Poppenk & Moscovitch, 2011) to show that differences in anterior and posterior hippocampal connectivity persist even under passive and active task demands. These results are consistent with recent notions of the trait-like properties of functional connectivity patterns detectable across time and tasks (Frank et al., 2019; Gratton et al., 2018; Horien, Shen, Scheinost, & Constable, 2019; Touroutoglou, Andreano, Barrett, & Dickerson, 2015). Our findings of stable connectivity patterns complement prior studies that have examined connectivity in the context of categorization but focused on task-related connectivity changes (Mack, Love, & Preston, 2016; Seger & Cincotta, 2006; Soto, Bassett, & Ashby, 2016; Turner, Crossley, & Ashby, 2017). Together, these results highlight that both task-related connectivity changes and stable connectivity patterns carry information relevant to our understanding on how the brain supports cognition.

Our findings of stable functional connectivity differences between anterior and posterior hippocampus may more broadly reflect their structural connectivity profiles. Rodent and primate literature have shown distinct structural connectivity between anterior (ventral) and posterior (dorsal) hippocampus both within the medial temporal lobe (Fanselow & Dong, 2010; Suzuki &

Amaral, 1994) and across the cortex (Catenoix, Magnin, Mauguière, & Ryvlin, 2011; Kier, Staib, Davis, & Bronen, 2004). Moreover, our pattern of findings is relatively consistent with structural connections of anterior and posterior hippocampus. In humans, white matter tracts connect anterior hippocampus with VMPFC and anterior lateral temporal cortices (Catenoix et al., 2011; Kier et al., 2004). The body and tail of the hippocampus are connected to parietal regions through more complex pathways (Duvernoy, Cattin, Risold, Vannson, & Gaudron, 2013), but direct connections exist between ANG and posterior portions of the medial temporal lobe surrounding hippocampus (Rushworth, Behrens, & Johansen-Berg, 2006; Uddin et al., 2010). Inferior frontal gyrus forms connections that span the entire hippocampus (Kier et al., 2004; Oishi et al., 2008). Though future investigation is required, our findings of functional connectivity differences between anterior and posterior hippocampus may arise from differences in structural connections.

The IFG was one exception to the otherwise stable connectivity, showing increased connectivity from rest to task (both passive viewing and categorization). IFG is part of a larger frontoparietal network that orients attention to behaviorally relevant stimuli (Corbetta & Shulman, 2002; Raichle, Fox, Corbetta, Snyder, & Vincent, 2006) and increases in activation when participants engage in an externally-oriented task compared to rest or an internally-oriented task (Cabeza & Nyberg, 2000; Scheibner, Bogler, Gleich, Haynes, & Bermpohl, 2017; Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010). The nature of the task at hand may dictate the degree to which hippocampus interacts with IFG, as has been previously reported for hippocampal interactions with the frontoparietal control network (Westphal, Wang, & Rissman, 2017). The IFG is also recruited for learning statistical regularities in the temporal sequence of stimuli (Karuza et al., 2013; Schapiro et al., 2013, 2016), with hippocampal-IFG connectivity

modulated at boundaries in the temporal structure (Schapiro et al., 2016). Thus, hippocampal-IFG connectivity may more strongly reflect dynamic task demands than stable traits of individuals. However, it is not possible to rule out that what we interpret as task-related increases in background connectivity may be to some degree driven by co-activation related to task features occurring below the filter cutoff frequency.

The current findings are complementary to other frameworks that propose hippocampal interactions with distinct networks to serve multiple memory functions. For example, Ranganath and Ritchey (2012) propose that the hippocampus interacts with two medial temporal lobe networks: a posterior-medial network that includes the parahippocampal cortex and represents the spatial and temporal context of memory and an anterior-temporal network that includes perirhinal cortex and represents individual items and their features. The hippocampus integrates item and contextual information into a coherent representation (Diana, Yonelinas, & Ranganath, 2007). Consistent with this proposed function, Cooper & Ritchey (2019) found increased connectivity between the hippocampus and both posterior-medial and anterior-temporal networks during retrieval of memories with multidimensional features (i.e. spatial, visual and emotional), with connectivity increases scaling with the quality of memory retrieval. Interestingly, differences emerged along the hippocampal axis such that posterior hippocampal connectivity with both medial temporal lobe networks demonstrated greater scaling with retrieval quality, which would be consistent with its hypothesized role in memory specificity. How these different conceptualizations of distinct hippocampal functions complement or interact with each other is an interesting area for future research.

The current study provides novel evidence for differential functional interactions along the hippocampal long axis, showing distinctions in connectivity patterns of anterior v. posterior

hippocampus with cortical regions that align with their putative role in memory specificity and generalization and that persist across levels of task engagement. The distinct cortical interactions with anterior and posterior hippocampus may provide one mechanism for how a single region—the hippocampus—may form both specific and generalized representations supporting multiple memory functions. More broadly, the findings add to our understanding of functional organization along the hippocampal long axis and highlight the utility of functional connectivity measures in the study of cognition.

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CHAPTER IV

HIPPOCAMPAL CONNECTIVITY PREDICTING INDIVIDUAL DIFFERENCES IN MEMORY SPECIFICITY AND GENERALIZATION

Memory allows us to remember specific episodes (memory specificity) and link across them to form new knowledge (generalization). While the role of the hippocampus in memory specificity is well established (Eichenbaum, Otto, & Cohen, 1992; Scovill & Milner, 1957; Squire, 1992), recent evidence suggests it also plays a role in generalization (Schapiro et al., 2017; Schlichting & Preston, 2015; Zeithamova & Bowman, 2020). For example, the hippocampus is recruited for drawing inferences between related experiences (Schlichting, Zeithamova, & Preston, 2014; Zeithamova, Schlichting, & Preston, 2012), updating new information with existing knowledge structures (Bein, Reggev, & Maril, 2014; van Kesteren et al., 2010), and building conceptual knowledge (Bowman, Iwashita, & Zeithamova, 2020; Bowman & Zeithamova, 2018). How the hippocampus supports the two different types of learning is still unclear.

The hippocampus does not work in isolation to support memory specificity or generalization. Generalized memories, like schemas and concepts, rely on the extraction and integration of regularities across our experiences (McClelland, McNaughton, & O'Reilly, 1995; van Kesteren et al., 2012; Zeithamova & Bowman, 2020). These processes are supported by a number of regions, including the basal ganglia (Carpenter et al., 2016; Knowlton, Mangels, & Squire, 1996), ventromedial prefrontal cortex (Ashby & Zeithamova, 2022; Bowman & Zeithamova, 2018; Guo & Yang, 2020), middle temporal gyrus (Ashby & Zeithamova, 2022; Mummery et al., 2000) and more (Ashby & Zeithamova, 2022; Baldassano, Hasson, & Norman, 2018; Patterson, Nestor, & Rogers, 2007; Schapiro et al., 2013; Wei et al., 2012). Specific

memories, on the other hand, are processed by a separate set of regions that span the visual cortex, ventral temporal cortex, lateral prefrontal cortex, and lateral and medial parietal cortices. These regions are crucial for representing specific features of a memory (Eger et al., 2008; Kuhl & Chun, 2014; Xiao et al., 2017; Zeithamova, de Araujo Sanchez, & Adke, 2017), maintaining their fidelity and vividness (Lee et al., 2019; Wais, Jahanikia, Steiner, Stark, & Gazzaley, 2017; Xue et al., 2010), and separating overlapping memories to prevent interference (Badre et al., 2005; Bowman & Dennis, 2016; Brice A. Kuhl, Dudukovic, Kahn, & Wagner, 2007; Zhao, Chanales, & Kuhl, 2021). As different regions are recruited for memory specificity and generalization, the hippocampus may contribute to the different forms of learning through distinct cortical interactions.

Evidence from task-based studies suggest this may be the case. The formation and retrieval of specific memories recruits hippocampal interactions with cortical regions, like visual cortex, lateral prefrontal cortex, and medial and lateral parietal cortices (McCormick et al., 2010; Ranganath et al., 2005). On the other hand, hippocampal interactions with the ventromedial prefrontal cortex (VMPFC) are thought to drive memory integration and updating processes (Schlichting & Preston, 2015; van Kesteren et al., 2012). Importantly, studies have largely focused on interactions during or following learning (van Kesteren et al., 2010; Zeithamova, Dominick, & Preston, 2012). Recent work demonstrates the important of intrinsic or trait-like connections in predicting individual cognition (Finn et al., 2015; Fong et al., 2019; Poole et al., 2016; Touroutoglou et al., 2015). Thus, the present study asks how intrinsic hippocampal connections with distinct sets of brain regions may differentially contribute to memory specificity and generalization.

Functional specialization along the long axis of the hippocampus may further explain its dual function in memory. Research suggests the posterior hippocampus represents information on a fine-grained scale, while the anterior hippocampus maintains more coarse-grained representations (Brunec et al., 2018; Kjelstrup et al., 2008; Poppenk et al., 2013). Accordingly, memory specificity may be supported by the posterior hippocampus and generalization by the anterior hippocampus. In a recent study (Frank, Bowman, & Zeithamova, 2019), we found that posterior and anterior hippocampus form intrinsic connections with cortical memory regions that are consistent with these hypothesized roles, such that anterior hippocampus was more connected to presumed generalization regions and posterior hippocampus was more connected to presumed specificity regions. Without a clear link to behavior, however, it remains unknown how these distinct connections may serve different types of learning. Building off our prior findings, the present study tests the prediction that anterior hippocampal connections contribute to generalization and posterior hippocampal connections to memory specificity.

Using an individual differences approach, the current report examined how distinct hippocampal connections at rest contribute to memory specificity and generalization. As the different types of learning rely on separate networks of regions, we predicted that distinct hippocampal connections contribute to generalization and specificity. We further tested if anterior and posterior hippocampal connections differentially serve the two types of learning. Based on prior theories, we predicted individual differences in anterior hippocampal connectivity would track individual generalization abilities and posterior hippocampal connectivity would track individual specificity abilities. This paper furthers our understanding of the hippocampal processes underlying different types of memory and the intrinsic connections that contribute to learning.

