Shifting The Balance Between Pattern Separation and Pattern Completion

by

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Abstract

Are people’s memories influenced by neurocognitive states? If so, what establishes them? Theoretical models suggest that after detecting familiarity, as opposed to novelty, the hippocampus is biased towards pattern completion due to decreased cholinergic input. I investigated the behavioral implications of this theory by designing a paradigm which assesses how recent familiarity influences aspects of memory retrieval that differentially depend on pattern completion: associative retrieval and item recognition. I found that recent familiarity selectively benefited associative retrieval (Experiment 1). I then measured the time course of this mnemonic state by varying the ISI between retrieval trials (Experiment 2). I found that recent familiarity robustly benefited associative retrieval at short ISIs, but that the benefit decreased at long ISIs. This decay is consistent with the timescale of cholinergic modulation of the hippocampus. Thus, I used a subtle, biologically motivated manipulation to bias basic memory computations.
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Cheers!
# Table of Contents

Table of Contents .................................................................................................................. iv  
List of Figures ......................................................................................................................... vi  
List of Appendices ................................................................................................................... vii 

Chapter 1 ................................................................................................................................. 1  

1 Introduction ............................................................................................................................. 1  
1.1 Effect of Novelty on Brain and Behavior ............................................................................. 3  
1.2 Memory and the Medial Temporal Lobe .............................................................................. 3  
1.2.1 Encoding and Retrieval Processes in the Medial Temporal Lobe ................................ 4  
1.2.2 Anatomy of the Hippocampus ...................................................................................... 6  
1.3 Pattern completion versus pattern separation ................................................................... 6  
1.4 Effect of Novelty on Episodic Memory Encoding ............................................................ 8  
1.5 Effect of Novelty on Episodic Memory Retrieval ........................................................... 9  
1.6 Thesis Overview ................................................................................................................. 10 

Chapter 2 ................................................................................................................................. 12 

2 Experiment 1 .......................................................................................................................... 12  
2.1 Introduction ........................................................................................................................ 12  
2.2 Methods .............................................................................................................................. 13  
2.2.1 Participants .................................................................................................................. 13  
2.2.2 Stimuli ......................................................................................................................... 13  
2.2.3 Procedure .................................................................................................................... 13  
2.2.4 Data Analysis ............................................................................................................. 15  
2.3 Results & Discussion ........................................................................................................ 16 

Chapter 3 ................................................................................................................................. 20 

3 Experiment 2 .......................................................................................................................... 20  
3.1 Introduction ........................................................................................................................ 20  
3.2 Methods .............................................................................................................................. 20  
3.2.1 Participants .................................................................................................................. 20  
3.2.2 Stimuli ......................................................................................................................... 21
List of Figures

Figure 1. Task Schematic for Experiments 1 & 2  .............................................................. 42

Figure 2. Experiment 1: Source Memory and Item Memory as a function of Preceding Response - 43

Figure 3. Experiment 1: Source Memory as a function of preceding subjective experience------- 44

Figure 4. Experiment 1: Recognition Decision Criteria as a function of Preceding Response------ 45

Figure 5. Experiment 2: Source Memory and Item Memory as a function of Preceding Response and ISI  ......................................................................................................................... 46

Figure 6. Experiment 2: Source Memory as a function of preceding subjective experience for both ISIs. ................................................................................................................................. 47

Figure 7. Experiment 2: Recognition Decision Criteria as a function of Preceding Response and ISI ................................................................................................................................. 48

Figure 8. Task Schematic for Experiment 3............................................................................ 49
List of Appendices

Appendix A. Experiment 2 Supplemental Material 50
Chapter 1

1 Introduction

For a memory to be useful, it must go beyond signalling familiar aspects of our world; it must also be capable of using familiar cues to reactivate relevant associations from the past. For example, to avoid an embarrassing encounter at a grocery store, you need to both recognize the face of an acquaintance (item memory) and be able to recall their name (associative memory). As anyone who has been in this situation can attest, associative memory can be as challenging as it is indispensable. This raises the question; why do familiar cues evoke detailed memories of a past episode on some occasions but fail to evoke memories on others?

This is a central question motivating decades of episodic memory research. The question has generally been approached by relating encoding strength or retrieval accuracy to the processes evoked by discrete events. This method, however, can reveal only part of the story. It treats each stimulus and trial as though it occurred in isolation, ignoring the ongoing cognitive and neural processes in which they occur. Endel Tulving first proposed that successful retrieval does in fact depend on processes unfolding before a retrieval cue (Tulving, 1985). He specifically postulated the existence of a retrieval mode, a neurocognitive attentional state which permits conscious awareness of reactivated memories. The prospect that neurocognitive states can also influence the mnemonic reactivation process itself, however, has not been explored.

To explore this possibility, I turned to neurocomputational models that formally characterize how the brain reactivates associative memories (Treves & Rolls, 1992). Associative retrieval is mediated in these models through pattern completion, a computational process through which a partial, noisy cue can reactivate stored patterns of neural activity related to an event. Pattern completion is thought to occur in the hippocampus, a brain structure shown to support associative memory. Critically, the likelihood of the hippocampus engaging in pattern completion may not be constant, but instead could be biased by shifts in cholinergic input; lower cholinergic input is
postulated to bias the hippocampus towards pattern completion whereas higher cholinergic input biases the hippocampus away from pattern completion (Hasselmo & Schnell, 1994; Hasselmo, Schnell, & Barkai, 1995; Easton, Douchamps, Eacott, & Lever, 2012). The slow acting nature of such neuromodulation implies that, once induced, pattern completion biases could be temporally extended on the order of a few seconds (Hasselmo & Fehlau, 2002; Meeter, Murre, & Talamini, 2004). The neurochemical state of the brain prior to a retrieval cue, thus, could affect the likelihood of that cue triggering pattern completion, irrespective of the strength of the memory trace itself.

Here I asked whether this neurocomputational framework can be used to make mechanistic predictions about (1) manipulations that have the power to elicit prolonged memory states and (2) the specific aspects of memory retrieval that can be biased by these memory states. Inspired by a recent study which biased the complementary process of pattern separation (computational process by which similar events can be stored into distinct memory traces) in human behaviour (Duncan, Sadanand, & Davachi, 2012), I assessed whether exposure to familiar vs. novel images influences subsequent retrieval. The crux of this manipulation is that familiarity reduces acetylcholine release but novelty increases it. I, thus, reasoned that if behavioural biases follow the same time course as the physiological biases described above, recent exposure to familiarity should facilitate pattern completion dependent retrieval whereas recent exposure to novelty should impair it. To test whether familiarity does, in fact, selectively facilitate pattern completion dependent memory retrieval, I tested whether this manipulation influences different aspects of memory retrieval, specifically, associative memory (pattern completion dependent) and item memory (pattern completion independent).

In the next few sections, I will provide background on the neural underpinnings of episodic memory to motivate why novelty and familiarity could bias episodic memory retrieval.
1.1 Effect of Novelty on Brain and Behavior

Responding to novelty is evolutionary significant – novel stimuli can be indicative of unknown opportunities or threats that might lead to fruitful or harmful outcomes, respectively. Novelty has been shown to affect different aspects of cognition. For example, human neuroimaging studies have shown that novelty interacts with reward processing (Guitart-Masip, Bunzeck, Stephan, Dolan, & Düzel, 2010; Bunzeck, Doeller, Dolan, & Duzel, 2012). Novelty can also enhance visual perception by eliciting a transient attentional response (Schomaker & Meeter, 2012) and visual working memory encoding (Mayer, Kim, & Park, 2011). Importantly, novelty’s effect on episodic memory processes has gained some attention in the past few years (Davis, Jones, & Derrick, 2004; Li, Cullen, Anwyl, & Rowan, 2003), but as I will discuss later, this influence is only beginning to be understood in humans.

1.2 Memory and the Medial Temporal Lobe

To understand the mechanisms through which novelty may influence episodic memory, it is first critical to review our current understanding of how the brain supports memory. Key structures known to be vital for episodic memory are found in the medial temporal lobe (MTL), which consists of the hippocampus, and the underlying entorhinal, perirhinal, and parahippocampal cortices.

