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An Evaluation of the Influences of Extra-Hippocampal Processes on Pattern Separation

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Doctor of Philosophy
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ABSTRACT

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Long-term declarative memory depends on pattern separation, which reduces the degree of overlap between similar representations, to maintain memory specificity, and on pattern completion, which occurs when a degraded cue is used to retrieve a previously stored memory. Previous studies aimed at evaluating the underlying neuronal substrates of these computational processes have used a mnemonic discrimination paradigm and fMRI to focus on the hippocampus, to the exclusion of cortical processing. We aim to investigate the influences extra-hippocampal processes have on pattern separation in the following two studies.

Study 1. Computational models of pattern completion suggest it occurs cortically and results in generalized memories whereas pattern separation occurs in the hippocampus and results in memory specificity. It is unknown how the incongruity of these two neuronal processes is resolved. Many studies evaluating the neuronal correlates of pattern separation have used fMRI to evaluate activity in the hippocampus. The sluggish time resolution of fMRI and the restricted spatial focus leave room for considerable differences between pattern completion and pattern separation to go undetected. Here, we use encephalography (EEG) and an event-related potential (ERP) analysis to examine neuronal activity during pattern separation and pattern completion to investigate whether or not cortical processing is employed to resolve the discrepancy between these two neuronal processes. We largely did not observe differences between the ERPs associated with pattern separation and pattern completion. Failure to identify neuronal differences could result from the bulk of neuronal processing differentiating between the two processes occurring deeper in the brain than can be measured by ERPs.

Study 2. Extrinsic rewards contingent on memory performance can boost memory and learning. However, the effects of extrinsic rewards on memory specificity, particularly in regards to the process of pattern separation, are not well understood. In this behavioral study, we evaluate how extrinsic rewards affect behavioral performance in a task that taxes pattern separation. Our data show that rewards given for participation at the time of encoding boost mnemonic discrimination between target-lure pairs while rewards given for memory performance at the time of retrieval do not. We hypothesize this is because pattern separation is an encoding dependent process. This boost in discriminability is only seen when the rewarded stimuli are blocked together in separate blocks from the non-rewarded stimuli. When the rewarded and non-rewarded stimuli are interspersed within blocks, discriminability does not significantly differ between the rewarded and non-rewarded trials. Overall, performance was better when rewards were contingent on performance than when rewards independent of performance, although this difference is eliminated when attention during encoding is controlled.

Keywords: pattern separation, mnemonic discrimination, hippocampus, extrinsic rewards, attention, episodic memory, event-related potentials

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CHAPTER 1: Literature Review

Introduction

Memory, defined as the process of encoding, storing, and retrieving information, can be classified into several sub-types. Numerous models of memory exist, each one classifying the sub-types differently (Tulving, 2007). In 1968, Richard Atkinson and Richard Shiffrin proposed a model called the Atkinson-Shiffrin model (Atkinson & Shiffrin, 1968), outlining three main branches of memory: sensory, short-term, and long-term (Figure 1.1A). These branches are mainly classified according to the duration of memory in time. The duration of sensory information varies, however it usually lasts less than a second. The main function of sensory memory is to act like a buffer by sensing information and holding it until it can be processed in short-term memory systems. While short-term memory (often referred to as working memory) is defined as lasting less than one minute and having a limited amount of information that can be retained, long-term memory can be held for a life-time and is thought to be virtually limitless in the quantity of information that can be stored.

Another memory model categorizes memories according to the type of information (Figure 1.1B). Using this classification system, the two main branches are: declarative (explicit) memory and non-declarative (implicit) memory. Non-declarative memory, also referred to as implicit memory, occurs outside of conscious awareness. Several different types of non-declarative memory have been identified, with one example being procedural memory. Procedural memory aids in the development of motor skills (Willingham, Nissen, & Bullemer, 1989) and is developed by engaging in the same activity repeatedly, such as riding a bike. The neostriatum, basal ganglia, and cerebellum are brain regions associated with the development and execution of non-declarative memory (L. R. Squire, 2004). Declarative memory, on the other

hand, is the ability to encode, store, and recall facts and events (Eichenbaum, 1997) and has been localized to the hippocampus and adjacent cortical areas collectively known as the medial temporal lobe (MTL) (Eichenbaum, 1997; Squire, 1992; Squire, Stark, & Clark, 2004). Declarative memory can be further divided into episodic and semantic memory. Semantic memories are those that are independent of personal experience and are based on general factual knowledge (Tulving, 1984) such as one gallon equals 128 ounces or James K. Polk was the 11th president of the united states. Episodic memory refers to events that one has experienced, such as a family vacation, the birth of a child, or even something as simple as a meal one ate last week (Baars & Gage, 2007; Terry, 2006). It is this type of memory that allows one to engage in mental time travel to recall information about previous experiences (Tulving, 1983). One of the hallmarks of episodic memory is that although individual episodes may overlap a great deal, it is possible, nevertheless, to store and retrieve representations unique to a specific episode. The computational process that allows this to happen is known as pattern separation.

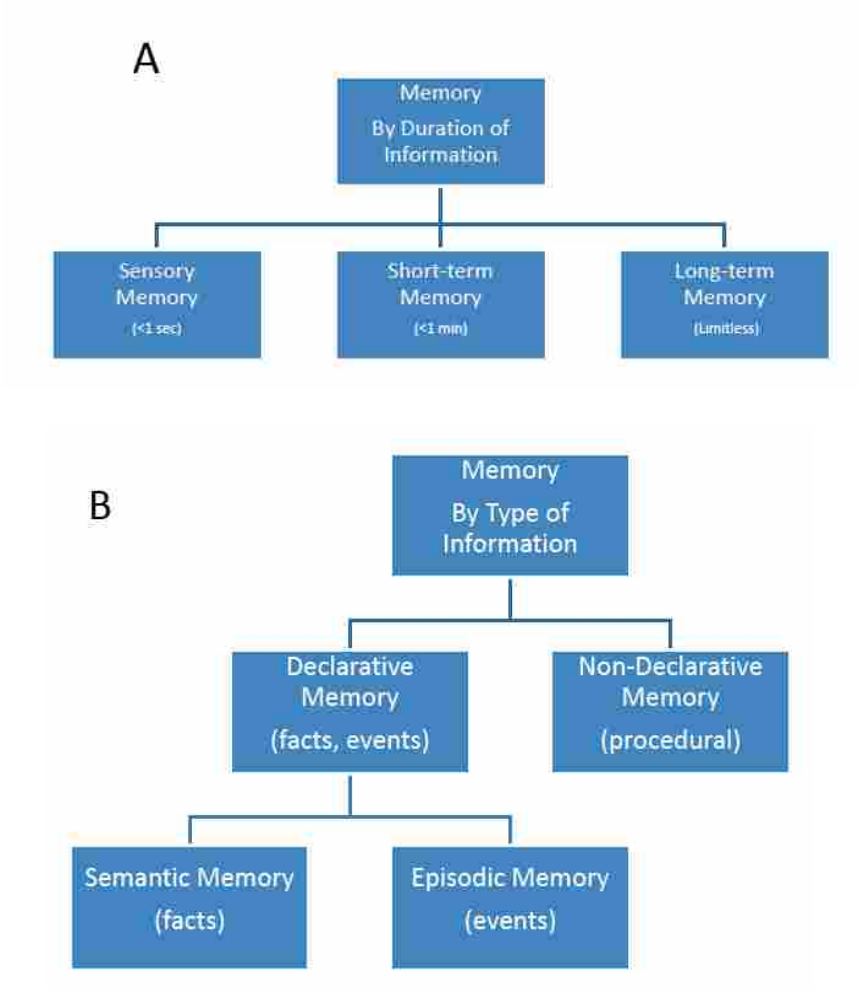


Figure 1.1: Types of Memory.
A) Memory classified by duration of the information being held according to the Atkinson-Shiffrin model. B) Memory classified by information type.

Pattern Separation

Behaviorally, pattern separation is necessary for a subject to be able to distinguish between two similar memory representations. If, for example, one eats dinner at roughly the same time every day, at the same place, and with the same people, and was asked to recall what they had for dinner five days ago, they would most likely struggle to retrieve this information. The difficulty in recalling this fact is not due to the length of time from the event; most people are able to recall events that occur five days ago without trouble. Rather, what makes this

difficult is the interference caused by the similarity between each occurrence: eating dinner at the same time, in the same place, with the same people, etc. With so many overlapping representations associated with each dinner memory, it is challenging to recall the specific differences between each event. The process of pattern separation allows one to establish distinct memory representations in spite of the similarity between different events.

Pattern separation is a computational process occurring at the neuronal level. It functions to reduce the degree of overlap between similar mnemonic representations (Hunsaker & Kesner, 2013; Yassa, Mattfeld, Stark, & Stark, 2011), thus making similar representations more distinct from one another and resulting in separate memories for experiences with overlapping elements, or in other words, increased memory specificity (Deng, Aimone, & Gage, 2010; Hunsaker & Kesner, 2013; Yassa & Stark, 2011). When an event is experienced, such as dinner on Monday night, a unique neuronal code is generated to represent that specific event. When a similar event is experienced, such as dinner on Tuesday night, a separate and distinct neuronal code is generated that has the fewest overlapping neuronal traces as the memory of Monday night's dinner as possible. This reduced similarity allows memory representations to be stored independent of each other and is crucial in providing the ability to maintain different and distinct memories for overlapping experiences (Deng et al., 2010). Because pattern separation functions to generate distinct neuronal codes when encountering an experience, it is referred to as an encoding dependent process.

Complementary to the process of pattern separation is pattern completion. This process occurs during the retrieval of a memory when a partial or degraded cue is used to retrieve a previously stored memory (Hunsaker & Kesner, 2013; Yassa & Stark, 2011). If the input neuronal firing of the second cue is too similar to the output firing of the first, both cues are

recognized as the same, although differences may be present (Deng et al., 2010). This process results in a more generalized memory by matching the overlapping representations of a current cue with a previously stored memory. Without the complementary processes of pattern separation and pattern completion, memory representations with too much similarity would trigger catastrophic interference when attempting to retrieve a single, distinct memory representation (McCloskey & Cohen, 1989). This catastrophic interference results in generalized overlapping memories for two different experiences.

Pattern separation and pattern completion are complementary processes. Both processes hold advantages and disadvantages depending on the context. Pattern separation is extremely pertinent when one needs to attend to minor deviations in a routine. However, an extreme bias toward pattern separation resulting in too much attention to details may be involved in disorders such as autism or obsessive compulsive disorder (Sahay, Wilson, & Hen, 2011). Conversely, pattern completion is optimal for maintaining a routine when subtle deviations occur, but becomes problematic when over-generalization is involved in disorders such as anxiety, depression, and post-traumatic stress disorder (Sahay et al., 2011; Shelton & Kirwan, 2013). In addition to these disorders, studies using tasks that tax pattern separation and pattern completion processes have led to inferences about how the balance between these two processes may be altered in Alzheimer's disease (Ally, Hussey, Ko, & Molitor, 2013), age-related cognitive changes (Holden, Toner, Pirogovsky, Kirwan, & Gilbert, 2013; Stark, Stevenson, Wu, Rutledge, & Stark, 2015; Toner, Pirogovsky, Kirwan, & Gilbert, 2009), or by exercise (Dery et al., 2013). Therefore an optimal balance between pattern separation and pattern completion is necessary.

While there is much about learning and memory that we do understand, there is still a large portion of how memory works that remains elusive. Developing our understanding of the

mechanisms that underlie learning and memory are crucial for developing treatments to memory impairments, as well as enhancing and strengthening learning and memory in general. Maintaining the optimal balance between pattern completion and pattern separation, and restoring balance once it has been disturbed, are some of the aspects of memory we do not fully understand yet. In order to do so, we first must gain a better understanding of the mechanisms that underlie pattern completion and pattern separation. Doing so will help us understand how learning and memory work, and will lay the foundation for preventative, restorative, and memory enhancing techniques.

Mnemonic Discrimination Task

Previous research has employed a mnemonic discrimination paradigm (e.g., Kirwan and Stark, 2007) that places high demands on pattern separation and pattern completion processes. In this paradigm, participants are shown a series of objects and asked to classify each object as either "new" to novel images that have not previously been viewed in the study, "old" if the image is an exact repeat of a previously shown image, or "similar" if they are shown a lure object that is like a previously viewed image, but with slight deviations from the original. Novel items called "new" are referred to as "Correct Rejections" (CRs) and repeats called "old" are referred to as "Hits" (Figure 1.2). Evaluation of the neural and behavioral responses to similar images (called lures) provides insight into the underlying pattern separation and pattern completion processes. Correctly identifying lures as "similar" images (Lure correct rejections or Lure CRs) places a high demand on the process of pattern separation since the participant must be able to detect subtle differences between the two similar images and identify them as different. Alternatively, identifying the lures as "old" (Lure false alarms or Lure FAs) places greater demands on the process of pattern completion because the lure image acts as a degraded

cue that results in the retrieval of a previously encoded memory representation. Therefore, in the context of this mnemonic discrimination paradigm, Lure CRs are used to evaluate pattern separation processes and Lure FAs are used to evaluate pattern completion processes. In addition to the numerous behavioral studies (Ally et al., 2013; Duncan, Sadanand, & Davachi, 2012; Holden et al., 2013; Kim & Yassa, 2013; Kirwan & Stark, 2007; Stark et al., 2015; S. M. Stark, M. A. Yassa, J. W. Lacy, & C. E. Stark, 2013; Toner et al., 2009) that use this paradigm, many fMRI studies have used it to evaluate hippocampal activity (Bakker, Kirwan, Miller, & Stark, 2008; Doxey & Kirwan, 2015; Lacy, Yassa, Stark, Muftuler, & Stark, 2011; Motley & Kirwan, 2012a).

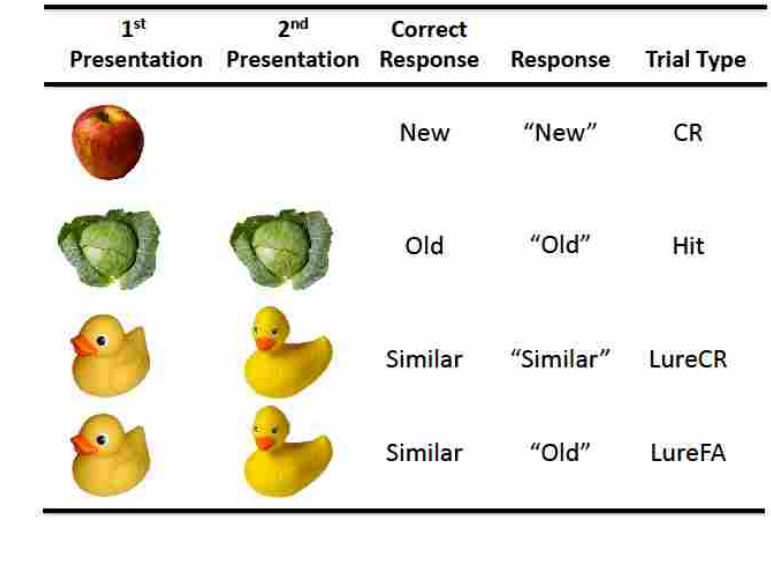


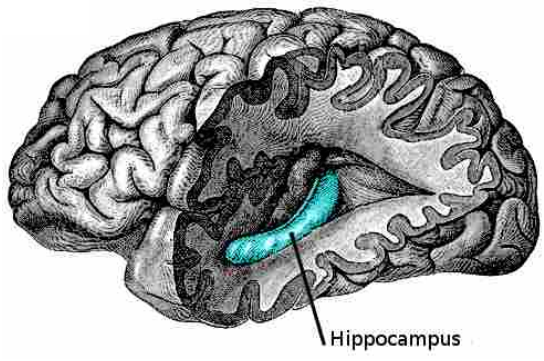
Figure 1.2: Mnemonic Discrimination Task.
Examples of the different stimuli, responses, and trial types in the mnemonic discrimination task.

Hippocampal Anatomy

While pattern completion is thought to occur in the hippocampus and in cortical regions, pattern separation is believed to be hippocampal dependent (Edmund T. Rolls, 2013; Treves & Rolls, 1994). Additionally, the hippocampus is biased toward pattern separation (E. T. Rolls &

Kesner, 2006). The hippocampus is a bilateral structure located within the medial temporal lobe (Figure 1.3A) and is composed of multiple sub regions (Figure 1.3B). Information from various regions of the neocortex is funneled through the parahippocampal gyrus and perirhinal cortex. Neuronal projections from these two structures converge on the entorhinal cortex, which is the gateway for incoming signals to the hippocampus. The flow of neuronal processing through the hippocampus is quite complex. A simplified pathway (Figure 1.4) outlines the neuronal connections that allow information to be sent from the entorhinal cortex to the dentate gyrus via the perforant pathway. The dentate gyrus is composed of three layers of neurons, the most prominent one being the middle layer, which is composed of granule cells. Neuronal projections from these granule cells are unidirectionally organized, synapsing on the pyramidal cells of the CA3. Next, mossy fibers connect the dentate gyrus to the CA3. In the CA3, two main pathways exist: the recurrent pathway synapses back onto CA3 neurons, while Shaffer collaterals extend from the CA3 to the CA1. From the CA1, information is transmitted to the subiculum and then to the neocortex.

A



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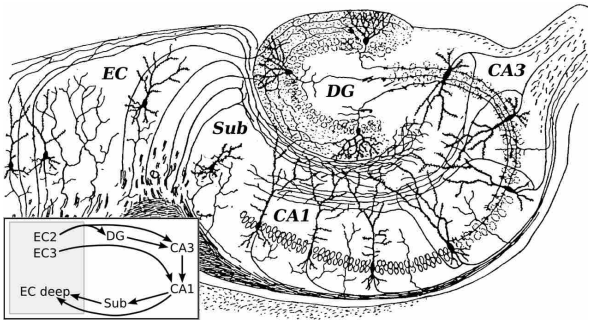

Figure 1.3 Hippocampal Anatomy.
A)The hippocampus is a bilateral structure located within the medial temporal lobe. B) The hippocampus is composed of multiple sub regions shown here.

Computational models specific to hippocampal function suggest different neuronal processes occur within the hippocampus during pattern separation and pattern completion. Pattern separation is thought to result from an increase in the sparseness of neural representation in the dentate gyrus (Hunsaker & Kesner, 2013; Edmund T. Rolls, 2013; Treves & Rolls, 1994). This is supported by rodent research that shows a significant increase in synaptic projections from the entorhinal cortex to the dentate gyrus aiding in the ability to increase the possible neuronal activity patterns (Amaral & Witter, 1989; Leutgeb, Leutgeb, Moser, & Moser, 2007). Pattern completion, on the other hand, is thought to occur via the recurrent pathways of the CA3, which are able to re-instantiate a previously encoded representation when partially activated by a noisy or degraded cue (Rodriguez & Levy, 2004; E. T. Rolls & Kesner, 2006; E. T. Rolls & Treves, 1994). Yassa and Stark (2011) note that pattern completion is not unique to the hippocampus, but, rather, is a computational process that may occur throughout the cortex. Indeed, computational models, such as the complementary learning systems (CLS) models (e.g., Norman and O'Reilly, 2003), propose that the hippocampus stores pattern-separated representations, while the cortex makes use of overlapping representations so as to generalize novel stimuli based on their shared features with previous representations. While the cortex is thought to be biased toward pattern completion, the hippocampus is thought to be biased toward pattern separation (Bakker et al., 2008). In the case of a target-lure pair where the lure is an image very similar to the target, yet different, the CLS model posits that the cortex would encode the lure with the previously established memory trace for the corresponding target, while the hippocampus would generate a new memory trace, differentiating the lure from the target representation. Currently, the mechanism underlying how the brain interprets and processes these

two different memory traces, one resulting in pattern completion, and the other resulting in pattern separation, is unknown.

