THE EFFECTS OF HIPPOCAMPAL AMNESIA ON RETRIEVAL ORIENTATION AND NOVELTY PROCESSING

BY

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DISSERTATION

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Abstract

The medial temporal lobes (MTLs), and in particular the hippocampus, have been the focus of a large body of research since the discovery of a memory deficit in patient H.M. following surgical removal of those brain regions. This research has pointed to the role of the hippocampus in supporting a particular kind of memory, namely relational memory, and has attempted to explain how the hippocampus allows one to retrieve information given some cue (such as on a recognition memory test). However, persistent evidence has also appeared throughout the literature suggesting that the hippocampus is important for novelty processing. Several experiments presented here explore what novelty processing may be exactly, how it relates to typically-discussed memory processing, and how hippocampal function impacts these processes.

The broad umbrella of 'novelty processing' has been used to describe a few potentially distinct phenomena. One is a differential response to novel as opposed to familiar stimuli, which refers to stimuli with different amounts of previous exposure; a word being seen for the first time in an experiment is novel compared to a word that has already been studied. This will be referred to as stimulus-based novelty. A second is a similar finding but where novel refers to unexpected or unusual stimuli given the experimental context; a green picture presented in a stream of red pictures is novel in this way. This will be referred to as contextual novelty. Finally, novelty processing can refer to the intention to find novelty as opposed to the goal of finding familiar or studied stimuli; the latter 'familiarity processing' is what occurs in typical recognition memory experiments. This will be referred to as novelty orientation. Each of these novelty processes has been empirically associated with the hippocampus, although other authors have questioned if the first two actually represent a novelty process per se and the third has received little attention. For that reason, three experiments were designed that investigated novelty as a goal, or more specifically as a retrieval orientation, in contrast to a familiarity-based goal.

Previous research has found that participants are easily able to follow familiarity and novelty instructions; as demonstrated by eye movement data they will direct viewing to a familiar stimulus when asked to and will similarly direct viewing away from a familiar stimulus when asked to look at novel stimuli. However, familiar stimuli seem to automatically grab viewing such that it takes longer to direct viewing away. This paradigm (Ryan et al, 2007) was examined using patients with hippocampal damage and intact comparison participants. Famous and non-famous faces were used to provide different levels of stimulus-based novelty, some famous faces were not seen during study to provide a source of unexpectedness or contextual novelty, and viewing instructions were manipulated to provide a contrast between novelty and familiarity orientation. Eye movement data revealed that both amnesic and comparison participants directed different levels of viewing to the different types of faces, supporting the idea that they varied in their memory content. Hippocampal damage did reduce the ability of the patients to distinguish familiar faces from novel lures, but both groups showed the same relative viewing to the studied famous, studied non-famous, and unexpected famous faces; hippocampal damage had no influence on stimulus-based or contextual novelty. Similarly, both groups directed viewing properly following the familiarity and novelty instructions.

Recent evidence has suggested that the hippocampus may be important for memory over a short delay in addition to the long-held view of its role in long-term memory. These results were examined

along with novelty orientation in a second experiment that expanded on the results of the first. Complex computer-generated stimuli were used instead of faces, and retrieval orientation was manipulated at the trial level instead of across blocks. Behaviorally the amnesic group performed normally when memory was tested after a short unfilled delay, but they were impaired after a long delay. Eye movement data showed that both groups were again able to direct viewing appropriately given the instruction. Critically, there was again no evidence that hippocampal lesions impaired performance under novelty instructions, either behaviorally or with regard to eye movements. Moreover, the eye movement data suggest that participants may have a preference to search for the familiar item at test, raising the question of the necessity of 'novelty processing' in addition to familiarity.

While other authors have questioned the stimulus-based and contextual novelty effects found in previous research, the first two experiments here implied that novelty processing as a retrieval orientation may also be an unnecessary construct. The final experiment tested that hypothesis more directly using a paradigm that has demonstrated the later consequences of instantiating a particular retrieval strategy or goal. College-age adults studied two lists of words, one under deep (semantic) instructions and the other under shallow (word length) instructions. They then received separate recognition memory tests for these two lists with the knowledge that the old words came from those distinct lists. Previous research (Jacoby et al, 2005a) has shown that participants are able to use this information to focus their memory search, which has the effect of producing deep and shallow processing on the foil items on the two recognition tests; this is demonstrated on a final test where the deep foils are better recognized than shallow foils (called the memory for foils effect). The current experiment manipulated novelty orientation during the middle phase when participants performed the two recognition tests, with one group receiving familiarity instructions and a second receiving novelty instructions. The familiarity group replicated the previous results, demonstrating both a depth of processing effect on the initial recognition tests and a memory for foils effect on the final test. The novelty group produced a reduced depth of processing effect but a normal memory for foils effect. The intention to look for novel stimuli thus does appear to produce different effects than the intention to look for familiar stimuli, although in a complicated manner.

The results described here extend the novelty processing literature by attempting to differentiate familiarity and novelty retrieval orientations. Other authors have suggested that novelty processing is not really about novelty at all, but more of a priming effect; that is, brain regions such as the hippocampus are conducting less of their normal memory processing on familiar stimuli than on novel stimuli. The results of the first two experiments support that view; hippocampal lesions had no effect on novelty processing regardless of how novelty was defined. The third experiment instead demonstrated that novelty processing can be distinct from typical memory processing. I discuss why, however, it is unclear that this represents some manner of novelty processing per se as opposed to representing a shift in the meta-mnemonic processes engaged by participants. While the data are unable to definitively determine whether novelty and familiarity orientations are distinct goals or strategies, I demonstrate that novelty processing is not a necessary construct at the mnemonic level.

To my wife and family

And

All of my wonderful teachers

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They say that psychologists (and maybe all scientists) study what they're bad at, and as such I will surely forget to thank some people that I should. But I will do my best to thank everyone I can remember.

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1. Introduction

1.1. A Brief Overview of Relational Memory

Memory comes in a variety of flavors. Some researchers study motor learning, others semantic networks and language (see figure 1.1 for a partial taxonomy). My work has focused broadly on declarative memory. More specifically I have typically focused on a subset of declarative memory called relational memory and how it relates to a part of the brain called the hippocampus. Declarative memory is typically described as being what it sounds like: memory that supports anything a person might declare or explicitly state, such as a fact or personal event. Memory for facts, such as Lincoln being the 16th President, have typically lost any associated context and are called semantic memories. One doesn't need to remember when or where they learned that Lincoln was the 16th President to express that knowledge. Memory for personal events, such as what one had for breakfast yesterday, is considered to be an episodic memory and is typically contrasted to semantic memory in that context is very important. The memory is associated with yesterday, not any day, and remembering breakfast involves some manner of 'mental time travel' or re-experiencing of the event. The breakfast memory might be associated not only with the time and what was eaten but also who else was there, what was going on during breakfast, or what happened before or afterward.

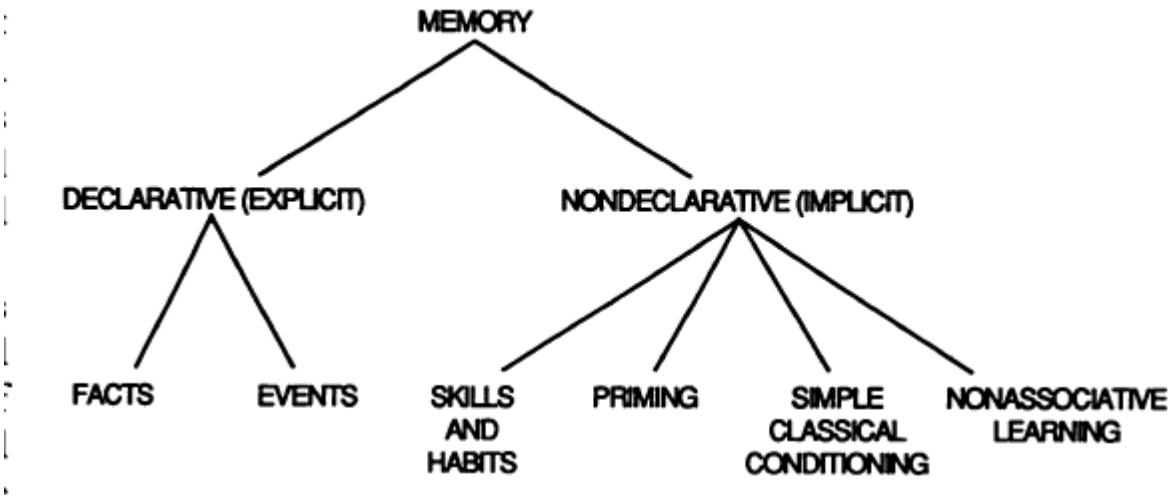

Figure 1.1. A partial taxonomy of memory systems. From Squire and Zola-Morgan, 1991.

Relational memory is thought to support both these kinds of memories, although in different ways. Relational memory is the ability to bind together different, arbitrary pieces of information into a single whole that can be flexibly used with other information (Cohen and Eichenbaum, 1993; Eichenbaum and Cohen, 2001). For example, when someone meets a new acquaintance they need to remember the name that goes with the face. Faces and names are arbitrary associations; given a picture of an unknown person, it is unlikely that a name would jump to mind or that it would be the correct name. This is why relational memory is fundamental to episodic memory: a person must be able to combine arbitrary elements (e.g. who was at breakfast with the day or what was eaten or the contents of the newspaper) to form a complete episodic memory. It is unusual to think of them this way, but facts (semantic memories) begin as arbitrary pieces of information. When someone learns that Lincoln was President, those words previously had nothing to do with each other and must be remembered by brute force. After repeated use, however, such combinations become inflexible facts and no longer rely on relational memory to be remembered. Consistent with this description, amnesic patients with relational memory deficits have difficulty learning new semantic information after their injury (e.g. Gabrieli, Cohen, & Corkin, 1988). On the other hand, they have no trouble remembering semantic information learned sufficiently before their injury. In contrast, amnesic patients have difficulty remembering episodes from before their injury with the full detail and experience that defines episodic memory; the memories appear to have become more like semantic memories (Rosenbaum et al., 2008). Amnesia has made it difficult, if not impossible, for these patients to create new episodic or semantic memories, as well as retrieve episodic memories. The critical aspect of these results is the importance of contextual detail.

Beyond describing a kind of memory, the relational memory theory provided by Cohen and Eichenbaum also makes claims about which brain regions support different psychological processes. The 'items', or individual pieces of information themselves (such as the face or name of a new acquaintance), are processed by regions of cortex in the medial temporal lobes (MTLs). Specifically, it is thought that the perirhinal cortex creates item memories. The actual combining of items (or of items to other information) into a relational memory is accomplished by the hippocampus. The hippocampus differs from the perirhinal cortex in a variety of ways, but there are two key features that allow it to support relational memory: its position in the brain and its own internal structure (Brown & Aggleton, 2001; Eichenbaum, Yonelinas, & Ranganath, 2007; Lisman & Otmakhova, 2001). The hippocampus is located in the MTL at the end of a number of sensory processing pathways. The most studied is the ventral visual pathway, which takes visual information from the occipital lobe and passes it through inferior temporal cortex and into the perirhinal cortex. Meanwhile, more spatial aspects of the environment seem to pass through a dorsal pathway that includes the parietal cortex and into the parahippocampal cortex. These

two types of information then pass into entorhinal cortex, remaining differentiated, and on into the hippocampus. Similar stories can be told for the other sensory modalities. Thus the hippocampus has all the information necessary to form a complete episodic memory: visual information sounds, smells, spatial locations, and so on. The importance of the hippocampus' structure is discussed later.

It is worth noting that the hippocampus has not always been associated with relational memory. Since initial reports of memory loss in patient H.M. after his hippocampus was removed during surgery (Scoville & Milner, 1957, the hippocampus has been described as supporting cognitive mapping, spatial maps, declarative memory, episodic memory, explicit memory, and recollection as well as relational memory (Cohen et al., 1999; Konkel & Cohen, 2009). In fact, to the extent that all of these claims are plausible, they support the relational memory theory because each reflects a portion of the theory. While spatial accounts of hippocampal function have been prominent over the years, particularly in animal research, it is notable that memory for locations is one kind of relational memory. As has already been noted, relational memory is a fundamental feature of episodic and declarative memory. Recollection is a more recent process attributed to the hippocampus (Eichenbaum et al., 2007); recollection is the ability to remember the context or details associated with a particular stimulus. It is frequently compared to familiarity, which is remembering that a stimulus was seen before but without any subjective ability to remember the details of the prior event. For example, one might study the word 'omelette' and be reminded of breakfast during the weekend. If this memory comes back again when omelette is seen at test, it should be called 'recollected'. If the person feels that omelette was studied before but has no details to go along with it, it should be called 'familiar'. Recollection is also typically invoked if a person is able to remember the font color a word was presented in or the side of the screen is was displayed on (examples of source memory). Given the nature of relational memory described above, the connection between it and recollection should be obvious. One key difference between relational memory theory and a number of these alternative accounts (such as recollection, or more important to this thesis, novelty processing) is that the other theories function at the level of psychological processes as opposed to representations. Further discussion of this issue is found in the conclusion section.

1.2. Recognition Memory: Strength or Something More

Despite the fact that the hippocampus appears to play a role in a wide range of situations (such as language (Duff, Hengst, Tranel, & Cohen, 2007; Hassabis, Kumaran, Vann, & Maguire, 2007) or imagination (Hassabis et al., 2007)), most of the recent debate over hippocampal function is based on evidence from recognition memory tests. After being exposed to a list of stimuli, participants are presented with a test list consisting of both previously encountered ('old') and not recently experienced ('new') stimuli. The participant is then asked to determine if any given stimulus was previously seen or

not. This type of test can be contrasted to recall, in which the participant is asked to generate the studied material directly from memory. While recall is broadly accepted to rely on the hippocampus (and be related to recollection), recognition provides a more murky case. Since participants get to see each stimulus, they have the opportunity to feel that they have seen it before without retrieving any detailed information about the episode (the process of familiarity described earlier). Thus recognition may rely on a combination of memory processes, and perhaps equivalently a number of brain regions. This point has been heavily debated, however (Eichenbaum et al., 2007; Squire, Stark, & Clark, 2004; Wixted, 2007).