The link between the MTL and memory was first characterized in 1957 when patients with bilateral temporal lesions showed memory deficits (Scoville & Milner, 1957). Most notably, patient H.M. underwent a MTL resection to treat his epilepsy. As a result, he suffered from severe anterograde and partial retrograde amnesia; he was unable to form new memories and could only remember memories that were more than a decade old. However, his intelligence was intact, and his procedural memory and working memory were unaffected. This discovery led to the finding that the MTL plays an important role in episodic memory formation and retrieval.
1.2.1 Encoding and Retrieval Processes in the Medial Temporal Lobe

Over the past decade, numerous neuroimaging studies have provided insights into how the intact human brain supports memory. Using the difference in memory (DM) or subsequent memory paradigm (Paller & Wagner, 2002) approach, studies have been able to ask how distinct MTL subregions contribute towards memory formation (Davachi, 2006; Eichenbaum, Yonelinas, & Ranganath, 2007; Wixted & Squire, 2011). For example, encoding activity in the hippocampus has been shown to be greater for trials on which contextual details were later recalled (Davachi, Mitchell, & Wagner, 2003; Haskins, Yonelinas, Quamme, & Ranganath, 2008; Kirwan & Stark, 2004; Staresina & Davachi, 2008, 2009). This is consistent with the role of hippocampus in relational binding; it implies that the hippocampus is more involved in binding together relations between elements of an event (Cohen et al., 1999). Additionally, related work has also demonstrated that activity in the perirhinal cortex is related to whether individual items are later recognized, regardless of whether additional source details are retrieved. Together these findings suggesting that MTL regions contribute differently towards item and associative memory formation (Davachi et al., 2003; Staresina & Davachi, 2008, 2009).

Relatedly, hippocampal activation is also related to successfully recognizing item associations at the time of retrieval (Giovanello, Schnyer, & Verfaellie, 2004; Kirwan & Stark, 2004). A recent study has also demonstrated that hippocampal activations during the presentation of a retrieval cue, i.e., prior to the memory decision, predicts how accurately the participant recalls associative memory following the cue (Chen, Olsen, Preston, Glover, & Wagner, 2011). This suggests that neural reactivation during cue presentation is hippocampally mediated and is related to subsequent retrieval. It has also been found that damage to the MTL cortical regions, sparing the hippocampus, results in item recognition deficits (Bowles et al., 2007; Zola-Morgan, Squire, Amaral, & Suzuki, 1989). Thus, there is consistent evidence of a division of labour across MTL regions of its contributions towards item and associative memory during both encoding and retrieval.
An alternative perspective on this division of labour is the dual-process theories of recollection and familiarity (Yonelinas, 2002). Recollection is a slow deliberate process by which events and their contextual details are recalled, whereas familiarity is a fast, global measure of memory strength (Yonelinas, Aly, Wang, & Koen, 2010). Consistent with this perspective, human neuroimaging studies have shown that activations in the hippocampus are enhanced during the conscious recollection of studied episodic events (Cansino, Maquet, Dolan, & Rugg, 2002; Dobbins, Rice, Wagner, & Schacter, 2003; Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Wheeler & Buckner, 2004). Human patient work has also revealed that damage to the hippocampus disproportionately impairs recollection compared with item recognition (Giovanello, Verfaellie, & Keane, 2003; Vann et al., 2009). Rodent work has provided converging evidence that lesions to the rat hippocampus impair recollection but not familiarity, thereby enabling recognition judgments (Fortin, Wright, & Eichenbaum, 2004).

A third perspective on hippocampal contributions to memory is defined at a more computational level of analysis. Inspired by the distinctive circuitry of the hippocampus, detailed below, computational models (Marr, 1971; Treves & Rolls, 1992) propose that this network is uniquely configured to perform two key functions, namely, pattern completion and pattern separation. Pattern completion, a computational process by which patterns of neural activity can get reactivated from a partial noisy cue (see 1.3), is particularly central to my thesis. The reactivation of neural patterns supported by pattern completion could then produce phenomenological states like recollection and support processes like relational binding. It could, thus, be an underlying computation that is consistent with prevailing models of MTL function. The mnemonic outcomes of pattern completion are best assessed by presenting retrieval cues and asking participants to recall other details that were previously associated with the cues. By contrast, item recognition is less dependent on pattern completion because it simply requires recognizing if an event occurred earlier or not, without reactivating the associated details.
1.2.2 Anatomy of the Hippocampus

Understanding how the hippocampus could support pattern completion requires a review of its internal structure. The hippocampal formation consists of a set of interconnected regions known as the dentate gyrus (DG), the fields of cornu ammonis (CA), namely, CA1, CA2, CA3, CA4, and the subiculum. The hippocampus has intricate connections with surrounding cortical regions as well as within itself. The entorhinal cortex (EC) receives sensory input from the perirhinal cortex and the parahippocampal cortex and projects it the DG and CA3 via the perforant path projections and to the CA1 via a different projection from the EC. Granule cells of the DG then project via their mossy fibers to the CA3, which has recurrent collaterals that interconnect neurons within the CA3. Pyramidal cells in the CA3 also provide input to the CA1 via the Schaffer collaterals. The CA1 finally projects to the subiculum and the EC. The subiculum also projects back to the EC (Amaral & Witter, 1989). Such intricate interconnections allow for integration of information as it is passed along the hippocampal subfields, permitting the encoding and reactivation of associations.

In addition to these intrinsic connections, the hippocampus also receives cholinergic input through the septohippocampal pathway (Dutar, Bassant, Senut, & Lamour, 1995), dopaminergic input from the nucleus accumbens (Groenewegen, Vermeulen-Van der Zee, Te Kortschot, & Witter, 1987) and the ventral tegmental area (Lisman & Grace, 2005), and noradrenergic input from the locus coeruleus (Berridge & Waterhouse, 2003). Although each of these neuromodulatory pathways has the potential to shape hippocampal processing, thereby impacting memory, cholinergic modulation of the hippocampus will be the focus of my thesis because it has been implicated in regulating pattern completion.

1.3 Pattern completion versus pattern separation

There is ample evidence that the hippocampus is responsible for storing details of an event and recalling these details when necessary. How does it accommodate the distinct computational demands of these processes? On one hand, while encoding memories, it is thought that similar events need to be represented within the hippocampus as distinctly
as possible to avoid interference. This process, known as pattern separation, reduces the similarity of overlapping input thereby making stored patterns more distinct from each other. On the other hand, the hippocampus must also be capable of using a partial or noisy cue to retrieve previously stored patterns. This is thought to be achieved through the process of pattern completion, whereby an event can reactivate the full representation of past similar events, essentially making the representations more overlapping.

According to the Hebb-Marr model (Hebb, 1949; Marr, 1971; McNaughton & Morris, 1987), the feedforward pathway from the EC to the CA3 is important for pattern separation and pattern completion, whereas the recurrent connectivity within the CA3 is important for pattern completion. Consistent with these models, evidence from animal and human studies for pattern separation and pattern completion has been found within the DG and CA3 (Bakker, Kirwan, Miller, & Stark, 2008; Leutgeb, Leutgeb, Treves, Moser, & Moser, 2004) and CA3 (Gold & Kesner, 2005; Jackson, 2013), respectively.

How then is the CA3 network capable of performing both pattern completion and separation? One possibility has been proposed by neurocomputational models of the hippocampus (Hasselmo & Schnell, 1994; Hasselmo et al., 1995; Hasselmo, Wyble, & Wallenstein, 1996). According to these models, when a stimulus is presented, CA3 is thought to reinstate past memories via pattern completion thereby generating an “expectation”. Sensory input from EC is compared with this expectation computed by the CA3. This comparison takes place in the CA1 (Duncan, Ketz, Inati, & Davachi, 2012). Based on the match/mismatch detection, neuromodulatory input is said to project to the DG and CA3 (Hasselmo & Schnell, 1994; Hasselmo et al., 1995, 1996). Matched expectations, i.e. familiarity, lead to decreased release of acetylcholine (ACh), whereas mismatched expectations, i.e. novelty, lead to an increased release. ACh is released in the layers of CA3 that contain the recurrent collaterals, which are thought to support pattern completion. On one hand, high concentrations of ACh can inhibit these recurrent connections, thereby limiting reactivation of past memories and facilitating pattern separation. On the other hand, low concentrations of ACh can inhibit the feedforward input from the EC and DG and facilitate reactivation of past memories by encouraging pattern completion. In
this way, the hippocampus can be biased either towards pattern separation or pattern completion.

As explained in the models, acetylcholine has been proposed to mediate the shifts between pattern separation and pattern completion. Aspects of this model have been tested empirically: Ach depletion, by administering cholinergic antagonists, can produce proactive interference, impair encoding of new information but have little effect on the retrieval of old information. This has been shown in both humans (Atri et al., 2004) and rats (De Rosa & Hasselmo, 2000). This suggests that lower levels of acetylcholine in the hippocampus would discourage encoding and encourage retrieval, which is consistent with the theoretical model.