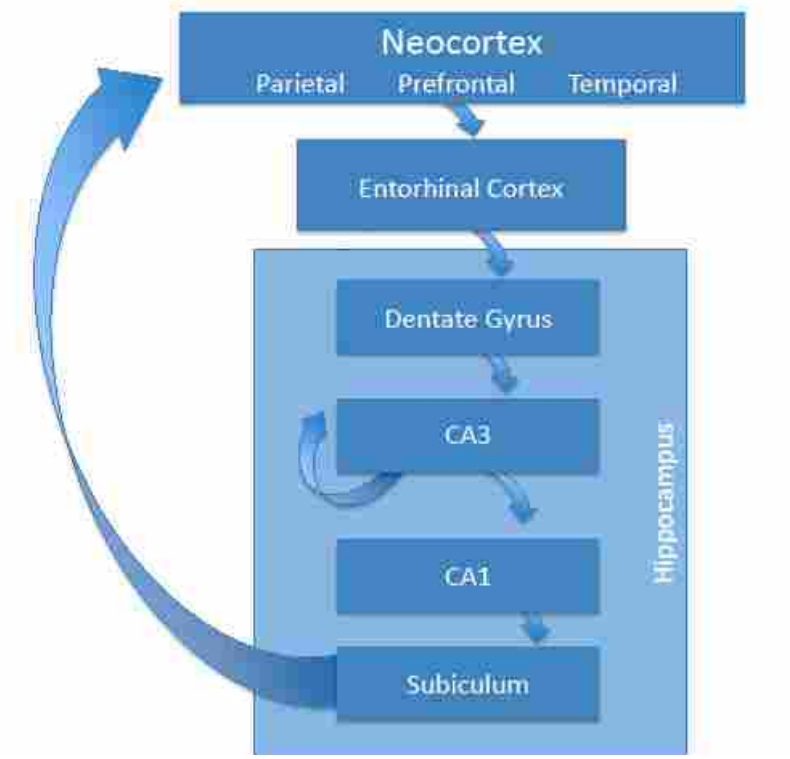

Figure 1.4 Hippocampal Processing.
A simplified representation of the flow of neuronal processing through the hippocampus

Stages of Memory

Memory can also be broken down into different stages: encoding, storage, and retrieval (Melton, 1963). The first stage, encoding, is the process of taking sensory input and converting it to neuronal activity that can be stored and later recalled. This is accomplished by receiving incoming sensory stimuli, then converting it into neuron signals. The three main sensory inputs are: visual , acoustic, and semantic.

Once information is encoded, it is then available to transfer into long-term storage, either short- or long-term. Short-term storage is limited in its quantity and duration. Generally, it is accepted that short-term memory is limited to 5-9 items. Miller (1956) identified seven as the

magic number of average items that can be held in short-term memory. However, the capacity of these seven slots has never been identified. One way to increase the amount of information held in short term memory is to "chunk" information together (Simon & Chase, 1973). Instead of recalling each piece of information individually, clustering several pieces of information into seven "chunks" provides a way to increase this limited capacity. Long-term memory seems to be unlimited in the duration the information can be held as well as the amount of information that can be retained.

Retrieval, or recall, allows us to access information that has been stored. Information stored in short-term memory can be recalled for approximately 30 seconds, after it is encoded. Information is maintained in short-term memory via rehearsal (Campbell, 2008). Information stored in long-term storage can be recalled after a significant time has passed from the initial encoding event. Organization of information aids deeply in the ability to retrieve it (Hunt & Mcdaniel, 1993). For instance, if instructions or a list of tasks are given in sequential order, the probability of a person correctly recalling all the tasks or instructions, increases drastically compared to when that same information is given in a random order (Brewer, 1977).

The memory processes underlying the encoding, retrieval, and encoding can be very different. For example, pattern completion is thought to be retrieval dependent mechanism since it occurs when a given cue leads to the recall of a certain memory representation. Conversely, pattern separation is thought to be mainly an encoding dependent process, as it is defined as the process of generating a distinct memory trace when an event is encountered.

Extra-hippocampal Processing

To date, the majority of studies evaluating pattern separation and pattern completion processes have focused on the processing that occurs in the hippocampus and medial temporal

lobe structures. As these structures are anatomically connected to other brain regions, it is very plausible that extra-hippocampal processing can influence pattern separation processes. A few studies have begun to investigate the effects of extra-hippocampal processing on both pattern separation and pattern completion (Morcom, 2015; Motley & Kirwan, 2012b; Pidgeon & Morcom, 2016). These studies have shown promising evidence that the hippocampus is influenced by extra-hippocampal processing. However, there are limitations to these studies and they leave plenty of material to be investigated. The following two studies are designed to investigate the influences extra-hippocampal processes have on pattern separation and pattern completion processes.

CHAPTER 2: Effects of Cortical Processing on Pattern Separation (Study 1)

Introduction Experiment 1

Computational models, such as the complementary learning systems (CLS) model (e.g., Norman and O'Reilly, 2003), propose that the hippocampus stores pattern-separated representations, while the cortex makes use of overlapping representations so as to generalize novel stimuli based on their shared features with previous representations. In the case of a target-lure pair where the lure is an image very similar to the target, yet different, the CLS model posits that the cortex would encode the lure with the previously established memory trace for the corresponding target, while the hippocampus would generate a new memory trace, differentiating the lure from the target image. Currently, the mechanism underlying how the brain interprets and processes these two conflicting memory traces, one resulting in pattern completion and the other resulting in pattern separation, is unknown. Although the neuronal processing for pattern separation occurs deep in the hippocampus, and pattern completion may be cortically driven. The processing that mediates the two may also been cortically located where many executive functioning processes are carried out (Alvarez & Emory, 2006).

Several high-resolution functional magnetic resonance imaging (fMRI) studies have used the continuous recognition memory task to investigate pattern separation and pattern completion processes (Bakker et al., 2008; Bakker et al., 2012; Lacy et al., 2011; Yassa et al., 2010). In these experiments, analyses took advantage of the novelty response in the brain, whereby neural signals are reduced for the second (or repeated) presentation of a stimulus. The reasoning in these analyses was that regions which perform pattern completion should treat stimuli that are similar to previously seen stimuli as old, resulting in a decrease of neural activation. On the other hand, regions that perform pattern separation should treat similar stimuli as new and should have

elevated activation relative to true repeats. While MRI provides excellent spatial resolution, one limitation of functional neuroimaging techniques that exploit the hemodynamic response (such as fMRI) is that they have a temporal resolution on the order of seconds. Much of the neurocognitive processing that occurs in the mnemonic discrimination task is thought to happen at much shorter time scales (milliseconds) and may be obscured by the sluggishness of the hemodynamic response. For example, Kirwan and Stark (2007) hypothesized that participants perform a "recall-to-reject" process when evaluating similar lure stimuli in this task, in which they first must retrieve the previously stored representation in order to compare and decide if it is the same or different. This interpretation was supported by reaction time data in that experiment, which must be long enough to allow for the processing to occur (around 1,000 ms) (Rotello & Heit, 2000), but the sluggish nature of the hemodynamic response as measured by fMRI may have obscured activity occurring on a shorter time scale. Furthermore, due to technical limitations, the high-resolution fMRI studies performed previously have sacrificed the amount of spatial coverage in favor of increasing spatial resolution in the hippocampus and medial temporal lobe. Thus, these studies have not been able to address the role of cortical processing in the mnemonic discrimination task.

Event-related potentials (ERPs) from electroencephalograms (EEGs) are able to measure electrical potential changes on the order of milliseconds (Toga & Mazziotta, 1996). Measuring and comparing the mean amplitudes of ERPs gives insight on the relative degree to which underlying neural generators are active during certain task conditions. Previous literature has established a difference in mean amplitudes between novel items and repeated items (i.e., an old-new effect) in two ERP components: one negative-going component that peaks approximately 400 ms after stimulus onset over anterior electrode sites (referred to here as the FN400), and a

positive-going component that peaks approximately 600 ms after stimulus onset over posterior electrode sites (referred to here as the late positive component; LPC). In both components, repeated stimuli reliably elicit more positive mean ERP amplitudes than novel stimuli (Curran & Cleary, 2003; Friedman, Hamberger, & Ritter, 1993). In addition to demonstrating old/new effects, both of these components have been used to study memory. The FN400 and LPC have previously been associated with familiarity and recollection, respectively (Addante, Ranganath, & Yonelinas, 2012; Curran & Cleary, 2003; Curran & Hancock, 2007; Paller & Kutas, 1992; Paller, Kutas, & Mcisaac, 1995; Wilding, 2000). Although there are overlapping features between pattern completion and familiarity, as well as between pattern separation and recollection, these processes are not identical (Kim & Yassa, 2013). Source localization studies have shown that the likely neural generators of the FN400 and LPC are both cortical (e.g., Herzmann, Jin, Cordes, & Curran, 2012). While the cortex is widely accepted as being able to engage in pattern completion processes, it is not highly associated with pattern separation process. Since the FN400 (which indexes the neuronal processing underlying general familiarity) and LPC (which indexes the neuronal processing underlying recollection) are like cortically generated, it seems as though there may be a cortical process that mediates the memory specificity that results from pattern separation preformed in the hippocampus and the pattern completion processes of the cortex.

A recent study, (Morcom, 2015), has used a mnemonic discrimination task to investigate pattern separation and pattern completion processes using the LPC and FN400. There were several important differences between the study by Morcom (2015) and previous studies of pattern separation processes in the MTL. For example, Morcom (2015) used study-test recognition memory test format while previous studies employed a continuous recognition

paradigm (e.g., Kirwan and Stark, 2007). Additionally, prior studies (e.g., Motley and Kirwan (2012a)) have demonstrated that pattern separation effects are more prominent in the highest similarity levels, which was not explicitly manipulated by Morcom (2015). Consequently, we include an analysis considering target-lure pair similarities below.

Hypothesis Experiment 1

In this study we evaluated whether ERPs provide neural correlates that differentiate between behaviors associated with pattern separation and pattern completion in the mnemonic discrimination task. Specifically, we examined ERP amplitude differences between trials in which stimuli were novel, repeated, or lures (i.e., similar to previously viewed stimuli). We further distinguished lure trials in which participants responded “similar,” from lure trials in which participants responded “old”. In the case of "similar" responses to lures (Lure CRs) we propose that the presentation of the lure stimulus must trigger the retrieval or reactivation of the previous target memory representation but that a further mismatch is detected resulting in a "similar" response. Otherwise, if there were no reactivation of the previous representation of the target, one would expect a "new" response. Thus, we take Lure CRs as evidence of pattern separation as the participant is able to correctly separate the old from the new memory representation. In the case of "old" responses to lure stimuli (Lure FAs), we propose that the presentation of the lure stimulus triggers enough of a match signal to result in an "old" response. Further, this depends on some form of pattern separation process, whereby the previous memory representation is re-activated based on the similar-but-not-identical lure stimulus.

We hypothesized that the repeated images would produce ERPs, which were more positive than novel images, consistent with the old-new effect observed in previous literature. Because “similar” responses to lure stimuli (Lure CRs) are thought to reflect pattern separation processes,

while "old" responses to lure stimuli (Lure FAs) are thought to reflect pattern completion processes, we predicted differences in the amplitudes of ERPs associated with these two conditions in both the FN400 and the LPC. Consistent with the fMRI literature, we predicted that ERP amplitudes associated with Lure CRs would more closely associate with ERP amplitudes for correctly identified new stimuli (or Correct Rejections), while amplitudes associated with Lure FAs would more closely associate with amplitudes for correctly identified repeated stimuli (or Hits). We also hypothesize that ERPs of Lures with the highest degree of similarity between the target-lure pairs will have a distinct ERP from Lures with the lowest degree of target-lure similarity.

Methods Experiment 1

Participants

Informed consent was obtained from 83 healthy participants who were recruited from the university community and received credit or monetary compensation for participation. The experiment was conducted as approved by the Brigham Young University Institutional Review Board protocol for research with human participants. Participants with fewer than 10 trials in any of the four bins (Hits, CR, Lure CR, Lure FA) (n=14) or with excessive artifacts (n=16) were discarded from further analysis (see Methods) for final n=53 (age range =17-29; mean age =21; 37 female). Using a more conservative 16 trials per bin criterion resulted in a final sample of n=41. However, as an analysis with this more stringent criterion did not significantly alter our findings, we chose to include all 53 subjects in the analyses reported below.

Stimuli and Behavioral Procedures

Participants performed a mnemonic discrimination task in which images of everyday objects were presented one at a time on a white background for 1500 ms followed by a 1000 ms inter-stimulus interval in which a fixation cross was shown (Figure 2.1). Objects were novel (never before presented in the context of the experiment), repeats (exact repeats of previously seen objects) or lures (visually similar, but not identical to previously seen objects; see Figure 2.1B for examples). The mean interval between first and repeat/lure presentations was 14.78 trials (range 4-31).

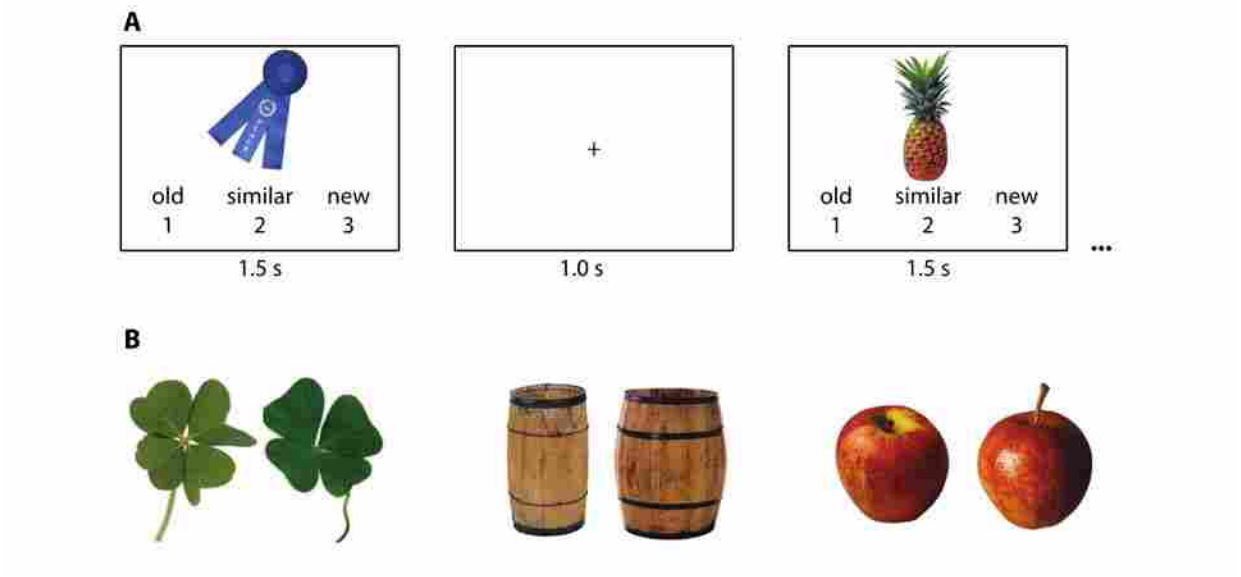

Figure 2.1: Continuous Recognition Mnemonic Discrimination Task.
The continuous recognition mnemonic discrimination task. A) Objects were presented on a white background for 1500 ms, followed by a fixation cross for 1000 ms. The possible responses "New," "Old," and "Similar" were shown at the bottom of the screen with their corresponding numbers. B) Examples of target-lure pairs.

Participants were asked to make one of three judgments about each image using one of three buttons on a key pad: "new" for novel objects, "similar" for lures, and "old" for repeats. Response options were displayed on the screen below the object on each trial in each version (see Figure 2.1A). Stimuli were presented in eight blocks of 150 trials each. Each block consisted

of 75 novel images, 25 repeat images, and 50 lure images. A large number of stimuli were used to increase the number of trials in each of the bins described below (see Methods: Behavioral Results). Participants were allowed to take untimed breaks between each block

Electroencephalogram Acquisition and Analysis

To reduce artifacts in the EEG, participants were instructed to sit still and to minimize yawning, jaw movements, eye movement, and blinks. The EEG was recorded from 128 scalp sites using a HydroCel Geodesic Sensor Net and an Electrical Geodesics Inc. (EGI; Eugene, Oregon, USA) amplification system (amplification 20K, nominal band-pass 0.10-100 Hz). The EEG was referenced to the vertex electrode and digitized at 250 Hz. Impedances were maintained below 50 kΩ. EEG data were processed off-line beginning with a 0.01 Hz first-order high-pass filter and a 30 Hz low-pass filter. ERPs were segmented based on trial type criteria (specified below). Eye blinks were removed from the segmented waveforms using independent components analysis (ICA) in the ERP Principle Components Analysis (PCA) Toolkit version 2.23 (Dien, 2010). The ICA components that correlated at 0.9 with the scalp topography of a blink template generated based on the current data set were removed from the data (see Dien, 2010). Artifacts in the EEG data, due to saccades and motion, were removed from the segmented waveforms using PCA in the ERP PCA Toolkit (Dien, 2010). Channels were marked bad if the fast average amplitude exceeded 100 mV, or if the differential average amplitude exceeded 50 mV: and bad channels were replaced via interpolation. Data were re-referenced to the mean of the two mastoid electrodes, and waveforms were baseline corrected using a 200 ms window prior to stimulus presentation.

Stimulus-locked ERP averages were derived spanning 200 ms pre-stimulus to 1000 ms post-stimulus. Electrode clusters of interest were identified *a priori* based on previous research

using a similar 128-channel EGI recording system to observe FN400 and LPC components (Curran & Doyle, 2011) (see Figure 2.2).

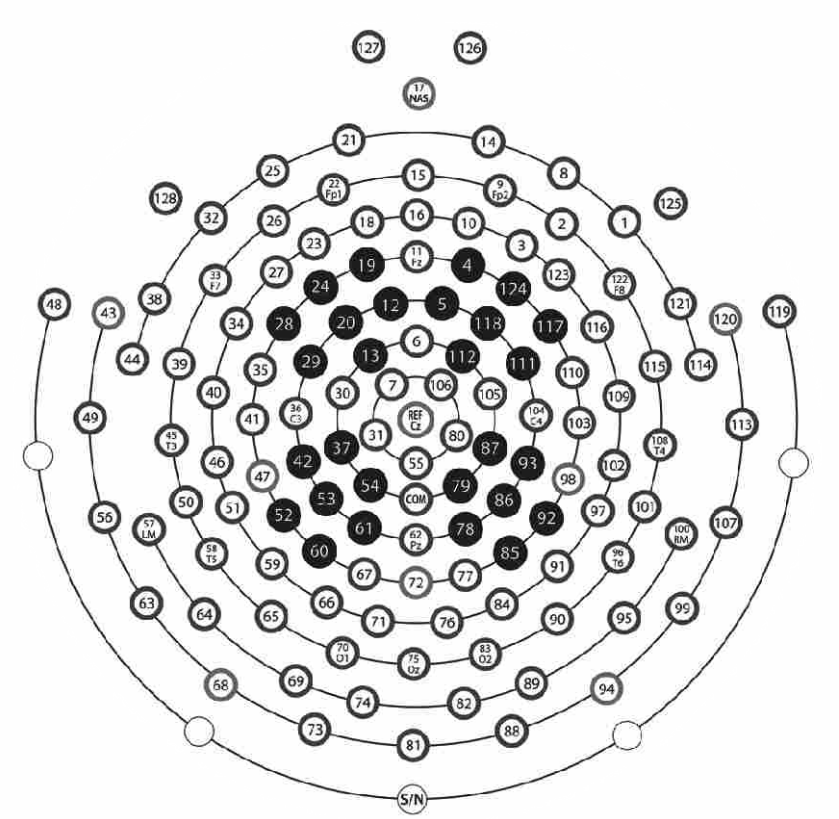

Figure 2.2: Electrode Clusters.
EEG data were collected using a 128 electrode net. Clusters of interest used for data analysis are shaded in the above figure.

The FN400 amplitudes were extracted as the mean amplitude within the 300-500 ms post-stimulus window. The amplitudes for the LPC were extracted as the mean amplitude within the 500-800 ms post-stimulus window. Left and right hemispheres were analyzed separately to examine effects specific to each cluster of interest, as has been done in previous studies (Curran, 2004; Mecklinger, 2006; Woodruff, Hayama, & Rugg, 2006).

Results Experiment 1

Behavioral

Trials were sorted according to stimulus type (novel, repeat, and lure) and behavioral response ("new", "old", and "similar"). Due to low trial counts for incorrect responses to novel and repeat images, only correct trials (Hits – repeated images called "old," and Correct Rejections or CRs – novel images called "new") were analyzed for these stimulus types. We also analyzed Lure Correct Rejections or Lure CRs (lures called "similar") and Lure False Alarms or Lure FAs (lures called "old"). The range and mean of the number of trials for each condition are as follows: Hits, range: 14-154, mean: 69; CRs, range: 45-535, mean: 262; Lure CR, range: 11-276, mean: 109; and Lure FA, range: 10-125, mean: 49. In order to assure there would be enough trials per bin, participants were presented with a large number of trials. The behavioral performance per blocks is displayed in (Figure 2.3). Statistical comparisons of performance between blocks are located in the appendix.