Methods

Participants

A sample size of 166 (Mean age = 19.63, 113 females, 49 males, 4 other) participants were recruited from the University of Oregon and surrounding community. A subset of 71 participants were recruited for the MRI portion of the study based on eligibility (i.e., right-handed, native English speaker, no MRI contraindications, no psychiatric or neurological illnesses, no medications known to affect brain function). Eight participants were excluded for having a significant neurological history (1 person), non-compliance with study protocols (1 person), participating in the same or similar study (2 people), and falling asleep during the resting-state scan (four people). Three MRI participants dropped out of the study early due to the SARS-CoV-2 lockdown and four did not complete the MRI portion due to scheduling conflicts (2 people), having non-removable piercings (1 person), and being color blind (1 person). Participants received written informed consent and were financially compensated for their time. All experimental procedures were approved by Research Compliance Services and the University of Oregon.

Measuring Individual Differences in Memory Abilities

Procedures. Participants were given a battery of tasks assessing memory specificity and generalization abilities. Several different paradigms were included to evaluate overall performance in the two forms of learning. Descriptions of each task are provided in Figures 4.1 & 4.2. Measures of working memory (Adam et al., 2015; Unsworth et al., 2005) and fluid intelligence (Carpenter, Just, & Shell, 1990; Verguts & De Boeck, 2002) were included in the battery of tasks but are not included in this report. To reduce fatigue, behavioral testing was split across two visits that were separated by at least one day (typically 1-7 days, except for one

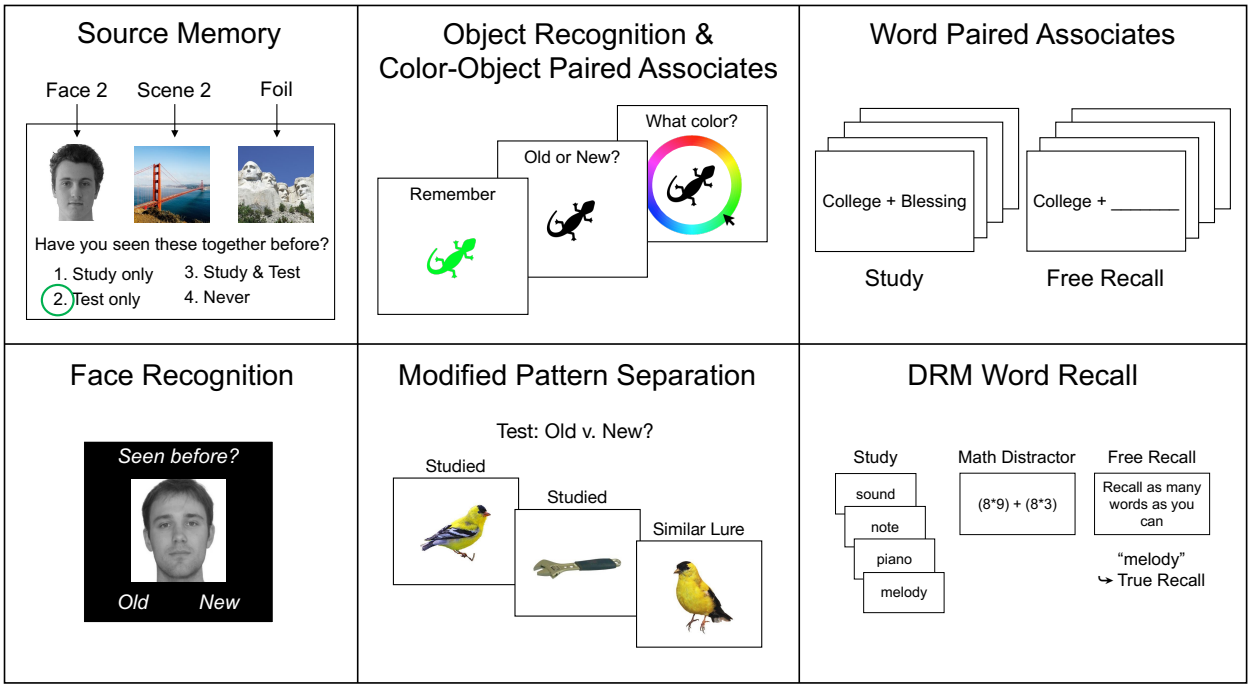

Figure 4.19. Paradigms used to assess specificity abilities. **Source memory** – In the acquired equivalence task, participants also completed a test of source memory. On each trial, participants were shown a face with two scenes and were asked when they saw the three images together (during the study portion only, during the test only, during both study and test, or not at all). Source memory was measured by how well participants could correctly identify seeing the transferred pair only during test. **Face recognition** – Following training on the face category learning task, participants completed an old v. new recognition test on a set of trained and novel faces. Corrected hit rate was calculated as the difference in correct recognition of old faces and false recognition of novel faces (hit rate – false alarm). **Object recognition** – Participants encoded color-object associations. The colors varied along a 360-degree color wheel. Participants first completed an old v. new recognition test with old and new uncolored objects. Corrected hit rate was calculated as correct recognition of old objects minus false recognition of new objects (hit rate – false alarm). **Color-object paired associates** – After the object recognition task, participants were asked to recall the color associated with each shape by selecting a color on a 360-degree wheel. Mixture models were fit to the responses for each participant to estimate the precision of responses and the probability of guessing. Memory for the color-object associations was measured as the probability of a hit (1 – probability of guessing). **Modified pattern separation** – Participants studied images of animals and tools. They then completed an old v. new recognition task with the studied images and similar lures. The difference between correct recognition of the old images and false recognition of similar lures was calculated as a measure of corrected hit rate. **Word Paired Associates** - Participants studied randomly generated word pairs. During each test trial, they were shown a word and asked to recall the word that was paired with it during study. The rate of correctly recalled word pairs . **DRM word recall** – Participants were tested on how many words they could correctly recall from each word list on the DRM task (see DRM false memory).

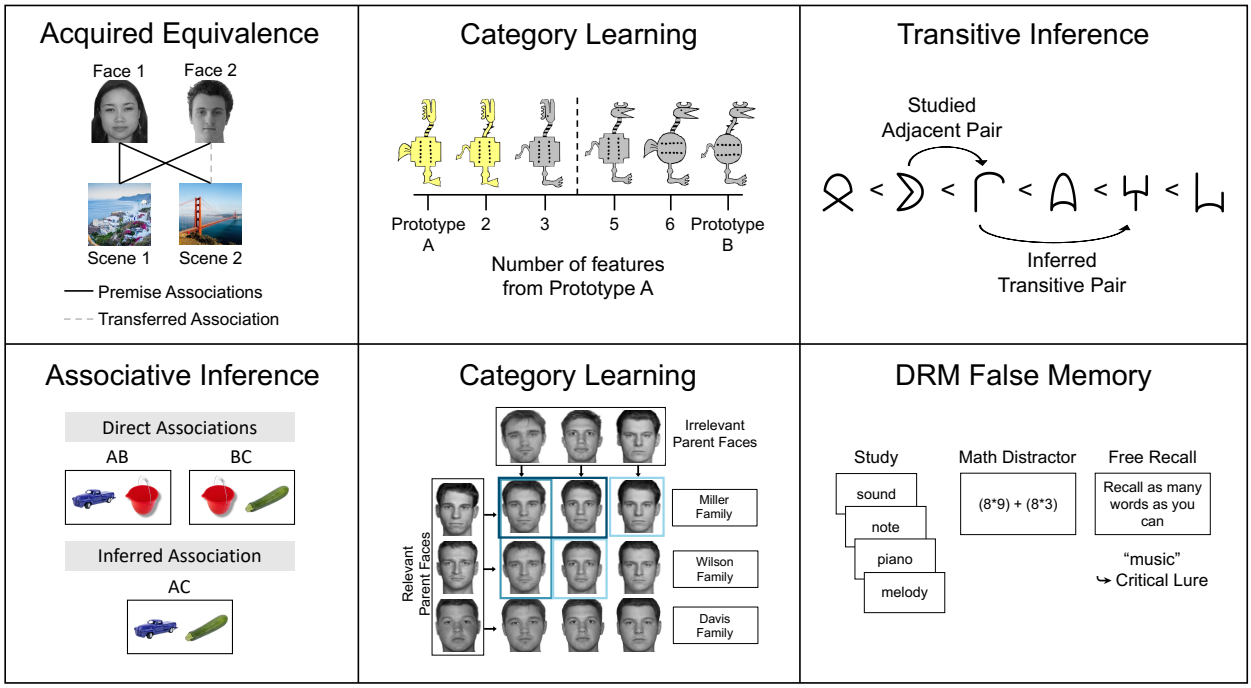

Figure 4.20. Paradigms used to assess generalization abilities. **Acquired equivalence** – Through feedback, participants learned that two faces prefer Scene 1 (F1-S1, F2-S1). They then learned that Face 1 also prefers Scene 2. Participants were then tested on their memory for the premise associations and novel associations (F2-S2). Generalization was measured by how likely they were to transfer the preference for Scene 2 to Face 2 (F2-S2), given both faces shared an association with Scene 1. **Associative inference** – Participants studied overlapping pairs of colored objects (AB, BC), with each pair sharing an object (B). They were then tested on their memory of the direct associations (AB, BC) and their ability to infer the association between A and C given their shared relation to B. **Category learning (animals)** – Participants learned to categorize novel cartoon animals into one of two categories. The animals varied along 8 binary features (e.g., yellow or gray, round or square body, etc.), with the prototype for category A exactly 8 features away from the prototype of category B. Through feedback, participants learned to sort the animals into each category. Following training, participants were tested on their ability to categorize the trained animals and novel animals. The novel animals were used to assess how well participants could generalize their category knowledge. **Category learning (faces)** – Participants learned to sort faces into one of three families. The training set consisted of nine faces that were 50%-50% blends of one relevant parent face and one irrelevant parent face. The relevant parent faces were associated with a last name that indicated to which family the blended faces belonged. Irrelevant parent faces contained no information regarding category membership. Participants were tested on how well they could categorize the trained faces and how well they could generalize the category structure to novel faces. **Transitive inference** – Participants were tested on how well they could form a relational hierarchy of six novel symbols (A<B<C<D<E<F). They completed feedback-based training on the 5 directly adjacent associations (e.g., B<C). They were then tested on all possible pairs of symbols, including transitive pairs that were separated by at least one symbol (B<D, C<E). Successful inference of the transitive pairs indicated that participants integrated the orderly relationships into a single relational structure. **DRM false memory** – Participants studied lists of semantically related words (e.g., bed, pillow, dream) and were then tested on their ability to recall the words. Between the study and test of each list, participants completed a 45 second math distractor task. Each word list was associated with a "critical lure" that was semantically related but never shown during study (e.g., sleep). Generalization was indexed by how often participants demonstrated false memory for the critical lure.