Before even addressing the issue of what brain regions support recognition memory, however, is the contentious issue of what psychological processes underlie recognition. As implied above, one theory is that recollection and familiarity combine to support recognition (thus commonly called the dual-process theory), with the question being how much of which process is brought to bear in different circumstances (Yonelinas, 2002). The main alternative theory is the signal detection theory (SDT; Macmillan & Creelman, 2005) of recognition, which is primarily described as a single-process theory (although, see Wixted, 2007). In the SDT framework, the single process can best be described as matching (Shiffrin & Steyvers, 1997 describe a compatible mathematical model). An incoming stimulus, such as one seen on a recognition test trial, is compared to potentially every representation in memory. The comparison process generates a single 'match' value, or evidence that the stimulus has been seen before. This evidence value is then judged as to whether or not it is sufficient to actually call the stimulus 'old'. The decision is based on two distributions of memory evidence. One distribution is made of new items and is typically called the noise distribution due to SDT's origin in psychophysics. Because of the many items stored in memory, even a completely novel stimulus (such as a non-word) has some amount of evidence that it is actually old due to it being similar to something that has been seen before. Of course, items differ in how 'old' they seem; a very unusual non-word like 'zyzyzyz' may have elicit little evidence and seem obviously novel whereas a non-word with typical features like 'tham' may be a more attractive lure. On the other hand, actually studied words elicit more of a match because they actually exist in memory and were recently activated. Due to factors like attention during study, inherent characteristics of the item (like word frequency), and person-specific idiosyncrasies, old items also take on a range of evidence values and thus create a 'signal' distribution. The match value that a particular item evokes is compared to the signal and noise distributions (or alternatively a criterion level of evidence established in relation to those distributions) to determine which one the item is more likely to have come from, and a decision is made (see figure 1.2).

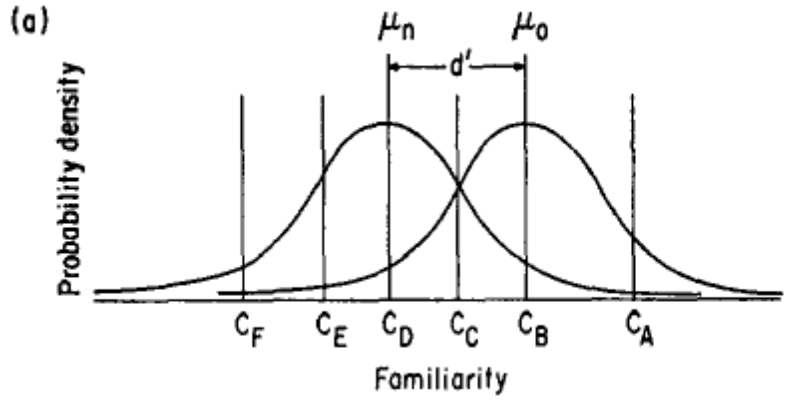

Figure 1.2. An illustration of the signal detection theory view of memory. The noise distribution (on the left) is made of unstudied items while the signal distribution (on the right) is made of studied items. Locations further to the right on the scale have more evidence of having come from the signal distribution. The ability to discriminate old from new items can be evaluated with the distance between the means of the two distributions, called d'. Any individual item is evaluated by comparing its evidence value to a criterion for responding "old" or "new". The figure shows 6 criteria points, as might be used when subjects also provide a rating of how confident they are in their response (e.g. "sure new", "probably new", "guess new", "guess", "guess old", "probably old", "sure old"). Any item with an evidence value between c_b and c_a would generate a 'probably old' response. Illustration from Banks (1970).

Behaviorally speaking, SDT models typically account for recognition performance better than dual-process models (Glanzer, Kim, Hilford, & Adams, 1999; Hilford, Glanzer, Kim, & DeCarlo, 2002). However, dual-process models provide very similar fits as well as additional theoretical accounts of performance (Wixted, 2007; Yonelinas, 2002). Additionally, evidence from neuroimaging and lesion studies suggests dissociations in the brain regions that support recollection and familiarity during recognition testing (Eichenbaum et al., 2007). However, a different perspective also suggests that a single-process view of recognition memory may not be correct. The matching process, at least as described by many models, is strictly a quantitative process. The test stimulus is compared to everything in memory, generates an evidence value, and the evidence is compared to some criterion for making an 'old' response. Jacoby, Shimizu, Daniels, & Rhodes (2005), in contrast, proposed that the recognition process can differ under different circumstances to reflect what they called source-constrained retrieval. For example, if a participants knows that any old items on a test were studied under one condition instead of another (such as aurally as opposed to visually), the participant can use that information to guide and limit his memory search. This is similar to how recall might be performed; given a cue 'tell me the words from the list you just saw', participants can limit their search to words seen in the recent past to retrieve what was studied. If participants can make different kinds of memory searches, and perform different kinds of processes on stimuli during this search as suggested by Jacoby et al. (2005), this implies a

qualitative aspect to retrieval that is not present in single-process accounts of recognition. It is not sufficient to describe a stimulus' status in memory or likelihood of being retrieved via a single strength value. The circumstances of the test as well as the different strategies that participants may use must also be taken into consideration.

Perhaps due to the advent of functional neuroimaging, the role of the hippocampus in recognition memory has become a popular research focus. More importantly, the relationship has become a two-way street as recognition tasks are used to examine the function of the hippocampus (see reviews by (Davachi, 2006; Diana, Yonelinas, & Ranganath, 2007; Eichenbaum et al., 2007; Henson, 2005; Konkel & Cohen, 2009; Mayes, Montaldi, & Migo, 2007; Squire, Wixted, & Clark, 2007), and entire issues of the journal Hippocampus, such as November 2010). Single-process theories of memory have been able to account for much of the behavioral data in this literature, at least compared to dual-process theory, and have been resilient in the face of contradictory data. However, when the full range of the hippocampal literature is considered, as well as evidence of meta-mnemonic effects like those found by Jacoby et al. (2005), it is clear that a single-process or strength-based account of recognition memory is incomplete. Thus SDT is better suited as a measurement technique than as the basis for a theory of memory function.

1.3. Novelty and Familiarity

While the hippocampus is typically thought of as a memory module, and the discussion so far has largely been in regards to how the hippocampus allows us to retrieve what we have seen before, there is a somewhat separate body of research that contends it also does the opposite: it tells us what we have not seen before. These two phenomena will be called familiarity processing and novelty processing. Familiarity processing refers to the processes engaged when a familiar stimulus is seen, not to be confused with the process of familiarity discussed above in regards to recollection. Novelty processing, on the other hand, refers to the processes engaged when a novel stimulus is seen. Due to the importance of exploration and learning new information, novelty processing has been called an essential function for survival (Knight & Nakada, 1998). Broadly speaking, familiarity processing can be viewed as what researchers discuss in regards to recognition tests: retrieval strategies, memory evaluations, decision making, and so on. Intuitively, however, novelty seems to be the 'other side of the coin' to familiarity; if something is familiar, it is not novel, and vice versa (Habib, 2001). Such a conclusion would be reasonable under a SDT model of recognition since any stimulus possesses only a single strength value in memory. A very familiar stimulus would be, by definition, not very novel. If novelty and familiarity exist only to different degrees, wouldn't they evoke the same psychological processes only to different degrees? As discussed previously, however, the single-process view is unappealing as a complete view of recognition memory, and so perhaps familiarity and novelty are separable in a multi-process view of

recognition that includes various mnemonic and meta-mnemonic functions. Thus the question at hand is: do we need to have separate novelty detection and recognition processes, or is recognition memory alone sufficient?

Beyond the intuitive account just described, some confusion over the distinction between novelty and familiarity is due to the use of a broad term ('novelty detection' or 'novelty processing') applied to potentially different phenomena. Kumaran & Maguire (2007) and Nyberg (2005) identify three different kinds of novelty, which will serve as a framework for discussing novelty processing relative to other functions, namely relational memory.

Stimulus novelty: Stimulus novelty is used to describe the situation where a single item is new. The strongest possible example is for a completely novel stimulus, such as a previously unseen face. However, most research has focused on what might called 'experimentally novel' stimuli: stimuli like words that have been seen before and already exist in memory, but have not been seen previously in the experimental context. It is unclear if these two kinds of novelty should be grouped together (the ideas of associative and contextual novelty, discussed next, argue that perhaps they shouldn't). Stimulus novelty effects are usually found by comparing some measure of processing of novel stimuli to a measure of processing of familiar stimuli. This is commonly done with functional magnetic resonance imaging (fMRI) and used to find the brain regions responsible for processing novelty. An early example (using positron emission tomography, PET) comes from Tulving, Markowitsch, Craik, Habib, & Houle (1996). On the first day of the experiment, participants were shown a series of presumably unfamiliar color pictures. On the second day, participants saw blocks of stimuli consisting mostly of these now-familiar pictures or mostly of novel pictures while brain data were collected. Comparing the novel blocks to the familiar blocks, the researchers found that the hippocampus, amongst a variety of areas, was more active during the novel blocks. Very similar paradigms were carried out with blocked (Stern et al., 1996) and event-related fMRI (Kirchhoff, Wagner, Maril, & Stern, 2000) and the hippocampus was consistently found to respond to novelty.

However, there is reason to believe that the hippocampus is not actually critical for processing stimulus novelty. Even in those early reports (Stern et al., 1996; Tulving et al., 1996), the authors noted that the hippocampus may be active due to encoding, particularly for the complex materials used as stimuli. Kirchhoff et al. (2000) extended that intuition by demonstrating that many of the same brain regions that responded to novelty, including the hippocampus, also were active in a subsequent memory analysis. That is, the same regions that appear to be responsible for novelty processing are also responsible for memory encoding. This raises the question of if the hippocampus is involved in novelty

processing per se or if it is carrying out its usual role in memory formation and simply does so more for novel materials (Kumaran & Maguire, 2009).

Another issue with stimulus novelty is its relationship with priming (Habib, 2001; Ranganath & Rainer, 2003). As described above, novelty activation in fMRI is found by comparing novel to familiar stimuli. This is exactly the same procedure for finding priming effects in the brain. Priming effects are associated with reduced activity to repeated stimuli (also called repetition suppression or adaptation); it is thought that reduced activity reflects more efficient processing (Henson, 2003). However, this is exactly the same pattern of results that is used to define novelty processing, more activity for novel than familiar stimuli. Thus it is impossible to distinguish the two at the data level; they can only be distinguished conceptually and any given research article tends to approach their data from one viewpoint and not the other. In fact, Kumaran & Maguire (2009) have suggested using novelty effects to determine hippocampal function in a manner very similar to how priming effects have been used to deduce the function of various regions of visual cortex. In other words, they are suggesting that the novelty effects found in the hippocampus are, in fact, a kind of priming or repetition suppression and not at all related to novelty processing per se.

In summary, there are two issues related to concluding that the hippocampus supports stimulus novelty processing: these effects could just be encoding activity, or the effects could be priming. They could reflect both, given that the hippocampus is involved in both encoding and retrieval. These two concerns will carry on into the other varieties of novelty processing.

Associative novelty: Associative novelty is defined as a novel combination of previously seen items (Kumaran & Maguire, 2007). A common experimental example is word pairs: pair A-B could be studied and later pair C-D; if pair A-D is seen at test it is associatively novel. The items or elements themselves are familiar but the combination as a whole is new. As has been mentioned, this type of processing seems to fit well with relational memory theories of hippocampal function. The hippocampus has been connected to a variety of types of associations, such as item-item, item-location, and item-time (or sequential order) (Konkel & Cohen, 2009; Konkel, Warren, Duff, Tranel, & Cohen, 2008). Providing quite the parallel within the novelty literature, the hippocampus has been associated with item-item (Köhler, Danckert, Gati, & Menon, 2005), item-location (Köhler et al., 2005), and item-time novelty processing (Kumaran & Maguire, 2006). Kumaran and Maguire (2007) take this evidence as a sign that if the hippocampus is involved in novelty processing at all, it should be associative (relational) novelty.

While a broad view of the data supports an association-based (as opposed to item-based) view of hippocampal function, it is still unclear if the hippocampus should be associated with novelty processing

in this domain. As noted previously, a novelty processing view needs to contend with fact that it is conflated with both encoding and priming. That is, the relational memory theory would predict that a new combination of studied stimuli would need to be bound together, requiring hippocampal activity. Previously studied combinations will not need as much binding (and in fact could eventually become independent of the hippocampus as semantic memories). Thus increased hippocampal activity for novel associations is not a surprising result and need not be a consequence of a special novelty process. This conclusion holds whether one views the results as encoding or priming.

Contextual novelty: Contextual novelty refers to a stimulus being unexpected given the context it occurs in. The primary paradigm examining this kind of novelty is perhaps the novelty oddball paradigm, often studied with event-related potentials (ERPs) but also occasionally with fMRI (Knight & Nakada, 1998). In the novelty oddball paradigm, three types of stimuli are presented to the participant: standards, targets, and oddballs. The standard is a single stimulus (such as a pure tone) presented the majority of the time (perhaps 80% of trials) that the participant is told requires no response. The target is also a single stimulus (such as a pure tone at a different pitch) presented infrequently (10% of trials) that the participant is told to respond to. The oddball is the actual stimulus of interest, however. The oddball is infrequently presented, like the target, but is usually of a different character than the target or standard (such as a dog bark or car horn or other environmental sound). The oddball is unexpected due to its rarity and distinct character relative to the majority of stimuli presented on other trials. It is also literally unexpected since participants are often not told that it will be presented. The oddball stimulus has been found to evoke its own ERP component, the P3a or novelty P3. The novelty P3 is considered to reflect an orienting response or capture of attention by an unexpected stimulus (Knight & Nakada, 1998). Important to the current discussion, the novelty P3 is reduced or eliminated in patients with hippocampal damage (Knight, 1996). Additionally, hippocampal activity showed a similar pattern of results to those found in ERPs (namely, habituation) in an fMRI investigation of the oddball paradigm (Yamaguchi, Hale, D'Esposito, & Knight, 2004).

However, similar caveats apply to a contextual novelty account of hippocampal function as were discussed with associative novelty. Indeed, it is unclear if item-context associations are fundamentally different from other item associations mentioned earlier. The context provided by an experimental session can easily be viewed as temporal or more concrete pieces of information (the location of the testing, the experimenter, what the room looks like, other items in the experimental list, etc.). Items to be remembered, or simply presented as in the novelty oddball paradigm, can be associated to that information as much as to experimenter-manipulated information like other words or computer screen

locations. Due to its role in relational memory, the hippocampus would be expected to form a memory for the ongoing context of an experiment just as much as it would for other associations.