Exploration of a novel environment has been shown to increase levels of acetylcholine in the hippocampus (Giovannini et al., 2001). By contrast, familiarity would lead to decreased levels of ACh. Together, the above empirical and theoretical work suggests that detecting novelty or familiarity may have the power to bias fundamental memory processes. Specifically, if these physiological mechanisms do have behavioural consequences then recent exposure to novelty or familiarity should facilitate memory behaviour that relies on pattern separation and pattern completion, respectively. Furthermore, if the mnemonic biases are indeed mediated by the slow-acting cholinergic inputs, then we should expect the biases to extend in time (Hasselmo & Fehlau, 2001; Meeter et al., 2004), impacting memory performance for seconds after the initial detection of novelty or familiarity.

1.4 Effect of Novelty on Episodic Memory Encoding

Recent studies have shown that active and passive exposure to novelty, and even anticipation of novelty alone, can enhance memory encoding of unrelated information (Bunzeck et al., 2012; Fenker et al., 2008; Schomaker, van Bronkhorst, & Meeter, 2014; Wittmann, Bunzeck, Dolan, & Düzel, 2007). Most of these studies, however, implicate the recruitment of the dopaminergic rather than cholinergic system, in part because these
effects operate on the timescale of minutes rather than seconds. Converging evidence from rodent work has shown that novelty detection enhances induction and maintenance of long-term potentiation (LTP) in the hippocampus for up to 20 minutes following novelty exposure and that this effect is mediated by dopamine receptors (Davis et al., 2004; Li et al., 2003). This suggests another mechanism through which novelty could influence the memory system, but leaves questions about how novelty impacts memory on the timescale of seconds and whether it can impact memory through cholinergic means.

1.5 Effect of Novelty on Episodic Memory Retrieval

Most studies to date have focused on the effect of novelty on memory encoding, with much less research investigating its effect on memory retrieval. In the only study that has investigated how novelty influences retrieval, Duncan and colleagues demonstrated that recent exposure to novelty as opposed to familiarity improves subsequent identification of subtle changes (2012b). Participants were shown old, similar, and new objects in a continuous recognition paradigm, which was initially developed to study pattern separation in the human hippocampus (Bakker et al., 2008). Participants were asked to decide whether each object was old, similar, or new. Similar trials were used to measure pattern separation and pattern completion biases; if the memory system were biased towards pattern completion, similar trials should more often be incorrectly identified as old, whereas if the system were biased towards pattern separation, the likelihood of noticing slight changes should be enhanced. As predicted by the cholinergic framework described above, similar trials were more accurately identified as being similar when they were preceded by new trials than when they were preceded by old ones. In fact, the effect was stronger when subjective novelty of the preceding trials was considered (i.e., judging the trial as old or new). They demonstrated that these memory decision biases persist only for a few seconds, thereby implicating the role of acetylcholine in these biases.

While these results are consistent with the cholinergic model described above, this study did not exclude an alternative explanation to the findings; it is possible that a novelty
induced shift in the decision criterion caused participants to be more accurate at identifying similar trials. Specifically, judging a trial as new could also have a linger impact on decision criteria, perhaps making people more conservative (i.e., less willing to think an item is old). This would make participants more likely to be accurate on the subsequent “similar” trials because errors on these trials are most often driven by incorrectly thinking the image is old. Hence, this line of research needs to be further explored to rule out the effects of criterion shift. One possible way to do this would be to measure memory performance in terms of associative memory rather than item recognition; deciding amongst multiple source options is less likely to be influence by biases towards thinking the retrieval cue is old or new.

1.6 Thesis Overview

In the preceding review I described theoretical and empirical motivation for the proposal that the hippocampus can be biased towards pattern separation or pattern completion. This work also suggested that this bias may be established by shifts in cholinergic input evoked by the detection of novelty or familiarity, the effects of which would, thus, be temporally extended. Although empirical support for this claim in humans is scarce, Duncan et al. (2012b) has inspired the two experiments presented in this thesis.

In Chapter 2, I tested whether there is behavioural evidence of the existence of memory states. I hypothesized that familiarity detection would result in a subsequent bias towards pattern completion. Consistent with the hypothesis, I found evidence for such a bias following familiarity decisions; participants made more accurate associative memory judgments after making familiarity responses as compared to novelty responses. Critically, recent familiarity vs. novelty did not influence item recognition accuracy, suggesting that recent familiarity specifically facilitates memory retrieval operations that depend on pattern completion.

In Chapter 3, I tested the time course of this mnemonic bias by varying the time between consecutive memory decisions. I hypothesized that the bias would extend in time due to
the slow acting nature of acetylcholine, but begin to decay after seconds. In line with the hypothesis, I found evidence for a temporally extended bias towards pattern completion following familiarity judgments.

In Chapter 4, I propose an experiment that would be better suited for functional MRI. Using fMRI would enable me to identify whether familiarity does in fact facilitate the neural reactivation of stored memories. I have laid out the study procedure for a pilot behavioural experiment and discussed proposed fMRI analyses.

Together, these experiments revealed that recent mnemonic processing can profoundly shape how people retrieve memories and identified a subtle, ecologically valid behavioural manipulation that can bias basic memory computations. My planned future directions will uncover the neural basis of this mnemonic bias, linking the new behavioural phenomenon to the neural models that inspired its discovery.
Chapter 2

2 Experiment 1

2.1 Introduction

Why do we remember certain events but not others? Retrieval may depend not only on the strength of the memory cue at the time of retrieval, but also on internal memory states. Neurocomputational models have drawn on physiological findings to formally define memory states in terms of hippocampal biases (Hasselmo & Schnell, 1994; Hasselmo et al., 1995). According to their model, memory states are established by shifts in cholinergic input to the hippocampus. In the presence of familiarity, as opposed to novelty, reduced cholinergic input biases neural networks towards pattern completion, and this could make the hippocampus more likely to retrieve associations. By contrast, in the presence of novelty, a high cholinergic input biases the neural networks towards pattern separation. Importantly, this neuromodulation is slow, suggesting that resulting memory states could last for seconds. Thus, the neurochemical state of the brain prior to an event may affect the manner in which it is processed by the hippocampus. If this physiological mechanism translates up to human behaviour, I would predict that recent familiarity would facilitate processes that rely on pattern completion, like associative retrieval, as opposed to item recognition, which is pattern completion independent.

To test these predictions, I designed a paradigm in which participants made a series of memory judgments about novel and familiar images. Each decision simultaneously assessed associative and item memory. Unbeknownst to the participants, I manipulated whether each memory decision was made shortly after viewing an unrelated novel or familiar image. This allowed me to test the influence of recent familiarity and novelty on different aspects of memory retrieval.
2.2 Methods

2.2.1 Participants

35 adults (mean age = 18.51, age range = 18-22) were recruited for this experiment. Data from 3 participants were excluded from the analyses due to prior participation in conflicting studies (N=2) and self-reported drowsiness throughout the experiment (N=1). Excluding their data did not change the pattern of results presented here. The final analyses included 32 participants (mean age = 18.53, age range = 18-22). A sample size of 32 was predetermined from an earlier pilot data set (N=36). This data was randomly sampled with replacement in a bootstrapping procedure to determine the number of participants required to achieve 80% power. Participants in all experiments were fluent in English and did not have any history of psychiatric disorders. They were given course credit for their participation. All experimental procedures were approved by the local ethics committee.

2.2.2 Stimuli

A total of 484 colored images of natural indoor and outdoor scenes (242) and common objects (242), along with three words (“ancient”, “plain”, “safe”) were used in the experiment. Stimuli were displayed on a gray background on a 21” iMac using PsychoPy (Peirce, 2007).

2.2.3 Procedure

The experiment consisted of an encoding session in which participants associated images with one of the three words and a retrieval test that simultaneously assessed source memory for the words and item recognition of the images.

Encoding Session: During each trial, an image-word pair was displayed on the screen for 3 seconds (Figure 1). Images were trial-unique; however, there were only three words used across the experiment. Each trial-unique image was pseudorandomly paired with one of three repeating words, such that all three words were paired with an equal number of
images. Participants were asked to vividly imagine a scenario in which the word could describe the image. These instructions were used to encourage deeper processing of the image-word pairs. After the pair disappeared, participants rated the imagined scenario on a 4-point continuous scale within 1.5 seconds (“h” (very vivid), “j”, “k”, “l” (not vivid at all)). A fixation cross was presented at the center of the screen for 1 second before each trial. A post-study debriefing session revealed that no participant used a memory encoding strategy that was inconsistent with the instructions. Participants were informed before the start of the encoding session that their memory would be assessed.