participant who returned for visit 2 after 315 days following the SARS-CoV-2 lockdown). Additional time was also allotted for breaks between the tasks. The tasks were pseudo randomized into six orders and counterbalanced across participants to control for order effects in performance. Generalization and specificity tasks were intermixed across sessions such that each visit contained assessments of both.

A subset of participants returned for a third visit to complete an MRI scan. While undergoing MRI, participants completed a resting-state scan and a category learning task. During rest, participants were instructed to keep their eyes open and fixated on a cross. The category learning task was taken from the larger battery of assessments and completed while in the scanner on visit 3, instead of during the second session like the remaining participants. Performance on the category learning task was included in the composite memory scores (see below), but the functional MRI data collected during this task is not included in the current report.

Outliers and Missing Data. Principal component analysis (PCA) was used to generate composite scores of performances on measures of memory specificity and measures of generalization. Prior to analysis, individual tasks were screened for outliers. Participants were excluded from a generalization task if they performed poorly (>3 SD below median) on tests of learned information (e.g., trained associations) or generalized information (e.g., inferred associations). Outliers (>3 SD below median) were also excluded from individual specificity tasks. For the DRM task, 2 participants were excluded for a high rate (>3 SD above mean) of false alarms to words other than the critical lure. Scores on the color-object paired associates learning task were also excluded if participants were color blind. Participants were excluded from all analyses if they were missing 2 or more generalization tasks or 3 or more specificity

tasks (11 participants). Finally, all missing or excluded scores were replaced with the mean prior to PCA.

Generating Individual Scores of Memory Abilities. The behavioral measures were standardized and subjected to PCA of the correlation matrix. The tasks selected *a prior* as measures of memory specificity correlated well together (Figure 4.3) and were thus submitted to a PCA to generate a single composite score of memory specificity. The *a priori* selected generalization measures also correlated well together, except for transitive inference and DRM false memory (Figure 4.3). Individual scores of transitive inference and DRM false memory other and were thus dropped from further analysis. Scores from the remaining generalization tasks were included in a PCA to generate a single composite score of generalization. A parallel analysis procedure was used to determine the number of components to retain for each analysis (Horn, 1965). For each PCA, 100 Monte Carlo simulations of eigenvalues based on random, uncorrelated data were run and used to generate a threshold for each component based on the 95% confidence interval of simulated eigenvalues. The components were not rotated as only one was retained from each analysis (see Results). Individual component scores were then generated using a regression approach, resulting in a single memory specificity score and a single generalization score for each participant.

Measuring Individual Differences in Hippocampal Connectivity

*fMRI Data Acquisition***.** Scanning was completed on a 3T Siemens Skyra at the UO Lewis Center for Neuroimaging using a 32-channel head coil. Foam padding was used around the head to minimize motion. The scanning session started with a localizer SCOUT sequence and was followed by an 8-minute resting-state scan. Functional data were acquired using a multiband gradient-echo pulse sequence (TR, 2000 ms; TE, 25 ms; flip angle, 90°; matrix size, 104×104; 72

contiguous slices oriented 15° off the AC-PC line to reduce prefrontal signal dropout; interleaved acquisition; FOV, 208 mm; voxel size: 2.0×2.0×2.0 mm; GRAPPA factor, 2; Multi-band acceleration factor, 3). Anatomical data was collected using a standard high-resolution T1-weighted MPRAGE anatomical image (TR, 2500 ms; TE, 3.43 ms; TI, 1100 ms, flip angle, 7°; matrix size, 256×256; 176 contiguous sagittal slices; FOV, 256 mm; slice thickness, 1 mm; voxel size 1.0×1.0×1.0 mm; GRAPPA factor, 2) and a custom anatomical T2 coronal image (TR, 13520 ms; TE, 88 ms; flip angle, 150°; matrix size, 512×512; 65 contiguous slices oriented perpendicularly to the main axis of the hippocampus; interleaved acquisition; FOV, 220 mm; voxel size, 0.4×0.4×2.0 mm; GRAPPA factor, 2).

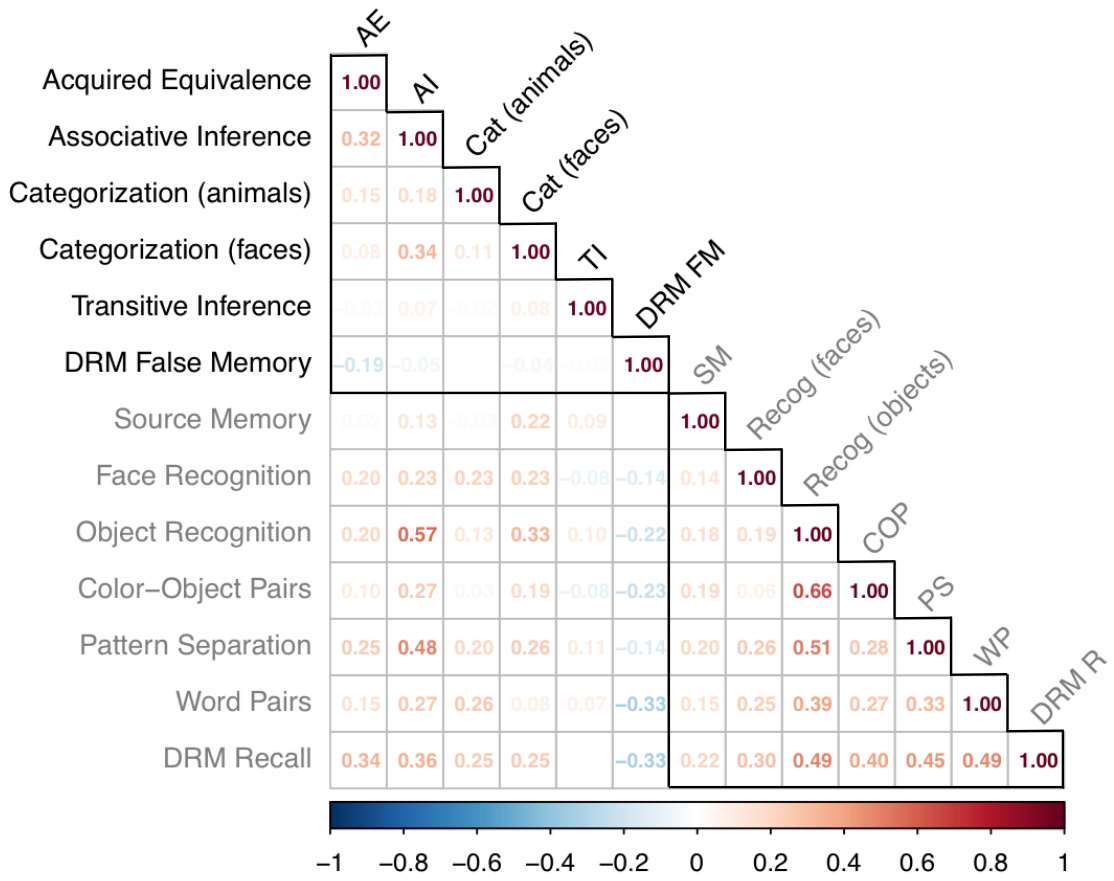

Figure 4.21. Correlation matrix between measures of generalization (black) and memory specificity (gray). The correlations between all generalization measures (top) and between all specificity measures (bottom) are bordered in black.

*Hippocampal Regions of Interest***.** The anterior and posterior hippocampus regions of interest (ROIs) were defined in MNI space. The hippocampus was first derived from the probabilistic Harvard-Oxford subcortical structure atlas and thresholded at 50%. The boundary used for dividing the hippocampus into anterior and posterior portions was similar to that proposed by Poppenk and colleagues (2013). The posterior hippocampus ended at y = -22 mm and the anterior hippocampus began at y = -18. The middle slice (y = -20) was dropped to avoid any overlap in signals between the two regions. The ROIs for right and left hemispheres were combined for subsequent analysis.

fMRI Preprocessing. Raw dicom images were converted to Nifti format using the dcm2nii function from MRIcron (https://www.nitrc.org/projects/mricron). The functional data were preprocessed and analyzed using CONN toolbox (www.nitrc.org/projects/conn, RRID:SCR_009550; Whitfield-Gabrieli & Nieto-Castanon, 2012), a software implemented on MATLAB 2018b (https://www.mathworks.com) and SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Motion correction was first conducted to realign all functional data to the first volume of the rest scan. Outlier volumes were then identified and marked for removal using a conservative threshold (global BOLD signal > 3 SD and framewise displacement > .5 mm). The anatomical and functional data were then normalized to the standard MNI space and segmented into gray matter, white matter, and cerebrospinal fluid (CSF). For group-level whole-brain connectivity analyses, the functional data were spatially smoothed using an 8-mm full width at half maximum Gaussian kernel. Noise components were generated from white matter (5 components) and CSF (5 components) signals using a component-based noise correction method (CompCor). To reduce the confounding effects of motion and physiological noise on connectivity estimates (Behzadi et al., 2007; Power et al.,

2012), the 10 noise components, outlier regressors, 12 motion parameters and their first order derivatives, and constant and first order linear session effects were regressed from the BOLD signal of each voxel. Finally, a high-pass temporal filter was applied to remove frequencies below 0.008 Hz.