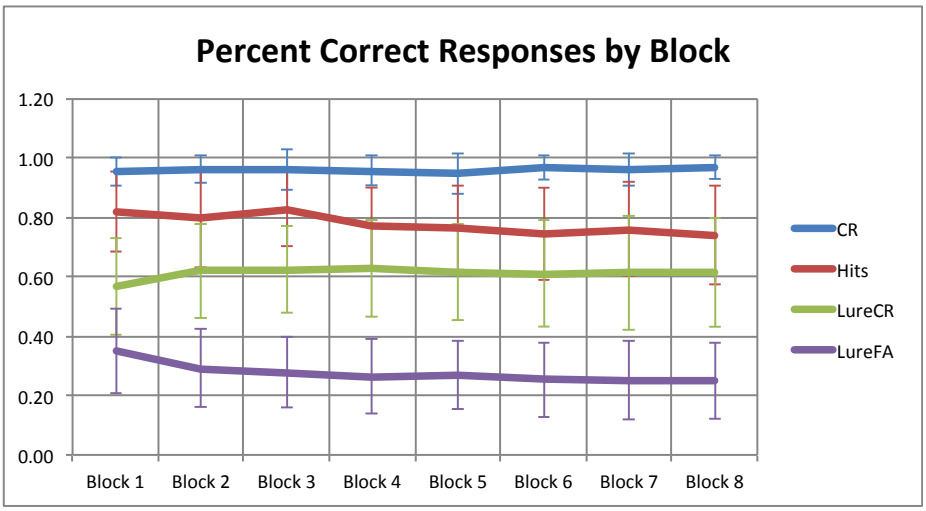

Figure 2.3: Behavioral Responses By Block.
Proportion of correct answers by block for CRs (Novel called "New"), Hits (Repeats called "Old"), Lure CRs (Lures called "Similar), and Lure FAs (Lures called "Old").

Participants had high accuracy for correctly identifying novel stimuli as "new" (correct rejections or CRs; mean ± SD = .96 ± .04) and identifying repeated stimuli as "old" (Hits; .78 ± .11). The majority of responses to lure stimuli were divided between "similar" (Lure correct rejections or Lure CRs; .61 ± .16) and "old" (Lure false alarms or Lure FAs; .28 ± .12). Figure 2.4 shows the proportion of responses and the reaction times for the categories of interest. Table 2.1 lists the proportion of behavioral responses and mean reaction times (RTs) for all trial types. A 3 (stimulus type) × 3 (behavioral response) repeated measures ANOVA conducted on RTs revealed a main effect of behavioral response ($F[2,156] = 154.38$, $p < .001$) and a behavioral response × stimulus type interaction ($F[4,312] = 37.33$, $p < .001$), but no main effect of stimulus type ($F[2,156] = .82$, $p > .05$). Post-hoc paired t-test comparisons for behavioral responses revealed that mean RTs for Hits were faster than both Lure FAs ($t[52] = 7.65$, $p < .01$) and Lure CRs ($t[52] = 2.02$, $p < .05$). However, RTs for Lure CRs were not different than Lure FAs ($t[52] = .45$, $p = .65$). For both repeat and lure stimuli, "old" and "similar" responses had longer RTs than "new" responses (all p values < .001).

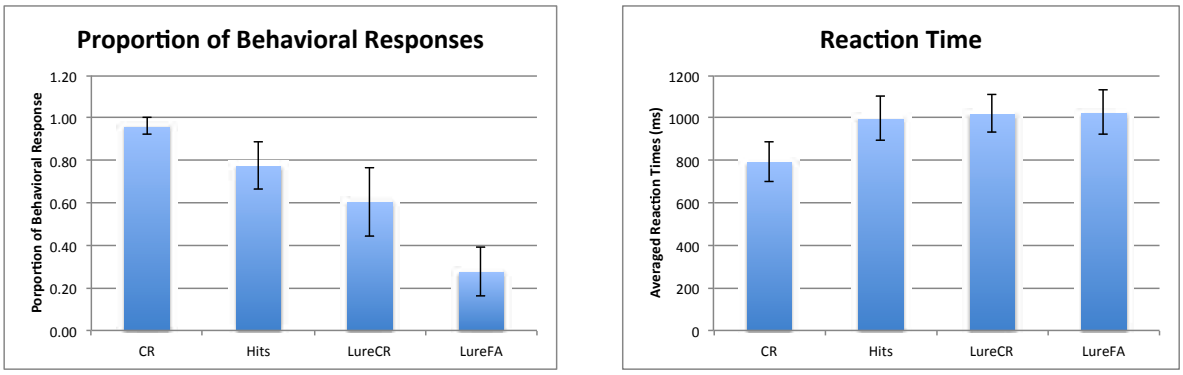

Figure 2.4: Proportion Behavioral Responses and Reaction Times.
Behavioral results for the mnemonic discrimination task. A) Percent of Behavioral Responses. B) Reaction Times.

Table 2.1: Proportion Behavioral Responses and Reaction Times.
The proportion of behavioral responses and their corresponding averaged reaction times for all trial types in the mnemonic discrimination task.

Behavioral Responses and Reaction Times			
Stimulus Type	**Behavioral Response**	**Mean Proportion Responses (SD)**	**Mean RT (SD) in ms**
Novel	Old	0.01 (0.02)	1084.0 (159.3)
	Similar	0.03 (0.02)	1059.0 (116.6)
	New (CR)	0.96 (0.04)	794.18 (93.1)
Repeat	Old (Hit)	0.78 (0.11)	999.1 (103.5)
	Similar	0.16 (0.09)	1035.9 (109.3)
	New	0.07 (0.06)	925.5 (181.3)
Lure	Old (Lure FA)	0.28 (0.12)	1025.9 (105.1)
	Similar (Lure CR)	0.61 (0.16)	1020.9 (86.6)
	New	0.12 (0.09)	898.8 (118.0)

We calculated a pattern separation score for all participants as the probability of responding "similar" to a lure stimulus corrected by the probability of responding "similar" to a novel foil (i.e., p("similar"|Lure) – p("similar"|New)). This method has been used previously in similar continuous recognition memory paradigms to protect against possible response bias (e.g., S. M. Stark, M. A. Yassa, J. W. Lacy, & C. E. L. Stark, 2013; Yassa, Lacy, et al., 2011). The mean pattern separation score was .58±.17, which is consistent with previous research and

indicates a lack of response bias (Dery et al., 2013; Kirwan et al., 2012; Shelton & Kirwan, 2013; Yassa, Lacy, et al., 2011).

Event-related Potential Analyses

We first asked whether ERP components that previously have been shown to distinguish between old and new stimuli (the FN400 and LPC) did so in our paradigm (i.e., whether there were old-new effects). Grand average waveforms are depicted in Figure 2.5. Mean amplitudes for the FN400 were evaluated in the 300-500 ms post-stimulus period over the two anterior electrode clusters (shaded in Figure 2.5A-B), while mean amplitudes for the LPC were evaluated in the 500-800 ms post-stimulus period over the two posterior electrode clusters (shaded in Figure 2.5D-E). We analyzed mean amplitudes for trial types (i.e. Hits, CRs, Lure CRs, and Lure FAs) using one-way repeated measures ANOVAs. Greenhouse-Geisser corrected p-values are reported below. During the 300-500 ms time window, there was a main effect of trial type in both left and right anterior clusters (Left: $F[3,156] = 31.17$, $p < .001$; Right: $F[3,156] = 32.567$, $p < .001$). Post-hoc paired t-test comparisons (Bonferroni corrected alpha criterion = 0.008) revealed significant differences in mean amplitude between Hit and CR conditions on both the left and the right (Table 2.2). During the 500-800 ms time window, there was a main effect of trial type in both left and right posterior clusters (Left: $F[3,156] = 19.75$, $p < .001$; Right: $F[3,156] = 13.706$, $p < .001$). Post-hoc paired t-test comparisons revealed significant differences between CR and Hit conditions (Table 2.3). As we hypothesized, we observed old-new effects in both the 300-500 ms and the 500-800 ms windows as the mean amplitudes for CRs were more negative than mean amplitudes for Hits in both the left and right hemispheres, consistent with previous literature (Fay, Isingrini, Ragot, & Pouthas, 2005; Rugg & Nieto-Vegas, 1999).

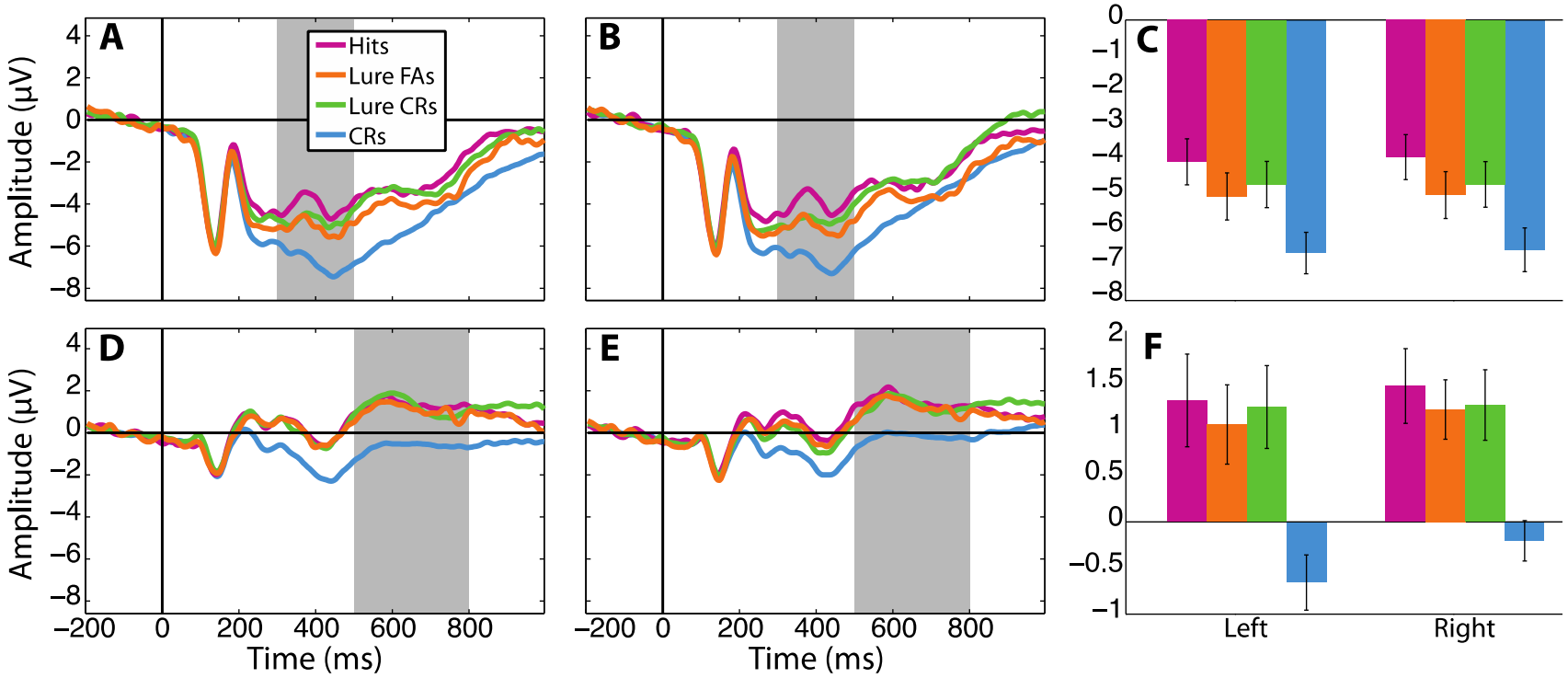

Figure 2.5: Experiment 1 Event-related Potentals.
Data for the continuous recognition memory task for correctly identified novel, repeat, and lure stimuli, and incorrect lures called "old." Event-related potentials (ERPs) for the left (A) and right (B) frontal electrode clusters. C) Bar graphs depicting mean amplitudes in the 300-500 ms post-stimulus-onset time window (shaded in A & B). ERPs for the left (D) and right (E) posterior electrode clusters. D) Bar graphs depicting the mean amplitudes in the 500-800 ms time window (shaded region in D & E).

Table 2.2: Mean Amplitude Comparisons 300-500 ms.
Mean amplitude comparisons for the mnemonic discrimination task in the 300-500 ms post stimulus onset time range obtained from frontal electrode clusters. Images are either "novel," "repeats," or "lures." Participants are asked to classify each image is either "new," "old," or "similar." Novel items called "new" are Correct Rejects (CR), repeated items called "old" are Hits, Lures called "old" are Lure False Alarms (Lure FA), and Lures called "similar" are Lure Correct Rejections (Lure CR).

	Left		Right	
Comparison	**t(52)**	**P-value**	**t(52)**	**P-value**
CR – Hit	-9.26	<0.001*	-11.58	<0.001*
CR – Lure FA	-5.44	<0.001*	-5.40	<0.001*
CR – Lure CR	-8.86	<0.001*	-7.88	<0.001*
Hit – Lure FA	2.89	0.006*	3.35	0.002*
Hit – Lure CR	3.11	0.003*	3.47	0.001*
Lure FA – Lure CR	1.09	0.280	-0.92	0.363

We next tested the hypothesis that the same components would have distinguishable amplitudes for the Lure FA and Lure CR conditions. In the 300-500ms time window (Table 2.2), there were no differences in the mean amplitudes between Lure CR and Lure FA conditions over either the left or right hemispheres. This was also the case in the 500-800 ms time window (Table 2.3). Therefore, contrary to our hypothesis, we found no differences in mean amplitudes between Lure CR and Lure FA conditions in either time window. Thus, the amplitudes of the Lure FA and Lure CR conditions indicate that these two trial outcomes result in similar ERP signatures. Scalp topographies of the three conditions of interests (Hits, Lure CRs, and Lure FAs) for the 300-500 ms and 500-800 ms windows are available in Figure 2.6.

Table 2.3: Mean Amplitude Comparisons 500-800 ms.
Mean ERP amplitude comparisons for the left and right 500-800 ms parietal clusters.

Comparison	Left t(52)	P-value	Right t(52)	P-value
CR – Hit	-5.81	<0.001*	-5.13	<0.001*
CR – Lure FA	-5.62	<0.001*	-4.68	<0.001*
CR – Lure CR	-6.59	<0.001*	-4.69	<0.001*
Hit – Lure FA	0.88	0.384	0.94	0.354
Hit – Lure CR	0.27	0.787	0.84	0.403
Lure FA – Lure CR	-0.65	0.516	-0.16	0.873

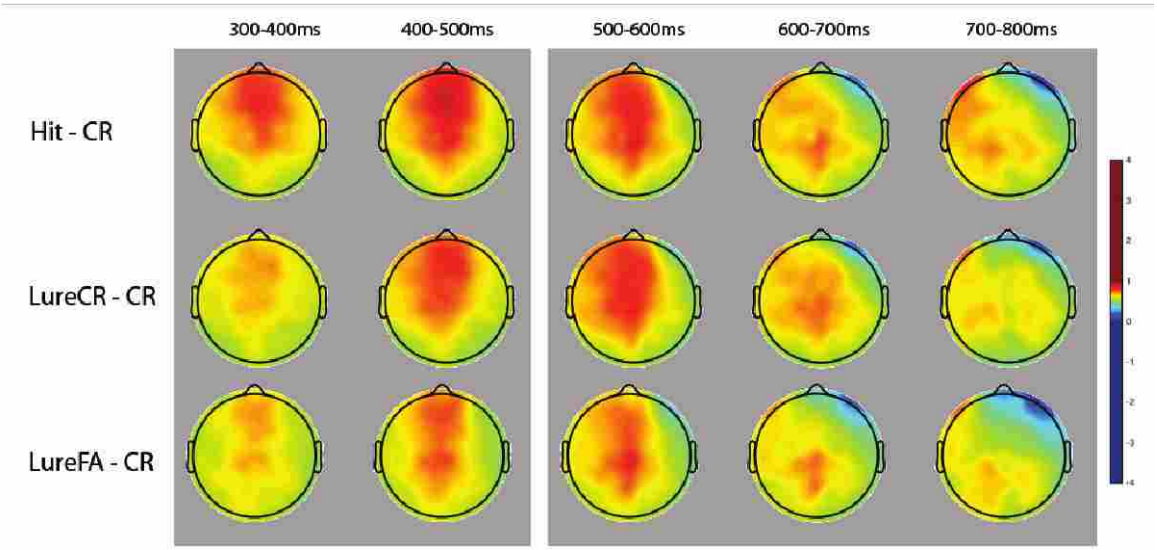

Figure 2.6: Scalp Topographies.
Scalp topographies are shown for Correct Rejections (CR) subtracted from the three conditions of interest in the 300-500 ms and 500-800 ms time windows. Topography maps are scaled from -4 microvolts to +4 microvolts.

Finally, we hypothesized that if the Lure CR condition reflects pattern separation processing, then the associated ERP amplitudes should more closely resemble those of the CR condition. Similarly, we hypothesized that if the Lure FA condition reflects pattern completion processing then the associated ERP amplitudes should be more similar to those of the Hit condition. In evaluating the amplitude of the Lure conditions relative to those of CRs and Hits,

we found that in the 300-500 ms window, the mean amplitudes for the lure stimuli (both Lure CR and Lure FA) were intermediate between mean amplitudes for Hits and CRs (Figure 2.5, Table 2.2). In the 500-800 ms window, the mean amplitudes of the lures (both Lure CR and Lure FA) were significantly different than the mean amplitudes of CRs but not distinguishable from the mean amplitudes of Hits (Figure 2.5, Table 2.3). Thus, contrary to our predictions, mean ERP amplitudes for both Lure FA and Lure CR conditions are consistent with pattern completion processes, at least in the 500-800 ms window for the posterior electrode sites.

The amplitude data in the 300-500 ms window indicate that here, Lures are intermediate between the Hit and CR conditions. Lures of varying similarity to their corresponding targets may have varying levels of familiarity, which could influence the amplitude of the FN400 component (Curran, 2000). Thus, the intermediate amplitude of the lures between Hit and CR conditions may have been due to selectively averaging together responses to stimuli that were more or less similar to the originally presented target stimulus (for a discussion of selective averaging, see Paller, Voss, & Boehm, 2007; Yu & Rugg, 2010). In short, treating all the lures as if they shared the same degree of similarity with their respective targets may have masked any effects that are dependent on the level of similarity shared between the two stimuli. To assess this possibility, we conducted a separate analysis in which we sorted trials according to the similarity of the lure stimulus to the target stimulus. In a separate behavioral experiment, we collected normative similarity ratings for each target-lure pairing. Thirty-five participants (independent from the sample who participated in the ERP experiment) rated the similarity of target-lure pairs on a 7-point Likert scale, ranging from “very similar” to “not similar.” Target-lure pairs were rank-ordered and divided into five equally sized similarity bins (1 = least similar, 5 = most similar) based on mean similarity scores.

Similarity Behavioral Results

Using data from the original 83 participants, we re-sorted ERP lure trials in order to examine mean ERP amplitudes for Hits, CRs, and lure stimuli sorted by similarity bin. The lures were sorted into similarity bins regardless of behavioral response due to the limited number of trials in each similarity bin. In this new analysis, 24 participants had fewer than 10 trials in at least one task condition (similarity bins 1-5, CRs, and Hits), and 16 had excessive artifacts, and were thus excluded from further analysis (final n=48; age range=17-29; mean age=21; 34 female).

First we analyzed the behavioral responses to lure stimuli to assess the influence of similarity ratings on "old" and "similar" responses with the hypothesis that higher similarity ratings would lead to more "old" responses (i.e., Lure FAs) and that the proportion would decrease with lower similarity ratings. A one-way repeated measures ANVOA for Lure FAs by the five similarity bins, revealed a main effect of similarity ($F[4,384] = 435.48$, $p < .001$). Consistent with our hypothesis, there was a strong linear trend in the proportion of "old" responses to lure stimuli across similarity ratings ($F[1,96] = 626.41$, $p < .001$) (Figure 2.7).