In short, at least three forms of novelty have fallen under the umbrella of 'novelty processing' and each has been associated with the hippocampus. However, each of these faces issues of interpretability. Stimulus and associative novelty effects are intertwined with priming and encoding while associative and contextual novelty effects are already predicted by the relational memory theory, which additionally predicts a wide range of results throughout the literature.

1.4. Searching for Novelty: Retrieval Orientation

If novelty and familiarity processing are two different psychological entities, then they should be clearly distinguished in both behavioral and neurological data. However, the discussion above has raised issues at both levels. Behaviorally, novelty has been called 'the other side of the coin' to familiarity (Habib, 2001). Within the brain, novelty effects have been found in regions (such as the hippocampus) with other prominent functional roles that provide other, and perhaps better, accounts of the data. At any level, it is unclear if novelty can be separated from memory encoding or priming. In sum, it is unclear if novelty processing needs to exist as a psychological construct if familiarity (or recognition memory) already explains all the same results.

However, another route to studying novelty processing is available. If novelty processing is different from familiarity processing, or if novelty is a feature or characteristic of stimuli different from familiarity, then participants should be able to invoke that process or look for those features when circumstances permit. As described previously, Jacoby et al. (2005) demonstrated that participants can constrain their memory search to certain categories or types of information. This happens even though the participants were not asked to, and may be a subconscious strategy. Thus, if they are in fact different, participants should be able to institute a 'novelty orientation' that is distinct from a 'familiarity orientation'. Only a few studies have compared these two. (Dudukovic & Wagner, 2007) asked participants to study a list of words and then take a recognition memory test with two types of trials. On each test trial participants saw three words, two studied and one novel, but before the trial the participant was cued to choose the novel word or the more recently studied word. Thus the stimuli on each test trial were identical but the participant modulated his retrieval orientation. The hippocampus was significantly more active during novelty than recency judgment trials. Thus it appears that the hippocampus might respond differently to novelty orientation than (temporal) source memory orientation. However, an earlier study from the same lab (Dobbins & Wagner, 2005) found that the hippocampus was equally active for novelty and a different source (task performed at study) memory orientations, and a study

investigating working memory (Monk et al., 2002) similarly found that the hippocampus was equally active for match-to-sample and non-match-to-sample tasks.

Given the discussion above, the manipulation of retrieval orientation while keeping stimulus content identical is a critical part of these studies. The evidence for novelty processing as a distinct function was all based on stimulus characteristics: a particular stimulus (such as the car horn in the oddball paradigm) was novel or familiar, and it was assumed that the stimulus itself evokes different processing. There would be better reason to distinguish novelty and familiarity processing if they could be brought to bear on any stimulus, as appears to be the case (at least quantitatively) in the study by Dudukovic and Wagner (2007). Duncan, Curtis, & Davachi (2009) have suggested that intention may in fact be the basis for seemingly contradictory fMRI results involving hippocampal activity. Despite the common finding of more activity for novel than familiar stimuli, it is not uncommon to find the opposite: more activity for familiar than novel stimuli (e.g., Giovanello, Schnyer, & Verfaellie, 2004; see Henson, 2005 for a discussion of the old-new effect). Duncan et al. (2009) note that this seems to occur in situations when familiarity is behaviorally relevant, such as during intentional retrieval. To test this hypothesis, Duncan et al. (2009) developed a working memory paradigm where participants viewed a pair of objects and then received a signal telling them to either maintain the objects or flip their spatial locations. After a delay, participants saw either the same items in the same locations as at study, the same items in flipped locations, one old and one new object, or the same objects with one in a new location. Thus a studied stimulus could be a goal match or a goal mismatch depending on instructions, as could a novel stimulus. The new item and new position conditions provided trials with stronger perceptual novelty. Duncan et al. (2009) found only match signals in the hippocampus: it was more active for familiar stimuli in the 'maintain' condition and novel stimuli in the 'swap' condition than for if the stimulus mismatched the goal. Further, no hippocampal region demonstrated mismatch activity. However, an array of MTL areas demonstrated novelty effects by being more active during the new object and new location conditions than any matching condition, replicating the stimulus/associative novelty response discussed earlier. These results demonstrate that the hippocampus can show both familiarity and novelty effects depending on the participants' goal; familiarity activity should occur under a familiarity orientation and novelty activity should occur under a novelty orientation.

1.5. Current Work

Novelty effects have been found consistently in the hippocampus, yet their interpretation is ambiguous. There is wide support for the role of the hippocampus in relational memory, and it is unclear if it additionally supports some manner of novelty detection or processing. The little research that has extended into the realm of goal states is promising, but conflicted. Duncan et al. (2009) found that the

hippocampus is sensitive to goal state, but only in regard to matching expectations. Perhaps supporting that match enhancement hypothesis, Dobbins and Wagner (2005) and Monk et al. (2002) found that the hippocampus was equally active under a novelty orientation as a variety of familiarity orientations. However, Dudukovic and Wagner (2007) found that the hippocampus was more active under a novelty orientation than a temporal orientation, suggesting that the hippocampus may respond to differences in goal state. More research is necessary to determine if the hippocampus is critical for instantiating different goal orientations, particularly in regards to novelty.

An additional limitation of the majority of novelty research is that it relies on fMRI and ERP data. While these methods provide data and test hypotheses that cannot be attempted with other techniques, they are inherently correlational. A stronger test is provided by examining novelty processing in patients with brain lesions. For example, Knight (1996) found that the novelty P3 component is missing in hippocampal lesion patients, suggesting that the hippocampus is necessary for detecting contextual novelty. More directly tied to the current work, Freed & Corkin (1988) tested patient H.M. with both familiarity and novelty-focused versions of recognition tasks. Having studied a list of pictures earlier, both H.M. and intact comparison participants performed yes/no, yes/no-new (participants looked for and responded positively to novel pictures), two-alternative forced choice, and two-alternative non-match (pick the novel picture) forced choice recognition tests. While the comparison group performed equally well regardless of the familiarity/novelty instruction, patient H.M. performed better, and in fact at normal levels, under the novelty orientation. The authors suggest that H.M. may have a novelty preference instead of a deficit, which appears to conflict with the conclusions drawn from the novelty literature discussed so far.

The current work aims to extend the novelty literature further in the realm of goal states by testing patients with hippocampal lesions. If the hippocampus is fundamentally involved in processing novelty, then hippocampal damage should impair the patients' ability to instantiate a novelty orientation. In fact, if the Freed and Corkin (1988) result generalizes, patients may even perform better under novelty instructions. However, following the relational memory theory of hippocampal function, it would be predicted that patients will not be impaired or benefit under novelty instructions. Another reason to predict a null result is that goals and retrieval orientation are generally understood to be controlled by the prefrontal cortex (e.g. Miller & Cohen, 2001) and not the hippocampus. Instead, amnesic patients should demonstrate a more generic memory impairment.

A first test of these hypotheses will come from a paradigm developed by Ryan et al. (2007). Participants studied a list of faces containing both famous and non-famous people. The following test

trials consisted of three faces. Excluding occasional catch trials consisting of three non-studied, non-famous faces, all test trials contained two completely novel (non-studied, non-famous) faces and one familiar face. The familiar face could be a studied non-famous face, a studied famous face, or a non-studied famous face. In one block participants were asked to look at the familiar face while in another they were asked to look at any novel face; eye movements were recorded to detect where participants were looking. This manipulation across blocks represents a manipulation of orientation; the participant is either attempting to find a familiar face or a novel face. In young adults Ryan et al. (2007) found that participants are able to find familiar faces quickly when instructed to do so; regardless of why the face was familiar, the familiar face drew more viewing than the novel faces only half a second after the faces appeared on-screen. Participants were also able to follow the novelty instruction, but the eye data suggested that something else may be going on. Eye movements away from the familiar face were relatively delayed, only dropping below the level of novel faces after a full second of trial time. Additionally, non-studied but famous faces were extremely delayed and only rejected after three seconds of viewing. Thus Ryan et al. (2007) found that 1) participants are able to direct their viewing according to their goal state, 2) memory has an obligatory effect on viewing such that familiar faces appear to draw viewing and are easier to look at than to look away from, and 3) contextually unexpected stimuli like the non-studied but famous faces may be especially difficult to reject.

The same paradigm will be used here with amnesic patients as well as intact comparison participants. This paradigm provides a number of benefits relevant to the current goals. First, it relies on eye movements instead of overt behavioral responses. Eye movements are an excellent way to gather data from a population like amnesic patients (Hannula et al., 2010), especially under an overt demand on their memory. Second, there are three kinds of novelty in the study that could prove to be affected by hippocampal lesions. Novelty orientation is examined by the instructional manipulation across blocks, stimulus novelty is examined by the use of famous and non-famous faces, and contextual novelty is examined by testing non-studied but famous faces. As mentioned previously, the relational memory theory predicts that the patients will not demonstrate any goal orientation deficits. Instead, they may have difficulty distinguishing studied faces from non-studied faces, consistent with their memory deficit. Despite showing the faces repeatedly during study, their memory impairment may be sufficient to reduce performance compared to normal controls. Additionally, there is the possibility that the patients will demonstrate a different pattern of viewing when tested with the non-studied famous faces. These faces appear to be contextually unexpected in young adults; since the hippocampus is associated with relational memory and creating the context of a task, the patients may not respond in the same way as the comparison group.

A second study will extend the results of the first into the domain of working memory as well as generalize by using different materials. Although the hippocampus has long only been associated with long-term memory, recent work has found that lesions can impair performance even on tasks with short or no appreciable delays if the conditions are right (Duff et al., 2011; Olson, Moore, Stark, & Chatterjee, 2006; Olson, Page, Moore, Chatterjee, & Verfaellie, 2006; Voss, Gonsalves, Federmeier, Tranel, & Cohen, 2011; Voss, Warren, et al., 2011; Warren, Duff, Jensen, Tranel, & Cohen, 2011; Warren, Duff, Tranel, & Cohen, 2010, 2011). The experiment will also use novel computer-generated stimuli (Konkel et al., 2008) as opposed to faces. While the non-famous faces in experiment 1 are also completely novel, they will have been studied extensively before being tested and may be easier to process given the large amount of experience people have with processing faces. The paradigm will involve a series of working memory trials with intermixed study trials for a later long-term memory test; the long-term memory test trials will be presented after the working memory phase. After studying a pair of items participants will be instructed to choose the familiar or choose the novel item at test; this experiment will thus examine the ability to change retrieval orientation trial-to-trial whereas the first experiment examined orientation in a more stable manner. Consistent with long-established results in the memory literature, the amnesic patients should perform worse than the comparison group on the long-term memory trials. It is possible that they will also be impaired on the working memory trials given recent research in that area. However, the task does not explicitly test any relational information, so the patients may also perform normally. More importantly, a relational view of hippocampal function again predicts that the patients will not be impaired in terms of the retrieval orientation manipulation. Demographic information and neuropsychological test results for the patient and comparison participants tested in experiments 1 and 2 are presented in table 1.1.

The final piece of the current work is to investigate the consequences of instantiating a novelty orientation. Many different paradigms demonstrate the effects of exposure to a novel stimulus, such as drawing additional viewing (Loftus & Mackworth, 1978) and being remembered better on a later test (Kishiyama & Yonelinas, 2003). However, the memory effects of looking for novel stimuli are far less known. The only experiment I am aware of is a follow-up study to an fMRI experiment by Dudukovic and Wagner (2007). Having demonstrated that the hippocampus, among other areas, is more active when participants are looking for a novel stimulus than a more recently seen stimulus, the authors performed a behavioral study to further examine the consequences of that orientation. A separate set of participants went through the same paradigm as the fMRI group (studying a list of words and then receiving trial-by-trial instructions to either choose the novel word or the more recently studied word out of two old and one novel words) followed by another test. This final test contained novel lures from the novelty test trials,

novel lures from the recency test trials, and completely novel lures; participants were told to endorse any word seen earlier in the experiment. Novel lures from novelty trials were endorsed more than lures from recency trials, leading the authors to conclude that the hippocampal activity may have reflected encoding as well as (or perhaps instead of) attentional effects.

To expand on this work, I am adapting the source-constraint experiment described previously by Jacoby et al. (2005). The critical manipulation will occur during the second phase, when participants take separate recognition tests for deeply and shallowly studied words. One group of participants will go through the same paradigm and should replicate the memory for foils effect: due to constraining their memory search to the appropriate study condition, lures from the deep test receive deep processing during the test and are better remembered on a later test than lures from the shallow test. A second group will go through the same initial encoding and final test for lures phases, but perform the tests in the second phase under novelty instructions. If searching for novelty is different from searching for familiarity, then this group should demonstrate differences for performance during the second and/or third phases due to the differences in their memory search. I hypothesize that a novelty orientation may shift participants away from deeper or more thorough memory searches; they may be less likely to constrain their memory search or engage in recollection. Instead they will focus on making simple yes/no decisions instead of considering where the old items come from. If this is true, the novelty orientation group may demonstrate reduced depth of processing as well as memory for foils effects due to their lack of constrained memory search.

ID	Etiology	Gender	Handedness	Onset	Education	WAIS VIQ	WAIS PIQ	WAIS FIQ	WMS GMI	WMS DMI
1846	Anoxia	F	R	1993	14	89	79	84	57	62
2308	HSE	M	L	1999	16	95	78	87	45	48
2363	Anoxia	M	R	1998	16	112	83	98	73	74
2563	Anoxia	M	L	2000	16	98	105	102	75	80
1846c	--------	F	R	-------	16	122	155	143	120	-----
2308c	--------	M	L	-------	16	112	113	113	114	-----
2363c	--------	M	R	-------	16	115	98	108	122	-----
2563c	--------	M	L	-------	16	135	91	115	98	-----

Table 1.1. Demographic and neuropsychological data for the patients and comparison participants (noted by a 'c' following the ID for the matched patient) tested in experiments 1 and 2. Note that 2308c and 2563c are also matches for each other's patients. WAIS - Wechsler Adult Intelligence Scale – III; VIQ – verbal IQ; PIQ – performance IQ; FIQ – full IQ; WMS – Wechsler Memory Scale – III; GMI – general memory index; DMI – delayed memory index; HSE – herpes simplex encephalitis. Etiology and onset are presented only for the patients. Education is measured in years. WMS DMI score was not available for the comparison participants.