Measuring Whole-Brain Connectivity. We measured whole-brain seed-to-voxel connectivity using anterior and posterior hippocampus as seed regions. The preprocessed BOLD signal from each hippocampal ROI and each voxel was correlated to produce an estimate of their strength of connectivity. This resulted in two whole-brain connectivity maps for each subject, one for anterior hippocampal connections and another for posterior hippocampal connections (Figure 4.4). The correlation maps were Fisher z transformed for group-level analysis.

Comparing Whole-Brain Anterior and Posterior Hippocampal Connectivity

Prior studies have demonstrated distinct connectivity profiles between the anterior and posterior hippocampus (Frank et al., 2019; Kahn et al., 2008; Persson et al., 2018), suggesting they may serve different functions. To ensure connectivity differences are present in our current sample, a paired samples t-test was conducted between the whole-brain connectivity maps for anterior and posterior hippocampus. In line with previous findings (Frank et al., 2019; Grady, 2020; Kahn et al., 2008; Persson et al., 2018), we expected to find greater anterior hippocampal connectivity with VMPFC, anterior lateral temporal regions, amygdala and perirhinal cortex. We also expected greater posterior hippocampal connectivity with medial and lateral parietal regions, lateral prefrontal regions, and parahippocampal gyrus. A voxel-wise threshold of $p < 0.001$ and an FDR cluster-corrected threshold of $p < 0.05$ was applied to the resulting contrast.

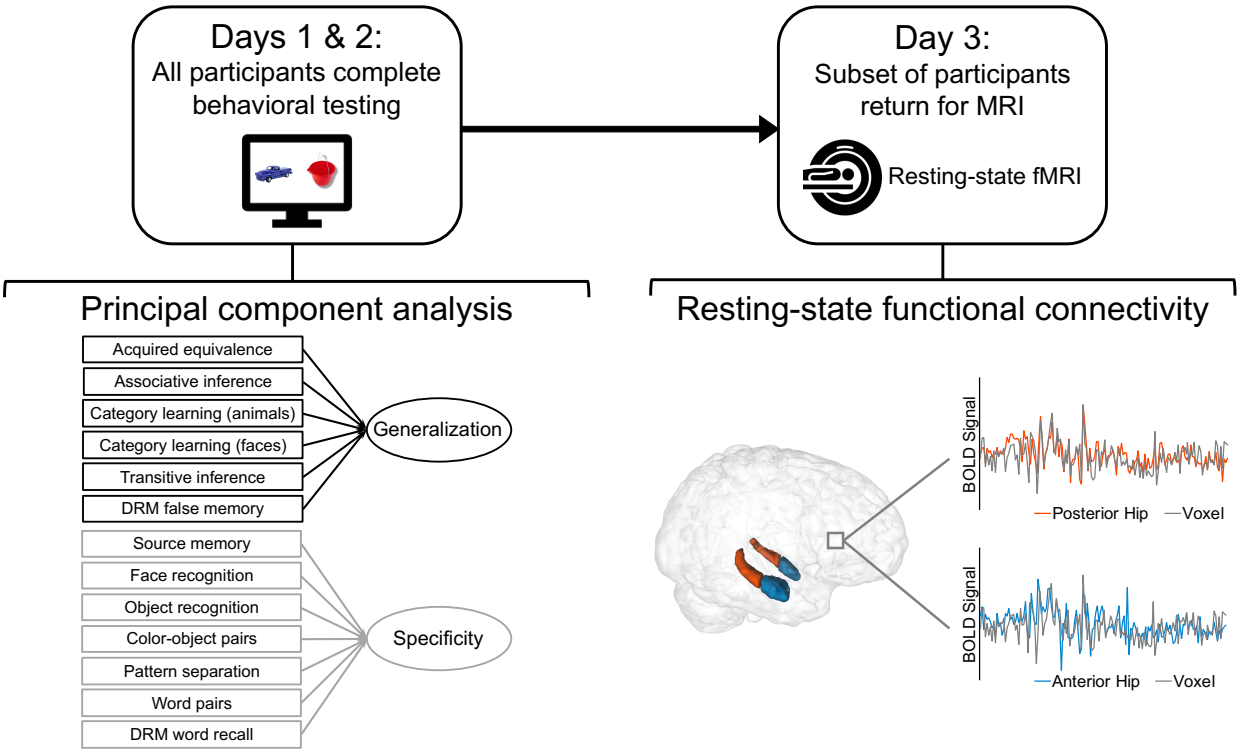

Figure 4.22. Overview of study procedures. All participants completed two separate sessions during which they completed assessments of memory specificity and generalization. Principal component analysis (PCA) was conducted to generate individual composite scores of memory specificity and generalization abilities. PCA was conducted separately on measures memory specificity and measures of generalization. A subset of participants returned for a third day to complete an MRI scan, including a resting-state functional MRI. Whole-brain functional connectivity for each hippocampal seed (posterior hippocampus in red, anterior hippocampus in blue) was calculated during the resting-state scan. The BOLD signal from each seed was correlated with the BOLD signal from each voxel to estimate their strength of connectivity.

Correlating Individual Memory Abilities and Hippocampal Connectivity

We next tested how individual memory abilities correlate with individual differences in the strength of hippocampal connectivity. We first asked whether individual specificity and generalization abilities were tracked by different hippocampal connections. We further asked whether anterior and posterior hippocampal connections differentially predict behavior, with anterior hippocampal connectivity predicting generalization abilities and posterior hippocampal connections predicting specificity abilities. To determine which whole-brain connections track behavior, individual anterior and posterior hippocampal connectivity maps were each correlated

with individual composite scores of specificity and generalization. A voxel-wise threshold of $p <$ .05 and an FDR cluster-corrected threshold of $p < .05$ was applied to each connectivity-behavior correlation map. We first predicted individual specificity and generalization composite scores would correlate with distinct hippocampal connections. We further predicted the distinct connections would be driven by functional differences between anterior and posterior hippocampus. That is, we expected anterior hippocampal connectivity to be more related to individual generalization abilities and posterior hippocampal connections to more strongly correlate with individual specificity abilities.

To further probe for a dissociation, we conducted a final analysis that directly tested for regions whose connectivity to anterior and posterior hippocampus differentially tracked behavior. Individual contrasts between posterior and anterior hippocampal connectivity were correlated with individual memory abilities, with separate correlations conducted for specificity and generalization (posterior–anterior x generalization and posterior–anterior x specificity). The resulting maps can be interpreted as regions whose connectivity to posterior hippocampus is more correlated with behavior than connectivity to anterior hippocampus (phip*generalization > ahip*generalization and phip*specificity > ahip*specificity). A voxel-wise threshold of $p < .05$ and an FDR cluster-corrected threshold of $p < .05$ was applied to each correlation map. To interpret the direction of significant correlations, we extracted anterior and posterior hippocampal connectivity scores with the significant clusters and plotted their correlation to behavior. We predicted anterior hippocampal connections would be more correlated with individual generalization scores compared to posterior hippocampal connections and posterior hippocampal connections would be more correlated with specificity compared to anterior hippocampal connections.

Results

Principal Component Analysis

Principal component analysis (PCA) was used to summarize individual performance across the tasks and generate composite scores of memory specificity and generalization abilities. For the generalization PCA, the following thresholds for component eigenvalues were determined using parallel analysis: 1.30, 1.12, 1.00, 0.90. The model produced principal components with the following eigenvalues: 1.62, 0.93, 0.87, and 0.57. Based on the thresholds determined by the parallel analysis, we retained the first component (eigenvalue = 1.62), which explained 41% of variance in the data. The unrotated component loadings are presented in Table 4.1. The measures showed moderate loadings on the first component, with associative inference having the strongest loading (0.79) and category learning with novel animals having the weakest loading (0.49).

Table 4.8. Component loadings

Generalization PCA	
	Comp 1
Acquired equivalence	0.61
Associative inference	0.79
Category learning (animals)	0.49
Category learning (faces)	0.61
Specificity PCA	
	Comp 2
Source memory	0.38
Face recognition	0.42
Color-object pairs	0.67
Object recognition	0.81
Pattern separation	0.70
Word pairs	0.65
Word recall	0.77

For the PCA of specificity measures, the eigenvalue thresholds for each component determined by the parallel analysis were: 1.41, 1.26, 1.15, 1.05, 0.97, 0.89, 0.79. The eigenvalues of the principal components obtained by the PCA were as followed: 2.95, 1.05 0.90, 0.70, 0.65, 0.47, 0.28. We retained the first component (eigenvalue = 2.95), which explained 42% of variance. The unrotated component loadings of each measure are presented in Table 4.1. The loadings ranged from weak to strong. Source memory demonstrated the weakest loading (0.38), and object recognition showed the strongest loading (0.81). The specificity and generalization component scores were moderately correlated (r (149) = .57, $p < .001$), with higher scores of

specificity associated with higher scores of generalization. Though the correlation was unexpected, it was also not surprising as an ability to link related memories may rely to some extent on an ability to remember those episodes.