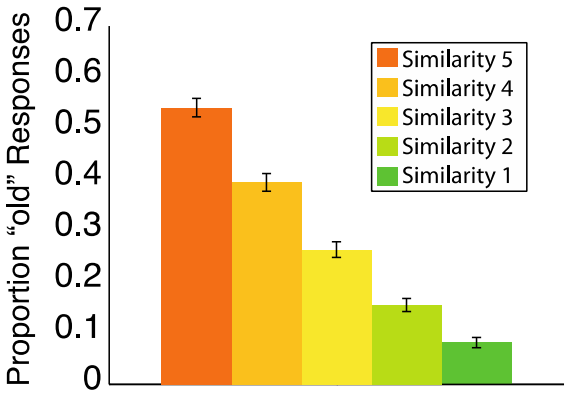

Figure 2.7: Proportion of Lures Called "Old."
Each of the lures was rated for similarity, 1 being the least similar and 5 being the most similar. The proportion of lures called "old" for each similarity bin is shown above. There is a strong increasing linear trend for the lures called "old" as the similar rating increases.

Similarity ERP Results

Mean amplitudes in the 300-500 ms post-stimulus period over the two anterior electrode clusters (Figure 2.8A) were analyzed using one-way repeated measures ANOVAs for trial t ypes (Hits, CRs, and Lures according to similarity bins 1-5). In both anterior clusters, there was a main effect of trial type (Left: $F[6,282] = 10.35$, $p < .001$; Right: $F[6,282] = 11.89$, $p < .001$). As in the previous analysis, post-hoc paired samples *t*-tests (Bonferroni-corrected alpha criterion = 0.0024) revealed that mean amplitudes for CRs were more negative than for Hits in both the left ($t[47] = -8.14$, $p < .001$) and right hemispheres ($t[47] = -9.62$, $p < .001$). Likewise, mean amplitudes for each of the similarity bins were more positive than mean amplitudes for CRs in both hemispheres (see Table 2.4). Mean amplitudes for Hits were more positive than those for similarity ratings of 1 (least similar) in the left hemisphere, and for similarity ratings of 1-4 on the right side. However, there were no significant differences in mean amplitudes between similarity bins themselves in either hemisphere. Linear trend analyses revealed strong linear

trends bilaterally (Left: $F[1,47] = 32.94$, $p < .001$; Right: $F[1,47] = 48.68$, $p < .001$); however, these appear to be highly influenced by the Hit and CR conditions, as indicated by significant cubic trends (Left: $F[1,47] = 11.83$, $p = .021$; Right: $F[1,47] = 12.61$, $p = .001$) and the absence of a linear trend when considering the mean amplitudes of the similarity bins without the Hit or CR conditions (Left: $F[1,47] = .32$, $p = .58$; Right: $F[1,47] = .62$, $p = .44$). Thus, target-lure similarity does not appear to exert a strong influence over the amplitude of the FN400.

Table 2.4: Mean Amplitude Comparisons for Similarity Bins 300-500 ms.
Mean amplitude comparisons for the mnemonic discrimination memory task in the frontal 300-500 ms electrode clusters. In this analysis, lures were broken down into similarity bins, 1 being the least similar pairs and 5 being the most similar pairs. Data for lures was used regardless of behavioral classification of lures).

	Left			Right		
Comparison	**t**	**df**	**P-value**	**t**	**df**	**P-value**
CR –Hit	-8.141	47	<0.001*	-9.618	47	<0.001*
CR - Similarity 1	-6.501	47	<0.001*	-5.033	47	<0.001*
CR - Similarity 2	-6.554	47	<0.001*	-5.233	47	<0.001*
CR - Similarity 3	-5.238	47	<0.001*	-5.696	47	<0.001*
CR - Similarity 4	-4.44	47	<0.001*	-4.678	47	<0.001*
CR - Similarity 5	-5.427	47	<0.001*	-5.851	47	<0.001*
Hit - Similarity 1	3.845	47	<0.001*	4.157	47	<0.001*
Hit - Similarity 2	2.572	47	0.013	4.057	47	<0.001*
Hit - Similarity 3	2.868	47	0.006	3.286	47	0.002*
Hit - Similarity 4	2.38	47	0.021	3.614	47	0.001*
Hit - Similarity 5	2.403	47	0.020	3.091	47	0.003
Similarity 1 - Similarity 2	-1.379	47	0.174	-0.692	47	0.492
Similarity 1 - Similarity 3	-0.534	47	0.596	-1.013	47	0.316
Similarity 1 - Similarity 4	-0.382	47	0.704	-0.244	47	0.809
Similarity 1 - Similarity 5	-1.016	47	0.315	-1.161	47	0.251
Similarity 2 - Similarity 3	0.489	47	0.627	-0.511	47	0.612
Similarity 2 - Similarity 4	0.478	47	0.635	0.243	47	0.809
Similarity 2 - Similarity 5	-0.016	47	0.987	-0.64	47	0.525
Similarity 3 - Similarity 4	0.054	47	0.957	0.703	47	0.486
Similarity 3 - Similarity 5	-0.608	47	0.546	-0.116	47	0.908
Similarity 4 - Similarity 5	-0.619	47	0.539	-0.994	47	0.325

* = significant; Bonferroni correction of 0.0024

In the 500-800 ms post stimulus period, a one-way repeated measures ANOVAs for trial types (Hits, CRs, and Lures according to similarity bins 1-5) revealed a main effect of trial type over both left and right posterior electrode clusters (Left: $F[6,282] = 10.85$, $p < .001$; Right:

$F[6,282] = 6.57$, $p < .001$). Similar to the 300-500 ms range, post-hoc paired *t*-tests revealed that mean amplitudes for CRs were more negative than those for Hits in both the left and right hemispheres (see Table 2.5). Mean amplitudes for each of the similarity bins 1-5 on the left and 2-5 on the right were significantly different from CRs, and only similarity bin 1 on the left was different from Hits. Additionally, there were no significant differences (p values > .0024) between mean amplitudes of similarity bins. Again, there were strong linear trends bilaterally (Left: $F[1,47] = 32.41$, $p < .001$; Right: $F[1,47] = 20.44$, $p < .001$), which were likely driven by the Hit and CR conditions as there was a strong cubic component ($F[1,47] = 5.60$, $p = .022$; Right: $F[1,47] = 6.00$, $p = .018$) and no linear trend when considering lure similarity bins in the absence of the Hit and CR conditions (Left: $F[1,47] = 2.84$, $p = .10$; Right: $F[1,47] = 1.25$, $p = .27$). In summary, there were no obvious trends in amplitude when considering the similarity ratings of the lures in any of the components we evaluated.

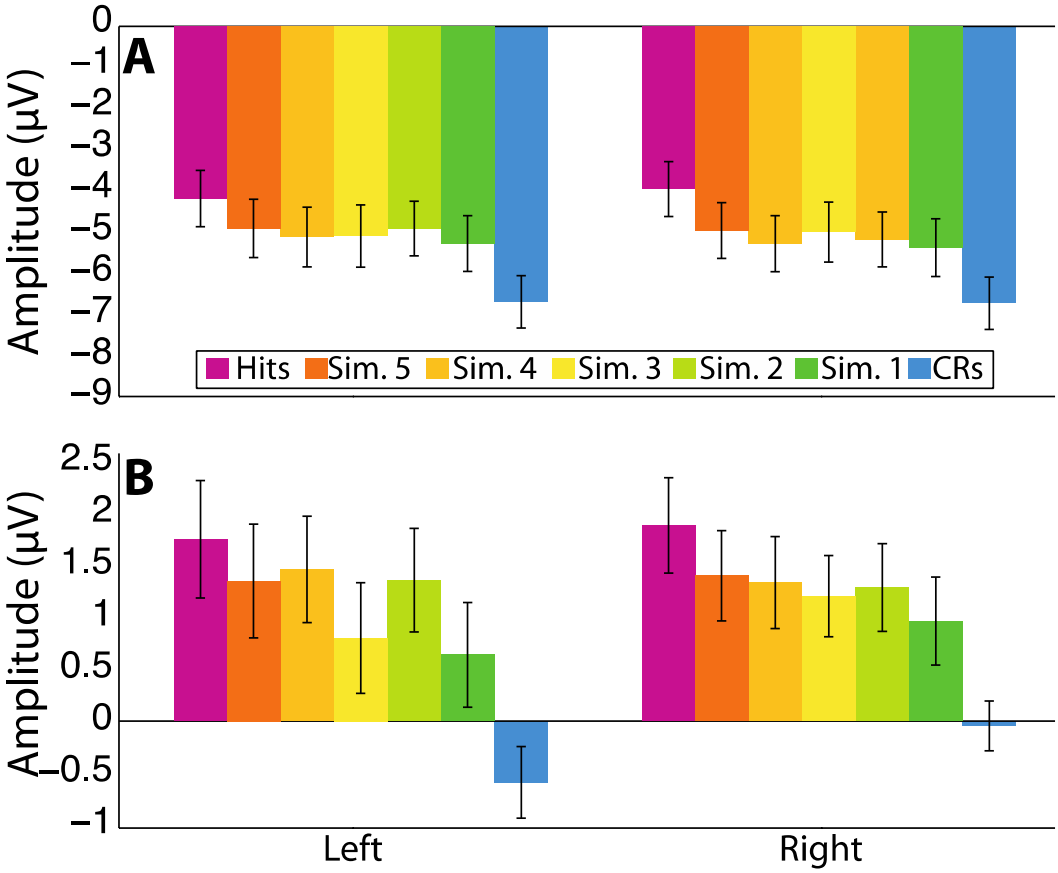

Figure 2.8: Event-related Potentials for Similarity Bins.
Mean amplitudes for the continuous recognition memory task for correctly identified novel and repeat stimuli with lures, regardless of response accuracy, binned according to similarity ratings: 1 being most similar and 5 being most different. A) ERP mean amplitudes for the left and right anterior electrode clusters 300-500 ms after stimulus onset. B) ERP mean amplitudes for the left and right posterior electrode clusters 500-800 ms after stimulus onset. None of the mean amplitudes for the similarity bins differed and there was no linear trend by similarity.

Table 2.5: Mean Amplitude Comparisons for Similarity Bins 500-800 ms.
Mean amplitude comparisons for the mnemonic discrimination memory task in the parietal 500-800 ms electrode clusters. In this analysis, lures were broken down into similarity bins, 1 being the least similar pairs and 5 being the most similar pairs. Data for lures was used regardless of behavioral classification of lures.

	Left			Right		
Comparison	**t**	**df**	**P-value**	**t**	**df**	**P-value**
CR –Hit	-6.658	47	<0.001*	-5.098	47	<0.001*
CR - Similarity 1	-4.198	47	<0.001*	-3.098	47	0.0030
CR - Similarity 2	-5.997	47	<0.001*	-3.932	47	<0.001*
CR - Similarity 3	-4.208	47	<0.001*	-3.97	47	<0.001*
CR - Similarity 4	-5.859	47	<0.001*	-3.826	47	<0.001*
CR - Similarity 5	-5.215	47	<0.001*	-4.129	47	<0.001*
Hit - Similarity 1	3.659	47	0.001*	3.022	47	0.004
Hit - Similarity 2	1.144	47	0.259	1.656	47	0.104
Hit - Similarity 3	2.961	47	0.005	2.318	47	0.025
Hit - Similarity 4	0.813	47	0.420	1.69	47	0.098
Hit - Similarity 5	1.302	47	0.199	1.821	47	0.075
Similarity 1 - Similarity 2	-2.484	47	0.017	-1.059	47	0.295
Similarity 1 - Similarity 3	-0.55	47	0.585	-0.827	47	0.412
Similarity 1 - Similarity 4	-2.428	47	0.019	-1.16	47	0.252
Similarity 1 - Similarity 5	-1.969	47	0.055	-1.323	47	0.192
Similarity 2 - Similarity 3	1.717	47	0.092	0.241	47	0.811
Similarity 2 - Similarity 4	-0.273	47	0.786	-0.131	47	0.896
Similarity 2 - Similarity 5	0.024	47	0.981	-0.315	47	0.754
Similarity 3 - Similarity 4	-1.789	47	0.080	-0.386	47	0.701
Similarity 3 - Similarity 5	-1.538	47	0.131	-0.617	47	0.540
Similarity 4 - Similarity 5	0.353	47	0.726	-0.23	47	0.819

* = significant; Bonferroni correction of 0.0024

Performance Based Analysis

Several studies have evaluated ERP effects based on behavioral performance (Curran & Cleary, 2003; Morcom, 2015). In a recent study employing similar stimuli and methods, Morcom (2015) did not observe Lure FA vs Lure CR differences in either hemisphere of the 500-800ms window. However, when the lure discrimination index, referred to here as the pattern separation score, was used as a covariate in the analysis, significant differences between Lure FA and Lure CR mean amplitudes emerged (only in the 500-800 ms window). Modeling our analysis after that of Morcom (2015), we preformed repeated measures ANOVAs for trial types for each of the

electrode clusters, including the pattern separation score as a covariate. These results (Table 2.6) showed no significant trial type (Lure FAs vs. Lure CRs) × pattern separation score interaction in any of the electrode clusters.

Table 2.6: Behavioral Performance Analysis.
A one-way ANOVA was used to evaluate trial types (Hits, Correct Rejections, Lure FAs, and Lure CRs) with pattern separation scores used as a covariate. All four clusters showed no statistical difference.

Electrode Cluster	F	df	*p*-value
Left 3000-500	.944	4, 47	.381
Right 300-500	1.927	4, 47	.158
Left 500-800	.213	4, 47	.838
Right 500-800	.312	4, 47	.870

Temporal Principle Components Analysis

Our previous analysis focused on components that have reliably demonstrated old/new effects (i.e., the FN400 and the LPC). In order to expand our analysis beyond these components, we conducted an exploratory analysis across all electrodes and time points. As a data reduction technique, we performed temporal principle components analyses (PCA). We used a Promax rotation (Dien, Khoe, & Mangun, 2007), which first applies a Varimax rotation, and then relaxes it to allow for correlated factors. A scree test indicated that retaining 17 factors accounted for 90% of the variance. The first three factors explained 34%, 14%, and 9% of the variance and peaked at 828ms, 360ms, and 580ms, respectively (Table 2.7). All three components had peak electrode sites within the left anterior cluster used for our *a priori* analysis outlined above. We extracted peak factor scores for these three components at their peak electrode sites (Figure 2.9). Repeated measures ANOVAs revealed significant main effects of condition for each of the factors (Table 2.8). Follow-up t-tests revealed that the comparison of Lure FAs to Lure CRs was only significant for the third factor, peaking at 580ms ($t(53)=2.26$, $p = .03$). Additionally, factor

scores for Hits differed from Lure CRs (but not Lure FAs) in the second and third factors (which peaked at 360ms and 580ms, respectively). Scalp topographies of the three conditions of interests (Hits, Lure CRs, and Lure FAs) for each of the electrode sites are available in Figure 2.10.

Table 2.7: Peak Factor Scores.
The peak factor scores and peak latencies are shown above for the three electrodes produced from the principle factor analysis.

				Peak Factor Score			
Factor Number	**% Variance**	**Peak Latency (ms)**	**Electrode Number**	**Hits**	**Lure FA**	**Lure CR**	**CR**
1	34	828	12	2.444	2.236	1.732	0.971
2	14	360	19	2.209	1.918	1.534	0.970
3	9	580	24	2.000	2.231	1.652	0.779

Table 2.8: Statistical Comparisons of Trial Types within Each Electrode.
Repeated measures ANOVA and t-tests for the three electrode sites.

		Main Effect of Condition			**Hits vs. Lure FA**		**Hits vs. Lure CR**		**Lure FA vs. Lure CR**	
Factor Number	**Electrode Number**	**F(3,159)**	***p***	**Parietal eta^2**	t(53)	p	t(53)	p	t(53)	p
1	12	4.020	0.014	0.071	0.445	0.658	1.934	0.058	0.906	0.369
2	19	3.523	0.022	0.062	0.596	0.554	2.074	0.043*	0.992	0.325
3	24	9.436	<.001	0.151	0.752	0.455	2.261	0.028*	2.261	0.028 *

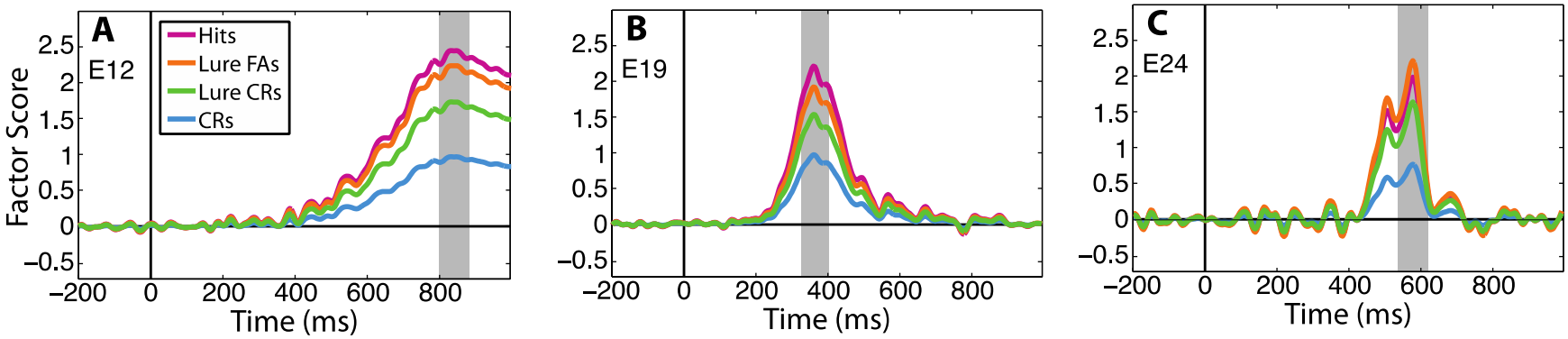

Figure 2.9: Exploratory Analysis Event-related Potentials.
Data for the continuous recognition memory task for correctly identified novel, repeat, and lure stimuli, and incorrect lures called "old." Event-related potentials (ERPs) for each of the three electrodes from the principle components analysis A) E12, B), E19, and C) E24. The time of the peak amplitudes are shaded in gray.

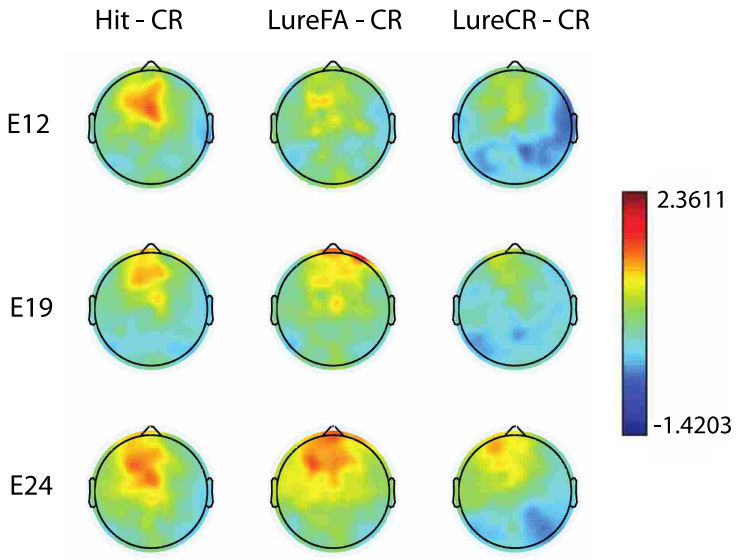

Figure 2.10: Scalp Topographies.
Scalp topographies are shown for Correct Rejections (CR) subtracted from the three conditions of for each of the three electrodes. Topography maps are scaled from -1.4203 microvolts to +2.3611 microvolts.

Discussion Experiment 1

Several of our ERP analysis (overall ERP analysis, ERPs broken down by similarity, and ERPs by behavioral performance) failed to show mean amplitude differences between the Lure FA and the Lure CR trial types in our *a priori* components. However, the temporal principle components analysis revealed differences between the Lure FA and Lure CR trials, indicating that ERPs are sensitive to differentiation between the neural correlates of pattern separation and pattern completion. However, our original hypothesis that ERP amplitudes for Lure CRs (pattern separation) would resemble those for CRs, while ERP amplitudes for Lure FAs (pattern completion) would resemble those for Hits was not confirmed. In fact, our findings indicate that amplitudes for both Lure FA and Lure CR trial types resembled those for Hits. We hypothesized

that this may have been caused by task demands of the intentional continuous recognition memory task. Previous studies that have shown differentiation of neural responses to lures relative to repeats have used an incidental memory task design, suggesting top-down processing (Duncan, Curtis, & Davachi, 2009; Motley & Kirwan, 2012a). Accordingly, we conducted an additional study using an incidental memory paradigm with similar methods to Experiment 1.