2. The Effects of Hippocampal Lesions on Novelty Orientation

2.1. Abstract

It has long been established that eye movements are sensitive not only to the contents of memory but also of goals or intentions. This feature was leveraged in the current experiment to examine the importance of the hippocampus for novelty processing as a retrieval orientation or goal. Novelty has been studied across a variety of paradigms and has consistently been associated with the hippocampus, but rarely in the realm of goals. The current study tested amnesic patients with hippocampal damage to neurologically intact control participants. Both groups studied famous and non-famous faces and then were asked to either look at these faces (familiarity orientation) or look at a novel face (novelty orientation), following a paradigm used by Ryan et al. (2007). Eye movements were monitored during the test phase to provide sensitive measures of how viewing was affected by both memory content and goal. The results show that hippocampal damage had no effect on the ability of the amnesic patients to follow a novelty orientation, although they did show viewing patterns consistent with a memory deficit. This result obtained even for a class of familiar stimuli (unstudied but famous faces) that evoke an odd pattern of viewing. We conclude that the hippocampus is not critical for novelty processing at the goal level, and following a claim from a recent review of the novelty literature (Kumaran & Maguire, 2007), it is possible that the hippocampus is not important for novelty processing at all.

2.2. Introduction

Eye movements have proven very useful in evaluating the contents of memory (Hannula et al., 2010). For example, the pattern and duration of eye movements change when participants view a famous face as compared to a novel face (e.g. Althoff & Cohen, 1999) or an experimentally-familiar (previously studied) as opposed to novel scene (e.g. Ryan, Althoff, Whitlow, & Cohen, 2000; Smith, Hopkins, & Squire, 2006). Eye movements can also demonstrate memory for elements within scenes using either pre-existing/semantic information (e.g. Loftus & Mackworth, 1978; Underwood, Templeman, Lamming, & Foulsham, 2008) or within-experiment/episodic information (e.g. Becker & Rasmussen, 2008; Brockmole & Henderson, 2006; Ryan et al., 2000). In short, eye movements are sensitive to the contents of both semantic and episodic memory and at both the whole-scene and within-scene scales. Indeed, eye movements have been said to be automatically and obligatorily affected by memory (Ryan, Hannula, & Cohen, 2007).

Along with their response to memory, eye movements are also strongly influenced by goals and intentions (e.g. Hayhoe & Ballard, 2005). An extremely simple example is the anti-saccade task. In this task, a visual target appears in the periphery while participants look at fixation. Participants must then override the automatic tendency to look at the target and instead look in the opposite direction. The anti-saccade task describes, in essence, only a single eye movement in response to a sudden stimulus onset, but goal-directed viewing can also occur with much more complex tasks and materials. As described by Hannula et al. (2010), Yarbus collected eye movement data while participants viewed the same scene under a variety of questions or prompts. When no particular prompt was given (i.e., free viewing) participants tended to look at the large objects and people in the scene. But if asked how old the people were, viewing shifted to focus on the people alone; if asked how wealthy the family was, viewing shifted to focus on their clothes and the furniture in the room. Thus eye movements can also respond to goals; when asked to find certain kinds of information, people's eyes will move in such a way that the sought-for information can be found.

Eye movements are thus a strong choice of technique for studying novelty. Novelty detection or processing has been described as an essential function (Dudukovic & Wagner, 2007; Knight & Nakada, 1998) and has been examined in a number of paradigms. Research on novelty has been reviewed several times recently (Knight & Nakada, 1998; Kumaran & Maguire, 2007; Ranganath & Rainer, 2003) with the conclusion that the hippocampus is a critical member of a number of brain regions that support novelty processing (although see Kumaran & Maguire, 2007, for some potential qualifications). However, novelty processing has rarely been studied as a goal. If novelty processing is a unique function, then one would expect that eye movements would appear different under that goal than under another goal, such as looking for familiar information. Similarly, one might expect that the hippocampus would be critical for supporting such eye movements given its involvement in novelty across so many other domains.

The current experiment aims to address exactly those two predictions by expanding on research conducted by Ryan et al. (2007). That study reported three different experiments. In the first, participants viewed unfamiliar faces three times before entering a 'testing' block. One group of participants was asked to look at and choose a familiar face from an array of two or three faces filled out with novel lures, while a second group simply viewed the arrays under no particular instruction. Ryan et al. (2007) found that participants under recognition memory instructions tended to look preferentially at the familiar face over the novel faces while the free viewing group showed the opposite pattern. Thus eye movements responded differentially to participants' goals. In the second experiment, participants again studied a list of faces but in this case there were both unfamiliar as well as famous faces. Afterward they viewed test trials consisting of two novel and one familiar face; the familiar face could be a studied but

non-famous face, a studied and famous face, or a unstudied but famous face. They were told to choose any familiar face. While studied familiar faces were selected with near-perfect accuracy, unstudied but famous faces were only chosen 57% of the time. Eye movement data (from correct trials only) indicated that any familiar face quickly drew viewing, being fixated longer than novel faces as soon as 500 milliseconds after stimulus onset. Indeed, the duration of the very first fixation to a face was longer if that face was familiar compared to novel faces.

These results stand in contrast to those from the third experiment, which followed exactly the same structure except participants were asked to not look at any familiar face. In that case, viewing of familiar faces dropped off quickly with fixations to novel faces lasting longer than fixations to familiar faces. This occurred more quickly for studied famous faces (after 1000 milliseconds) than studied non-famous faces (after 2000 milliseconds), but the pattern of viewing for unstudied famous faces was more odd: they evoked longer fixations than novel faces early, within the first second of viewing, and were only rejected (viewed less than novel faces) nearly four seconds into the trial. Similarly, studied famous faces were found to evoke shorter fixations than novel faces on the second fixation to a face, but this was not true for the unstudied famous faces, which were viewed just as much as the novel faces. Across the three experiments, Ryan et al. (2007) provided ample evidence that eye movements respond to the goals of the participants. But due to how quickly the effects occur, and the differences between the second and third experiments, they concluded that memory has an automatic effect in driving eye movements.

The current experiment aims to expand on the Ryan et al. (2007) results and address the role of the hippocampus in novelty goal processing by testing the same paradigm on patients with amnesia due to hippocampal damage. Ryan et al. (2007) demonstrated that participants can follow instructions to look at novel stimuli (or, more specifically, to not look at familiar stimuli), but found eye movement data that suggest that 'familiarity processing' can, in some circumstances, have priority even under novelty instructions. We aim to replicate their most striking finding, the difficulty in rejecting famous faces simply because they were not studied in that experimental session. Additionally, if novelty processing is broadly supported by the hippocampus, it would be predicted that amnesic patients would have difficulty following novelty instructions or would demonstrate different eye movement patterns under novelty instructions compared to a control group.

2.3. Methods

2.3.1. Participants

The participants included three patients (two men, one woman) with amnesia following damage limited largely to the hippocampus. They have been described in detail in several papers by ourselves and

colleagues (patients 1846, 2363, and 2563; Konkel et al, 2008; Allen et al, 2006; see table 1.1). In short, each has damage to the hippocampus subsequent to a hypoxic/anoxic episode. Patients 2363 and 2563 suffered anoxia due to heart attack while patient 1846 had an allergic reaction. Memory impairments were confirmed with standardized tests such as the Wechsler Memory Scale (WMS). While performance on the WMS was very impaired, performance on intelligence (such as the Wechsler Adult Intelligence Scale) and executive function tests (including the Tower of London, Trail Making, and Wisconsin Card Sorting tasks) were normal. The lesions are localized in the hippocampus with little if any parahippocampal cortex involvement; this was confirmed with structural MRI for two patients and CT for the third (2563, who has a pacemaker; Allen et al, 2006; Hannula et al, 2006). To serve as control participants, we also tested four intact comparison participants (three men, one woman) matched individually to the patients by age, gender, and handedness (two comparisons were matched to the same patient). The amnesic patients were tested at the University of Iowa Carver Hospital and compensated according to the University of Iowa Human Subjects Committee and Internal Review Board while the control participants were tested at the University of Illinois Urbana-Champaign and compensated $10 per hour of testing according to the University of Illinois HSC and IRB. All participants provided informed consent before each testing session.

2.3.2. Apparatus

Eye movement data were collected on an EyeLink 1000 (SR Research) eye tracker. The eye tracker shines infrared light on the eye and calculates eye position by the location of the pupil and changes in the angle of light reflected back from the cornea. Eye position data were collected at 1000 Hz while participants sat comfortably using a chin rest. Point of gaze is determined by a calibration phase. A number of fixation crosses are presented at predetermined locations on the computer screen one at a time while participants are directed to look at the cross. The eye tracker uses the observed eye position and the known fixation cross position to calculate point of gaze on experimental trials. Point of gaze is measured with an average accuracy of .5 degrees of visual angle.

The eye tracker reports the onset and offset times of fixations and blinks and sends them to a Windows-based computer. Fixations are calculated on-line by the EyeLink software; fixations are defined as viewing left after blinks and saccades have been marked. The software identifies blinks by pupil size or blockage and saccades by the acceleration and velocity of the eye position. The final data provided by the eye tracker are a list of fixation positions and onset/offset times relative to the beginning of the trial. These data were parsed using a MatLab script to attribute the fixations to one of three regions of interest (ROI), each being defined by the position of a face on the computer screen. Fixations outside the ROIs were discarded. Additionally, fixations of less than 82 milliseconds were discarded. Fixation

durations to the ROIs were analyzed themselves as well as used to calculate other eye movement measures as described in the analysis section.

Presentation software was used for stimulus display. The initial session (described below) used Microsoft Office PowerPoint 2007. Statistical analyses were carried out in R.

2.3.3. Materials

The materials consisted of a pool of 204 male non-famous faces, 200 female non-famous faces, 225 male famous faces, and 151 female famous faces (see also Althoff and Cohen, 1999; Ryan et al, 2007). The non-famous faces were collected from a variety of sources such as hairstyling magazines to ensure that the general attractiveness and quality of the photographs were similar to the pictures of the famous people. 360 non-famous faces were selected randomly from the pool for use in the experiment; 72 famous faces were selected as described in the next section. The faces were presented in color at a size of 470 by 475 pixels with a screen resolution of 1280 x 1024 pixels.

2.3.4. Task and Design

Each participant underwent three testing sessions: an initial session to establish their knowledge of famous people and two experimental sessions. In the initial session participants saw all famous faces from the pool intermixed with 40 non-famous faces; faces were presented one at a time for participants to identify by name if possible or to describe in general otherwise. The non-famous faces were included so that participants would not feel that they should find every person famous. The high threshold of naming was used to ensure that the famous faces were indeed famous and strongly familiar. Participants' ability to identify the famous faces was used to determine what famous faces they would see in the later experimental sessions. One patient (1846) did not identify a sufficient number of famous faces by name, so additional faces were used so long as the patient remembered other details (such as if the person were an actor or what show she was on) or described the face as familiar. These additional faces were concentrated in their own blocks (see procedure section) to allow for separate analysis. However, performance was similar and so the blocks for all participants were combined in the analyses presented below.

In the experimental sessions participants studied a mix of nine famous and nine non-famous faces. These 18 faces were then presented again in a new randomized order, and this was repeated so that each face was seen five times. Study trials were presented for five seconds separated by one second of fixation. The study block was followed by a test block consisting of 36 trials. Each trial involved presenting three faces. Nine trials were 'catch' trials, consisting of three non-studied, non-famous faces. Nine were 'studied famous' trials, consisting of two non-studied, non-famous faces and one studied

famous face. Nine were 'studied non-famous' trials, consisting of two non-studied, non-famous faces and one studied non-famous face. Finally, nine trials were 'non-studied famous' trials, consisting of two non-studied, non-famous faces and one non-studied famous face. Test trials lasted for 7.5 seconds and were separated by 1.5 seconds of fixation. Two study and tests blocks were completed in a session so in total there were 18 test trials of each type (studied famous, studied non-famous, non-studied famous, and catch) under each instruction (novelty and familiarity) for each participant. Examples of study and test displays are presented in figures 2.1 and 2.2.

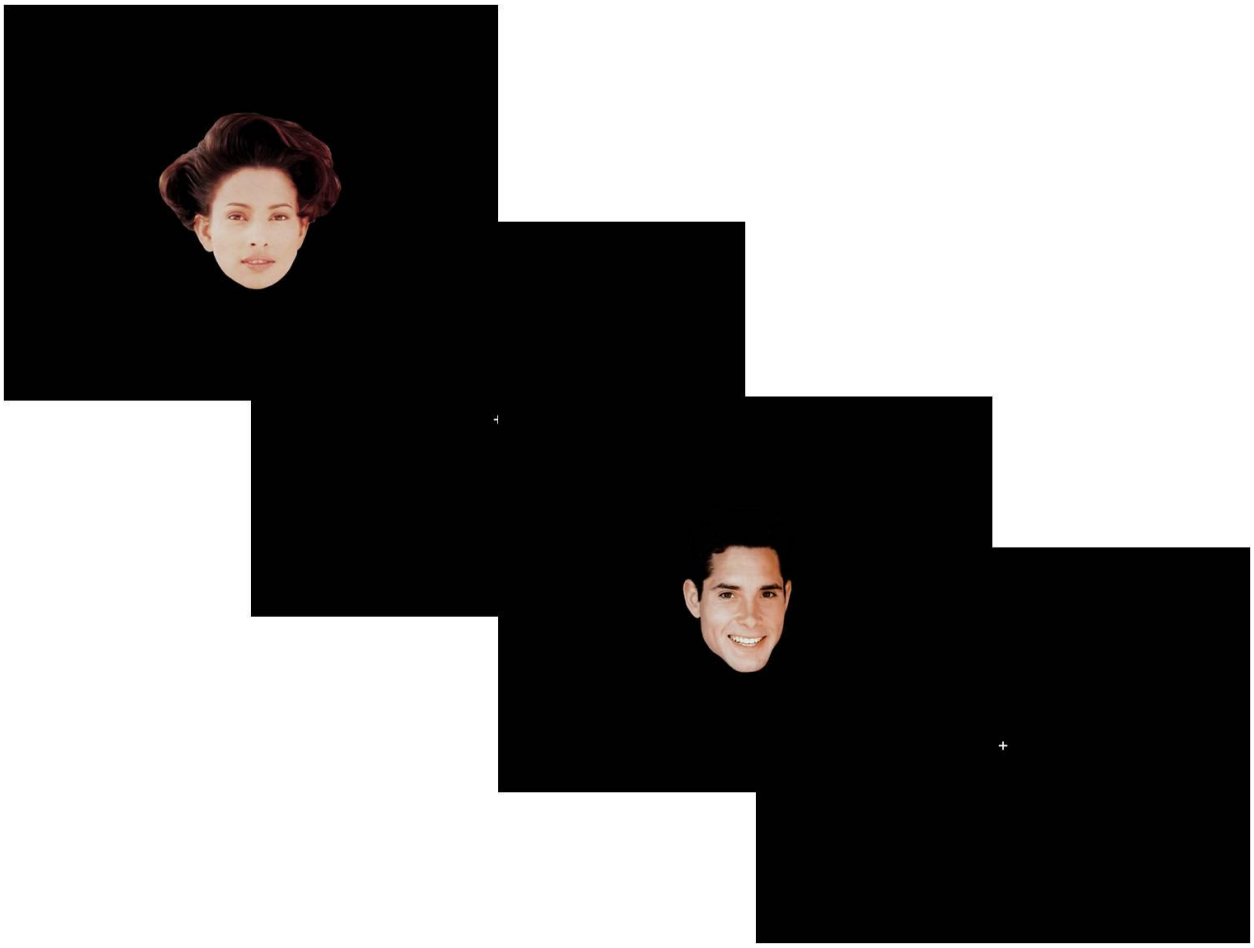

Figure 2.1. Sample study trials. Faces were displayed for five seconds and followed by one second of fixation. The examples are non-famous faces.