Anterior and Posterior Hippocampus Form Distinct Connections

We first contrasted anterior and posterior hippocampal connectivity to establish they form distinct connections across the brain (Figure 4.5). Anterior and posterior hippocampus demonstrated significant differences in intrinsic connectivity that were largely in line with previous findings (Frank et al., 2019; Kahn et al., 2008; Persson et al., 2018). Consistent with Frank and colleagues (2019), regions of the middle temporal gyrus and VMPFC showed greater connectivity with anterior compared to posterior hippocampus. Overall, lateral prefrontal and lateral parietal cortices were more connected to posterior hippocampus. However, smaller clusters in these regions were preferentially connected to anterior hippocampus, suggesting

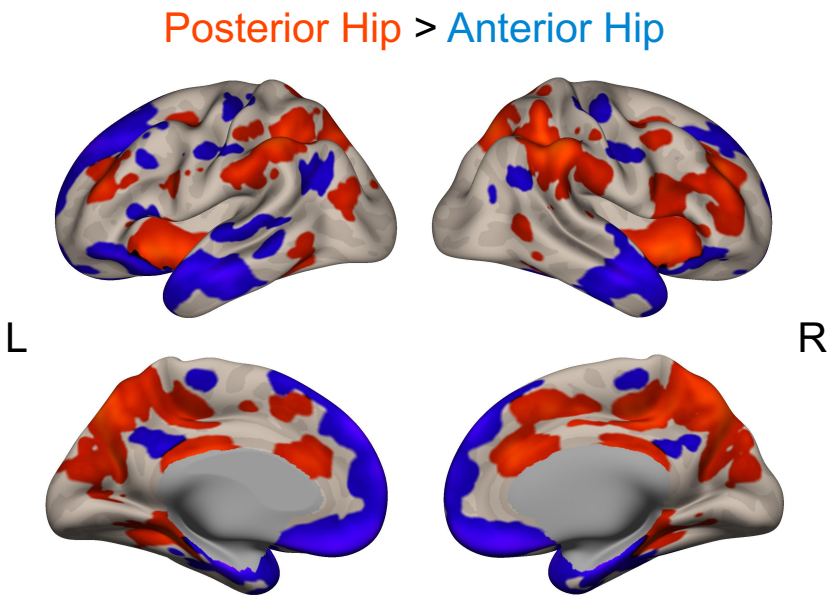

Figure 4.23. Contrast between posterior and anterior hippocampal whole-brain connectivity (posterior > anterior, voxel-wise threshold $p < .001$ and FDR-corrected cluster threshold $p < .05$.). Anterior and posterior hippocampus form distinct connections at rest. Medial prefrontal and anterior temporal gyrus preferentially

connected to anterior hippocampus and medial and superior parietal preferentially connected to posterior hippocampus.

Table 4.9. Whole-brain correlations between hippocampal connectivity and individual memory abilities

Cluster Label	Peak Voxel Coordinates (MNI)			Hemisphere	Cluster Size	Cluster p-FDR corrected	Voxel p-uncorrected
	x	y	z				
Anterior Hippocampal Connections x Generalization							
Occipital-temporal	34	-40	-14	R	3350	0.000256	0.000003
Occipital-temporal	-54	-78	6	L	1696	0.016384	0.000353
Medial/Dorsolateral prefrontal	-6	52	40	L	1449	0.025342	0.00073
Anterior Hippocampal Connections x Specificity							
Occipital lobe	-30	-96	14	L	1887	0.019026	0.000115
Posterior Hippocampal Connections x Generalization							
Occipital-temporal	36	-50	-10	R	9828	0	0.00001
Posterior Hippocampal Connections x Specificity							
Occipital-temporal-prefrontal	-4	-58	-12	L	8242	0	0.000008

collapsing across regions of interest may wash out more spatially refined differences in connectivity.

Specificity and Generalization are Predicted by Distinct and Overlapping Anterior and Posterior Hippocampal Connections

We next addressed 1) whether distinct hippocampal connections contribute to specificity and generalization, and 2) if correlations to behavior are differentially distributed between anterior and posterior hippocampus. In line with recent theories (Poppenk et al., 2013; Zeithamova & Bowman, 2020), we expected anterior hippocampal connections to predict generalization abilities and posterior hippocampal connections to predict specificity. The results of the correlations between whole-brain hippocampal connections and individual memory abilities are presented in Table 4.2 and Figure 4.6.

Partially supporting our first prediction, specificity and generalization abilities were to some degree tracked by different hippocampal connections. This finding, however, was limited

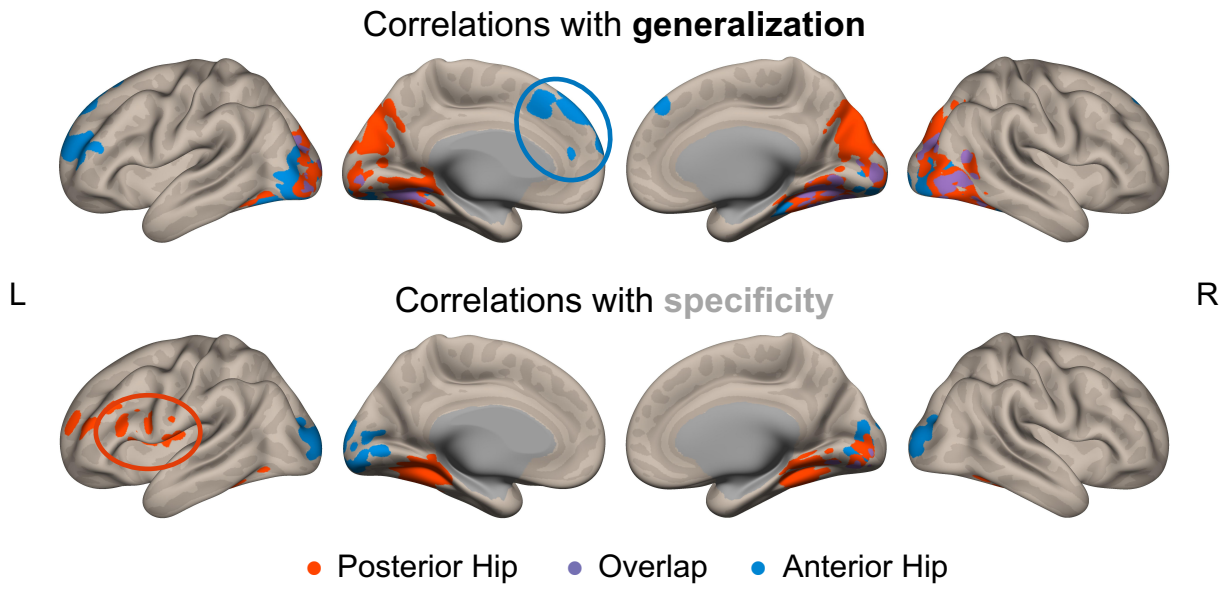

Figure 4.24. Whole-brain correlations between individual differences in anterior/posterior hippocampal connectivity and individual memory abilities (voxel-wise threshold of $p < .05$ and FDR-corrected cluster threshold of $p < .05$). Regions for which connectivity to both anterior and posterior hippocampus predicted behavior are shown in purple. Hippocampal connections to the prefrontal cortex were consistent with our predictions, with anterior hippocampal connectivity to medial prefrontal cortex tracking generalization (circled in blue) and posterior hippocampal connectivity to lateral prefrontal cortex tracking specificity abilities. Connections to the rest of the brain were not consistent with our predictions.

to the prefrontal cortex and was not found elsewhere in the brain. Within prefrontal cortex, hippocampal connectivity to a significant cluster in the medial prefrontal cortex (MPFC) was found to track individual generalization abilities, while specificity abilities were associated with hippocampal connectivity to the inferior frontal gyrus (IFG). Importantly, these connections differed between anterior and posterior hippocampus, revealing partial support for our second prediction. Anterior hippocampal connectivity to the MPFC cluster was positively associated with generalization, while connectivity between the posterior hippocampus and IFG positively correlated with specificity abilities.

Contrary to our initial prediction, we also found evidence that the different memory abilities are tracked by similar hippocampal connections, particularly along the ventral visual processing stream. Hippocampal connectivity to clusters in the occipital and temporal lobes were

found to positively correlate with both specificity and generalization. Furthermore, the occipital-temporal clusters did not differ between anterior and posterior hippocampus. When looking at correlations with individual generalization abilities, significant clusters spanning the occipital cortex and ventral temporal regions were found for both anterior and posterior hippocampus. This finding suggests that generalization may rely on interactions between visual processing regions and the *entire* hippocampus, rather than anterior and posterior subregions. Unlike generalization, the overlap between the anterior and posterior hippocampal connections predicting specificity were limited to a small cluster in the early visual cortex.

Anterior and Posterior Hippocampus Differentially Predict Memory

The relative lack of a functional differences between anterior and posterior hippocampus was unexpected. To further probe how anterior and posterior hippocampal connections relate to memory, we conducted two direct contrasts testing whether anterior and posterior hippocampal connections differentially predict individual specificity and generalization abilities (Table 4.3). In other words, are there regions in the brain where posterior hippocampal connectivity is more predictive of behavior compared to anterior hippocampal connectivity (posterior*generalization > anterior*generalization and posterior*specificity > anterior*specificity). If so, are anterior hippocampal connections stronger in their relationship to generalization compared to posterior hippocampal connections, and are posterior hippocampal connections more related to specificity abilities compared to anterior hippocampal connections? To determine the direction of anterior-posterior differences in each significant cluster, we plotted the correlation between individual behavior and the strength of each anterior and posterior hippocampal connection to that cluster (Figure 4.7).