Introduction Experiment 2

Bakker et al. (2008) used an incidental version of the mnemonic discrimination task where participants were asked to classify each image as one typically used "indoors" or "outdoors," instead of "old," "similar," or "new." In this study, the fMRI data evaluating hippocampal activation showed strong evidence of pattern separation even though the participants were not engaged in an overt memory task. Neural activity indicated that lures were treated more like novel stimuli (consistent with pattern separation processing) in the CA3/dentate gyrus of the hippocampus, while other hippocampal sub-regions (i.e., CA1) and cortical regions responded similarly to lures and repeats (consistent with pattern completion processing). In the explicit or intentional version of this experiment, the pattern of activation in the hippocampus was more complicated, likely due to overt task demands (Kirwan and Stark, 2007). Motley and Kirwan (2012) directly compared incidental and intentional task instructions using the same stimuli in both conditions and found that pattern separation processing changed according to task demands.

Hypothesis Experiment 2

Based on this premise, we conducted an incidental version of the task previously used in this study to evaluate if we could replicate data from the intentional version, suggesting cortical

processes are equally engaged in the two versions, or if differences in ERPs would emerge due to task demands. We hypothesize that we will be able to replicate the old/new effect in the intentional version and that Lure ERPs will be intermediate between Novel and Repeat ERPs, although closer to the Repeat stimuli then that Novel.

Methods Experiment 2

Participants

Informed consent was obtained from 38 healthy participants who were recruited from the university community and received credit for participation. The experiment was conducted as approved by the Brigham Young University Institutional Review Board protocol for research with human participants. Participants with excessive artifacts (n=7) were discarded from further analysis (see Methods Experiment 1) for final n=31 (age range =18-31; mean age =21.7; 18 female).

Stimuli and Behavioral Procedures

The incidental task was similar to the intentional task with a few minor changes. In the incidental version, participants were asked to judge if the item was typically used "indoors" or "outdoors." Stimuli were presented in three blocks of 150 trials each. Each block consisted of 75 novel images, 25 repeat images, and 50 lure images. In both the intentional and incidental versions, participants were allowed to take untimed breaks between each block. Response options were displayed on the screen below the object on each trial in each version.

Electroencephalogram Acquisition and Analysis

EEG acquisition and analysis was the same as Experiment 1.

Results Experiment 2

Behavioral Results

Since behavioral responses were used only to ensure each subject encoded the stimuli, and they did not explicitly indicate pattern separation and pattern completion processing, they were not analyzed.

Event-related Potential Analysis

Mean amplitudes for Novel, Repeat and Lure stimuli for each of the hemispheres (right and left) in the frontal 300-500 ms and parietal 500-800 ms (Figure 2.11) ranges were calculated using three-way repeated measures ANOVAs. In the left anterior cluster, there was a main effect of trial type (F[2,30] = 3.474, p = 0.037). Post-hoc t-tests reveal significant differences for Novel vs. Lure stimuli (t[30] =-2.726, p =.011), and Old vs. Lure stimuli (t[30] = -2.075, p = .047), but not for Novel vs. Old stimuli (t[30] = .461, p = .711). The right anterior cluster showed no main effect of trial type (F[2,30] = 1.93, p = 0.160). In both posterior clusters, there was no main effect of trail type (Left: F[2,30] = 3.156, p = .058; Right: F[2,30] = 1.539, p = 0.226).

Next we compared the ERPs from the incidental and intentional tasks. Figure 2.12 shows the mean amplitudes for Novel, Repeat, and Lure stimuli for the intentional and incidental versions of the task. Mean ERP amplitudes between the two versions were compared using independent samples T-tests (Table 2.9). For the intentional version, all lure stimuli, whether they were identified is “old”, “similar,” or “new,” were grouped together to mirror the ERP categories from the incidental version. For repeat stimuli, significant differences between ERPs were only seen in the right 500-800 parietal window. For novel and lure stimuli, no significant differences were seen between the incidental and intentional task in any of the four clusters of

interest. In summary, the incidental version did not enhance ERP signals in our conditions of interests as we had hoped.

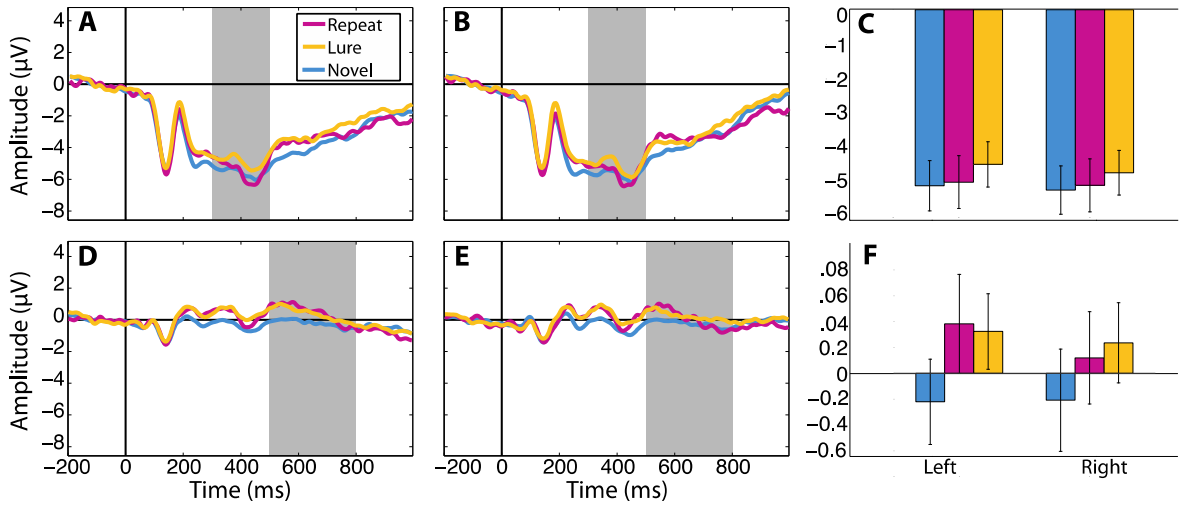

Figure 2.11: Incidental Task Event-related Potentials.
Data for the incidental version of the continuous recognition memory task for novel, repeat, and lure stimuli. Event-related potentials (ERPs) for the left (A) and right (B) frontal electrode clusters. C) Bar graphs depicting mean amplitudes in the 300-500 ms post-stimulus-onset time window (shaded in A & B). ERPs for the left (D) and right (E) posterior electrode clusters. D) Bar graphs depicting the mean amplitudes in the 500-800 ms time window (shaded region in D & E).

Table 2.9: Incidental vs. Intentional Mean ERP Amplitudes.
Mean ERP comparisons between the incidental and intentional version of the mnemonic discrimination tasks.

Electrode Cluster	Novel			Repeat			Lure		
	t	**df**	***p*-value**	**t**	**df**	***p*-value**	**t**	**df**	***p*-value**
Left 300-500	1.722	2, 81	0.089	-8.836	2, 81	0.405	0.971	2, 81	0.334
Right 300-500	1.46	2, 81	0.147	-1.067	2, 81	0.289	0.632	2, 81	0.529
Left 500-800	0.936	2, 81	0.352	-1.296	2, 81	0.199	-5.514	2, 81	0.608
Right 500-800	-0.007	2, 81	0.994	-2.267	2, 81	0.026*	-1.315	2, 81	0.192

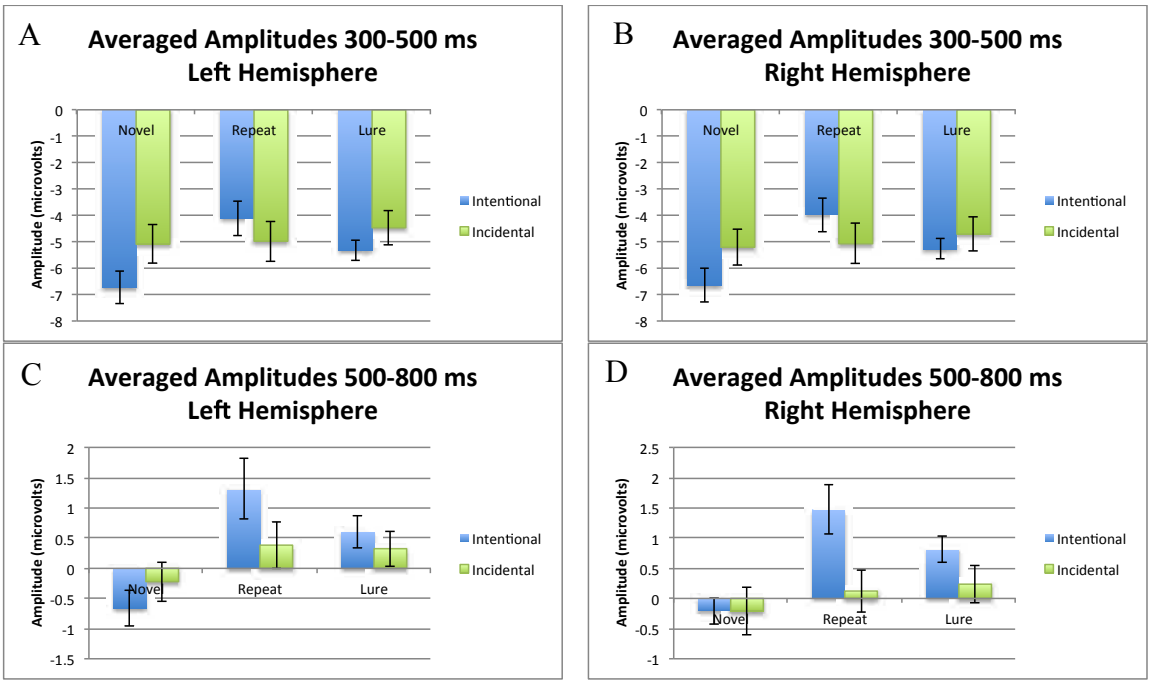

Figure 2.12: Intentional vs. Incidental Event-related Potential Comparisions.
Mean amplitudes for new, old, and similar stimuli are shown for both the intentional and incidental version of the mnemonic discrimination task. A) Left frontal cluster for the 300-500 ms range. B) Right frontal cluster for the 300-500 ms range. C) Left parietal cluster for the 500-800 ms range. D) Right parietal cluster for the 500-800 ms range.

Discussion Experiment 2

There is an old/new effect in the intentional version with the old items eliciting a more positive ERP signal then the new items. The lure ERPs fall between these two, making it difficult to conclude whether they look more like old items or like new items. We conducted the incidental version to see if ERP amplitudes would become more distinguished. However, in the incidental version, we saw no old/new effects at all, making it impossible to distinguish the lures from the old and new items. Perhaps adding the overt recognition memory component enhances memory processing and is necessary for observing an old/new effect with these stimuli. However, other studies have demonstrated an old/new effect in an incidental task (Curran, 1999; Paller, Kutas, & Mayes, 1987). Their task differs from ours in several aspects such as: it uses

words instead of pictures, it uses a study-test format instead of a continuous recognition paradigm, and the quantity of stimuli are different. Further research is needed to determine which aspects are resulting in a diminished old/new effect.

General Discussion Study 1

Computational models suggest different neuronal processes occur in pattern separation and pattern completion. Mnemonic discrimination tasks have been used in numerous behavioral and fMRI studies to evaluate these processes with the reasoning that lures called "similar" tax pattern separation processes while lures called "old" indicate pattern completion processes. In this study, we examined ERP responses to evaluate the neural correlates of these two conditions in the first 1000 milliseconds following stimulus onset.

Consistent with previous literature, we found old-new effects, such that mean ERP amplitudes were more positive for Hits than for CRs for anterior electrode sites in the 300-500 ms window, and for posterior electrode sites in the 500-800 ms window (Friedman, 1990; Kayser, Fong, Tenke, & Bruder, 2003; Rugg, 1985, 1987). Following the reasoning of previous studies (e.g., Bakker et al., 2008), we hypothesized that pattern separation processes would have neural signals more similar to novel items, while pattern completion processes would have neural signals more similar to repeated items. However, contrary to our hypothesis, we did not observe a difference between mean amplitudes for Lure CRs and Lure FAs, nor did we observe a difference in reaction times.

One possible explanation for the failure to observe differences in ERP amplitudes between Lure CRs and Lure FAs is that we selectively averaged more- and less-similar lure trials together. More-similar lure stimuli may have elicited ERPs that more closely resembled repeated stimuli, while less similar lure stimuli might have elicited ERPs that resembled novel stimuli. To

account for this possibility, we separated lure stimuli according to normative similarity ratings. When we examined mean amplitudes for lure stimuli based on target-lure similarity, we still did not observe a systematic relationship between similarity and mean ERP amplitude. Another possible explanation is that the medial temporal lobe is the main neuronal generator of differences in processing between Lure CRs and Lure FAs. High-resolution fMRI studies (e.g., Bakker et al., 2012) have demonstrated reliable differences in activation associated with lures in sub-regions of the hippocampus. Differential processing between the two processes in the hippocampus may not be reflected in the cortical activity that tends to drive the ERP components under investigation (Herzmann, Jin, Cordes, & Curran, 2012). In an exploratory principal components analysis, we observed a single component that explained 9% of the variance associated with differences between trial outcomes peaking at 580ms and centered over an electrode in our left anterior cluster. As this component overlapped temporally and spatially with the FN400 it may indicate that the FN400 partially dissociates pattern separation and pattern completion processing. However, we note that this component only accounted for a small portion of the variance associated with the different trial outcomes.

Behavioral responses to similar lure stimuli in our mnemonic discrimination task are thought to reflect pattern separation (for Lure CRs) and pattern completion (for Lure FAs) processes. However, the ERP amplitude data indicate that both behavioral outcomes engaged pattern completion processes as both Lure CRs and Lure FAs were more similar to Hits than CRs. It may be the case that the ERP amplitudes reflected a "recall-to-reject" strategy on the part of the participants for all of the Lure stimuli. In this strategy, when a participant encounters a lure image, the previously encountered image must first be recalled. If the degree of dissimilarity between the two is high enough, the participant will reject the lure as being the same as the

previously viewed image and will encode the current image as "similar" (pattern separation). If the degree of dissimilarity fails to trigger pattern separation, pattern completion will be employed as the participant matches the current image with a previously encountered image, and would classify the image as "old." In this case, the bulk of the cognitive processing between the two cases would be the same, with only the very end triggering a difference, which may depend on medial temporal lobe structures, such as the hippocampus, and thus may not be obvious in scalp-level recordings (Bakker et al., 2008). We evaluated data between 0-1000 ms. As noted in Table 2.1, response times for items called "similar" or "old" were between 900-1100 ms. Accordingly, stimulus evaluation and response selection necessarily occur prior to this time window, i.e., within 1000ms.

Models of pattern separation and pattern completion propose that regions performing pattern separation respond to small changes in input similarity with large changes in output similarity in order to reduce representational overlap (e.g., Yassa and Stark, 2011). Regions performing pattern completion, on the other hand, respond to small changes in input by reducing the representational changes in output in order to facilitate retrieval based on noisy or incomplete inputs. To examine the ERP responses to changes in input, we normalized ERP amplitudes for CRs, Hits, and lures of varying similarity ratings to range from 0 (for Hits, which have the least degree of change in similarity from encoding to retrieval) to 1 (for CRs, which have the highest degree of change in similarity) (Figure 2.13). Within this framework, responses above the diagonal represent pattern separation, while responses below the diagonal represent pattern completion processes. As can be seen in Figure 2.13, ERP amplitudes in both the FN400 and LPC mainly fall below the diagonal, with a clearer pattern completion response in the LPC. As the neural generators for both the FN400 and the LPC are likely found in the cortex (Herzmann

et al., 2012), this finding is consistent with computational models that posit that the cortex is more biased toward pattern completion (Norman & O'Reilly, 2003).

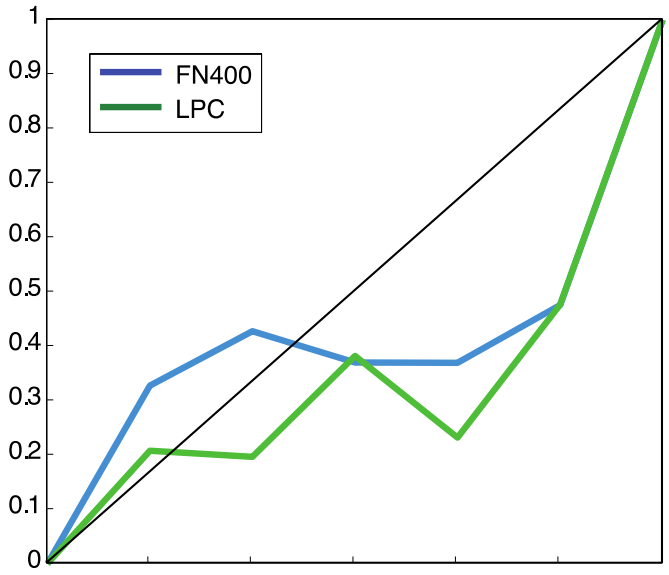

Figure 2.13: FN400 and LPC Model Pattern Completion.
A model of the transfer function represented by FN400 and LPC ERP amplitudes. Points falling above the diagonal correspond to pattern separation processes, while points falling below the diagonal correspond to pattern completion processes.

In a recent study employing similar stimuli and methods, Morcom (2015) observed an effect of true repeats relative to similar lures such that the parietal old-new effect was significantly greater for Hits than Lure CRs. The effect for Lure FAs was intermediate between Hits and Lure CRs and not statistically different from either. Analysis of individual performance indicated that better performance was correlated with a larger old-new effect for the Lure FA condition, but the correlation between behavioral performance and the old-new effect was weaker for the other conditions. As the parietal old-new effect was assumed to index recollection (see Curran and Rugg, 2007), the author interpreted these findings as indicating that participants do not rely primarily on a recall-to-reject strategy when considering similar lures in the mnemonic discrimination task. The recall-to-reject strategy suggests that when encountered with

a similar item, one first recalls competing representations and mentally compares the two. If they are not a match, the new item is rejected from being identified as the same of a previously encountered object. Our results are inconsistent with these findings in that we observe a strong old-new effect for both Lure FA and Lure CR conditions, consistent with a recall-to-reject strategy for both correct and incorrect responses to similar lure stimuli, at least initially. Additionally, we did not see any differences when individual performance was taken into account. Several differences in the behavioral paradigms between our study that of Morcom (2015) could be contributing factors to these incongruences. Morcom (2015) used a study-test design with an unspecified delay between the study and test phase, whereas we used a continuous recognition design, potentially resulting in differential neuronal processing. The duration of the stimuli presentation in the Morcom (2015) study was not reported so we are unable to determine if the timing of stimulus presentation may account for differences in our results. Further research (perhaps with greater spatial resolution) will be needed to determine what additional neural and cognitive processes allow participants to correctly distinguish similar lures from true repeats.

The principle components analysis revealed that Lure FAs and Lure CRs do contribute differentially to ERP components that appear to be memory related (i.e., exhibit an old/new effect). However, the nature of this contribution remains unclear as PCA factor scores for Lure CRs (pattern separation) are intermediate between those for Hits and CRs, similar to the ERP amplitudes. Removing the overt memory demands of the task as in the incidental version of the experiment did not help elucidate this point. To obtain a more robust comparison making ERPs a suitable method to evaluate pattern separation and pattern completion processing, we might have

to wait until technology develops or methods evolve that allow us to detect neuronal activity with a high temporal *and* spatial resolution.

In summary, participants performed a mnemonic discrimination task that places heavy demands on pattern separation and pattern completion processes. We did not observe reliable differences in the ERP characteristics (mean amplitudes) between behavioral conditions assumed to relate to these processes in the traditional analysis, but the exploratory analysis did reveal the ability of ERPs to detect a subtle difference. These data support the idea that participants engaged in a recall-to-reject strategy to evaluate similar lure stimuli, and that cortical structures involved in recognition memory performance are more biased toward pattern completion over pattern separation.

Limitations and Future Directions

Ideally, we would like to compare the Lure CRs to the Lure FAs within each of the five similarity bins. Due to a low trial number in each condition, this was not possible. In order to obtain these data, the task would have to be lengthened considerably. The task as is, takes about an hour to complete. Extending it longer would not only be taxing on participants, but it also increases the probability of electrode sponges drying out resulting in lost data. To prevent this, one possible option would be to use a gel-based system, which would circumvent the issue of sponges drying out. However, even with this alternative, it is likely that the task would have to be extended longer than what participants are able to complete while still maintaining a good level of engagement, making this option not very ideal. An alternative, and much more practical, option would be to reduce the similarity bins to just the highest, and lowest similarities only. Doing this would prevent the task from having to be extended to an unreasonable amount of time while still allowing for a differentiation of target-lure pairs based on similarity. There is a

possibility that differences in ERPs between Lure CRs and Lure FAs will emerge when they are broken down by the highest and lowest degree of similarity.