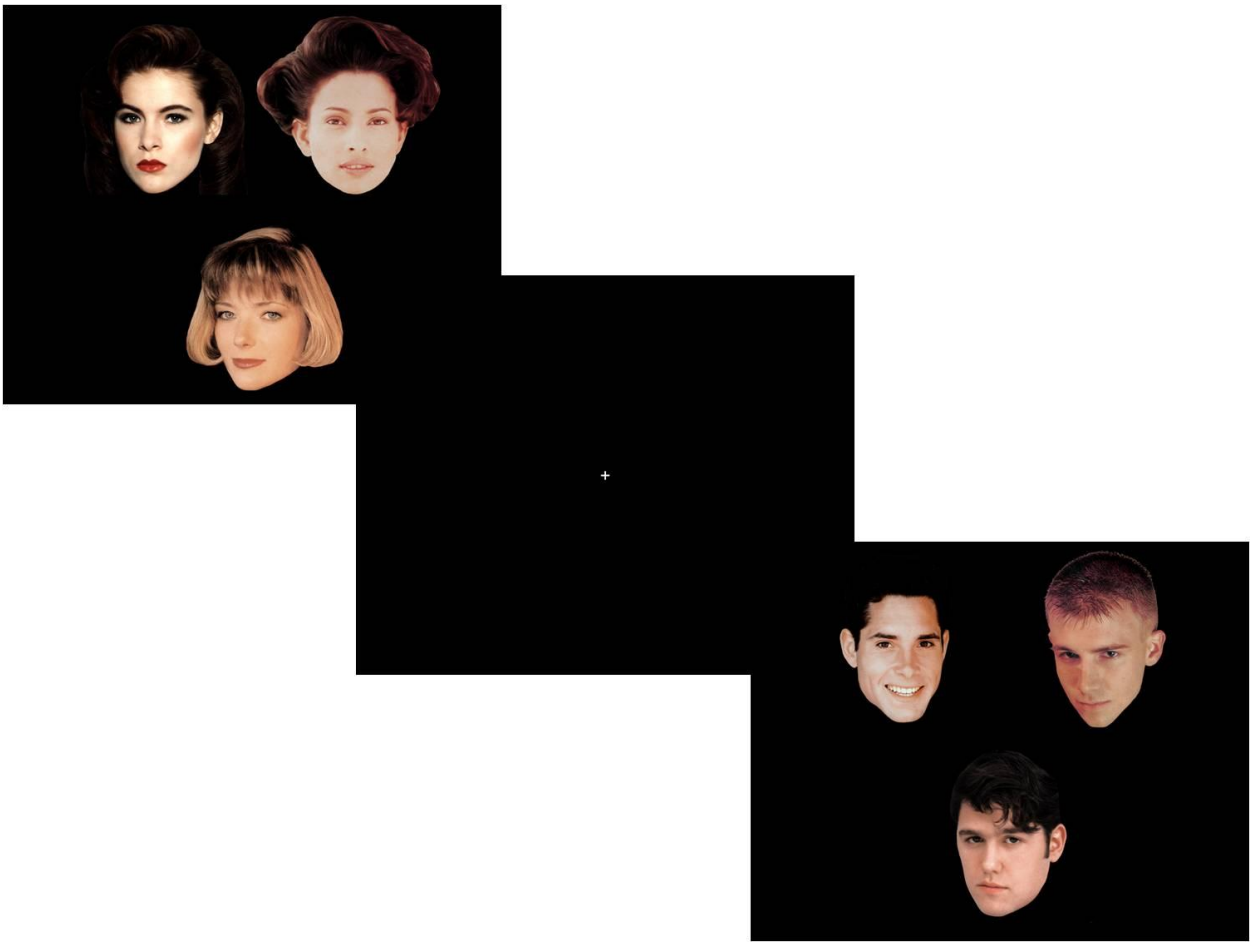

Figure 2.2. Sample test trials. Test trials lasted 7.5 seconds and were separated by 1.5 seconds of fixation. The examples are studied non-famous trials where the targets are the faces from figure 1 (top right face and then top left face).

Due to the small number of participants, no attempt was made to counterbalance the stimuli. Instead an experiment frame was created that assigned a role to each trial number; for example, study trial one was famous face number eight, study trial two was non-famous face number five, etc. Test trial one was a studied non-famous trial using non-famous face number two, and so on. Each participant then received the same order of trial types, which controls for any potential trial type order effects. The position of the familiar face on test trials was counterbalanced for each face type so that each of the three positions contained a familiar face equally often. Non-famous faces, whether seen at study or only at test, were constant across participants and always seen on the same trial number. Famous faces were randomly assigned to slots for each participant (e.g. famous face eight might be Demi Moore for one participant and Julia Roberts for another). When possible, the same famous faces were seen by all participants; 22 faces were used for all seven participants, 20 were used for six, and 28 were used for five. The same experiment frame was used to create each block for every participant.

Non-famous, non-studied faces seen on test trials were matched to the familiar face on gender. When possible, equal numbers of male and female faces were used throughout the experiment; however, two participants did not recognize enough female famous faces and thus saw more famous male faces.

2.3.5. Procedure

For the initial session, participants were seated in front of a laptop and received verbal instructions from the experimenter. They were told that they would see a series of faces one at a time and were to report (either verbally to the experimenter or by typing on the computer) the name of each person if possible, or what they knew about that person (if they were familiar, what their job was, or other details). They were also told that some non-famous faces were included so they should not expect to recognize every face. Participants had as much time as they wanted to respond to each face.

Several weeks to a month later, participants were tested in the experimental sessions. The experimental sessions were generally similar to experiments 2 and 3 in Ryan et al (2007). Each participants' first session used novelty instructions while the second experimental session was run under familiarity instructions. Sessions were separated by one to four weeks to avoid any potential contamination or confusion due to the different instructions, with the exception of one delay reaching two months and one delay being only a day due to patient availability. Participants went through two blocks in each session, with each block consisting of a study and test phase. The study phase consisted of nine famous and nine non-famous faces seen five times each for a total of 90 trials. Participants were asked to press the 'm' button on a computer keyboard if the face was male and the 'f' button if the face was female. Faces were presented for five seconds regardless of the participants' response; participants were asked to pay attention to the face for as long as it was on the screen. The gender judgment was used as an incidental task to ensure attention was given to the faces; responses were not actually recorded. Faces were separated by a fixation screen. Participants were not told that they would have their memory for these faces tested, although they may have expected it (particularly in the second block).

After the study phase, participants were given verbal instructions for the test phase. They were told that their eye movements would be collected during the test. On each trial, participants would see three faces. Under novelty instructions, participants were told that at least two of the three faces would be new, or novel faces that they had never seen before. No button response was needed, but participants were to find a novel face and look at it for as long as it was on the screen. No mention was made of famous or familiar faces; participants were encouraged to find a face that had never been seen before. Under familiarity instructions, participants were told that one face of the three would be familiar. It could be familiar either by being famous or by being a face they had just seen in the study phase. They were told to find the familiar face and look at it as long as it was on the screen. Participants were not told about

the catch trials (on which no face was familiar), but were told that if none of the faces seemed familiar they should still pick one face and look at it. After receiving instructions participants were asked if they had any questions, then settled into the chin rest. They were calibrated so that the eye tracker could determine their point of gaze (see apparatus section), then the test trials were presented. After the test block participants were told that the sequence would be repeated and they went through another study and test block under the same instructions.

2.4. Analysis and Results

The data from one familiarity block was lost from two comparison participants due to computer error and the data from one novelty block was lost from a third comparison participant due to an inability to track the participant's eyes because of her contact lenses. All statistical analyses were run with a significance threshold of alpha=.05; if an effect is described as significant but no p value is provided, the p is less than .00001.

Because no behavioral responses were required, all data analyses were conducted on the eye movement data collected during the viewing of test displays. These data take on two basic types: fixation durations and proportions of viewing time (see also Hannula et al., 2010). Fixation durations, as the name suggests, are the length of individual fixations to the display. The total viewing time for a test trial is the sum of the fixation durations on that trial. The proportion of viewing time is calculated for a given ROI (in this experiment, a face) on a given test trial by dividing the sum of the fixation durations to that ROI by the total viewing time on that trial. For example, if a participant fixated the three faces on one trial for a total of 5 seconds, and the fixation durations to a famous face on that trial summed to 2.5 seconds, the proportion of viewing time for the famous face on that trial would be .5. Proportion of viewing time can also be calculated for subsets of a trial by binning the data (e.g. Hannula, Ryan, Tranel, & Cohen, 2007; Ryan, Hannula, & Cohen, 2007). In the current experiment, bins were set to a size of 500 milliseconds, creating 15 bins per test trial. Seven trials were removed due to no fixations being recorded on those trials.

Fixation Durations: The data were analyzed following Ryan et al (2007). First the data set was partitioned by orientation (novelty or familiarity) and by face type (studied and famous, non-studied but famous, or studied but non-famous). Fixation durations were log-transformed to attempt to account for the large positive skew in the distribution. Ryan et al (2007) found memory effects even on the first few fixations to a face; we limited analysis to only the first fixation because some faces only received a single fixation during a trial. The mean first fixation durations for comparison and patient participants are below in figures 2.3 and 2.4.

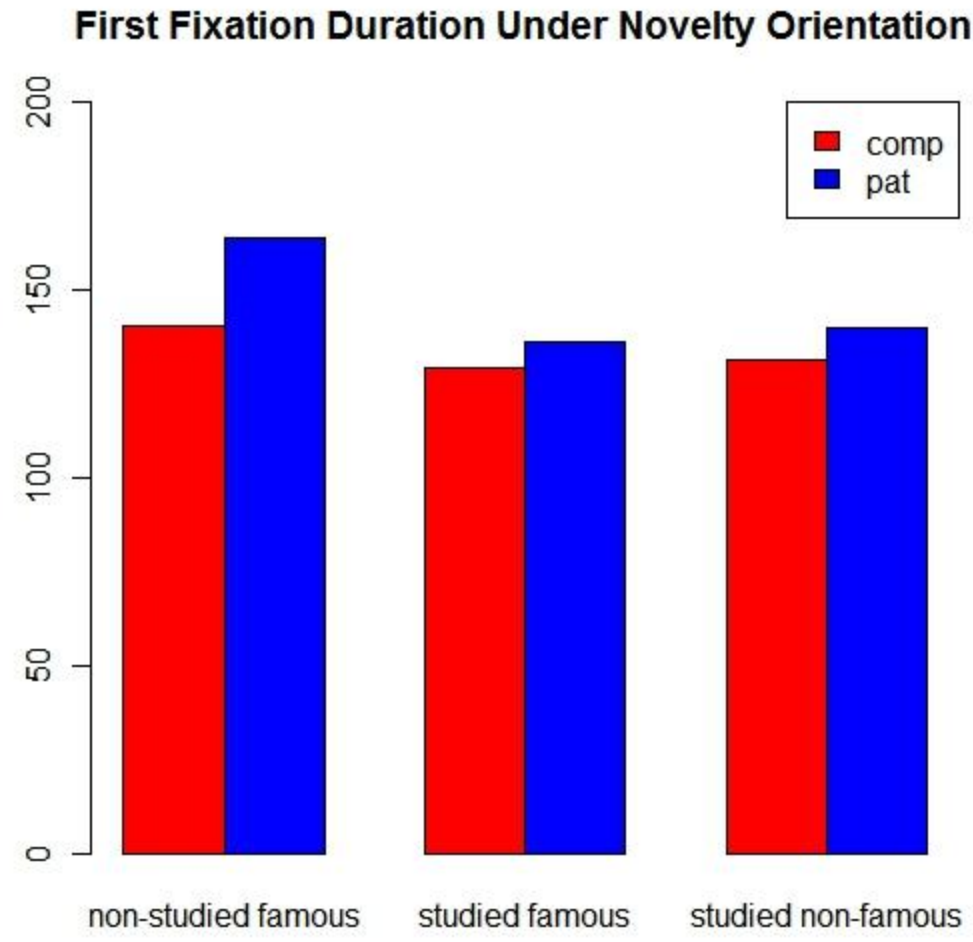

Figure 2.3. Mean first fixation duration to different familiar face types under novelty instructions for comparison and patient participants.