Table 4.10. Whole-brain correlations between hippocampal connectivity and individual memory abilities

Cluster Label	Peak Voxel Coordinates (MNI)			Hemisphere	Cluster Size	Cluster p-FDR corrected	Voxel p-uncorrected
	x	y	z				
*(Posterior Hip – Anterior Hip) * Generalization*							
Somatomotor cortex	-16	-42	66	L/R	1886	0.008675	0.000508
Anterior temporal lobe / Lateral orbitofrontal cortex	-44	-04	-20	L	1523	0.016133	0.000043
Precuneus / Angular gyrus	-38	-50	30	L	1202	0.037607	0.000538
*(Posterior Hip – Anterior Hip) * Specificity*							
Somatomotor cortex	20	-42	54	L/R	2496	0.001102	0.000351
Precuneus / Lateral occipital cortex	-12	-54	-12	L/R	1499	0.011391	0.000007

When inspecting posterior-anterior hippocampal differences and their correlation to generalization, we found a significant cluster in the somatomotor cortex that did not align with our predictions. In this cluster, connectivity to the posterior hippocampus was positively correlated with generalization, while connectivity to the anterior hippocampus was not. Interestingly, the correlation with specificity abilities revealed a highly overlapping cluster in the somatomotor cortex, which revealed a somewhat similar direction of posterior-anterior hippocampal differences. In this region, connectivity to the posterior hippocampus was only numerically positively correlated with specificity abilities, while connectivity to the anterior hippocampus was negatively correlated with specificity. In other words, the posterior > anterior finding for specificity abilities was driven primarily by a negative correlation with anterior hippocampal connectivity rather than a positive correlation with posterior hippocampal connectivity.

The rest of the findings were largely in support of our predictions. The correlations with generalization revealed two significant clusters that demonstrated a larger effect for anterior hippocampal connectivity compared to posterior hippocampal connectivity to those regions.

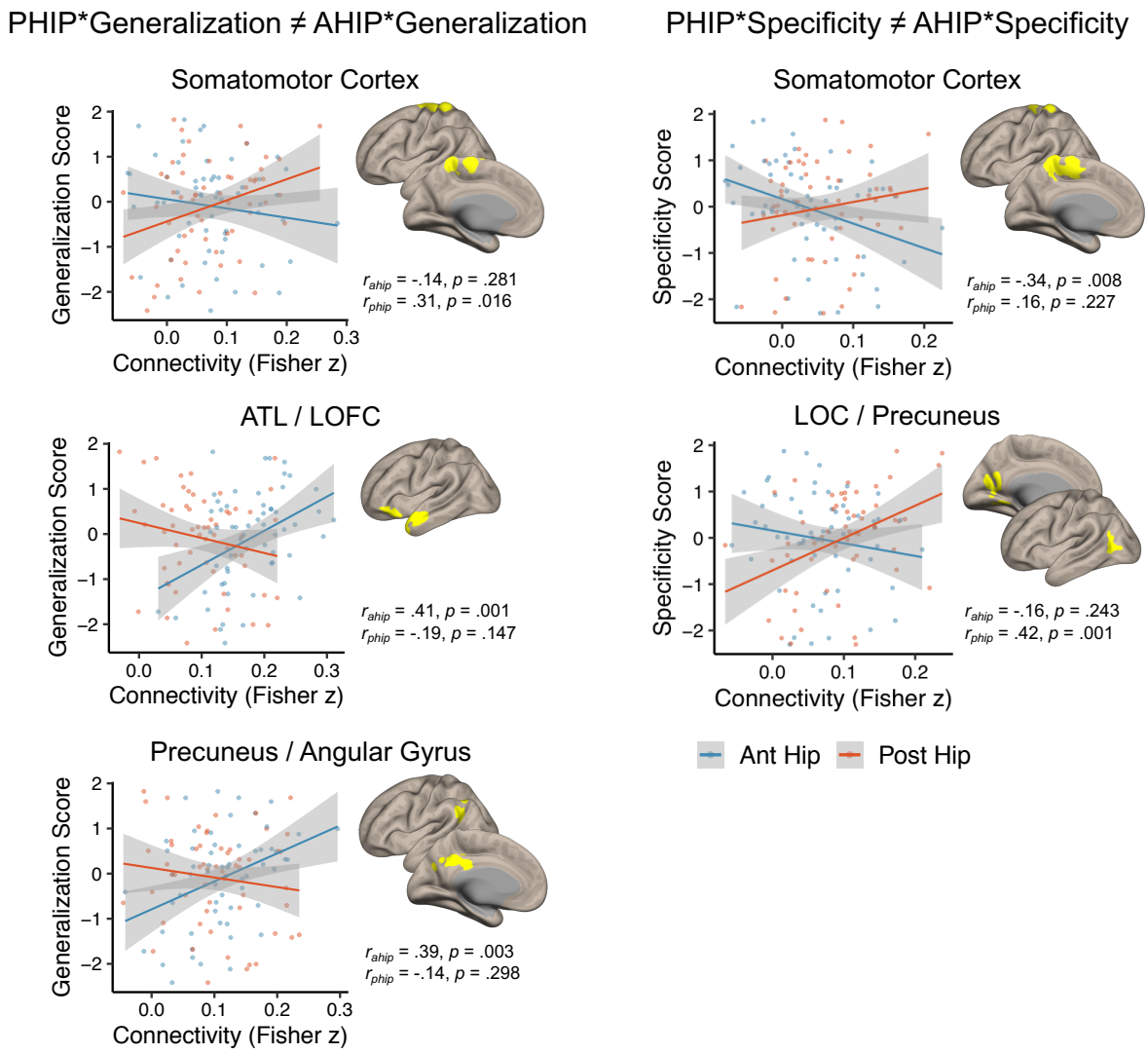

Figure 4.25. Differences in relationship between anterior/posterior hippocampal connectivity and behavior. Significant clusters were taken from correlating differences in anterior and posterior hippocampal (Post Hip – Ant Hip) with behavior. Separate analyses were conducted for generalization and specificity. ATL = anterior temporal lobe, LOFC = lateral orbitofrontal cortex, LOC = lateral occipital cortex.

Individual generalization abilities significantly and positively correlated with anterior hippocampal connectivity to a cluster spanning the precuneus, posterior cingulate cortex and angular gyrus and a separate cluster spanning the left anterior temporal lobe (ATL) and lateral orbitofrontal cortex (LOFC). Posterior hippocampal connectivity to these regions did not correlate with generalization abilities. When looking at posterior-anterior hippocampal

differences in tracking specificity, we found another cluster that showed the expected pattern of greater correlations to specificity for posterior compared to anterior hippocampal connections. Precuneus/lateral occipital cortex (LOC) connectivity to posterior hippocampus significantly and positively predicted specificity, while connectivity to the anterior hippocampus was not significantly related to specificity.

To summarize, we found compelling evidence they may differentially contribute to memory specificity and generalization. Anterior hippocampal connectivity was more strongly correlated with individual generalization abilities compared to posterior hippocampal connections. On the other hand, posterior hippocampal connectivity with regions of the LOC and precuneus were more strongly correlated with individual specificity abilities. While these findings were largely in line with our prediction that anterior hippocampal connections contribute more to generalization and posterior hippocampal connections to specificity, hippocampal connectivity to the somatomotor showed a different pattern. Somatomotor cortex connectivity to posterior hippocampus was more positively correlated with both specificity and generalization abilities compared to connectivity with anterior hippocampus. Though unexpected, connectivity with somatomotor cortex during rest have been linked to motor responses on independent tasks (Stillman et al., 2013; Sugata et al., 2020).

Discussion

The present study examined 1) whether individual memory specificity and generalization abilities track distinct intrinsic hippocampal connections, and 2) whether anterior and posterior hippocampal connections differentially contribute to the different types of learning. We predicted that hippocampal connectivity with regions important for maintaining accurate and vivid memories would predict individual specificity abilities, while generalization would be tracked by

hippocampal connectivity with regions known for extracting regularities across experiences. Furthermore, we predicted anterior and posterior hippocampal connections would differentially track behavior, with anterior hippocampal connections predicting individual generalization abilities and posterior hippocampal connections predicting specificity abilities. The present study revealed a more nuanced relationship between hippocampal connections in the different types of learning. In the prefrontal cortex, we found evidence for each prediction. Generalization abilities were tracked by anterior hippocampal connectivity to medial regions of the prefrontal cortex, and specificity abilities were predicted by posterior hippocampal connectivity to lateral regions of the prefrontal cortex. We also found evidence that anterior and posterior hippocampal connections differ in their relationship to behavior in alignment with their proposed roles in memory specificity and generalization. Anterior hippocampal connections were more strongly correlated with generalization abilities compared to posterior hippocampal connections, while posterior hippocampal connections were more correlated with specificity abilities. Contrary to our predictions, we also found specificity and generalization were associated with overlapping hippocampal connections, especially in visual processing regions. Moreover, anterior and posterior hippocampal connections were not unique to each of the memory abilities. Rather, specificity and generalization abilities were associated with both anterior and posterior hippocampal connections.

Unexpectedly, hippocampal connectivity to visual processing regions, like early visual cortex and fusiform gyrus, contributed to both specificity and generalization. There are two possible explanations for this finding. The first is that linking related information across our experiences relies to some extent on intact and detailed representations for specific episodes. While generalization decisions may call on representations that contain abstracted or integrated

information spanning multiple episodes (Bowman & Zeithamova, 2018; Minda & Smith, 2001; Schlichting et al., 2014; Zeithamova, Dominick, et al., 2012), some research suggests generalization can also occur on-demand by retrieving specific memories with common features (Banino et al., 2016; Carpenter & Schacter, 2017, 2018; Mack, Preston, & Love, 2013; for review, see Zeithamova & Bowman, 2020). Indeed, individual specificity and generalization scores were moderately correlated in the present sample, suggesting the two memory processes are not entirely independent. Another possibility is these regions maintain both specific and generalized representations. Several fMRI studies have shown how patterns of neural activity along the ventral visual processing stream capture event-specific content and the strength of these representations are associated with later memory (Eger et al., 2008; Xue et al., 2010; Zeithamova et al., 2017). However, representations in high-level visual regions, like the fusiform gyrus, also contain category-level information (Ashby & Zeithamova, 2022; Haxby et al., 2013; Kuhl & Chun, 2014; Zeithamova et al., 2017) and are subject to change as new associations or concepts are formed (Clarke et al., 2016; van der Linden, Murre, & van Turennout, 2008). More recently, it's been suggested that top-down influences on the formation of category representations can appear as early as the visual cortex. Accordingly, the hippocampus may modulate activity in these regions to align representations with task goals, such as attending to relevant category features or discriminating between exemplars (Ashby & Zeithamova, 2022; Folstein, Palmeri, & Gauthier, 2013; Folstein et al., 2015). Future studies are needed to differentiate between specific and generalized memory representations recruited for generalization and how they are each supported by hippocampal interactions.