CHAPTER 3: The Effects of Rewards on Pattern Separation (Study 2)

Introduction Experiment 1

Extrinsic rewards contingent on memory performance can boost memory and learning (R. Alison Adcock, Arul Thangavel, Susan Whitfield-Gabrieli, Brian Knutson, & John D. E. Gabrieli, 2006; Delgado & Dickerson, 2012; Gruber & Otten, 2010; Shigemune et al., 2010; Thornton et al., 2007; Wickens & Simpson, 1968; Wolosin, Zeithamova, & Preston, 2012). Although the exact mechanism underlying the benefit to learning and memory is not currently understood, dopamine has been demonstrated to be essential in these processes, first in rodents (Brozoski, Brown, Rosvold, & Goldman, 1979; Murphy, Arnsten, Goldman-Rakic, & Roth, 1996; Packard & White, 1991), and more recently in humans (Alvarsson, Caudal, Bjorklund, & Svenningsson, 2016; Cools & D'Esposito, 2011; Papenberg et al., 2014; Soderqvist, Matsson, Peyrard-Janvid, Kere, & Klingberg, 2014). Rewards are thought to modulate memory performance via dopaminergic projections to the medial temporal lobe (MTL) (Lisman & Grace, 2005; Samson, Wu, Friedman, & Davis, 1990; Swanson, 1982). Anatomically, projections of dopamine neurons extend from the ventral tegmental area (VTA) directly to MTL regions such as the hippocampus, entorhinal cortex, and perirhinal cortex (Akil & Lewis, 1993; Amaral & Cowan, 1980; Lewis et al., 2001; Samson et al., 1990) which are recognized regions associated with learning and memory (E. Duzel, Vargha-Khadem, Heinze, & Mishkin, 2001; Hunsaker & Kesner, 2013; Kesner, 1991; Olton & Papas, 1979; E. T. Rolls, 1991; Larry R. Squire, 2004). The presence of dopamine in these regions results in a decreased threshold for long-term potentiation (LTP) (Frey, Huang, & Kandel, 1993; Huang & Kandel, 1995; Li, Cullen, Anwyl, & Rowan, 2003; Otmakhova & Lisman, 1996), which is believed to facilitate memory formation and retention.

Extrinsic rewards, such as money, have been shown to increase dopamine release in neurons innervating the hippocampal memory system (Emrah Duzel, Bunzeck, Guitart-Masip, & Duzel, 2010; Haber & Knutson, 2010; Lisman & Grace, 2005; Samson et al., 1990; Schultz, 2002; Shohamy, 2011; Shohamy & Adcock, 2010). An fMRI study by Wolosin et al. (2012) found reward-related activation changes during encoding in the specific hippocampal subregions of the dentate gyrus/CA3 and enhanced functional connectivity during encoding and retrieval between the dentate gyrus/CA3 and dopaminergic midbrain regions. The dentate gyrus and CA3 are regions strongly associated with pattern separation processing (Bakker et al., 2008; Leutgeb et al., 2007).

Several high-resolution functional magnetic resonance imaging (fMRI) studies in healthy younger adults have confirmed that the mnemonic discrimination paradigm designed by Kirwan and Stark (2007) involves CA3/dentate gyrus activation (Bakker et al., 2008; Bakker et al., 2012; Lacy et al., 2011; Yassa et al., 2010). However, none of the above experiments have examined the effects of reward or manipulations of attention on mnemonic discrimination performance.

Hypotheses Experiment 1

In a series of experiments, we use a modified version of the mnemonic discrimination task to evaluate how extrinsic rewards affect pattern separation. Participant rewards were either contingent on their memory performance or independent of performance. Given the previous literature demonstrating effects of performance-based rewards on memory performance (e.g., (Wolosin et al., 2012)), we hypothesized that in general, and specifically referring to pattern separation processes, performance-based rewards would boost behavioral performance to a greater degree than participation-based rewards. Additionally we hypothesized that the

mechanism by which this increased performance is accomplished is via increased attention to stimuli during time of encoding.

Methods Experiment 1

Participants

Participants were recruited from the university community and received both course credit and monetary compensation for participation. Individuals with a traumatic brain injury, a psychological disorder, a neurological disorder, left-handedness, colorblindness, or non-native English speakers were excluded from the study. The experiment was conducted as approved by the local Institutional Review Board protocol for research with human participants. Informed consent was obtained for a total of 65 participants. One participant was excluded for failure to comply with instructions and four were excluded due to technical malfunctions occurring during the task. Participants (final n=60; 26 females, average age = 21, SD = 2.18) were randomly assigned to either the Paid-for-Performance (n=30) or the Paid-for-Participation group (n=30).

Stimuli

Stimuli consisted of 360 target-lure pairs of everyday images. Each pair of images contained a target image and a lure image, which was similar in appearance to the target image. In a separate experiment, an independent group of thirty-five participants rated 976 target-lure pairs of everyday objects on a 7-point Likert scale, ranging from "very similar" to "not similar." The target-lure pairs with the highest similarity tax pattern separation process to a greater degree than pairs with lower similarity (Yassa & Stark, 2011). To evaluate the effects on pattern separation, the current study employed the 180 target-lure pairs with the highest similarity ratings and 180 target-lure pairs with the lowest similarity ratings (Figure 3.1).

Figure 3.1: Target-Lure Pairs.
Examples of low and high similarity target-lure pairs are shown here. Stimuli consisted of 360 target-lure pairs.

Phase-scrambled images of the 360 target-lure pairs were generated using custom MATLAB scripts (Figure 3.2). The scrambled images maintain the same spatial frequency and color information as the original images. These images were included in the task to serve as a baseline for a subsequent study but were disregarded for this analysis.

Figure 3.2: Object and Scramble Stimuli.
Examples of object similar with their corresponding scrambles are shown here.

Behavioral Procedures

The task consisted of a study phase and a test phase. The study phase was framed to participants in terms of a card selection task. On each trial of the study phase, participants were presented with two selection options and were informed they represented decks of cards.

Participants were instructed to choose a card from one of the decks and were informed that their choice would be rewarded according to the contingencies described below. The participants were informed that one of the decks was rewarded more often than the other and that they were to determine the more advantageous deck through trial and error. In reality, the order of the rewarded and non-rewarded cards was predetermined according to a pseudo-random order. Once participants made a deck selection, the selected card was then flipped over, revealing a picture of an everyday object outlined in either blue or pink (Figure 3.3). The outlined color signified whether the image was a rewarded or non-rewarded stimulus. The rewarded color (blue or pink) was randomly assigned and was counterbalanced within groups. Participants were instructed that a memory test phase would follow the study phase. The contingencies for reward were as follows: Participants in the Paid-for-Participation (Participation) group were informed they would be paid $0.10 for every object they drew from the deck that was outlined in the rewarded color regardless of their performance on the memory test. Images were only outlined with a color during the study phase, but not during the test phase. For images that were outlined in the non-rewarded color, no monetary reward was received. Participants in the Paid-for-Performance (Performance) group were informed they would be paid $0.10 for every object that was outlined in the rewarded color during the study phase if they correctly identified it on the subsequent memory test. For images outlined in the non-rewarded color, no monetary reward was received when the card was drawn or if the images were correctly identified on the memory test. In both conditions, images were only outlined with a color during the study phase, but not during the test phase.

Participants were instructed to make their deck selection within 1000 ms during the study phase. If no selection was made within 1000 ms, a screen with “No Response” was shown for

2000 ms, followed by a 500 ms inter-stimulus interval, then the program moved on to the next trial without revealing an image. If a selection was made in less then 1000 ms, a blank screen was shown for the remainder of the 1000 ms span, then the stimulus was shown for 2000 ms followed by a 500 ms inter-stimulus interval. The study phase consisted of five blocks with 84 trails in each block (420 total trials, 180 low-similarity images, 180 high-similarity images, and 60 scrambled images). Untimed breaks were allowed between each block. The stimulus-types (scrambles, low-similarity, high-similarity) were presented pseudo-randomly while the stimuli within the stimulus-type were presented randomly.

Immediately after the study phase, participants were given instructions for a recognition memory test. For the memory test, only images from the target-lure pairs viewed in the study phase were used. Images for trials in which the participant failed to select a card and subsequently were not shown an image for that trial, were not used. Images were shown one at a time and participants were asked to classify each image as either an image similar to one they previously saw by pressing "1," or as an exact repeat of an image they saw during the study phase by pressing "2." Images were displayed for 2000 ms followed by a 500 ms inter-stimulus interval. All responses had to be made while the image was on the screen. Half of the low-similarity and half of the high-similarity images were shown as exact repeats while the other half were presented as lures. Participants were paid at the end of the test phase, with the amount of compensation depending on group assignment and performance.

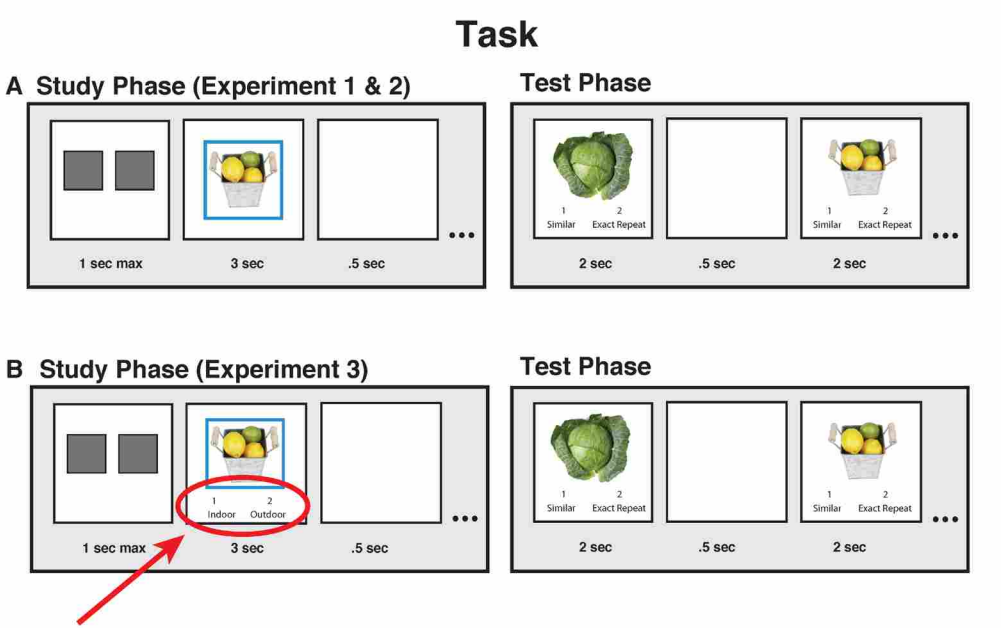

Figure 3.3: Task Design.
The behavioral task consisted of a study phase and a test phase. In the study phase, participants were presented with two decks of cards, the card they selected reveled a picture outlined in either blue or pink, which signaled a rewarded or non-rewarded trial. The test phase immediately followed the study phase. A) In Experiment 1, rewarded and non-rewarded stimuli were pseudorandomly interspersed in each block whilst in Experiment 2, rewarded and non-rewarded trials were grouped into blocks rather than being interspersed within a block. B) Experiment 3 replicated the pseudorandom order of Experiment 1 with the addition of an attention orienting task on the encoding slide during the study phase that asked the participant to classify each object as one used typically outdoors or indoors.

Participants in both groups could receive up to a total of $18. The final reward amount was rounded up to the nearest dollar. For participants in the Participation group, the total accumulated monetary rewards earned up to that point, was presented on the screen at the end of each block of the study phase. For participants in the Performance group, the total accumulated monetary rewards were presented on the screen at the end of each block of the test phase.

Results Experiment 1

Trials were sorted according to stimulus type (repeat or lure), behavioral response ("similar" or "exact repeat"), and reward type (rewarded or non-rewarded) for each similarity bin

(low similarity or high similarity) in each group (Performance or Participation). The proportion of correct responses and standard deviations for each condition are reported in Table 3.1.

Table 3.1: Experiment 1 – Proportion of Behavioral Responses (STDEV).
The proportion of behavioral responses for each trial type in Experiment 1. Target-lure pairs were classified as either high or low similarity.

	Response	Similar				Repeat				No Response			
	Stimulus Type	Repeat	Lure	Repeat	Lure	Repeat	Lure	Repeat	Lure	Repeat	Lure	Repeat	Lure
	Reward Type	Rewarded		Not Rewarded		Rewarded		Not Rewarded		Rewarded		Not Rewarded	
Low Similarity	Performance	0.3 (0.15)	0.8 (0.11)	0.3 (0.1)	0.81 (0.08)	0.7 (0.15)	0.19 (0.11)	0.7 (0.1)	0.18 (0.08)	0 (0.01)	0.01 (0.01)	0 (0.01)	0.01 (0.01)
	Participation	0.39 (0.16)	0.77 (0.12)	0.38 (0.17)	0.75 (0.11)	0.6 (0.17)	0.21 (0.11)	0.61 (0.17)	0.23 (0.11)	0.01 (0.04)	0.02 (0.05)	0.01 (0.03)	0.02 (0.03)
High Similarity	Performance	0.38 (0.13)	0.49 (0.11)	0.39 (0.13)	0.48 (0.11)	0.61 (0.13)	0.5 (0.11)	0.61 (0.13)	0.51 (0.11)	0 (0.01)	0.01 (0.02)	0 (0.01)	0.01 (0.01)
	Participation	0.48 (0.15)	0.55 (0.15)	0.47 (0.15)	0.54 (0.12)	0.51 (0.16)	0.43 (0.16)	0.51 (0.16)	0.44 (0.14)	0.01 (0.03)	0.02 (0.04)	0.02 (0.05)	0.02 (0.04)

To evaluate behavioral performance, we calculated discriminability scores (d′). The discriminability score provides a way to evaluate sensitivity in target-lure discrimination while simultaneously accounting for response bias. Larger d′ values represent enhanced ability to distinguish between target-lure pairs. To evaluate the pattern separation processes underlying behavioral performance we first separated the stimuli based on similarity ratings, then we compared d′ scores in rewarded vs. non-rewarded low-similarity stimuli to rewarded vs. non-rewarded high-similarity stimuli. High-similarity stimuli have more overlapping features resulting in a greater taxation of pattern separation processes relative to the low-similarity stimuli, which are more distinct. Consequently, if pattern separation processes are affected by extrinsic rewards, we expect to see a greater difference between the rewarded vs. non-rewarded trials in the high similarity stimuli then we do in the rewarded vs. non-rewarded trials in the low similarity stimuli (Figure 3.4).

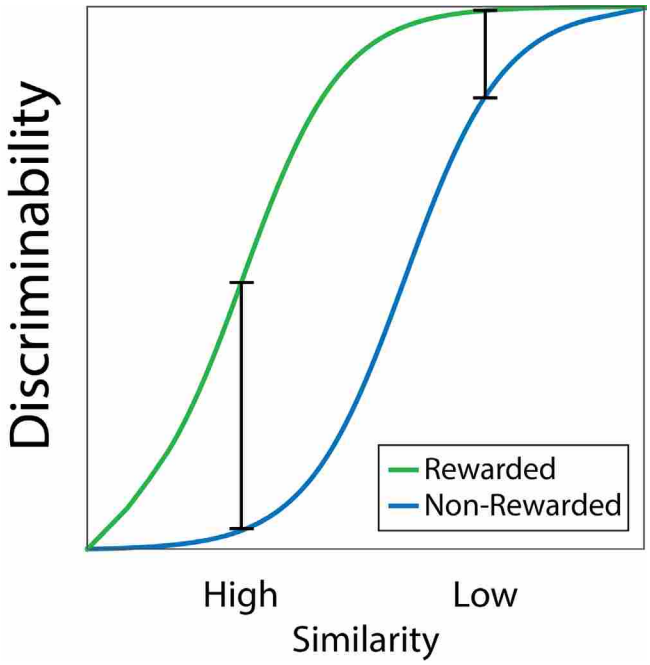

Figure 3.4: Calculating Pattern Separation.
We hypothesize extrinsic rewards will shift the d´ curve to the left, resulting in greater differences between the rewarded and non-rewarded trials in the high similarity stimuli then in the rewarded vs. non-rewarded trials in the low similarity stimuli.

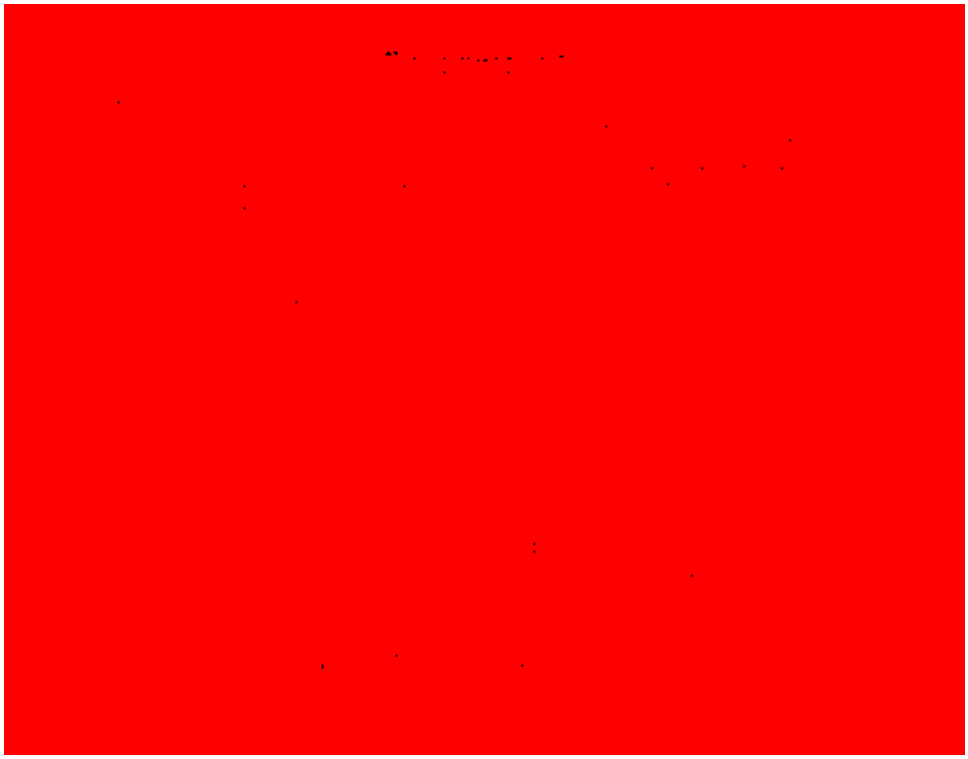

Figure 3.5: Behavioral Performance for Experiment 1.
Averaged discriminability (d′) scores are shown for Experiment 1. Trial types are separated by low- similarity and high-similarity, as well as rewarded and non-rewarded trials. Participants were either part of the Performance or the Participation group. * = $p < .05$

Experiment 1 d′ scores for each condition and trial type are shown in Figure 3.5. A 2 (Reward Condition: reward vs. non-reward) × 2 (Similarity: high vs. low) × 2 (Group: Participation vs. Performance) repeated-measures analysis of variance (ANOVA) revealed a significant main effect of Group ($F(1,58) = 6.09$, $p = 0.02$), and Similarity ($F(1,58) = 316.04$, $p < 0.00$), as well as a Group × Similarity interaction ($F(1,58) = 6.11$, $p = 0.02$). Post-hoc t-tests indicated that participants in the Performance group showed better discrimination than the Participation group in the low similarity condition (reward: $t(58) = 2.35$, $p = 0.02$; non-reward: $t(58) = 2.73$, $p = 0.01$). There was no main effect of Reward Condition ($F(1,58) = 0.44$, $p = 0.51$) and no three-way interaction ($F(1,58) = 0.17$, $p = 0.68$).