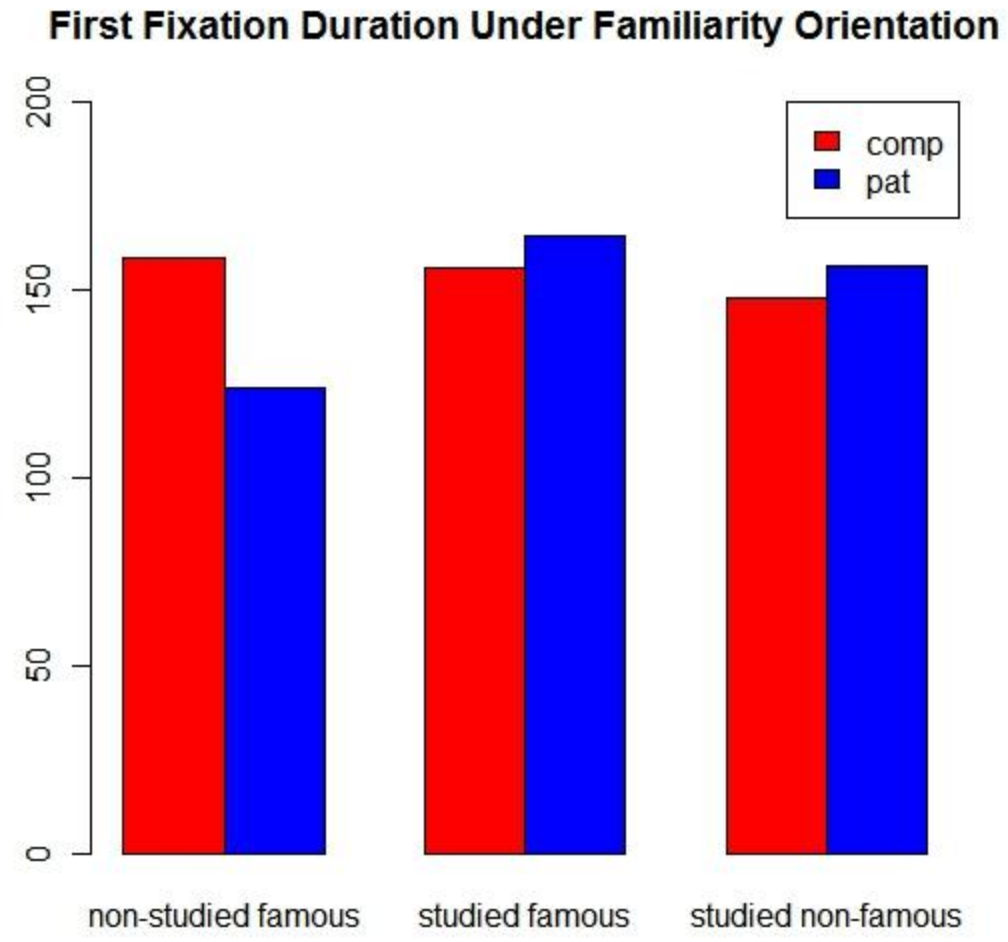

Figure 2.4. Mean first fixation duration to different familiar face types under familiarity instructions for comparison and patient participants.

The log-transformed fixation durations were analyzed with a regression model using group (patient or comparison), face type (non-studied famous, studied famous, or studied non-famous), and orientation (novelty or familiarity) as predictors. The three-way interaction was not significant so it was removed from the model. A significant two-way interaction (p=.044) was found between face type and orientation such that studied famous faces evoked shorter fixations than unexpected famous faces but only under novelty instructions; no other significant effects were found. This analysis included the novel lure faces (not shown in the figure); while non-significant, both groups demonstrated numerically longer first fixations to familiar faces under familiarity instructions and roughly equivalent fixation durations to familiar and novel faces under novelty instructions. The only exceptions were the unstudied famous

faces, which evoked longer fixations than novel faces under novelty instructions. Critically, there was no main effect or interaction due to group, indicating that at least on the first fixation to any given face hippocampal damage had no influence on viewing. To allay concerns that the lack of significant results was due to low power, the analysis was run again on both first and second fixations. The results did not change.

Following Ryan et al (2007), fixation durations were also partitioned into time bins throughout the trial. For example, the 0-500 millisecond bin contains the average fixation duration for fixations that happen in the first half second after stimulus onset. This allows for analysis of the changes in viewing patterns throughout the course of a trial. These data were analyzed as above, using the log-transformed durations in a regression model, but bin number was added as an additional predictor variable. The four and three-way interactions were not significant but, consistent with the analysis above, there was a significant two-way interaction such that in the novelty condition studied famous faces elicited shorter fixations than non-studied famous faces ($p=.009$). A similar effect was found for the studied non-famous faces, but only at a trend level ($p=.09$).

The trend interaction suggested that in the novelty condition, both groups had longer fixation durations over the course of a trial to the unexpectedly familiar (non-studied) famous faces than the studied face types. This may be an analogous effect to the one found by Ryan et al (2007) such that the unexpected familiar faces grabbed attention more than the studied familiar faces. However there was no effect of hippocampal damage, and in the current work the effect occurred throughout the trial whereas Ryan et al (2007) found that the non-studied famous faces were eventually rejected and received less viewing later in the trial.

Proportion of viewing: Initial analyses were carried out on proportion of viewing calculated over the full length of the trial. The mean proportion of viewing time for both groups to different face types is presented in figures 2.5 and 2.6. A generalized linear model was fit to the data predicting proportion of fixation from group, orientation, and face type. All coefficients were strongly significant, so follow-up analyses were conducted to explore the results.

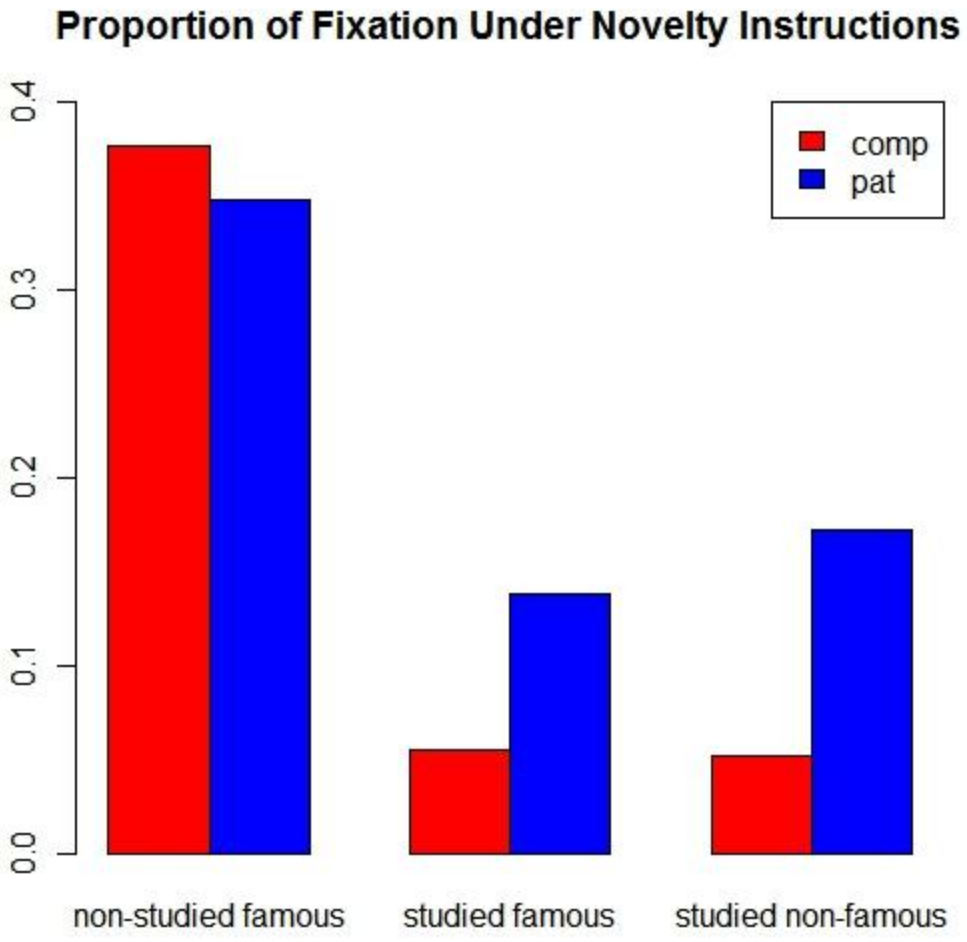

Figure 2.5. Proportion of viewing time over the whole trial separated by how a face was familiar and group under novelty instructions. Note that with three faces being present on screen, random viewing would be .33.

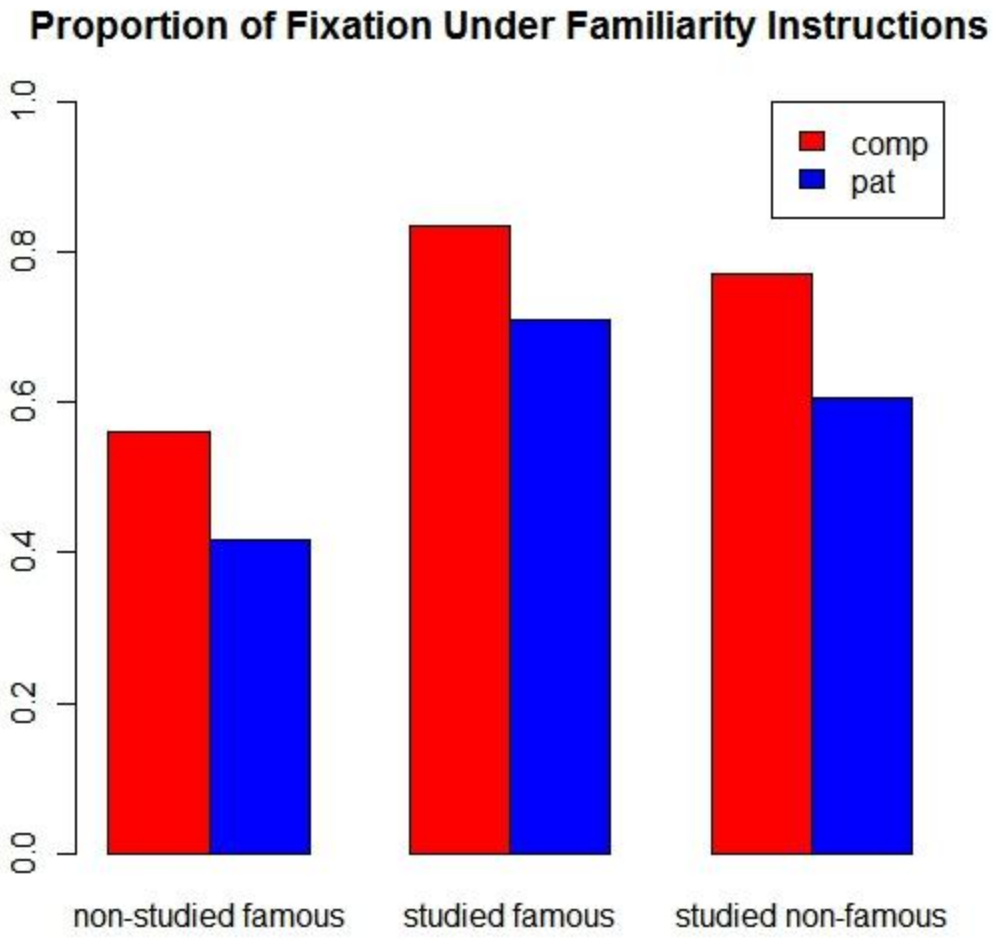

Figure 2.6. Proportion of viewing time over the whole trial separated by how a face was familiar and group under familiarity instructions. Note that with three faces being present on screen, random viewing would be .33.

As can be seen by comparing figures 2.5 and 2.6, participants were readily able to look at the familiar faces under familiarity instructions but not look at them under novelty instructions. However, non-studied famous faces evoked different amounts of viewing than studied famous or studied non-famous faces: the significant three-way interaction suggests that these effects differed between the patients and comparison participants. Similar regression models were fit to the data from the familiarity and novelty conditions separately to elucidate the results. In the familiarity condition, the two-way interaction between group and face type was significant; comparison participants directed more viewing to the familiar face than patients and this effect was exaggerated for the unexpectedly familiar famous faces. Conversely, the comparison participants were relatively worse at rejecting the unexpectedly

familiar famous faces; this effect was verified via a significant two-way interaction in the novelty condition data between group and face type.

To produce a timecourse of viewing, each trial was divided into 500 millisecond bins as was done for the fixation duration data. The proportion of viewing time was then calculated as above, but within each bin. Notably, the timecourse data can be analyzed to determine when viewing of familiar faces deviates from the chance level of .33. The timecourses corresponding to figures 2.5 and 2.6 are presented in figures 2.7 and 2.8.

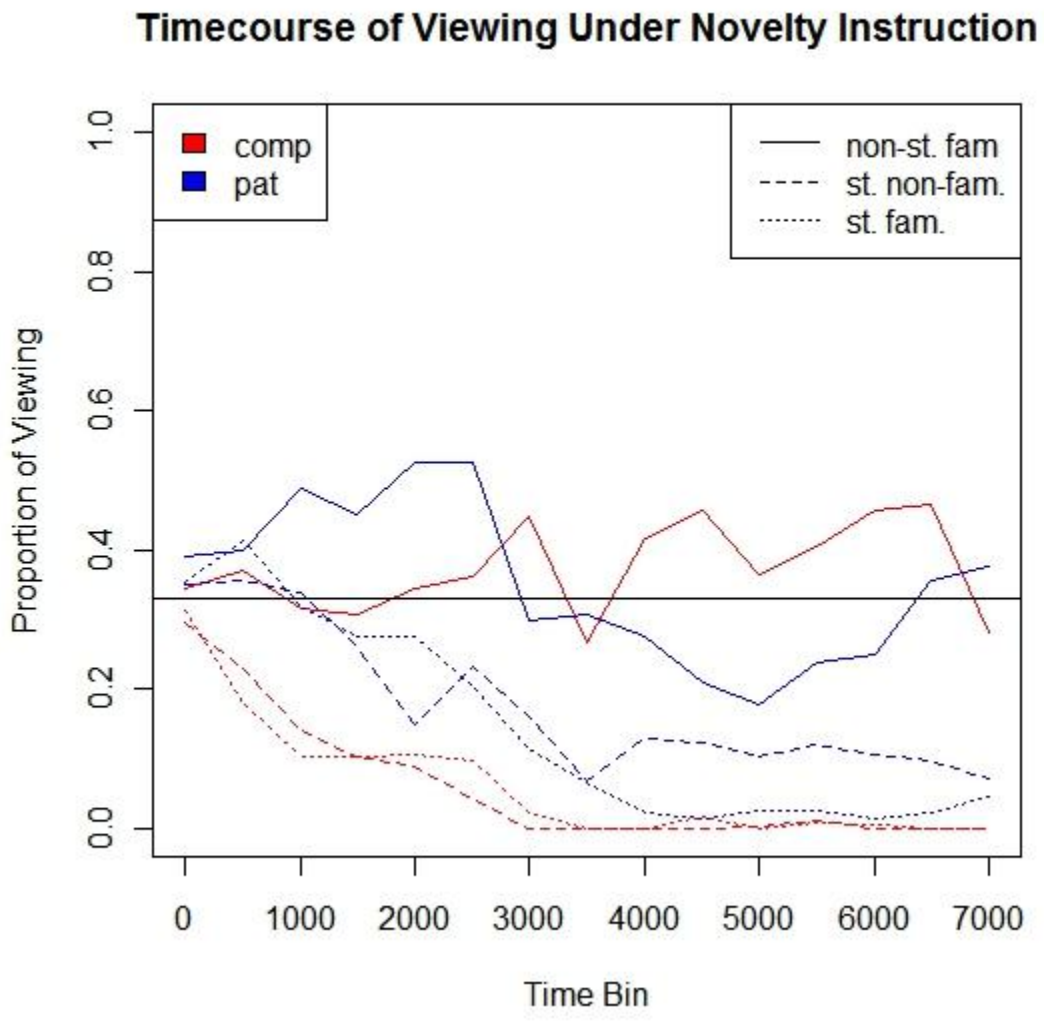

Figure 2.7. Timecourse of proportion of viewing time under novelty instructions. Note that chance viewing is .33 as indicated by the solid black line.