The encoding session was split into 8 3-minute blocks. Each block consisted of either scene-word or object-word pairs; 4 blocks of scene-word pairs and 4 blocks of object-word pairs were presented in a counterbalanced alternating order (see Figure 1).

Retrieval Session: During the memory test, I assessed participants’ item and associative memory simultaneously. Critically, I manipulated whether participants made each memory decision after an unrelated familiar or novel image. During each retrieval trial, an image was shown on the screen for 2 seconds. Participants were asked to decide if the image was new (‘d’), or old, in which case they were asked to recall the associated word (‘j’, ‘k’, ‘l’). They were asked to press the ‘f’ key if they thought that an image was old but were unable to recall the associated word. Note that these response options allowed us to simultaneously assess their item and source memory with a single response. A central fixation cross was presented during a 1s interstimulus interval.

There were 4 6-minute blocks in the retrieval session. Half of the images were studied during the encoding session, while the remaining were novel. Critically, the images presented during the memory test alternated between the two stimulus categories such that an object was always preceded and followed by a scene, and vice versa. This aspect of the design reduced the possibility of consecutive old images semantically priming each other because consecutive images always belonged to different stimulus categories and were studied during different encoding blocks. Stimulus presentation was predetermined
such that no more than 4 new stimuli appeared consecutively and so that the transition probability between seeing old and new images were all 0.5.

2.2.4 Data Analysis

Corrected source accuracy and $d$-prime ($d'; z(\text{hits rate})-z(\text{false alarm rate})$) were used to measure source and item memory, respectively. To obtain independent estimates of associative memory and item recognition, corrected source accuracy was calculated only for the trials on which participants correctly recognized an image as old, whereas $d'$ was calculated only for trials on which participants failed to give a correct source response.

I corrected for false alarms in source memory by calculating corrected source accuracy to account for the three source response options:

\[
\text{Corrected Source Accuracy} = \frac{\text{Proportion Source Hits} - \text{Proportion Source False Alarms}}{2}
\]

Thus, if a subject randomly made a source response on each trial, their corrected source accuracy would be $0.33 - (0.66/2) = 0$.

To directly compare source and item memory as a function of preceding trial decision, normalized difference scores ($[\text{preceding 'old' - preceding 'new'}/\text{average memory}]$) were calculated. Only participants with positive corrected source accuracy and $d'$ were included in this analysis to avoid negative denominators (1 participant excluded). Raw difference scores ($[\text{preceding 'old' - preceding 'new' }])$ were also calculated.

In addition to $d'$, I estimated criterion bias in recognition memory ($C: -(z(\text{hits rate})-z(\text{false alarm rate}))/2$). Positive values of $C$ indicate a conservative bias, i.e., less willing to guess old, whereas negative values of $C$ indicate a liberal bias, i.e., more willing to guess old.

Data were analyzed using R programming language. Separate 2 (preceding response: old vs. new) X 2 (stimulus: object vs. scene) repeated measures ANOVAs were used to analyze corrected source accuracy, RT on source correct trials, $d'$, and criteria. Paired t-tests were
used to examine simple effects. Pearson’s correlation was performed to assess the relationship between source accuracy and item memory. Generalized mixed-effects models (glmer function of the lme4 package in R (Bates, Maechler, Bolker, & Walker, 2014) were used to control for preceding trial’s reaction time and preceding trial type/response on a trial-by-trial basis. All models included within-subject predictors both as fixed effects and random slopes varying over participant.

Before any statistical tests were performed, trials for which the correct source response was the same as the participants’ response on the previous trial were removed. This was done to correct for response priming.

2.3 Results & Discussion

Vividness ratings did not differ by stimulus category (objects>scenes, $t(31)=0.37$, $p>0.250$, Cohen’s $d=0.06$). However, participants responded, on average, 30ms faster on object trials (scenes>objects, $t(31)=3.61$, $p=0.001$, Cohen’s $d=0.64$).

Participants completed a speeded memory test, which simultaneously assessed item and source memory. Item recognition was generally high ($d’=2.47±0.27$, $t(31)=18.55$, $p<0.001$; hit rate=$0.87±0.03$; mean false alarm rate=$0.16±0.07$). When participants correctly recognized an old trial, their corrected source memory was reliably above chance ($0.36±0.07$, $t(31)=10.60$, $p<0.001$). When they failed to retrieve the correct source, their recognition memory was still strong ($d’=2.01±0.23$, $t(31)=18.00$, $p<0.001$). Thus, my independent estimates of associative memory and item recognition both reflect reliable memory.

My main question was whether recognizing a familiar stimulus facilitates people’s subsequent ability to retrieve other unrelated associations. To assess this question, I ran a $2 \times 2$ (Preceding Response: preceding old, preceding new) x $2$ (Stimulus: objects, scenes) repeated measures ANOVA on corrected source accuracy. I found a main effect of preceding response ($F(1,31)=14.39$, $p<0.001$, $\eta^2_p=0.32$; Fig 2A), reflecting that recent familiarity judgments increased subsequent source accuracy by a robust $9.22\%±4.59\%$ as
compared to novelty judgments. Although there was also a main effect of stimulus category \( (F(1,31)=17.55, p<0.001, \eta^2=0.36) \), I did not find any significant interaction between preceding trial decision and stimulus category \( (F(1,31)=2.32, p=0.138, \eta^2_P=0.07) \). Hence, for follow-up analyses, I collapsed across the stimulus categories. I also ran a similar 2 x 2 repeated measures ANOVA on reaction time and found a main effect of preceding response \( (F(1,31)=7.13, p=0.012, \eta^2_P=0.19) \) and stimulus category \( (F(1,31)=54.96, p<0.001, \eta^2_P=0.64) \), with no significant interaction \( (F(1,31)=1.25, p>0.250, \eta^2_P=0.04) \). Together, these results suggest that preceding familiarity both increases associative memory accuracy and the speed with which these associations are retrieved, across multiple types of memory cues.

But what aspects of the preceding trial familiarity would drive this effect? I first assessed whether the subjective experience of familiarity vs. novelty is a better predictor of subsequent source memory than the objective old/new status of the preceding image. I used a generalized mixed-effects model to pit these predictors against each other on a trial-by-trial basis, and found that preceding response still affected source accuracy even after adjusting for preceding trial type \( (\beta=0.19, z=2.23, p=0.026) \) but preceding trial type did not \( (\beta=0.11, z=1.3, p=0.19) \). To further investigate the preceding subjective experience, I binned preceding old decisions according to whether a correct source was retrieved (source) or not (item). I found that both conditions led to more accurate memory as compared to preceding new responses (item>new: \( t(31)=3.78, p<0.001, \text{Cohen's } d=0.67 \); source>new: \( t(31)=3.41, p=0.002, \text{Cohen's } d=0.60 \); Fig 3). However, they did not differ from each other (source>item; \( t(31)=0.23, p<0.250, \text{Cohen's } d=0.04 \)), suggesting that successful associative retrieval is not required to facilitate source accuracy on subsequent trials.

It could be argued that rather than the novelty/familiarity of the preceding trial, the effect of familiarity may be driven by the difficulty of the preceding trial. To test this, I used the reaction time on the preceding trial as a proxy for difficulty level and included it, along with preceding trial decision, as a predictor of source accuracy in a generalized mixed-
effects model. I found that preceding familiarity judgments still influenced source accuracy even after adjusting for preceding trial’s reaction time (β=0.18, z=2.54, p=0.011).

Hence, my results demonstrate that recognizing something familiar results in a state that facilitates memory retrieval processes, like associative memory, which rely on pattern completion. This, however, begs the question; do all aspects of memory retrieval benefit from recent familiarity judgments or is this benefit selectively seen for pattern completion-dependent memory? To investigate this, I analyzed the effect of preceding response on item recognition. I ran a similar 2 (Preceding Response: preceding old, preceding new) x 2 (Stimulus: objects, scenes) repeated measures ANOVA on d' and found that, in contrast to the robust associative retrieval benefit, there was no reliable influence of recent familiarity decisions on recognition memory (F(1,31)=0.02, p>0.250, η²<0.01; Fig 2B). I did however find a main effect of stimulus category (F(1,31)=52.70, p<0.001, η²=0.63) and a significant interaction between preceding trial decision and stimulus category (F(1,31)=6.38, p=0.017, η²=0.17). The interaction was driven by recent familiarity having inconsistent effects on item recognition, depending on the stimulus category (scenes: old>new: t(31)=2.08, p=0.046, Cohen’s d=0.17; objects: old>new: t(31)=-1.41, p=0.168, Cohen’s d=0.25).