Individual memory specificity and generalization abilities were also supported by hippocampal connections to different prefrontal regions, with evidence for functional differences

between anterior and posterior hippocampus. Anterior hippocampal connectivity to medial prefrontal regions predicted generalization abilities, while posterior hippocampal connectivity to IFG predicted specificity. Moreover, the prefrontal regions are consistent with their proposed role in memory specificity and generalization. For example, the IFG is known for discriminating between related memories to prevent interference between overlapping or similar memories (Badre et al., 2005; Kuhl et al., 2007) and does so in coordination with the hippocampus (Bowman & Dennis, 2016; Manelis et al., 2013). The MPFC, on the other hand, is thought to support the integration of related memories to form and update complex knowledge structures, like schemas and concepts (Schlichting & Preston, 2015; Tompary & Davachi, 2017; van Kesteren et al., 2020; Zeithamova & Bowman, 2020). Anterior and posterior hippocampus may then differentially interact with the prefrontal cortex to determine whether information is integrated with or separated from existing memories.

The above findings indicated possible dissociations along the long axis of the hippocampus. To further corroborate these findings, a more direct contrast of anterior and posterior hippocampal connections was conducted to determine whether they differ in their relationship to behavior. Generalization was more strongly associated with anterior hippocampal connectivity than posterior hippocampal connectivity to regions of the LOFC, ATL, precuneus, posterior cingulate cortex and angular gyrus. Specificity, on the other hand, was more strongly associated with posterior hippocampal connectivity than anterior hippocampal connectivity, especially in the LOC and precuneus. These findings provide compelling support for the representational gradient hypothesis, which argues for fine-grained or specific representations in the posterior hippocampus and coarse-grained or generalized ones in the anterior hippocampus (Irish & Vatansever, 2020; Poppenk et al., 2013; Sekeres, Winocur, & Moscovitch, 2018). Our

prior work (Frank et al., 2019) found anterior and posterior hippocampus form stable, trait-like connections that are consistent with those predicted roles in specificity and generalization. The current findings extend this work by providing direct links between connectivity and behavior that demonstrate the potential functions of anterior and posterior hippocampal connections.

While we found some evidence anterior and posterior hippocampal connections differentially contribute to memory specificity and generalization, the connections implicated in our whole-brain analyses were not necessarily aligned with those anticipated based on prior work. For example, as ATL and VMPFC have been implicated in processing conceptual information (Ashby & Zeithamova, 2022; Bowman et al., 2020; Bowman & Zeithamova, 2018; Lambon Ralph et al., 2012), we expected connectivity to these regions would track individual generalization abilities. While hippocampal-ATL connectivity did predict generalization abilities, hippocampal-VMPFC connections were not significant. This was unexpected, as past studies demonstrate a clear role for hippocampal-VMPFC interactions during memory updating and integration (Schlichting & Preston, 2016; van Kesteren et al., 2010; Zeithamova, Dominick, et al., 2012). While generalization may largely be supported by on-demand engagement of hippocampal-VMPFC interactions, others have shown individual generalization performance is also tracked by those interactions found at rest (Frank et al., 2019; Gerraty et al., 2014).

We also anticipated lateral parietal and lateral prefrontal connections to the hippocampus would be related to specificity, as these regions are known to support episodic retrieval and the precision and vividness with which memories are recalled (Badre et al., 2005; Kuhl & Chun, 2014; Lee et al., 2019; Richter et al., 2016; Wais et al., 2017). While posterior hippocampal-IFG connectivity was associated with specificity abilities, anterior hippocampal connectivity to LOFC and angular gyrus predicted generalization abilities. Again, this may reflect

generalization's reliance on specific and detailed memories. Indeed, several studies have found that generalizing category knowledge is guided by memory for specific category exemplars represented in the lateral parietal and lateral prefrontal cortices (Bowman et al., 2020; Mack et al., 2013). Alternatively, lateral parietal and lateral prefrontal regions may maintain representations at different levels of granularity with task-demands determining the type of information required (Badre & Wagner, 2007; Favila, Samide, Sweigart, & Kuhl, 2018; Brice A. Kuhl, Johnson, & Chun, 2013; Schlichting, Mumford, & Preston, 2015).

Another unexpected finding was that hippocampal connectivity to somatomotor cortex tracked both specificity and generalization abilities. This finding may reflect the engagement of somatomotor cortex to coordinate successful motor responses during behavioral tasks. However, it was surprising to see connectivity to this region during a period of rest when participants are not required to give motor responses. Though unexpected, prior work has linked connectivity of somatomotor regions at rest to motor responses (Stillman et al., 2013; Sugata et al., 2020) and cognitive performance (Chen et al., 2022) on an independent task. Interestingly, there were anterior and posterior hippocampal differences in this finding, where posterior hippocampal connectivity with somatomotor cortex was positively correlated with behavior while anterior hippocampal-somatomotor connectivity was negatively correlated. The reason for such differences is unclear and presents an interesting area for future research.

The present study tested the role of anterior and posterior hippocampus in regard to the representational gradient hypothesis. However, this is just one theory of the possible functions of anterior and posterior hippocampal subregions. Other researchers consider functional differences between anterior and posterior hippocampus in terms of other cognitive processes, such as encoding v. retrieval (Fritch, Spets, & Slotnick, 2021; Kim, 2015) or episodic v. spatial memory

(Persson et al., 2018). The dissociation between anterior and posterior hippocampus may also be driven by differences in how they process visual stimuli. In her meta-analytic review, Grady (2020) found anterior hippocampus is preferentially recruited for tasks involving objects and words, while posterior hippocampus is primarily recruited for tasks involving scene or facial information. Differences in stimulus modalities between the tasks may explain why specificity abilities were associated with both anterior and posterior hippocampal connections to visual processing regions.

The present study addresses the role of intrinsic hippocampal connections in memory specificity and generalization, and how differences in anterior and posterior hippocampal connections may contribute to the different forms of learning. Our findings provide compelling evidence that the different forms of learning are, to some extent, associated with distinct hippocampal connections that may be driven by functional dissociations along the long axis of the hippocampus. Additionally, our findings suggest that some hippocampal connections recruited for memory specificity may also contribute to generalization, though the exact function of these connections remains unknown. Together, our findings begin to shed light on how exactly the hippocampus can contribute to memory at varying scales of granularity.

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CHAPTER V

GENERAL DISCUSSION

The hippocampus, most known for its role in episodic memory, is implicated in many other aspects of learning and memory (Kensinger, 2009; Schlichting & Preston, 2015; Scovill & Milner, 1957; Shohamy & Adcock, 2010; van Kesteren et al., 2012). H ow it contributes to different memory processes is still unclear. One proposal is that it works in coordination with different brain regions to support different functions. Functional connectivity is used to measure the level of coordination between brain regions and has begun to provide some insight into the different roles of hippocampal connections. Moreover, some researchers are leveraging intrinsic functional connectivity, such as that measured during resting-state fMRI, as they may provide more insight into individual behavior than task-driven interactions (Finn et al., 2015; Gratton et al., 2018). T hus, the present dissertation aimed 1) t o understand how different hippocampal connections serve different functions of memory, and 2) t o test whether intrinsic hippocampal connections predict individual memory abilities.

Different Hippocampal Connections Contribute to Different Memory Processes

The hippocampus is implicated in many aspects of learning and memory, like remembering specific episodes, prioritizing salient information, and generalization across experiences. Thus, the first goal of the dissertation was to address how the hippocampus interacts with different regions to support different aspects of learning. Chapter 2 first explored how hippocampal interactions with reward processing regions track reward effects on learning. As past studies have focused on hippocampal interactions with theoretically motivated structures (Lisman & Grace, 2005; Lisman, Grace, & Duzel, 2011; Shohamy & Adcock, 2010) , the

midbrain and ventral striatum, we used a meta-analytic approach to identify a broader network of reward-processing regions. Our findings demonstrated greater effects of reward on memory were associated with greater hippocampal connections to reward-processing regions. Behavior was primarily tracked by hippocampal connections with anterior cingulate cortex, orbitofrontal cortex, and ventral striatum, establishing a role for regions not previously considered. Unexpectedly, hippocampal-midbrain interactions were not related to the effects of reward on memory. Instead, they appeared to be relevant to overall memory performance, suggesting hippocampal-midbrain interactions are not specific to externally motivated learning but encoding and consolidation in general (Lisman et al., 2011).

Though traditionally thought to support memory for specific episodes (McClelland, McNaughton, & O'Reilly, 1995; Scovill & Milner, 1957; Squire, 1992), the hippocampus has also been shown to support generalization (Bowman, Iwashita, & Zeithamova, 2020; Schlichting, Zeithamova, & Preston, 2014; van Kesteren et al., 2010). While some argue the hippocampus supports generalization decisions by retrieving specific episodes (Banino et al., 2016; Carpenter & Schacter, 2017, 2018), other research suggests the role of the hippocampus goes beyond recalling specific memories and can actually integrate related information (Schlichting, Mumford, & Preston, 2015; Shohamy & Wagner, 2008; Zeithamova, Dominick, & Preston, 2012). To test this hypothesis, Chapter 3 examined whether hippocampal connectivity with putative generalization regions predicts category generalization. Connections with putative specificity regions were also measured to test whether the hippocampus contributes to generalization through memory specificity processes. Category generalization was associated with hippocampal connectivity to VMPFC, but no other connections. This finding was consistent with prior studies showing memory integration processes rely on interactions between the

hippocampus and VMPFC (Schlichting & Preston, 2016; van Kesteren et al., 2010; Zeithamova et al., 2012). Building off this work, Chapter 4 included measures of memory specificity to see if those connections that predict generalization are different from those that predict memory specificity. While specificity and generalization abilities were associated with distinct hippocampal-prefrontal connections, they were also related to hippocampal connectivity with ventral visual processing regions. One possible explanation for this finding is generalization may to some extent rely on the same hippocampal interactions that support intact and detailed memory for specific episodes. Together, these chapters highlight one avenue by which the hippocampus can serve seemingly different functions of memory.