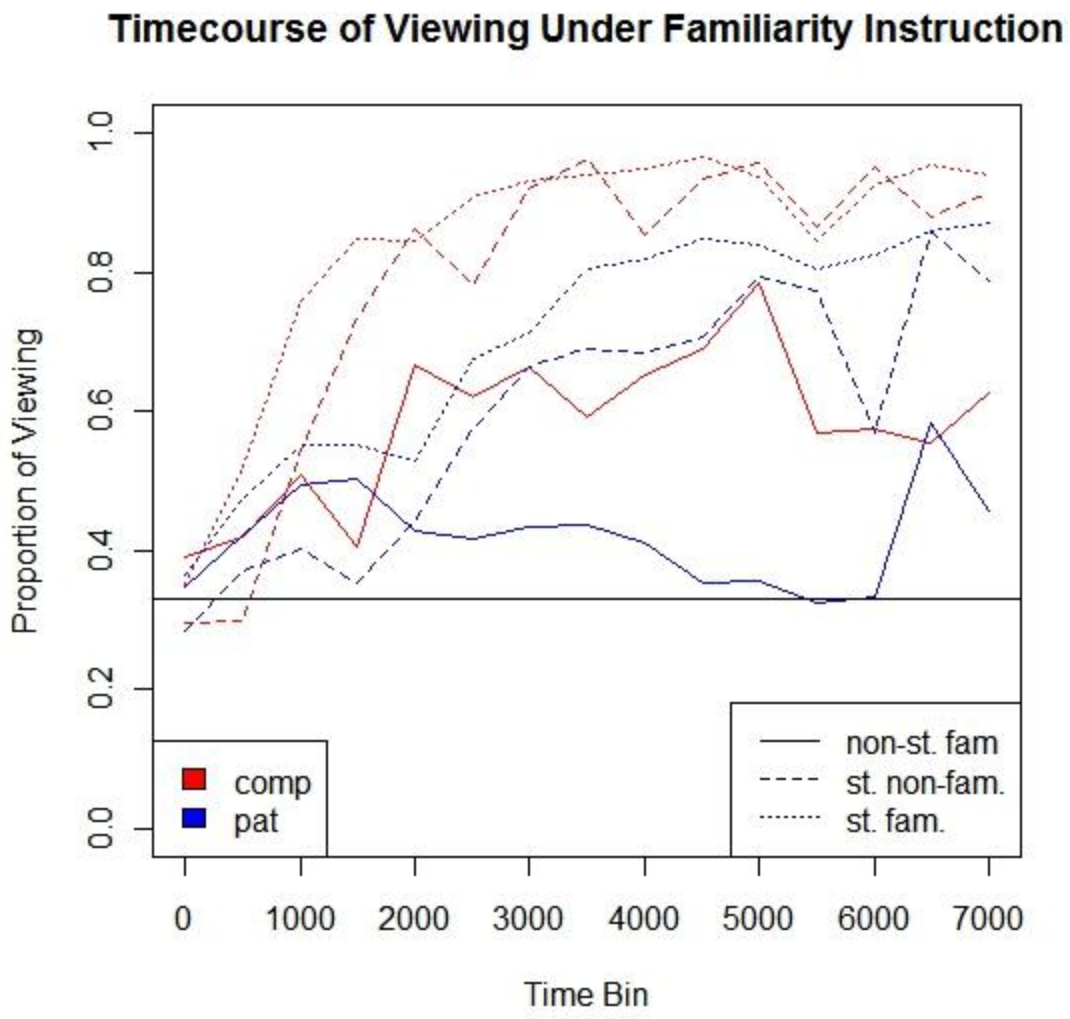

Figure 2.8. Timecourse of proportion of viewing time under familiarity instructions. Note that chance viewing is .33 as indicated by the solid black line.

Consistent with what was found for the whole-trial analysis, there was a significant interaction between group, orientation, and face type; this effect was mediated by a four-way interaction with bin number. The data were split into novelty and familiarity conditions as previously, and again the interaction between group, face type, and bin number was significant. Under novelty instructions, the comparison participants drove their viewing of familiar faces closer to 0 than patients did. However, this did not occur for the non-studied famous faces; the groups viewed these faces at approximately chance levels. The converse was true under familiarity instructions; comparison participants viewed the familiar faces at near-ceiling levels, higher than the patients. However, the non-studied famous faces did not

evoke as much viewing. And in contrast to the novelty condition, comparison participants appeared to begin to correctly view the non-studied famous face more as the trial went on; the patients did not.

To quantify those impressions, the patient and comparison participants' proportion of viewing in each time bin was tested to determine when viewing went above (for familiarity trials) or below (for novelty trials) chance. These proportions were tested with one-tail t-tests against a proportion of .33; due to the small sample size, they should be viewed with some caution. In the familiarity condition, patient viewing was significantly above chance after 500 milliseconds (in the second time bin) for studied famous faces ($p=.017$), 1000 milliseconds for studied non-famous faces ($p=.044$), and after 500 milliseconds for non-studied famous faces ($p=.01$). However, the viewing of non-studied famous faces decreased to chance levels in the next time bin and as the trial went on remained at chance levels. Comparison participants showed the same general pattern with viewing rising above chance for studied famous faces after 500 milliseconds ($p=.01$), after 1000 milliseconds for studied non-famous faces ($p=.015$), and after 1000 milliseconds for non-studied famous faces ($p=.045$). However, in contrast to the patients, viewing to non-studied famous faces remained numerically above chance and near trend levels of significance (unadjusted for multiple comparisons) for most of the remaining time bins. The patterns under novelty instructions were similar. Comparison participants directed lower than chance levels of viewing to studied non-famous faces after 1000 milliseconds ($p=.0005$) and studied famous faces after 500 milliseconds ($p=.018$) while patients did so after 2000 milliseconds ($p=.028$) and 1500 milliseconds ($p=.029$) respectively. However, both groups viewed the non-studied famous faces at chance levels throughout the length of the trial.

In summary, no effect of group was found on the fixation duration to the different kinds of familiar faces. The only significant effect of note, appearing in both the first fixation and timecourse analyses, was an interaction between orientation and face type. Under familiarity instructions, unexpectedly familiar famous faces evoked numerically shorter fixations than the two studied face types. However, under novelty instructions, fixation durations to studied faces decreased while the fixations to non-studied famous faces became slightly longer. The interaction with time bin was not significant, so this difference appears to have occurred throughout the trial, even in early viewing. Additionally, the effect did not differ between patients and comparison participants. It appears that the unexpectedly familiar faces provided a conundrum for the participants: under familiarity conditions they were unexpected or perhaps not familiar enough, evoking shorter fixations than the studied faces, but under novelty conditions they were familiar enough to evoke inappropriate viewing while the studied faces were rejected more thoroughly and thus evoked shorter fixations. A similar pattern was found in the proportion of viewing time data; both patients and comparison participants had difficulty properly viewing or

rejecting the non-studied famous faces. This effect was further complicated by the finding that the comparison participants appropriately raised their viewing of the non-studied famous faces above chance under familiarity instructions, but failed to ever reject these faces (i.e. view them at less than chance levels) under novelty instructions. A clearer pattern that is not present in the fixation duration data was found for the studied faces: famous faces were more easily accepted and rejected than non-famous faces, and amnesic patients had more difficulty separating their viewing of familiar faces from the novel lure faces. This preferential viewing happened quickly, in less than 1500 milliseconds for studied faces for both patients and comparison participants under both novelty and familiarity instructions (with one exception: studied non-famous faces fell below chance under novelty instructions for patients after 2000 milliseconds).

2.5. Discussion

The current experiment investigated the effects of hippocampal damage on novelty processing as a goal/retrieval orientation. The paradigm followed that of previous work by Ryan et al. (2007), who used instructions to manipulate what participants would search for while looking at three-face displays. Two questions were of primary concern: what effect does hippocampal damage have on novelty processing within the goal domain, and do unstudied but famous faces evoke odd patterns of eye movements, as in Ryan et al. (2007)?

Addressing the first question, we found no effect of hippocampal damage on retrieval orientation. Under both familiarity and novelty instructions, patients demonstrated eye movements similar to those of their comparison group. Under familiarity instructions both groups properly viewed the familiar face, with the effect becoming more prominent over the course of the trial; under novelty instructions, both groups demonstrated the opposite. The amnesic patients were less able to properly view or reject the familiar faces than the comparison group; while comparison participants viewed studied faces nearly 100% of the time late in a familiarity trial and novel faces 100% late in a novelty trial, the patients tended to still direct some viewing to inappropriate faces under either instruction. This is likely due to their memory impairment, an idea at least numerically supported by the difference in viewing for studied famous and studied non-famous faces. The non-famous faces, which should have weaker representation in memory, were viewed less appropriately than the famous faces, which should have a stronger representation in memory; eye movements are known to scale with repetition (Hannula et al., 2010), and thus probably also with memory strength. The full acceptance (or rejection) of studied faces by the comparison group is likely a sign that the five study trials were sufficient to drive memory of those faces to ceiling.

In regard to the second question, we confirmed the differential viewing of famous but unstudied faces found by Ryan et al. (2007). However, our pattern of results was somewhat different. Ryan et al. (2007) observed that participants directed longer fixation durations to unstudied famous faces early in a trial under novelty instructions but that this effect went away and reversed after several seconds, when participants correctly started to direct more viewing to the novel faces. Under familiarity instructions, participants correctly viewed these faces early and throughout the trial. In the current experiment, the comparison group did direct above-chance levels of viewing to unstudied famous faces but the effect was smaller than what was observed for the two classes of studied faces. The amnesic patients also directed viewing to these faces early, but the effect then dropped off to chance levels throughout the rest of the trial. Under novelty instructions, however, neither group ever viewed the unstudied famous faces differentially from chance; they were viewed roughly as much as the novel faces over the entire course of the trial and were never rejected. It is unclear why the pattern of viewing differed from what was found by Ryan et al. (2007); there were small changes in the paradigm and analyses as well as a larger change in the participant sample. However, both studies agree that unstudied famous faces evoke a far different pattern of viewing than either studied non-famous or studied famous faces.

Ryan et al. (2007) proposed two reasons that the unstudied famous faces could elicit this odd pattern of viewing: it could be because the unstudied face has no exact match in memory, or because the face is so novel in the experimental context that it automatically captures viewing. We believe that the second explanation is more likely; the unstudied famous faces are unexpected and thus participants are unsure of how to treat them. It is important to note, however, that these faces are still famous (a fact verified by each participant having provided the name matching the face in the initial session of the study), and other famous faces are also presented equally often during the testing phase. Thus the unstudied famous faces can only be unexpected if the participant has some expectation that familiar faces will come from the study phase, even though they are told to look at (or not look at) a face that is familiar for any reason. This would imply that the differential viewing of the unstudied famous faces is a kind of contextual effect. Alternatively, it is possible that participants set a high criterion for deciding a face is familiar due to the extensive viewing during study. An unstudied famous face, while famous, could potentially be less familiar during the test phase than a non-famous face that was studied five times just prior to test. These faces would then be more familiar than a completely novel face, yet fall below the threshold set for most familiar faces. Further research is necessary to tease out exactly why the unstudied famous faces elicit different viewing than the studied faces, but the effect does appear to be real. Additionally, the effect does not appear to depend on the hippocampus.

In conclusion, hippocampal amnesics demonstrated no deficit in regards to novelty processing as a goal. The patients appeared to perform the task in the same manner as the comparison group, although their viewing was not as strongly differentiated due to their memory deficit. Even in the case of unexpectedly familiar stimuli, namely unstudied but famous faces, their viewing patterns were similar to those of intact control participants. Thus hippocampal lesions had no effect on novelty processing due to memory strength (i.e. famous faces were viewed more appropriately than non-famous faces), expectations (the unstudied famous faces), or retrieval orientation. Given extant theories of hippocampal function in regards to memory (e.g. Kumaran & Maguire, 2007), it is possible that the hippocampus isn't involved in novelty processing at all, and instead only appears to do so because of its role in encoding and retrieval processes. Further investigation and clarification of the representations and computations involved in novelty processing is necessary, however, before such a claim is made in such a long-standing body of research.

3. The Effects of Hippocampal Lesions on Retrieval Orientation and Working Memory

3.1. Abstract

Novelty processing is described as a critical function for survival, and has often been connected to the hippocampus. However, little research has examined novelty as a goal, and the experiments that have found mixed evidence that the hippocampus is important for supporting novelty processing in that domain. The current experiment expanded on the literature by testing hippocampal damaged (amnesic) patients under both novelty and familiarity goals at both short and long delays. Additionally, eye tracking data was collected to give a more complete view of performance. We found that hippocampal damage had no impact on performance after a short delay, but did impair performance after a long delay. Critically, hippocampal damage had no influence on the novelty manipulation. Additionally, the eye tracking data provides some evidence that even under novelty instructions, participants prefer to work from a familiarity goal. These data are consistent with typical views of the hippocampus' role in memory as opposed to novelty processing.