Since it is difficult to infer from null and inconsistent findings, I directly compared the influence of preceding familiarity judgments on item recognition and source accuracy using normalized memory scores and found that the benefit of recent familiarity judgments was higher for source memory as compared to item recognition (source>item, t(30)=2.42, p=0.022, Cohen’s d=0.43; Fig 2C). Moreover, the correlation between recent familiarity’s influence on source and item memory reliably negative across participants, r(30)=−0.48, p=0.006 (Fig 2C), suggesting that there is a negative relationship between the benefit of familiarity on source memory and its actions on item recognition. Together these results suggest that recent familiarity judgments do not benefit memory retrieval as a whole; the benefit is selectively seen for pattern completion dependent associative memory.
Lastly, although the preceding trial response did not reliably affect item recognition accuracy, but it could change the way participants made memory decisions. For example, after judging a trial as new, participants might be more likely to judge the next trial as new as well if evidence for novelty vs. familiarity also lingers over time. To investigate this further, I assessed decision criteria. I ran a similar 2 (Preceding Response: preceding old, preceding new) x 2 (Stimulus: objects, scenes) repeated measures ANOVA on C and found no main effect of preceding response (F(1,31)=1.84, p=0.185, η²_p=0.06). I did find a trending effect of stimulus category (F(1,31)=3.83, p=0.06, η²_p=0.11) but no significant interaction between preceding trial decision and stimulus category (F(1,31)=0.91, p>0.250, η²_p=0.03). It should be noted, however, that when combining across stimulus categories, I observed, surprisingly, that recent familiarity actually increased the criterion (preceding old>preceding new; t(31)=2.50, p=0.018, Cohen’s d=0.44; Fig 4), meaning that participants were more likely to think an image was new after identifying an unrelated image as old rather than new. Such a bias would act against one’s ability to detect associations on the subsequent trial. Despite these criterion results, I found such robust subsequent associative retrieval benefit, which increases my confidence in the latter results.

In summary, this experiment demonstrated that recent familiarity selectively benefited pattern completion dependent memory processes. When participants failed to recollect the correct source, recent familiarity also influenced their decision criteria such that they became more conservative with their memory decisions.
Chapter 3

3  Experiment 2

3.1  Introduction

The results of Experiment 1 suggest that recent familiarity evokes a mnemonic bias that facilitates associative memory. However, there are still two unanswered questions from the predictions of the theoretical models.

Firstly, neurocomputational models predict that the mnemonic biases may be caused by shifts in cholinergic input to the hippocampus. If that were true, then this slow acting cholinergic modulation would also cause the resulting mnemonic state to be extended in time but decay on the time scale of seconds.

Secondly, as discussed earlier, the models predict that recent familiarity would enhance subsequent pattern completion. Conversely, this prediction can also be posed from the novelty perspective, such that, recent novelty could be inhibiting subsequent pattern completing rather than recent familiarity enhancing it. Experiment 1 could not answer this question because there was no condition.

In Experiment 2 I varied the interstimulus interval between retrieval trials with the aim of (1) measuring whether the time course of this mnemonic bias is consistent with cholinergic mechanisms and (2) using the longer ISI condition as a baseline to evaluate the relative influence of familiarity and novelty.

3.2  Methods

3.2.1  Participants

51 adults (mean age = 18.40, age range = 18-22) were recruited for this experiment. Data of 3 participants were excluded from the analysis because of low response rates (non-responses were >4SD, N=2) and high false alarm rate (>5SD; N=1). Thus, the final analyses
included 48 participants (mean age = 18.40, age range = 18-22). A sample size of 48 was predetermined by a power analysis which used a bootstrapping procedure with Experiment 1 data. I assumed that there would be no influence of preceding familiarity at long ISIs, and estimated the number of participants needed to show an interaction between ISI and preceding response with 80% power.

3.2.2 Stimuli

A total of 392 colored images of natural indoor and outdoor scenes (196) and common objects (196), along with three words (“ancient”, “plain”, “safe”) were used in the experiment. Stimuli were displayed on a gray background on a 21” iMac using PsychoPy (Peirce, 2007).

3.2.3 Procedure

The experiment procedure was similar to that of Experiment 1 except for modifications made to the timing and number of trials:

Procedure: The experiment consisted of an encoding session in which participants associated images with one of the three words and a retrieval test that simultaneously assessed source memory for the words and item recognition of the images.

Encoding Session: During each trial, an image-word pair was displayed on the screen for 3 seconds (Figure 1). Images were trial-unique; however, there were only three words used across the experiment. Each trial-unique image was pseudorandomly paired with one of three repeating words, such that all three words were paired with an equal number of images. Participants were asked to vividly imagine a scenario in which the word could describe the image. These instructions were used to encourage deeper processing of the image-word pairs. After the pair disappeared, participants rated the imagined scenario on a 4-point continuous scale within 1.5 seconds (“h” (very vivid), “j”, “k”, “l” (not vivid at all)). A fixation cross was presented at the center of the screen for 1 second before each trial. A post-study debriefing session revealed that no participant used a memory
encoding strategy that was inconsistent with the instructions. Participants were informed before the start of the encoding session that their memory would be assessed.

The encoding session was split into 6 3-minute blocks. Each block consisted of either scene-word or object-word pairs; 3 blocks of scene-word pairs and 3 blocks of object-word pairs were presented in a counterbalanced alternating order (see Figure 1).

Retrieval Session: During the memory test, I assessed participants’ item and associative memory simultaneously. Critically, I manipulated whether participants made each memory decision after an unrelated familiar or novel image. During each retrieval trial, an image was shown on the screen for 2 seconds. Participants were asked to decide if the image was new ('d'), or old, in which case they were asked to recall the associated word ('j', 'k', 'l'). They were asked to press the ‘f’ key if they thought that an image was old but were unable to recall the associated word. Note that these response options allowed us to simultaneously assess their item and source memory with a single response. A central fixation cross was presented during a 1s interstimulus interval.

There were six 5-minute blocks in the retrieval session: 2 blocks used a 1-second ISI between trials (short) while the remaining 4 used a 4-second ISI (long). Half of the images were studied during the encoding session, while the remaining were novel. Critically, the images presented during the memory test alternated between the two stimulus categories such that an object was always preceded and followed by a scene, and vice versa. This aspect of the design reduced the possibility of consecutive old images semantically priming each other because consecutive images always belonged to different stimulus categories and were studied during different encoding blocks. Stimulus presentation was predetermined such that no more than 4 new stimuli appeared consecutively and so that the transition probability between seeing old and new images were all 0.5.
3.2.4 Data Analysis

Data were analyzed using R programming language. Separate 2 (preceding response: old vs. new) x 2 (stimulus: object vs. scene) x 2 (ISI: short vs. long) repeated measures ANOVAs were used to analyze corrected source accuracy, RT for correct source trials, $d'$ and criteria. For the 3-way ANOVAs on $d'$ and criteria, participants with missing cells were excluded from the analysis (N=3). Paired t-tests were used to examine simple effects. Pearson's correlation was performed to assess the relationship between source accuracy and item memory. Generalized mixed-effects models (glmer function of the lme4 package in R (Bates, Maechler, Bolker, & Walker, 2014)) were used to control for preceding trial's reaction time and preceding trial type/response on a trial-by-trial basis. All models included within-subject predictors both as fixed effects and random slopes varying over participant.

3.3 Results & Discussion

During the associative encoding task, vividness ratings were higher for objects than scenes (objects>scenes, t(47)=2.58, p=0.013, Cohen's d=0.37) and participants also responded, on average, 20ms faster on object trials (scenes>objects, t(47)=2.75, p=0.009, Cohen’s d=0.40).

As was the case in Experiment 1, memory performance was strong in Experiment 2. Item recognition is generally high ($d'$: 3.14±0.16, t(47)=38.50, p<0.001; hit rate=0.91±0.02; false alarm rate=0.05±0.01). When participants correctly recognized an old trial, their source memory was reliably above chance (0.48±0.05, t(47)=18.71, p<0.001). When they failed to retrieve the correct source, their recognition memory was still strong ($d'$: 2.60±0.16, t(47)=33.31, p<0.001).

I ran a 3-way repeated measures ANOVA on corrected source accuracy with preceding trial decision, stimulus category and ISI as within-subject independent variables. Consistent with Experiment 1, there was a main effect of preceding trial decision (F(1,47)=41.17, p<0.001, $\eta_p^2=0.47$; Fig 5A), replicating the facilitatory influence of preceding
familiar judgments on associative memory, along with a main effect of stimulus category (F(1,47)=47.05, p<0.001, η²_p=0.50).