Discussion Experiment 1

We manipulated the contingencies of rewards in order to determine if rewards have an effect on pattern separation processing. Whilst participants in the Performance group had enhanced mnemonic discrimination in the low-similarity condition, this enhancement did not carry over into the high-similarity condition where pattern separation demands are highest. Thus, we cannot conclude that reward enchanted pattern separation processing. Further, the enhanced performance in the low-similarity condition was present for both rewarded and non-rewarded trials for the Performance group. As previous studies have shown significant reward effect on memory performance (R. A. Adcock, A. Thangavel, S. Whitfield-Gabrieli, B. Knutson, & J. D. E. Gabrieli, 2006; Gruber & Otten, 2010; Lisman & Grace, 2005; Shigemune et al., 2010; Swanson, 1982; Thornton et al., 2007; Wickens & Simpson, 1968; Wolosin et al., 2012) in conditions similar to our Paid-for-Performance condition, we hypothesized that interference from large number of stimuli to be remembered (360) may have caused participants to adopt a strategy of remembering all stimuli rather than just those that would be rewarded. That is, rather then trying to differentiate between rewarded and non-rewarded trial types *and* focus on remembering only the rewarded trials, we hypothesized that participants in the Performance condition strategized to maximize their rewards by preforming their best on all trial types (rewarded and non-rewarded) to ensure they would do well on all the rewarded trials. To test this hypothesis, we conducted a follow-up experiment in which rewarded and non-rewarded stimuli were presented in blocks and the overall number of stimuli were reduced.

Introduction Experiment 2

In Experiment 2 (63.3A) rewarded trials were clustered together (2 blocks) and all non-rewarded trials were clustered together (2 blocks). Additionally, the number of trails were

reduced from 360 to 288, subsequently reducing the maximum possible earnings to $15. The objective of Experiment 2 was to evaluate whether clustering the rewarded trials from the non-rewarded trials and reducing the number of total trials would produce a difference in behavioral performance between rewarded and non-rewarded trials, which was not observed in Experiment 1.

Hypothesis Experiment 2

We hypothesize that clustering the trials into blocks that solely contain either rewarded trials or non-rewarded trials will result in behavioral performance differences between the rewarded and non-rewarded trials. We also hypothesize that if rewards affect pattern separation processes, they differences will emerge as performance varies between rewarded and non-rewarded trials.

Methods Experiment 2

Participants

Participants were selected using the same criteria as in Experiment 1. A total of 64 individuals participated. Data from 4 participants were excluded due to failure to comply with instructions (final n=60; 31 females, average age = 21.8, SD = 2.90).

Stimuli

The stimuli used in Experiment 2 were the same 360 target-lure pairs used in Experiment 1. No scrambled images were used in this experiment.

Behavioral Procedures

The task was similar to Experiment 1 (Figure 3.3A), with the exception that in this experiment there were 4 blocks of 72 images each (288 total images; 144 low-similarity and 144 high-similarity). Rather than reward and non-rewarded trials being intermixed throughout a block, each block was restricted to all rewarded trials or all non-rewarded trials and rewarded/non-rewarded blocks alternated. The order was counterbalanced within groups

Results Experiment 2

The proportion of correct responses and standard deviations for each condition are reported in Table 3.2.

Table 3.2: Experiment 2 – Proportion of Behavioral Responses (STDEV).
The proportion of behavioral responses for each trial type in Experiment 2. Target-lure pairs were classified as either high or low similarity.

	Response	Similar				Repeat				No Response			
	Stimulus Type	Repeat	Lure	Repeat	Lure	Repeat	Lure	Repeat	Lure	Repeat	Lure	Repeat	Lure
	Reward Type	Rewarded		Not Rewarded		Rewarded		Not Rewarded		Rewarded		Not Rewarded	
Low Similarity	Performance	0.47 (0.29)	0.61 (0.26)	0.61 (0.27)	0.82 (0.11)	0.51 (0.29)	0.35 (0.25)	0.35 (0.26)	0.1 (0.13)	0.01 (0.02)	0.04 (0.15)	0.04 (0.17)	0.01 (0.02)
	Participation	0.22 (0.15)	0.79 (0.1)	0.25 (0.15)	0.83 (0.11)	0.76 (0.15)	0.19 (0.1)	0.74 (0.15)	0.16 (0.11)	0.01 (0.02)	0.01 (0.03)	0.01 (0.01)	0.01 (0.02)
High Similarity	Performance	0.3 (0.16)	0.39 (0.21)	0.51 (0.22)	0.69 (0.18)	0.69 (0.15)	0.58 (0.22)	0.46 (0.21)	0.19 (0.22)	0.01 (0.02)	0.03 (0.12)	0.03 (0.11)	0.02 (0.03)
	Participation	0.27 (0.15)	0.47 (0.13)	0.3 (0.17)	0.46 (0.13)	0.72 (0.15)	0.51 (0.13)	0.69 (0.16)	0.53 (0.14)	0.01 (0.02)	0.02 (0.03)	0.01 (0.02)	0.01 (0.02)

As with Experiment 1, d′ scores were used to evaluate behavioral performance (Figure 3.6). A 2 (Reward Condition: reward vs. non-reward) × 2 (Similarity: high vs. low) × 2 (Group: Participation vs. Performance) ANOVA revealed a significant Reward Condition × Similarity × Group interaction ($F(1,58) = 19.90$ $p < 0.001$) as well as a main effect of Similarity ($F(1,58) = 314.89$, $p < 0.001$), a main effect of Reward ($F(1,58) = 10.692$, $p = 0.02$), and a Group × Reward interaction ($F(1,58) = 7.00$, $p = 0.01$). Consistent with previous studies, post-hoc t-tests revealed significantly better discrimination scores for rewarded than non-rewarded stimuli in the Performance low-similarity group ($t(1,29) = 2.12$, $p = 0.04$). Thus, clustering the rewarded and non-rewarded stimuli resulted in significantly different discriminability performance between rewarded conditions, supporting our hypothesis. Further, blocking the rewarded and non-rewarded trials resulted in better discriminability for the rewarded than for the non-rewarded stimuli in the Participation high-similarity group ($t(1,29) = 4.93$, $p < 0.001$), indicating increased pattern separation processing at the time of encoding in the context of sustained reward for the Participation group.

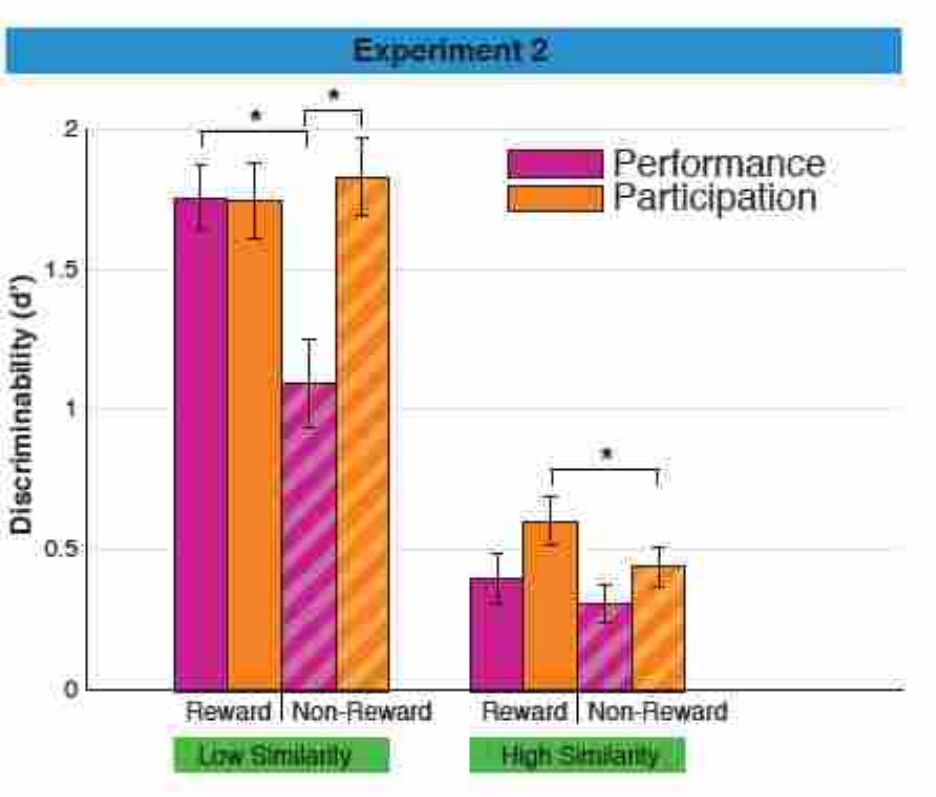

Figure 3.6: Behavioral Performance for Experiment 2.
Averaged discriminability (d´) scores are shown for Experiment 2. Trial types are separated by low- similarity and high-similarity, as well as rewarded and non-rewarded trials. Participants were either part of the Performance or the Participation group. * = $p < .05$

Discussion Experiment 2

We attribute the differential performance seen in rewarded vs. non-rewarded conditions in Experiment 2 to the clustering of rewarded trials into blocks making it easier to distinguish between rewarded and non-rewarded trials. Furthermore, separating the rewarded from the non-reward trials may have affected a putative sustained dopamine response in the rewarded blocks (see General Discussion). By blocking the rewards, increases in pattern separation performance are seen in the Participation group. This is contrary to our hypothesis that pattern separation performance would increase for the Performance group. We hypothesize the reason for this is because the Participation group is receiving the rewards during the encoding phase when the

stimuli are being presented whereas the Performance group receives these awards during the recall phase. Pattern separation is a encoding dependent processes, therefore, it makes sense that rewards eliciting a dopamine response (potentially up regulating long-term potentiation) during the encoding phase, would boost encoding dependent processes such as pattern separation.

A remaining question, however, is whether the difference in behavioral performance between the rewarded and non-rewarded conditions in the Performance condition was due to rewards increasing participants' motivation to remember the rewarded stimuli, resulting in increased attention during encoding. To test this hypothesis, we conducted a third experiment that mirrored Experiment 1 with only one minor change meant to control for any differences in attentional processes during encoding.

Introduction Experiment 3

In the study phase of Experiment 3, participants were instructed to indicate if each object is used typically indoors or outdoors (Figure 3.3B). Thus participants were required to attend to both rewarded and non-rewarded stimuli equally in the encoding phase. The purpose of this experiment was to determine whether or not rewards improved behavioral performance by increasing motivation to encode the stimuli and thereby attentional processing during the study phase.

Hypothesis Experiment 3

We hypothesize that the differences previously seen between the performance and participation groups, as well as the differences seen between the rewarded and non-rewarded trials, will diminish significantly or even vanish altogether, when attention is controlled for.

Methods Experiment 3

Participants

Participants were recruited using the same criteria as in Experiment 1. A total of 71 individuals participated. Data from 6 participants were discarded due to computer errors during the task and 5 were excluded due to participants failing to comply with instructions (final n=60; 34 females, average age = 21.3, SD = 3.63).

Stimuli

The stimuli used in Experiment 3 were the same 360 target-lure pairs used in Experiment 1. No scrambled images were used in this experiment.

Behavioral Procedures

The task was the same as Experiment 1 with only one difference. In Experiment 3, instead of just viewing the image revealed after deck selection, participants were asked to classify each object as either an object that is typically used indoors by pressing "1", or an object that is typically used outdoors by pressing "2." The choice options were printed on the screen and the participants were required to respond while the images were being presented. This addition was used to ensure that both participants in the Performance and Participation groups devoted equal attentional processing during stimulus encoding. Behavioral responses to the indoor/outdoor classification were used to determine which study trials would be used during the test phase but otherwise were not analyzed. For the test phase, only images with an encoding response made during the study phase were used.

Results Experiment 3

The proportion of responses and standard deviations for each condition are reported in Table 3.3. As with Experiment 1, d´ scores were used to evaluate behavioral performance (Figure 3.7). A 2 (Reward Condition: reward vs. non-reward) × 2 (Similarity: high vs. low) × 2 (Group: Participation vs. Performance) ANOVA revealed no significant three-way interaction ($F(1,58) = 0.96$ $p = 0.33$) indicating that discrimination did not improve differentially in any of the groups. This is consistent with the results of Experiment 1, where there was no significant behavioral difference between rewarded and non-rewarded trials. However, the main effect of Group ($F(1,58) = 0.50$, $p = 0.48$) and the Group × Similarity interaction ($F(1,58) = 0.01$, $p = 0.91$) seen in Experiment 1 now failed to reach significance when attentional processes during encoding are controlled. Consistent with the previous two experiments, there was a main effect of similarity ($F(1,58) = 58.00$, $p < 0.001$).

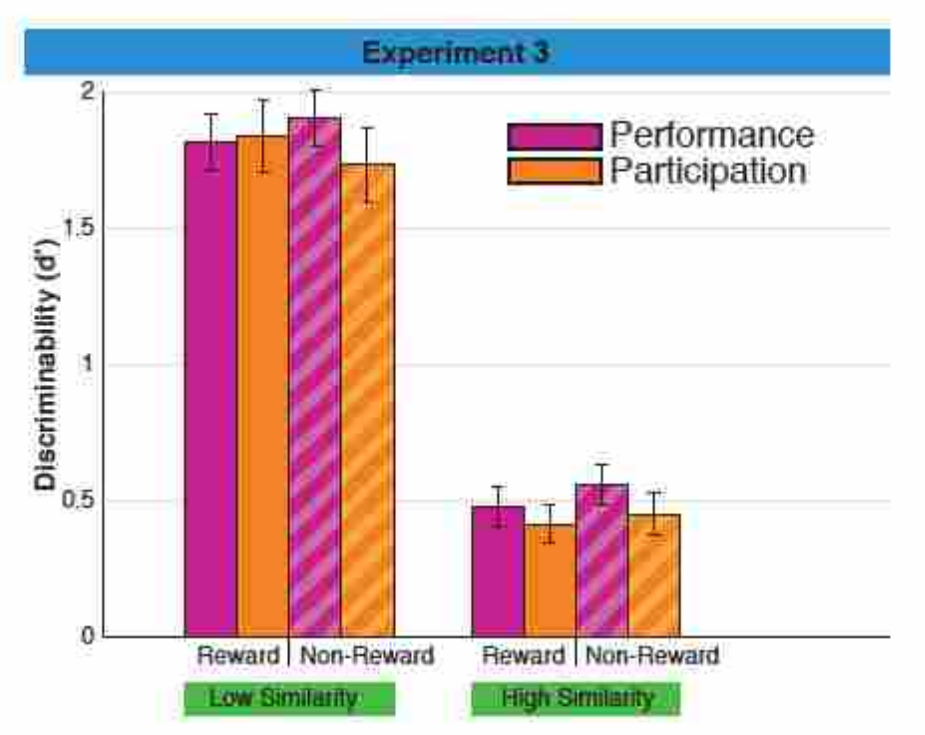

Figure 3.7: Behavioral Performance for Experiment 3.
Averaged discriminability (d´) scores are shown for Experiment 3. Trial types are separated by low-similarity and high-similarity, as well as rewarded and non-rewarded trials. Participants were either part of the Performance or the Participation group.

Table 3.3: Experiment 3 – Proportion of Behavioral Responses (STDEV).
The proportion of behavioral responses for each trial type in Experiment 3. Target-lure pairs were classified as either high or low similarity.

	Response	Similar				Repeat				No Response			
	Stimulus Type	Repeat	Lure	Repeat	Lure	Repeat	Lure	Repeat	Lure	Repeat	Lure	Repeat	Lure
	Reward Type	Rewarded		Not Rewarded		Rewarded		Not Rewarded		Rewarded		Not Rewarded	
Low Similarity	**Performance**	0.19 (0.09)	0.79 (0.1)	0.17 (0.09)	0.78 (0.11)	0.8 (0.09)	0.2 (0.09)	0.83 (0.09)	0.2 (0.11)	0.01 (0.02)	0.01 (0.02)	0.01 (0.01)	0.01 (0.02)
	Participation	0.21 (0.11)	0.8 (0.09)	0.22 (0.11)	0.78 (0.11)	0.79 (0.12)	0.19 (0.09)	0.78 (0.11)	0.21 (0.11)	0.01 (0.01)	0.01 (0.02)	0.01 (0.01)	0.01 (0.02)
High Similarity	**Performance**	0.23 (0.1)	0.38 (0.12)	0.24 (0.11)	0.42 (0.14)	0.76 (0.1)	0.61 (0.11)	0.76 (0.11)	0.57 (0.14)	0 (0.01)	0.01 (0.02)	0.01 (0.02)	0.02 (0.03)
	Participation	0.26 (0.1)	0.4 (0.12)	0.23 (0.11)	0.38 (0.1)	0.73 (0.1)	0.59 (0.12)	0.76 (0.11)	0.62 (0.1)	0.01 (0.01)	0.01 (0.02)	0.01 (0.01)	0.01 (0.01)

Discussion Experiment 3

In Experiment 1, we observed a main effect of reward group, with better performance for both high- and low-similarity stimuli in the Performance group compared to the Participation group. We hypothesized that this may have been due to the Performance group devoting more attentional resources at time of encoding than the Participation group in Experiment 1. In Experiment 3, we used an orienting task to control the amount of attentional processing between the two groups. The data from this experiment confirm the hypothesis that attentional differences explained the differential group effects observed in Experiment 1.

Comparison of Three Experiments

Although the tasks are slightly different between the three experiments, we wanted to get an idea of how behavioral performance compared to one another. To compare the behavioral performance between the three Experiments (Figure 3.8), we conducted a 2 (Group: Participation vs. Performance) × 2 (Reward Condition: reward vs. non-reward) × 2 (Similarity: high vs. low) × 3 (Experiment: 1 vs. 2 vs. 3) ANOVA which revealed a significant main effect of Experiment ($F(2,87) = 10.564$ $p < 0.001$). Further t-tests (Table 3.4) reveal both blocked rewards (Experiment 2) and encoding (Experiment 3), produced better performance compared to the unblocked rewards. However, the behavioral performance for the blocked rewards and the encoding version were comparable. The fact that the encoding task did not produce significantly better behavioral performance in participants compared to the blocked rewards, supports the idea that blocked rewards increase performance via increasing attention.

Table 3.4: Comparisons of Behavioral Performance Between Experiments.
Behavioral performance between for each trial type compared between Experiments. Green cells represent significance, $p < .05$.

			Regular vs. Blocked		Regular vs. Encode		Encode vs. Blocked	
			Exp 1 vs Exp 2		Exp 1 vs Exp 3		Exp 2 vs Exp 3	
Trial Type		**Group**	**t**	***p* value**	**t**	***p* value**	**t**	***p* value**
Low Similarity	**Rewarded**	**Perf**	-1.683	0.098	-2.243	0.029	0.359	0.721
		Part	-3.414	0.001	-3.999	<0.000	0.476	0.636
	Non Rewarded	**Perf**	2.184	0.033	-3.135	0.003	4.281	<0.000
		Part	-4.06	<0.000	-3.571	0.001	-0.507	0.614
High Similarity	**Rewarded**	**Perf**	-0.904	0.37	-1.773	0.082	0.619	0.539
		Part	-4.01	<0.000	-2.288	0.026	-1.794	0.078
	Non Rewarded	**Perf**	-0.515	0.608	-2.949	0.005	2.444	0.018
		Part	-2.67	0.01	-2.644	0.011	0.034	0.973

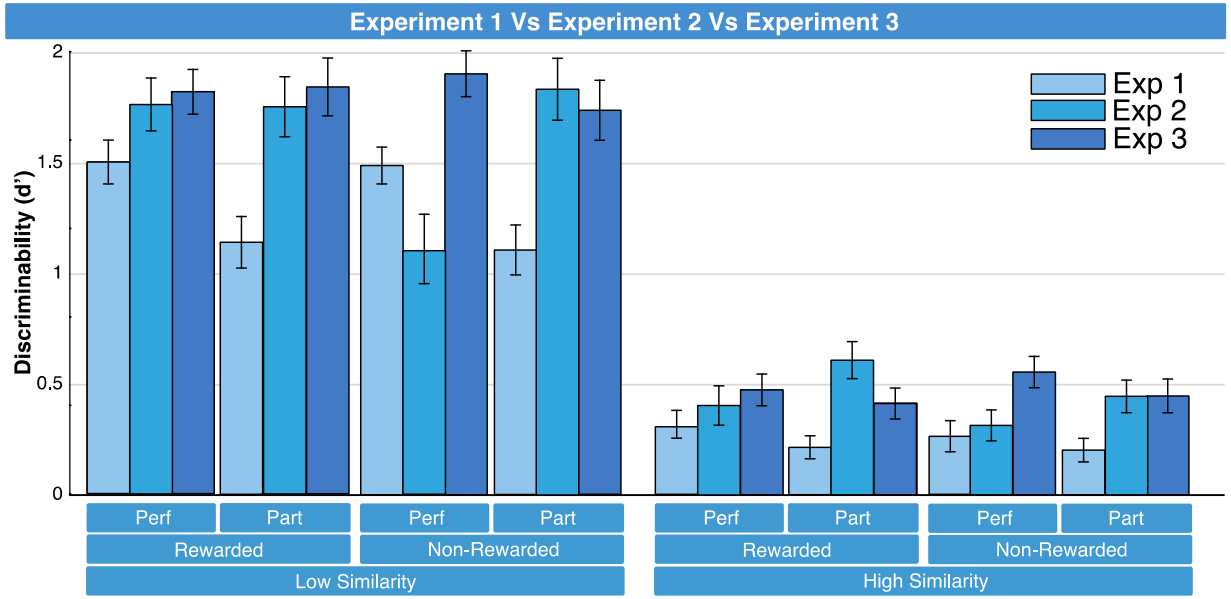

Figure 3.8: Comparison of d´ Scores Between the Three Experiments.
Averaged d´ scores from each of the three Experiments

General Discussion Study 2

In this study we set out to evaluate the effects of extrinsic rewards on mnemonic discrimination in a task that taxes pattern separation processing. Consistent with our hypotheses, rewards enhanced mnemonic discrimination, consistent with increased pattern separation processes. However, contrary to our hypothesis, this was seen only in the Participation group when stimuli were encoded in the context of a block of rewards (i.e., in Experiment 2). This group received extrinsic rewards when a rewarded image was displayed, meaning the rewards were received during the encoding phase. As pattern separation processes are viewed as encoding dependent processes (Hunsaker & Kesner, 2013; Lee & Kesner, 2004), presenting rewards during the encoding phase may explain the increased mnemonic discrimination performance seen in the Participation group relative to the Performance group. The Performance group on the other hand received a reward upon correctly identifying a rewarded stimulus on the memory test. These data suggest that rewards given during encoding may boost encoding dependent processes, such as pattern separation. However, when the rewards are given during retrieval, pattern separation processes remain unaffected.