Functional differences along the long axis of the hippocampus may be another way in which it contributes to different types of learning. In two empirical studies, we tested whether differences between anterior and posterior hippocampal connections are consistent with the representational gradient hypothesis, which posits coarse-grained or generalized representations in the anterior hippocampus and fine-grained or specific ones in the posterior hippocampus (Poppenk et al., 2013). While Chapter 3 provided evidence that anterior and posterior hippocampus form connections consistent with their predicted roles in generalization and specificity, they did not differentially relate to category generalization. Rather, we found that both anterior and posterior hippocampal connectivity to VMPFC predicted behavior. While there was a lack of evidence for a dissociation between anterior and posterior hippocampal connections, the study was underpowered and provided no link to memory specificity for comparison. Chapter 4 extended this work by including measures of memory specificity. Again, findings revealed partial support for functional differences between anterior and posterior hippocampus. There were some anterior hippocampal connections that were more correlated

with generalization compared to posterior hippocampus, and some posterior hippocampal connections that were more correlated with specificity compared to anterior hippocampus. However, generalization performance was largely associated with both anterior and posterior hippocampal connections, as was memory specificity. The lack of clear support for the representational gradient hypothesis may stem from generalization's reliance on maintaining and recalling specific memories (Banino et al., 2016; Carpenter & Schacter, 2017, 2018; Medin & Schaffer, 1978), highlighting an area of exploration for future research.

Individual Differences in Intrinsic Connectivity Predict Individual Behavior

The second goal of the dissertation was to test whether individual differences in memory performance can be predicted by individual differences in intrinsic hippocampal connections. Recent work suggests intrinsic functional connections, such as those found during rest, can be leveraged to identify individuals (Finn et al., 2015; Horien et al., 2019) and predict individual behavior (Fong et al., 2019; Poole et al., 2016; Rosenberg et al., 2015). However, it is less known whether hippocampal connections can provide insight into individual memory performance. Across three empirical studies, I demonstrated how individual differences in the strength and pattern of hippocampal connections can predict individual memory performance. In Chapter 2, the relationship between connectivity and behavior was present even prior to the encoding task, suggesting trait-like properties of hippocampal connections contain information about individual behavior. A similar connectivity-behavior relationship was found in Chapter 3, with hippocampal-VMPFC connectivity predicting individual generalization performance. The relationship to behavior did not reach significance during the beginning rest period, though the study may have been underpowered. Finally, Chapter 4 demonstrated how individual differences in the strength of resting-state hippocampal connectivity can predict individual memory

performance that was measured on a separate day. Notably, because resting-state connectivity was measured on a separate day from behavior, it is unlikely that this connectivity-behavior relationship was driven by temporary brain states or recent tasks. Instead, this finding provided compelling evidence that trait-like hippocampal connections can still provide insight into individual memory performance.

The present dissertation used both resting-state functional connectivity and background connectivity during tasks to index trait-like hippocampal connections. While the relationship between the two measures has been debated (Gratton et al., 2018; Jiang et al., 2020), Chapters 2 and 3 revealed the pattern of intrinsic hippocampal connections are consistent during rest and task, suggesting they may reflect stable, trait-like properties of the hippocampus. This aligns with prior studies showing background connectivity during different tasks are largely explained by connections found at rest, with only modest task-evoked changes (Cole et al., 2014; Gratton, Laumann et al., 2016; Gratton et al., 2018). Some have found task-evoked changes in functional connectivity are associated with individual behavior (Gruber et al., 2016; Tambini, Ketz, & Davachi, 2010; Tompary, Duncan, & Davachi, 2015), and may even serve as better predictors compared to resting-state connectivity (Finn et al., 2017; Greene et al., 2018; Jiang et al., 2020). However, the present dissertation found that while some task-evoked increases in background connectivity were present, they did not affect the overall pattern of connections. Thus, background connections may capture the same behaviorally relevant information as connections at rest.

Broader Implications

The current dissertation furthers our understanding of how hippocampal connections contribute to different forms of learning and provides compelling evidence for how intrinsic

hippocampal connections can be used to predict individual memory abilities. Mapping intrinsic functional connections to different memory processes is an important yet underexplored area of research. Over the years, research has demonstrated the utility of functional connectivity as a type of neural "biomarker" for predicting diseases or disorders (Bai et al., 2009; Castellanos et al., 2013; Kessler et al., 2016; Reinen et al., 2018; Tsiaras et al., 2011). Resting-state connectivity, in particular, provides a quick tool for assessing individuals to identify disruptions or abnormalities in healthy brain function (Castellanos et al., 2013). Understanding the link between intrinsic hippocampal connections and different memory processes will allow clinicians to better identify learning impairments that may follow disease or injury. Indeed, some researchers have already begun to link memory deficits to disruptions in hippocampal connectivity (Bai et al., 2009; Voets et al., 2014). The current dissertation adds to this literature by identifying connections important to other memory processes, such as prioritizing encoding for motivationally salient information and generalizing across memories. Mapping out functional connections also informs targeted treatments for impairments that may occur due to disruptions in connectivity. For example, studies have begun to explore the utility of transcranial magnetic stimulation (TMS), showing how targeted stimulation of hippocampal connections can improve learning and memory (Tambini, Nee, & D'Esposito, 2018; Wang et al., 2014; Warren, Hermiller, Nilakantan, & Voss, 2019). These findings underscore the potential of hippocampal connectivity "biomarkers" and targeted TMS treatments, directing to an important area of exploration for future research.

Limitations & Future Directions

The dissertation explored how functionally distinct subregions of the hippocampus may contribute to different learning processes. While the current dissertation examined differences

between anterior and posterior portions of the hippocampus, there are other ways to separate it into functionally meaningful units. The hippocampus is comprised of anatomically distinct subfields, including CA3, dentate gyrus, and CA1. Importantly, the subfields differ in how they code for or represent information, which may also explain how the hippocampus supports memories with varying scales of specificity (Guzowski, Knierim, & Moser, 2004; Yassa & Stark, 2011). For example, it is argued that sparse coding in the CA3/DG subfields enables separation of similar or overlapping memory representations (Norman & O'Reilly, 2003; Schapiro et al., 2017; Yassa & Stark, 2011). Representations in the CA1 subfield are less sparse and more overlapping, potentially allowing the hippocampus to pick up on regularities and connections between memories (Morton, Sherrill, & Preston, 2017; Schapiro et al., 2017; Schlichting et al., 2014). It is important for future studies to explore the role of intrinsic hippocampal subfield connections and how they might also contribute to different types of learning.

The present dissertation has shown how useful intrinsic connectivity can be when predicting individual memory performance, but how it relates to task-driven interactions is still unclear. It is well-established that generalization recruits both the hippocampus and VMPFC (Bein, Reggev, & Maril, 2014; Bowman & Zeithamova, 2018; Schlichting & Preston, 2016; van Kesteren et al., 2010; Zeithamova et al., 2012), but this was not reflected clearly in our findings. While Chapter 3 found hippocampal-VMPFC connectivity predicted individual category generalization performance, there was no evidence it was related to generalization abilities in Chapter 4. Though unexpected, prior studies have focused almost exclusively on task-driven interactions between the hippocampus and VMPFC (Schlichting & Preston, 2016; van Kesteren et al., 2010; Zeithamova et al., 2012). Thus, one possibility is that intrinsic connections and task-

evoked interactions can explain different aspects of behavior (Geerligs et al., 2015), with hippocampal-VMPFC connections only engaged during on-demand processing. In Chapter 3, participants learned the category structures prior to scanning. Hippocampal-VMPFC binding processes may have been engaged following learning to continue building representations for the new categories (Schlichting & Preston, 2016; Tompary & Davachi, 2017). This may also explain the negative relationship between connectivity and category generalization, as better learners may have formed category representations early on and no longer needed those binding processes at the time of scanning. Alternatively, task-evoked activations or interactions do not explain behavior beyond what one can learn from resting-state connections (Fox & Raichle, 2007). Research has shown functional connections found at rest are engaged during different tasks (Bzdok et al., 2016; Gess et al., 2014; Shah et al., 2016; Smith et al., 2009) and can even predict task-driven activations (Mennes et al., 2010; Ritchey, Yonelinas, & Ranganath, 2014; Tavor et al., 2016). Indeed, the negative relationship between connectivity and behavior in Chapter 3 also points to the possibility that intrinsic connections prime crosstalk between regions and are "de-activated" when offline (Cole et al., 2016). Future studies should explore the relationship between intrinsic and task-driven connections to better understand the role of hippocampal interactions in learning.

General Conclusion

The present dissertation moves beyond the localization view of brain function to show how the hippocampus works in coordination with different brain regions to support different functions of memory. Moreover, it demonstrates how intrinsic hippocampal connectivity, measured during rest or in the background of an external task, can provide insight into individual learning and memory. Importantly, clinicians can leverage this information as a quick tool for

identifying learning impairments that may follow disease or injury and develop targeted treatments. Together, these findings inform our understanding of the different functions of hippocampal connections and underscore the potential of intrinsic functional connectivity in future research.

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