Critically, Experiment 2 included two ISIs to assess the time course of the preceding trial’s influence. In line with the timescale of cholinergic modulation, I found a significant two-way interaction of preceding response and ISI (F(1,47)=6.13, p=0.017, η²_p=0.12; Fig 5A), indicating that the influence of the preceding trial decayed over the 4-second delay. I further unpacked this interaction to identify that memory performance decreased with time following a familiar trial (short>long, t(47)=2.44, p=0.019, Cohen’s d=0.35) rather than increasing over time following a novel trial (long>short, t(47)=0.95, p>0.250, Cohen’s d=0.14). This suggests that recent familiarity that enhances subsequent retrieval rather than recent novelty inhibiting it (Fig 5A). No interactions with stimulus category were significant at the p=0.05 threshold, but I confirmed that the preceding responses influenced source accuracy for both objects and scenes to account for a trending three-way interaction (F(1,47)=3.51, p=0.067, η²_p=0.07; see Appendix A). A similar 3-way ANOVA on reaction time did not reveal a main effect of preceding response (F(1,47)=1.58, p=0.215, η²_p=0.03) but there was a significant interaction between preceding response and stimulus category (F(1,47)=4.33, p=0.043, η²_p=0.08). A 2 (Preceding Response) x 2 (ISI) ANOVA revealed that preceding familiarity speeded RT for objects (F(1,47)=5.62, p=0.022, η²_p=0.11), but not for scenes (F(1,47)=0.05, p>0.250, η²_p<0.01).

I replicated the follow-up analyses from Experiment 1 to confirm that subjective familiarity drove source accuracy benefits in Experiment 2. I confirmed that preceding response still affected source accuracy even after adjusting for preceding trial type at the short ISI (β=0.32, z=2.13, p=0.033) but not the long ISI (β=0.13, z=0.92, p>0.250). Additionally, preceding familiarity still influenced source accuracy after correcting for preceding trial’s RT for the short ISI (β=0.39, z=3.79, p<0.001) but not for the long ISI (β=0.11, z=1.24, p=0.214). Lastly, these effects did not depend on correctly recalling the source on the preceding trial (source > new; t(95)=5.30, p<0.001, Cohen’s d=0.54; item>new; t(95)=4.77, p>0.001, Cohen’s d=0.49; Fig 6), but there was no interaction
between ISI and these three levels of preceding subjective familiarity (F(2,94)=1.87, p=0.16, η²_p=0.04).

Critically, recent familiarity selectively benefited pattern completion dependent source memory. Item recognition accuracy was not influenced by the preceding trial decision (F(1,44)=0.61, p>0.250, η²_p=0.01) or the interaction between ISI and preceding trial decision (F(1,44)=1.51, p>0.250, η²_p=0.03; Fig 5B), although there was a main effect of stimulus category (F(1,44)=61.51, p>0.250, η²_p=0.58). A direct comparison of item and source memory revealed a main effect of memory type (F(1,46)=7.40, p<0.001, η²_p=0.27; Fig 5C), but no main effect of ISI (F(1,46)=0.02, p>0.250, η²_p<0.01) or interaction of ISI and memory (F(1,47)=0.05, p>0.250, η²_p<0.01), suggesting that there was a selective benefit for source accuracy for both ISI conditions. Additionally, there was a reliable negative correlation between the influence of recent familiarity on associative and item memory at the short ISI, r(45)=−0.31, p=0.033, but an unreliable positive one at the long ISI, r(45)=0.12, p=0.431 (Fig 5C). These replications support my hypothesis that recent familiarity selectively facilitates associative memory retrieval and provide us a window onto the lingering nature of the memory bias.

Lastly, I investigated whether the preceding trial response also influenced the decision criteria used to make item recognition judgments. I ran a 2 (Preceding Response: preceding old, preceding new) x 2 (ISI: short, long) x 2 (Stimulus: scenes, objects) repeated measures ANOVA on C and found a main effect of preceding response (F(1,44)=4.79, p=0.034, η²_p=0.10) and ISI (F(1,44)=7.74, p=0.008, η²_p=0.15) and a significant interaction between preceding trial decision and stimulus category (F(1,47)=5.50, p=0.024, η²_p=0.11; Fig 7). Consistent with the results of Experiment 1, participants were more conservative (i.e. less willing to judge old) after making familiarity responses and became more liberal (i.e. more willing to judge old) at the long ISI.

In summary, Experiment 2 was able to replicate the results of Experiment 1 for the short ISI condition. For the long ISI condition, there was a significant reduction in the effect of
the preceding response on associate retrieval. This suggests that the boost in the associative retrieval was time-dependent, which is consistent with the timescale of the cholinergic modulation of the hippocampus.
Chapter 4

4 Proposed Future Directions

Now that I have shown behavioural evidence for the existence of a memory state, I plan to investigate how these memory states influence the neural reactivation of memories. The first step towards this goal is to adapt my current paradigm to better suit the temporal requirements of functional MRI and to optimize my ability to decode the neural reactivation of memories through the use of stimulus categorizes that are decodable using MVPA techniques.

In this new paradigm, participants will be alternating between two different source memory tasks, each involving retrieval of different stimulus categories. This will allow me to see how recent familiarity influences neural reinstatement and to identify neural networks that modulate this effect.

4.1 Methods

4.1.1 Stimuli

A total of 198 colored images will be used: common objects (192), 3 famous landmarks (CN Tower, Niagara Falls, Rogers Center), and 3 famous Canadian personalities (Ryan Gosling, Celine Dion, Justin Trudeau), along with two words (“plain”, “safe”). Stimuli will be displayed on a gray background on a 21” iMac using PsychoPy (Peirce, 2007).

4.1.2 Procedure

The following procedure describes the behavioral version of the planned experiment. If the predicted effects are found, the timing will be modified for the fMRI version.

Participants will perform 3 experimental blocks, with each block comprised of an object encoding session, a word encoding session and a retrieval session (see Fig 8). Each block will be less than 10 minutes long.
Object Encoding: Participants will be shown a series of object images (96) paired with one of two repeating words, “Plain” or “Safe”, and will be asked to imagine a scenario in which the word could describe the image. This will encourage deep encoding of the object-word pairs. Each pair will be shown for 2.5 seconds. After that, they will be asked to rate the vividness of the association on a scale of “very vivid” to “not vivid at all”. This will be followed by a 1-second fixation cross.

Word Encoding: Participants will be shown a series of concrete nouns (96) paired with one of six repeating images of culturally appropriate famous landmarks (CN Tower, Niagara Falls, Rogers Center) or celebrities (Ryan Gosling, Celine Dion, Justin Trudeau). The word will be presented on the left side of the screen by itself for 1 second, and then concurrently with one of the six images to its right. The pair together will be shown for 2.5 seconds. This presentation sequence and time was established to maximize later memory performance through pilot studies. If the word is paired with a landmark (scene), participants will be asked to imagine themselves in that scene/context using that object from a first-person perspective. If the word is paired with a celebrity (face), participants will be asked to imagine the celebrity using that object without any particular context in mind. After this, they will be asked rate the vividness of the imagery, which will be followed by a 1-second fixation cross.

Retrieval Session: Participants will then perform an associative retrieval session with alternating trials of objects (96 old and 96 new) and words (96 old and 96 new). Each trial will simultaneously assess participants’ source and item memory.

- Object Trial: An object will be shown on the screen. If the participants have seen the object image in the experiment before, it is ‘old’; if they haven’t, it is ‘new’. If they recognize an ‘old’ image, they should try to recall the word (“plain” or “safe”) that was paired with it. Participants will respond using their left hand. They will press the “A” key if they think the object image is ‘new’. If they recognize the image as ‘old’ and can recall the associated word, they can press ‘D’ for ‘plain’ and ‘F’ for ‘safe’. However, if they find the object image familiar but they cannot recall the
associated word, they can press ‘S’. Each image along with the response options will be shown for 2.25 seconds and participants will be asked to respond within this time frame.

- **Word Trial:** A word will be shown on the screen. If the participants recognize the word from the experiment, they should try to recall which image category (scenes or faces) it was paired with. Participants will respond using their right hand. They will press the ‘H’ key if the word is ‘new’. If the word is ‘old’ and they recall the image category it was paired with, they can press ‘K’ for scene and ‘L’ for face. If they find the word familiar but they cannot recall the associated image category, they can press ‘J’. They will again have only 2.25 seconds to make a response.