We propose that the improvement observed in mnemonic discrimination is likely mediated via dopamine interactions during encoding. Previous studies have demonstrated increased dopamine release in medial temporal regions (MTL) for rewarded trials relative to non-rewarded trials resulting in increased memory performance (Emrah Duzel et al., 2010; Wittmann et al., 2005; Wolosin et al., 2012). When rewarded and non-rewarded trials were interspersed within a block as in Experiment 1, we did not observe an effect of reward. One possible explanation for this failure to differentiate rewarded and non-rewarded stimuli is that non-rewarded stimuli, when interspersed with rewarded stimuli, can elicit a dopamine response. In a study conducted by Kobayashi and Schultz (Kobayashi & Schultz, 2014), electrophysiology

was used to demonstrate dopamine activations occurred in non-rewarded trials when presented in the context of a rewarded environment. According to Mather and Schoeke (Mather & Schoeke, 2011), reward anticipation, in addition to the actual rewards, can improve memory recall and recognition. When the rewarded trials are mixed with the non-rewarded trials, the reward anticipation can thus affect behavioral performance on non-rewarded trials whereas this is less likely to occur when non-rewarded trials are blocked together and separate from rewarded trials. Kobayashi and Schultz (Kobayashi & Schultz, 2014) further show that these neuronal dopamine activations are reduced in a graded fashion as the rewarded and non-rewarded stimuli are increasingly separated. Our data support these findings as we observed no discriminability differences between rewarded and non-rewarded trials when they were interspersed within blocks (Experiment 1), but when trials were separated into blocks consisting of entirely rewarded or entirely non-rewarded trials (Experiment 2), we observed increased discriminability in rewarded trials only.

In addition to the effects of rewards on mnemonic discrimination, we also set out to evaluate how overall recognition memory performance was affected by rewards. Numerous studies have shown that rewards increase memory performance (R. A. Adcock et al., 2006; Gruber & Otten, 2010; Lisman & Grace, 2005; Shigemune et al., 2010; Thornton et al., 2007; Wickens & Simpson, 1968; Wolosin et al., 2012) however, these studies fail to address whether or not the rewards must be contingent on performance in order to elicit a boost in memory. We hypothesized that performance-based rewards would boost behavioral performance to a greater degree then non-performance-based (participation-based) rewards. Additionally we hypothesized that the mechanism by which this increased performance is accomplished is via increase attention to stimuli during time of encoding.

In Experiment 1, although no differences were seen between the rewarded and the non-rewarded trials, the Performance group demonstrated significantly better overall performance then the Participation group, suggesting performance-based rewards drive behavioral performance to a greater degree then participation-based rewards. When we controlled for attentional processing at encoding, as in Experiment 3, the group differences in behavioral performance were no longer produced, nor were there differences in rewarded versus non-rewarded trials. Taken together, this suggests that the promise of extrinsic rewards motivates participants to pay more attention during encoding, subsequently resulting in increased recognition memory performance.

Several studies have suggested that the increased behavioral performance in rewarded trials resulted from a mechanism in which the participants mentally rehearsed the items (Tarpy & Glucksberg, 1966; Wickens & Simpson, 1968). While we cannot rule out a rehearsal mechanism, our data strongly demonstrate increased behavioral performance results from attentional processing during encoding, as the promise of extrinsic rewards may have caused the Performance group to attend more to stimuli than the Participation group during encoding in Experiment 1. In support of this interpretation, when we controlled for attentional processing at encoding in Experiment 3, The group differences in behavioral performance were no longer observed, nor were there differences in rewarded versus non-rewarded trials. Thus, consistent with our hypothesis, the boost in overall recognition memory performance does not appear to be a direct result of rewards, but rather an indirect effect that acts via increasing attention during encoding.

In summary, we show that rewards received during the encoding phase boost encoding dependent processes such as pattern separation only when rewarded trials are clustered together.

We also show that the increased behavioral performance resulting from performance-based rewards is driven by an increased attentional processes during encoding.

Limitations and Future Directions

In the current study we see increased performance in Experiment 2, when the rewards are blocked rewards, and in Experiment 3, when the encoding task is added to all stimuli. We would like to combine these into one experiment that contains blocked rewards and the encoding task and see if performance on this version is significantly better than performance on the task in Experiment 2 or Experiment 3.

Additionally, there is a significant amount of literature that reports enhanced effects of rewards on memory after consolidation (Atherton, Dupret, & Mellor, 2015; Miendlarzewska, Bavelier, & Schwartz, 2016; Kou Murayama & Kitagami, 2014; K. Murayama & Kuhbandner, 2011; Nielson & Bryant, 2005). Some of these studies failed to observe differences in memory performance on immediate memory tests, but did see performance differences when the memory test was administered after a significant delay. We would like to run the blocked rewards version and the encoding version with a greater delay between the study and test phase to allow for consolidation processes to occur.

We would also like to examine neuronal activity in addition to behavioral performance by using fMRI employing whole brain coverage. Using fMRI analysis, we would like to examine activity in the hippocampus, ventral tegmental area, and striatum to evaluate the activity in areas of the brain associated with memory and the dopamine reward system as well as the areas associated with pattern separation processes.

CHAPTER 4: Discussion

Our current understanding of the brain has allowed us to identify and associate specific functions with specific brain regions. It is widely accepted that the hippocampus and medial temporal lobe are imperative for learning and memory, specifically for pattern separation processing. Accordingly, much of the research on pattern separation has focused exclusively on the hippocampus and medial temporal lobe. However, it is also widely accepted that brain regions are highly interconnected with each other and do not function independently from one another. To better understand and appreciate the complex processing of the brain, we need to evaluate surrounding brain structures and better understand how multiple regions interact and influence processing functions.

The two studies presented here show clear evidence that behavioral outcomes resulting from hippocampal-dependent pattern separation processing are influenced by extra-hippocampal processes. Currently, it is well accepted that the hippocampus encodes unique neuronal representations for images, even when behaviorally, those images are classified as "old" rather than similar, while the cortex engages in pattern completion processes. While these two processes occur simultaneously in different locations, it remains unclear how the behavioral result of one processing event wins out over the other. EEG data presented here suggest the differential processing occurs deeper than the cortical level. The current EEG technology and ERP analysis are not able to detect differences at the cortical level. However, further advances in technology may allow us to detect these changes. Additionally, more sensitive methods of analysis may also allow us to detect differences that currently aren't visible.

Behavioral data suggests rewards can assist one in boosting behavioral memory accuracy. It is likely that the mechanism through which this is accomplished is through increasing

intentional processing. Thus, dopamine release alone does not appear to significantly increase memory performance. Rather, it is the processing effect that results from dopamine (via additional attention processes) that influences pattern separation processes. These two studies just scratch the surface of how extra-hippocampal processes affect hippocampal dependent processes, such as pattern separation. Much more research is needed to delve deeper into uncovering the interactions these extra-hippocampal processes have on pattern separation before we begin to understand the extent and limitation of these influences.

Our current understanding of the pattern separation process is that the hippocampus does encode differences between two similar memory representations, but whether or not those differences rise to the level of conscious awareness could be mediated by extra-hippocampal processing via attentional processing. It is highly likely that other processes are involved as well. Hopefully, further research will be able to answer questions such as: What exactly are the processes that cause a person to identify two different episodes as the same even though the hippocampus has generated a unique neuronal representation for each one? What is the threshold of similarity between two representations that is required to result in the hippocampus encoding a unique neuronal code versus the same neuronal code for each representation? Is it possible for us to increase our conscious ability to differentiate between two similar representations by altering the extra-hippocampal processing? Finally, and perhaps most exciting, is that even if we are not able to alter the processing that allows us to consciously differentiate between two similar memory representations, will we one day develop the technology and methods to be able to evaluate neurological signals to assess whether the conscious classification is in accordance with the neurological processing? There is still a plethora of knowledge regarding the mechanism and

inner workings of the brain that we currently do not understand. Elucidation of these unknowns may possibly open a world of knowledge and opportunity.

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APPENDIX

Table A.1: ANOVA Comparisons by Block
ANVOA comparisons between each of the 8 blocks in the EEG mnemonic discrimination task for each of the trial types.

	F	**df**	***p***
CR	1.252	7, 301	.274
Hits	4.862	7, 301	< .0001
Lure CR	2.635	7, 301	.012
Lure FA	11.843	7, 301	< .0001

Table A.2: T-test Comparisons by Block
T-test comparisons between each of the 8 blocks in the EEG mnemonic discrimination task for Hits, Lure CRs, and Lure FAs.

	Hits			Lure CR			Lure FA		
	t	df	p	t	df	p	t	df	p
Block1 - Block2	0.946	49	0.349	-3.285	49	0.002	3.848	49	< .0001
Block1 - Block3	-0.418	49	0.677	-3.298	49	0.002	4.654	49	< .0001
Block1 - Block4	2.418	48	0.019	-3.688	48	0.001	5.819	48	< .0001
Block1 - Block5	2.41	47	0.02	-2.373	47	0.022	4.85	47	< .0001
Block1 - Block6	3.05	47	0.004	-1.975	47	0.054	5.092	47	< .0001
Block1 - Block7	2.523	46	0.015	-2.15	46	0.037	5.594	46	< .0001
Block1 - Block8	3.486	44	0.001	-2.912	44	0.006	6.756	44	< .0001
Block2 - Block3	-1.765	49	0.084	-0.349	49	0.729	1.299	49	0.2
Block2 - Block4	1.618	48	0.112	-0.565	48	0.575	2.149	48	0.037
Block2 - Block5	1.475	47	0.147	0.109	47	0.913	2.061	47	0.045
Block2 - Block6	2.415	47	0.02	0.312	47	0.757	2.552	47	0.014
Block2 - Block7	1.477	46	0.147	-0.022	46	0.983	3.318	46	0.002
Block2 - Block8	2.346	44	0.024	-0.606	44	0.548	3.605	44	0.001
Block3 - Block4	3.333	48	0.002	-0.287	48	0.775	1.074	48	0.288
Block3 - Block5	3.85	47	< .0001	0.387	47	0.701	1.144	47	0.258
Block3 - Block6	4.175	47	< .0001	0.838	47	0.406	1.454	47	0.153
Block3 - Block7	3.445	46	0.001	0.567	46	0.573	1.902	46	0.063
Block3 - Block8	3.888	44	< .0001	0.012	44	0.991	2.129	44	0.039
Block4 - Block5	0.139	47	0.89	0.652	47	0.518	0.274	47	0.785
Block4 - Block6	1.081	46	0.285	0.919	46	0.363	0.795	46	0.431
Block4 - Block7	0.597	45	0.554	0.922	45	0.362	1.103	45	0.276
Block4 - Block8	1.508	43	0.139	0.311	43	0.757	1.513	43	0.138
Block5 - Block6	0.979	46	0.333	0.411	46	0.683	0.517	46	0.608
Block5 - Block7	0.463	45	0.646	0.348	45	0.729	0.664	45	0.51
Block5 - Block8	1.339	43	0.187	-0.33	43	0.743	1.016	43	0.315
Block6 - Block7	-0.866	46	0.391	-0.241	46	0.811	0.276	46	0.784
Block7 - Block8	0.408	44	0.686	-0.823	44	0.415	0.336	44	0.739
Block1 - Block2	1.306	44	0.198	-0.631	44	0.531	0.152	44	0.88

CURRICULUM VITAE

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EDUCATION

Ph.D. Candidate Neuroscience — June 2016
Brigham Young University-Provo
Focus: Learning and Memory
Dissertation Chair: C. Brock Kirwan, Ph.D.

M.S. Physiology & Developmental Biology — August 2011
Brigham Young University-Provo
Focus: Electrophysiology
Thesis Chair: Sterling Sudweeks, Ph.D.

B.S. Physiology & Developmental Biology — August 2008
Brigham Young University-Provo
Cum Laude

RESEARCH EXPERIENCE

Research Associate — Provo, UT Aug 2015-Present
Brigham Young University, MRI Facility

Assisting principle investigators from BYU in experimental design, data collection, and data analysis for fMRI based research projects. Responsible for training new MRI users in how to to use the scanner and prepare them for level 3 certification.

Research Assistant — Provo, UT 2012-Present
Brigham Young University, Memory and Cognition Lab

Investigating the role of pattern separation and pattern completion in learning and memory using EEG and fMRI.

Research Assistant Provo, UT 2009-2011

Brigham Young University, Electrophysiology lab.

Investigated the kinetics of neuronal nicotinic acetylcholine receptors in response to beta-amyloid. Techniques included two-electrode voltage clamp electrophysiology, plasmid preparation, and gene expression in Xenopus oocytes. Masters thesis title: "The Effects of β-amyloid on α7 Nicotinic Acetylcholine Receptors Expressed in Xenopus Oocytes."

Research & Development Research Assistant Salt Lake City, UT 2008-2009

Idaho Technologies (Biofire)

Developed and optimized new PCR protocols for JABAIDS and RAZOR instruments in the detection of biological warfare agents. Responsible for giving company wide progress updates.

Research Internship Madrid, Spain 2008

Spanish National Center for Cancer Research (CNIO)

Evaluated the role of microRNAs in regulating gene expression in lymphomas. Techniques included PCR, sequence analysis, designing primers, transfection, restriction enzyme digestion, cloning, luciferase assay, western blot, and RNA/DNA extraction from tissue samples.

Research Assistant Provo, UT 2006-2007

Brigham Young University, Cancer Research Lab

Correlated with another student to design and carry out a project to compare the intracellular quantity and activity of thymidine kinase. Trained new lab members, assigned teams weekly assays, and data compilation. Research techniques included flow cytometry, Bradford assay, radioassay, tissue culture, ELISA, and preparation of media and reagents. Radiation certified.

PUBLICATIONS

Anderson, M., James, J., & Kirwan, C.B (Submitted). An Event-related Potential Investigation of Pattern Separation and Pattern Completion Processes.

Anderson, M., & Kirwan, C.B. (Submitted). The Effects of Rewards on Pattern Separation Processes.

ABSTRACTS AND PRESENTATIONS

M. Anderson, C. Doxey, M. Nash and B. Kirwan. *An fMRI investigation of memory specificity paradigms.* Poster presentation at the Society for Neuroscience meeting (October 2015) Chicago, IL.

Malia Anderson, MaryJo Talley, Brock Kirwan. *The Effect of Reward on Memory Specificity*. Poster presentation at the Cognitive Neuroscience Society Meeting (March 2015) San Francisco, CA.

Malia Anderson and Brock Kirwan. *An event-related potential investigation of pattern completion and pattern separation processes.* Poster presentation at the Society for Neuroscience meeting (November 2013) San Diego, CA.

S.N. Sudweeks, M.L. Anderson, C. Jacobsen, C. Stoddard, K. Carpenter, D. Hansen, B. Tullis. *The effects of beta-amyloid on neuronal nicotinc acetylcholine receptors expressed in Xenopus oocytes.* Poster presentation at the Society for Neuroscience (October 2012), New Orleans, LA.

Sterling Sudweeks, Malia Anderson, Doris Clark, Andrew Romney, Gabriel Kelly, Brandon Tompson, Amanda Berbert. *Characterizing the effects of beta-amyloid on neuronal nicotinic acetylcholine receptor subtypes found in the rat hippocampus.* Poster presentation at the International Conference for Alzheimer's Disease (July 2010), Honolulu, HI.

Kristie Aamodt, Malia Anderson, Melissa Tovar, Breanne Loosle, Daniel Sjoberg, Byron Murray, and Kim O'Neill. *Development of a direct ELISA for intracellular human thymidine kinase I.* Poster presentation at the American Association for Cancer Research (April 2008) San Diego, CA.

ML Anderson, AM Hamblin, AM Clement, NJ Clement, JR Staples, DG Fuja, BK Murray, KL O'Neill. *Therapeutic Activity of a Monoclonal Antibody to Thymidine Kinase 1 on Xenograft Breast Tumors in Nude Mice.* Oral presentation at the American Society for Microbiology (April 2007) Grand Junction, CO.

TEACHING EXPERIENCE

Westminster University

Adjunct Professor

Neuroscience 301: Neuroanatomy

Fall 2014

Developed course curriculum of brain and spinal cord anatomy and systems circuitry, developed and administered assessments, gave lectures, maintained course web page (Canvas), maintained grade book, and assigned grades.

Brigham Young University

Teaching Assistant

Neuroscience 380: Behavioral Neuroscience

Fall 2014-2015

Located journal articles that correlated with course content and created discussion questions for class assignments. Taught lectures when needed. Tutored students and held review sessions.

Teaching Assistant

Psychology 711R: fMRI Design and Analysis

Spring 2014

Graded exams and maintained grades in Learning Suite. Attended lectures and assisted students when needed.

Teaching Practicum

Neuroscience 205: Neurobiology

Winter 2014

Created and presented ten (75 minute) lectures to Neuroscience 205 students, wrote, administer, and graded quizzes and exams, maintained the grade book, created the course syllabus, maintained online course page in Learning Suite and held weekly reviews. Taught lectures when the professor needed, graded assessments, maintained online class page (Learning Suite).

Teaching Assistant

Neuroscience 205: Neurobiology

2013-2014

Wrote, administered and graded quizzes and exams, maintained online course page (Learning Suite), held weekly review session for students, gave lectures when the professor was absent.

Student Instructor

Physiology 305: Physiology lab
2009-2014

Supervised four sections of a two-hour lab each semester. Instructed students on course material and lab procedures. Created PowerPoint slides, maintained and submitted grades via Blackboard and Learning Suite

Teaching Assistant

Biology 240: Molecular biology
Winter 2007

Taught exam reviews, weekly reviews and tutored students. Graded papers, assignments and maintained grade book on Blackboard.

GRANTS AND SCHOLARSHIPS

Research Assistant Tuition Scholarship	2013-2016
University Travel Award ($400)	Fall 2015
Department Travel Award ($1000)	Fall 2015
Mary Lou Fulton Award ($300)	Winter 2015
Physiology and Developmental Biology Travel Grant ($400)	Winter 2015
Purell Scholarship ($5,000)	Winter 2015
Great Lakes National Scholarship ($2,500)	Summer 2014
BYU Graduate Studies Research Presentation Award ($400)	Fall 2013
BYU Research Assistantship	Spring/Summer 2013
BYU Research Assistantship	Fall 2010
BYU Graduate Studies Research Presentation Award ($400)	Fall 2010
Ted and Della Hanks Scholarship (Partial Tuition)	Fall 2010
Life Science Annual Fund Scholarship (Partial Tuition)	Fall 2010
Office of Research and Creative Activities Research Grant ($1,500)	Winter 2008

PROFESSIONAL AFFLIATIONS

American Association for Cancer Research
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