A 1-second fixation cross will follow each object and word trial.

### 4.1.3 Proposed Data Analysis

For the behavioural experiment, the following analysis will be performed using R:

- An ANOVA will be run on corrected source accuracy with stimulus category (objects/words) and preceding response (old/new) as IV.

- An ANOVA will be run on reaction time for correct source responses with stimulus category (objects/words) and preceding response (old/new) as IV.

- An ANOVA will be run on d’ with stimulus category (objects/words) and preceding response (old/new) as IV.

- A paired t-test will directly compare the benefit of preceding familiarity responses for associative accuracy and item accuracy.

### 4.2 Discussion & Proposed fMRI Experiment

The key difference between this proposed experiment and the first two experiments is that this experiment involves two separate source decision tasks. In the previous paradigm, participants were always retrieving the same sources (“ancient”, “plain”, “safe”)
on each retrieval trial, whereas in this new experiment, they will be actively switching between two retrieval tasks. If the influence of preceding familiarity is replicated, it would mean that recent familiarity judgments can influence later associative memory even when the memory decisions involve searching for different source memories (i.e. words vs. faces and scenes).

In the fMRI version, the object trial will serve as a novelty/familiarity detection trial and the word trial (when they will be searching their memory for famous faces and famous places) will be used to probe the reactivation of associative memories. Participants will be scanned during both encoding and retrieval. I plan to use Representational Similarity Analysis (Kriegeskorte et al., 2008) to decode on a trial-by-trial basis the patterns of activation in ventral temporal cortex that are associated with individual retrieval trials when participants are trying to recall the famous face or place. I will do this by comparing the correlation between the pattern of activity on each retrieval trial to the pattern of activity evoked by encoding trials that contain the same famous face/scene or different faces/scenes.

Specifically, my main questions are:

- Is there any RSA evidence of the reactivation of famous faces or famous places at the time of retrieval?

- Is there any effect of preceding familiarity or novelty on RSA evidence of memory reactivation?

- Is the univariate signal from object trials (novelty/familiarity detection) related to the multivariate reactivation of famous faces or famous places on the following word trials?
Chapter 5

5 General Discussion

In my thesis, I used a subtle, biologically motivated manipulation to investigate the existence of neurocognitive states. I showed that recent familiarity can influence subsequent memory performance; after identifying an image as being familiar, participants were more likely to retrieve other unrelated associations. These results provide the first behavioural evidence that recent familiarity judgments have the power to elicit prolonged memory states that can facilitate subsequent pattern completion-dependent memory retrieval.

The design allowed me to further unpack which features of the recent mnemonic experience evoke a memory state. Firstly, by pitting subjects’ preceding memory judgments against the stimulus condition, I determined that the subjective rather than the objective oldness of the recent experience elicits a memory state. Secondly, by including item and associative questions, I could further probe which aspects of subjective familiarity vs. novelty are required to evoke memory states. I found that it is not necessary for the recent mnemonic experience to involve successful associative retrieval; recent retrieval of an association and recent identification of a familiar image facilitated subsequent associative memory performance equally. This suggests that simply recognizing familiarity may be sufficient to initiate a memory state. Alternatively, attempting to recover the recollective experience, even when the attempt is unsuccessful, may also be required. This pattern of results could also be explained by recent detection of novelty impeding pattern completion rather than recent familiarity inhibiting it. However, examining how the effect decays across time (Fig 5A) suggests that it was the recent familiarity that enhanced subsequent retrieval rather than recent novelty inhibiting it. Together, these results suggest that recent subjective experiences of familiarity, whether accurate or not, can facilitate subsequent associative retrieval.
I also employed several control procedures to ensure that it was the familiarity and novelty of the recent experience that drove its influence on subsequent memory. To mitigate the possibility that familiar images directly primed memory on the subsequent trial, I designed the experiment in such a way that the preceding trial was always from a different stimulus category and was encoded at a different time. It, thus, did not share semantic information with the current trial ruling out semantic priming as an alternative explanation. Similarly, to reduce response priming, I removed preceding trials with the same response as the current trials’ correct source response. Follow-up analyses also revealed that the preceding trial’s difficulty (operationalized by RT) could not explain the influence of recent familiarity. Thus, the most parsimonious explanation of the results is that recent familiarity, per se, influenced subsequent memory performance.

This pattern of results can be best accounted for by neurocomputational models (Hasselmo & Schnell, 1994; Hasselmo et al., 1995; Hasselmo et al.; 1996). The process of pattern completion is thought to allow a partial cue to reactivate hippocampal patterns of activity. Conversely pattern separation is thought to allow similar/overlapping input to the hippocampus to be stored in distinct memory traces. As defined by these models the processes of pattern completion and separation are computationally incompatible (O’Reilly & McClelland, 1994). Thus, memory states could allow the hippocampus to deal with the competing demands of pattern completion and separation by prioritizing one process over the other through shifts in cholinergic input. On one hand, in the presence of novelty, high cholinergic input could bias hippocampal neural networks toward pattern separation, thereby preparing the hippocampus to form distinct representations. On the other hand, in the presence of familiarity, reduced cholinergic input could bias these networks toward pattern completion, thereby preparing the hippocampus to retrieve associations based on partial cue.

The associative retrieval effects found in my experiments may be driven by recent familiarity judgments evoking a pattern completion state via dips in cholinergic levels. This could explain why familiarity only benefited memory judgments that rely on pattern
completion and not item recognition judgments, which could be supported by MTL cortical processes. Also, I found that the associative memory benefit decayed over seconds, which is consistent with the time course of cholinergic modulation (Hasselmo & Fehlau, 2002; Meeter et al., 2004).

My experiments serve as a complement to the single prior study that assessed the implications of this model in human behaviour. Duncan and colleagues (2012b) used a behavioural paradigm that taxes pattern separation to identify how recent exposure to novelty can also benefit memory performance. They showed that recent exposure to novelty evoked a temporally extended pattern separation bias, thereby giving behavioural evidence for part of the cholinergic model. As a complete test to this model, my experiments investigated if the pattern completion biases can also be established by recent familiarity. The double dissociation between my study and Duncan et al. provides strong evidence that familiarity and novelty have selective effects on memory, affecting performance based on the computational demands of the cognitive task at hand.

Though my hypothesis was driven by neurocomputational models, Tulving (1985) first proposed the existence of a “retrieval mode”, which he conceptualized as a state that could make it possible to mentally travel back in time to a particular “episode” and re-experience its unfolding. While in a retrieval mode, information stored at the time of encoding can be recovered through the process of ephory. It is important to note that Tulving’s retrieval mode is different from the memory states proposed in this paper; in fact, my hypothesis is that recent familiarity directly influences ephory rather than retrieval mode. The two experiments in this thesis, provide some evidence that recent familiarity does not influence retrieval mode: Whereas Tulving’s retrieval mode is strategic and goal-directed, I have shown that subtle manipulations can evoke memory states without conscious awareness. Tulving’s retrieval mode would also apply equally to recognizing a familiar item and recalling associated details; in fact, many studies that assessed the theory used old/new recognition judgments. By contrast, I found a selective benefit for associative memory over item recognition. This finding is directly predicted by
my hypothesized cholinergic mechanism but could not be accounted for by Tulving’s retrieval mode. Thus, while additional neuroimaging research is required to demonstrate that recent familiarity directly promotes the reactivation of stored memories, the pattern of results reported here is more parsimoniously explained by this mechanism than a controlled attentional mode.

Although my research questions were focussed on modulating memory accuracy, I also serendipitously biased the criterion which participants used to make recognition judgments. I found that after making familiarity judgments as compared to novelty judgments, participants were more likely to be conservative with their memory decisions, i.e., they were less willing to judge the next item as old. These findings are directly in contrast with those reported in a recent paper where they found that old responses rather than new responses were more likely to follow old responses (Malmberg & Annis, 2012). However, there are some key differences between the two studies. Firstly, Malmberg & Annis did not control for response priming and semantic/conceptual priming. Secondly, Malmberg & Annis did not account for transitional probability between old and new retrieval trials. There is ample evidence that people are sensitive to statistical structure even without awareness (Turk-Browne, Scholl, Chun, & Johnson, 2009), so it is possible that subjects might generate expectations about upcoming trials based on previously experienced contingencies. By contrast, the transitional probabilities between old and new trials were always .5 in the two experiments contained in my thesis. Finally, Malmberg & Annis only assessed old/new judgments and, thus, performance on each trial may be driven by familiarity with an item or by recollections of associated details. My studies demonstrate that recent familiarity judgments have distinct effects on item and associative memory, and the associative memory component was removed from the data used to identify the criterion bias. Thus, the pattern of results reported by Malmberg & Annis may be the net result of the combination of effects reported here. Nevertheless, my findings need to be further investigated to understand if recent familiarity truly affects the mnemonic process (the evidence for oldness/newness) or if it affects the decision process (how the evidence is used to make a judgment). One possible approach to
resolving this issue would be to separate the memory decision from memory by using implicit memory measures, like eye-tracking (Ryan, Althoff, Whitlow, & Cohen, 2000).

My results are also relevant for the study of cognition, more broadly. Salient events, such as novelty, induce a release of acetylcholine throughout the cortex. Because cholinergic modulation is rather slow acting, carry-over effects similar to those seen in my experiments could be tested in other aspects of cognition. There is already a vast pharmacological literature showing the influence of acetylcholine on cognitive functioning. For instance, several pharmacological studies in both animals and humans have shown that cholinergic agonists can improve working memory function (e.g. Warburton & Rusted, 1993) and visual selective attention (e.g. Furey, Pietrini, Haxby, & Drevets, 2008). This suggests that endogenous fluctuations in acetylcholine, which could be evoked by novelty and familiarity, may establish lingering cognitive states that influence people's ability to engage in a variety of cognitive operations.

Lastly, my results demonstrate that processes that unfold prior to a stimulus onset can have profound behavioural consequences. Neuroimaging research has traditionally focused on neural processes evoked by and that occur during isolated trials. This approach is not sensitive to the influence that prolonged neurocognitive states have on behaviour. Although there is growing interest in pre-stimulus neural activity and its subsequent influence on cognition (Otten, Quayle, & Puvaneswaran, 2010; Park & Rugg, 2010; Addante, Watrous, Yonelinas, Ekstrom, & Ranganath, 2011), much of this emerging field has focussed on studying the neural activity that is spontaneously present prior to the stimulus onset. my work contributes to this growing literature by identifying factors which may elicit these prestimulus states, thereby opening the door for interventions that can harness memory states to create tailored learning environments.
References


patients with extended hippocampal system damage revealed by 3 convergent methods. *Proceedings of the National Academy of Sciences, 106*(13), 5442-5447.


Figure 1. Task Schematic for Experiments 1 & 2

A. Associative Encoding

Objects Block

- Safe
- Ancient
- Plain

Scenes Block

- Ancient
- Safe

B. Retrieval

Retrieval Block

- preceding new
- preceding old

Example Retrieval Trial

- new old? A P S

A. During the associative encoding session, participants are presented with trial-unique images of objects and scenes paired during separate blocks. Each image was paired with one of three words (“ancient”, “plain”, “safe”). B. During retrieval, participants are presented with alternating images of scenes and objects. They make simultaneous item and source decisions on each image, i.e., they are asked to identify if the image is new, old but they cannot recollect the source, and the specific source options if they can remember them (“A”, “P”, “S” correspond to “ancient”, “plain”, “safe”, respectively.)
Figure 2. Experiment 1: Source Memory and Item Memory as a function of Preceding Response

A. Source Memory

<table>
<thead>
<tr>
<th>Preceding Response</th>
<th>New</th>
<th>Old</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrected Source Accuracy</td>
<td><strong>3.5</strong></td>
<td><strong>4.0</strong></td>
<td><strong>3.5</strong></td>
</tr>
</tbody>
</table>

B. Item Memory

<table>
<thead>
<tr>
<th>Preceding Response</th>
<th>New</th>
<th>Old</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>d' (Item Recognition)</td>
<td><strong>2.0</strong></td>
<td><strong>2.5</strong></td>
<td><strong>-0.5</strong></td>
</tr>
</tbody>
</table>

C. Source Memory vs. Item Memory

<table>
<thead>
<tr>
<th>Memory</th>
<th>Source</th>
<th>Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalized Difference Scores</td>
<td><strong>0.6</strong></td>
<td><strong>0.4</strong></td>
</tr>
</tbody>
</table>

**Correlation Plot**

- **r(30) = -0.48**
- **p = 0.006**

Influence of preceding response on A. source memory B. item memory. Bar graphs compare accuracy on trials that were preceded by a new response or an old response. Boxplot shows the distribution of the difference score (preceding “old” – preceding “new”). C. Comparing the influence of preceding response on different aspects of memory. Bar graph compares the normalized difference scores (preceding “old” – preceding “new”) for source and item memory. Correlation plot tracks the relationship between the raw difference scores (preceding “old” – preceding “new”) for the source and item memory. Error bars represent the standard error of the mean.

* p<0.05  *** p<0.001
**Figure 3.** Experiment 1: Source Memory as a function of preceding subjective experience

Influence of preceding response, as a function of whether a source response was given or not, on source memory. Bar graphs compare corrected source accuracy on trials that were preceded by a new response, a response with an incorrect source response (item), or a correct source response (source). Boxplot shows the distribution of the difference score (preceding “old” – preceding “new”) for each difference. Error bars represent the standard error of the mean.

**p<0.01  *** p<0.001
Figure 4. Experiment 1: Recognition Decision Criteria as a function of Preceding Response

Influence of preceding response on recognition decision criteria. Bar graphs compare criteria on trials that were preceded by a new response or an old response. Boxplot shows the distribution of the difference score (preceding “old” – preceding “new”). Error bars represent the standard error of the mean.

*p<0.05
Figure 5. Experiment 2: Source Memory and Item Memory as a function of Preceding Response and ISI

Influence of preceding response and ISI on A. source memory B. item memory. Line graphs compare accuracy on trials that were preceded by a new response or an old response for each ISI. Boxplot shows the distribution of the difference score (preceding “old” – preceding “new”) at each ISI. C. Comparing the influence of preceding response on different aspects of memory. Bar graph compares the normalized difference scores (preceding “old” – preceding “new”) for source and item memory at each ISI. Correlation plots track the relationship between the raw difference scores (preceding “old” – preceding “new”) for the source and item memory. Error bars represent the standard error of the mean.

* p<0.05 ** p<0.01 *** p<0.001
Figure 6. Experiment 2: Source Memory as a function of preceding subjective experience for both ISIs.

Influence of preceding response, as a function of whether a source response was given or not, on source memory, for A. short and B. long ISI. Bar graphs compare corrected source accuracy on trials that were preceded by a new response, a response with an incorrect source response (item), or a correct source response (source). Boxplot shows the distribution of the difference score (preceding “old” – preceding “new”) for each difference. Error bars represent the standard error of the mean.

**p<0.01  *** p<0.001
Figure 7. Experiment 2: Recognition Decision Criteria as a function of Preceding Response and ISI

Influence of preceding response on recognition decision criteria. Bar graphs compare criteria on trials that were preceded by a new response or an old response for each ISI. Boxplot shows the distribution of the difference score (preceding “old” – preceding “new”) for each ISI. Error bars represent the standard error of the mean.

* p<0.05
A. There are two encoding sessions: During the object encoding session, participants are presented with trial-unique images of objects paired with one of two words “plain”, “safe”). During the word encoding, participants are presented with trial-unique nouns paired with repeating images of famous faces and scenes. B. During retrieval, participants are presented with alternating images of objects and words. They make simultaneous item and source decisions on each trial, i.e., they are asked to identify if the image is new, old but they cannot recollect the source, and the specific source options if they can remember them ("P", "S", "Sc", "Fa" correspond to “plain”, “safe”, “scene”, “face” respectively.)
Appendix A. Experiment 2 Supplemental Material

In Experiment 2, a 3-way ANOVA on corrected source accuracy with preceding trial decision, stimulus category and ISI as within-subject independent variables revealed a trending significant three-way interaction (F(1,47)=3.51, p=0.067, $\eta^2_p=0.07$). To investigate this further, I ran a 2 x 2 repeated measures ANOVA with preceding trial decision and ISI as within-subjects IVs separately for object and scene trials. I found a main effect of preceding trial decision for both stimulus classes (scenes: F(1,47)=20.86, p<0.001, $\eta^2_p=0.31$; objects: F(1,47)=24.83, p<0.001, $\eta^2_p=0.35$). I found a significant interaction for scenes (F(1,47)=6.96, p=0.011, $\eta^2_p=0.13$), but not for objects (F(1,47)=0.16, p>0.250, $\eta^2_p<0.01$), reflecting that object trials continued to be influenced by the preceding response, even after a 4-second time delay. This could be driven by either of the following: (1) the more memorable preceding objects eliciting a more robust memory state or (2) the less memorable objects being more susceptible to memory states.