3.2. Introduction

Novelty detection has been called an essential function for organisms to survive (Dudukovic, Preston, Archie, Glover, & Wagner, 2011; Knight & Nakada, 1998). It is certainly necessary for exploratory behavior; in order to explore new environments or investigate changes within familiar locations, first an organism must determine that something is in fact novel. Thus it is fitting that novelty detection and processing has been studied in a variety of paradigms and with a variety of techniques. For example, novelty processing has been studied with event related potentials (ERPs) in the novelty oddball paradigm (e.g. Cycowicz & Friedman, 1999), behaviorally and with ERPs in the von Restorff paradigm (e.g., Karis, Fabiani, & Donchin, 1984; Kishiyama & Yonelinas, 2003), and behaviorally and with positron emission tomography/functional magnetic resonance imaging (PET/fMRI) in a familiarization paradigm (e.g., Tulving & Kroll, 1995; Tulving, Markowitsch, Craik, Habib, & Houle, 1996).

Interestingly, given the range of paradigms involved, many types of novelty processing have been tied to the hippocampus. Knight (1996), for example, found that lesions to the medial temporal lobes (MTLs) focusing on the hippocampus reduced or eliminated the novelty P3 component. Converging evidence was found by Yamaguchi, Hale, D'Esposito, & Knight (2004) during an fMRI version of the novelty oddball paradigm, observing hippocampal activity that matched up well with patterns predicted by the ERP literature. Kishiyama, Yonelinas, & Lazzara (2004) found that hippocampal lesions eliminated the mnemonic benefit of novel materials in the von Restorff paradigm. And Tulving et al (1996) found that the hippocampus is more active while participants saw lists composed mostly of novel,

previously unstudied words compared to lists composed mostly of familiar, previously studied words; similar comparisons by Kirchhoff, Wagner, Maril, & Stern (2000) and Stern et al. (1996) confirmed this finding. In short, novelty is often found to produce more activity in the hippocampus than familiar or expected materials, and hippocampal damage often destroys novelty-based effects.

One arena in which novelty processing has received relatively less study is within the domain of goals. Novelty is typically an incidental feature of stimuli as far as participants are concerned; novel stimuli are unexpected and unresponded-to in the novelty oddball paradigm and novel stimuli are to-be-remembered just as all stimuli are in the von Restorff and familiarization paradigms. What happens when participants intentionally search for novel materials? Only a few experiments we are aware of have examined this question. Monk et al. (2002) measured hippocampal activity with fMRI while participants performed both delay-match-to-sample (DMS) and delay-non-match-to-sample (DNMS) tasks. Because the current experiment follows a similar design, the Monk et al (2002) study will be described in some detail. Participants underwent trials consisting of four phases: encoding, delay, test, and the inter-trial interval. During encoding an abstract stimulus was shown; each stimulus consisted of a square made up of four smaller, differently-colored squares with various abstract patterns contained within. Participants were told to remember the stimulus and then did so across the delay period, which was a 15-second unfilled time gap. In the test phase they were shown two stimuli, one that was the same as the encoded stimulus and one that was different. In DMS blocks, participants were asked to chose the matching stimulus at test; in DNMS blocks, participants were asked to chose the novel stimulus. Thus the trial layout and stimulus presentation were identical for the DMS and DNMS tasks, but in one case the participants' goal is to find a familiar (studied) stimulus while in the other their goal is to find a novel stimulus. Compared to a color-counting baseline task, the hippocampus was more active during the encoding phase under both DMS and DNMS instructions. However, it was not significantly more active during the delay or testing periods. Relevant to the current question, this suggests that novelty and familiarity goals may not be different (behavioral performance was also the same under both instructions), and moreover that the hippocampus may not be differentially involved in processing novelty as a goal.

Supporting the Monk et al (2002) null result, Dobbins & Wagner (2005) found that the hippocampus was equally active while participants made a novelty decision or one of two different source judgments in a long-term memory paradigm. However, using a temporal recency judgment instead of source memory, Dudukovic & Wagner (2007) found that the hippocampus was more active when participants made novelty judgments. While a one-in-three success rate for finding differential hippocampal activity is not particularly strong, Dobbins & Wagner (2005) noted two reasons that their

design may not be optimal for finding a difference. First, analyses were conducted only on correct trials. If the hippocampus were sensitive to different retrieval goals, it may also be sensitive to retrieval success; analyzing only correct trials would reduce this potential difference. Second, the forced-choice test trials mean that each test trial contains both novel and familiar stimuli, which may have evoked a similar response regardless of the test instruction. The second reason applies to all three studies just discussed, but Monk et al (2002) did analyze all trials, not just those with correct responses.

In addition to these fMRI studies, we are aware of one experiment that has compared novelty and familiarity goals using a patient with hippocampal damage. Freed & Corkin (1988) tested patient H.M.'s memory for pictures six months after they had initially been encoded. H.M. received additional study time compared to his control group so that initial memory (after a 10 minute delay) would be at an equivalent level. At this later test, H.M. was given standard yes-no recognition and two-alternative-forced-choice (2-AFC) tests and performed worse than the controls. However, H.M. was also given yes-no recognition and 2-AFC tests with instructions to look for novel stimuli, and he performed as well as the control group. Part of that is due to the control group performing numerically worse on the novelty versions of the tasks, but H.M. also performed numerically better on the novelty versions of the tasks. The authors claimed that H.M. may have developed a novelty preference as a result of his surgery.

The current experiment aimed to further investigate novelty processing in the goal domain and to examine the role that the hippocampus plays in supporting such judgments. Following Monk et al (2002), Dobbins and Wagner (2005), and Dudukovic and Wagner (2007), forced-choice was used as the testing paradigm. Following the experiments from the Wagner group, goal (novelty or familiarity) was manipulated at the trial level. However, the current experiment expands on the literature by testing after both short and long delays as well as testing multiple patients with hippocampal damage. It also uses eye tracking to supplement the behavioral data. Following the majority of the novelty literature, it would be predicted that hippocampal damage should impair performance on novelty goal trials.

3.3. Methods

3.3.1. Participants

The participants included three patients (two men, one woman) with amnesia. They have been described in detail in several papers by ourselves and colleagues (patients 1846, 2363, and 2308; Konkel et al, 2008; Allen et al, 2006; see table 1.1). In short, two have lesions limited largely to the hippocampus (1846 and 2363) subsequent to anoxia (2363 due to heart attack, 1846 due to allergic reaction) while the third (2308) has a much larger lesion due to herpes simplex encephalitis. Memory impairments were confirmed with standardized tests such as the Wechsler Memory Scale (WMS). While performance on

the WMS was very impaired, performance on intelligence (such as the Wechsler Adult Intelligence Scale) and executive function tests (including the Tower of London, Trail Making, and Wisconsin Card Sorting tasks) were normal. The lesions in the anoxic patients are localized in the hippocampus with little if any parahippocampal cortex involvement; this was confirmed with structural MRI (Allen et al, 2006). Patient 2308 has a larger lesion due to encephalitis; it includes the hippocampus and amygdala in the right hemisphere but is more widespread on the left and includes the entorhinal and perirhinal cortices (Konkel et al, 2008). While 2308 has a lower WMS memory score, his performance on other standardized tests is similar to the two anoxic patients.

To serve as control participants, we also tested four intact comparison participants (three men, one woman) matched individually to the patients by age, gender, and handedness (two comparisons were matched to the same patient). The amnesic patients were tested at the University of Iowa Carver Hospital and compensated according to the University of Iowa Human Subjects Committee and Internal Review Board while the control participants were tested at the University of Illinois Urbana-Champaign and compensated $10 per hour of testing according to the University of Illinois HSC and IRB. All participants provided informed consent before the testing session.

3.3.2. Apparatus

Eye movement data were collected on an EyeLink 1000 (SR Research) eye tracker. The eye tracker shines infrared light on the eye and calculates eye position by the location of the pupil and changes in the angle of light reflected back from the cornea. Eye position data were collected at 1000 Hz while participants sat comfortably using a chin rest. Point of gaze is determined by a calibration phase. A number of fixation crosses are presented at predetermined locations on the computer screen one at a time while participants are directed to look at the cross. The eye tracker uses the observed eye position and the known fixation cross position to calculate point of gaze on experimental trials. Point of gaze is measured with an average accuracy of .5 degrees of visual angle.

The eye tracker reports the onset and offset times of fixations and blinks and sends them to a Windows-based computer. Fixations are calculated on-line by the EyeLink software; fixations are defined as viewing left after blinks and saccades have been marked. The software identifies blinks by pupil size or blockage and saccades by the acceleration and velocity of the eye position. The final data provided by the eye tracker are a list of fixation positions and onset/offset times relative to the beginning of the trial. These data were parsed using a MatLab script to attribute the fixations to one of two regions of interest (ROI), each being defined by the position of an item on the computer screen. Fixations outside the ROIs were discarded. Additionally, fixations of less than 82 milliseconds were discarded. Fixation

durations to the ROIs were analyzed themselves as well as used to calculate other eye movement measures as described in the analysis section.

Presentation software was used for behavioral data collection and stimulus display. Statistical analyses were carried out in R.

3.3.3. Materials

The materials consisted of a pool of 503 computer-generated images (hereafter called 'items'; Konkel et al 2008). Examples of the items can be seen in figures 3.1, 3.2, and 3.3. All items are based on a rectangle but were created by changing the color, pattern, and texture of the rectangle as well as by adding or taking out various shapes. 480 items were randomly assigned to 160 triplets for use in the experiment proper and an additional 21 were randomly assigned into triplets for use in the practice phase. The items were presented at a size of 305 x 300 pixels with a screen resolution of 1280 x 1024 pixels.

3.3.4. Task and Design

The paradigm consisted of a series of short delay or working memory (WM) trials followed by long delay or long-term memory (LTM) test trials; the study phases for the LTM trials were intermixed with the WM trials. Within each triplet two items were assigned to be studied and one to be presented as a new item at test. Four types of trials were used: WM with a familiarity instruction (a DMS task), WM with a novelty instruction (a DNMS task), LTM with a familiarity instruction, and LTM with a novelty instruction. WM trials required the maintenance of two items for three seconds with no intervening stimuli or task whereas LTM trials required remembering the items for at least 10 minutes while performing the WM task on intervening items. Examples of the trial types are presented in figures 3.1 through 3.3.

Figure 3.1. A working memory trial with familiarity instruction (WMF; analogous to the DMS paradigm). The correct response would be to press the left button. Displays are presented for 2, 3, 3, and 4 seconds, respectively.

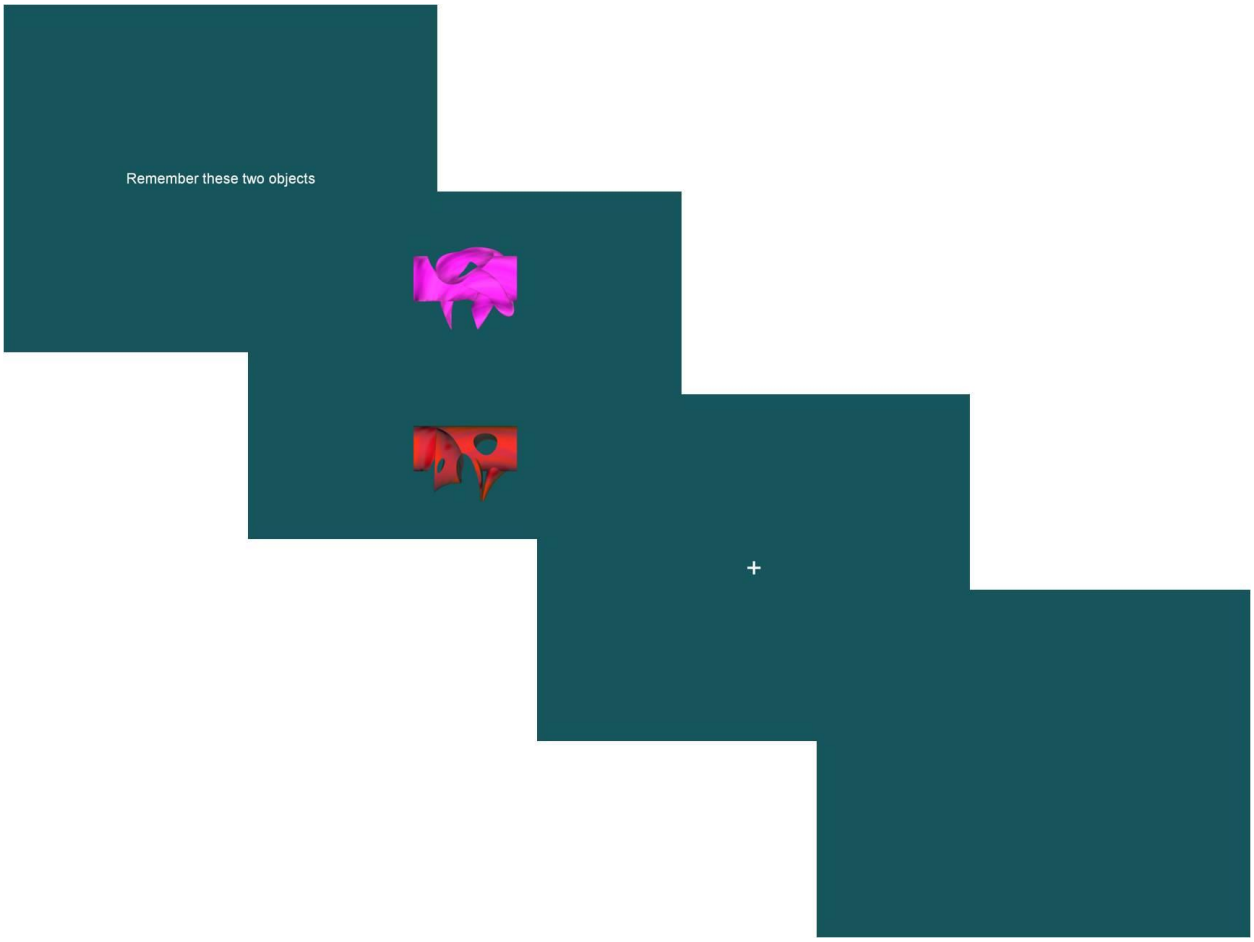

Figure 3.2. A long-term memory (LTM) study trial. These trials are intermixed with the WM trials. Timing is the same as on WM trials (2, 3, 3, and 4 seconds for each display, respectively).

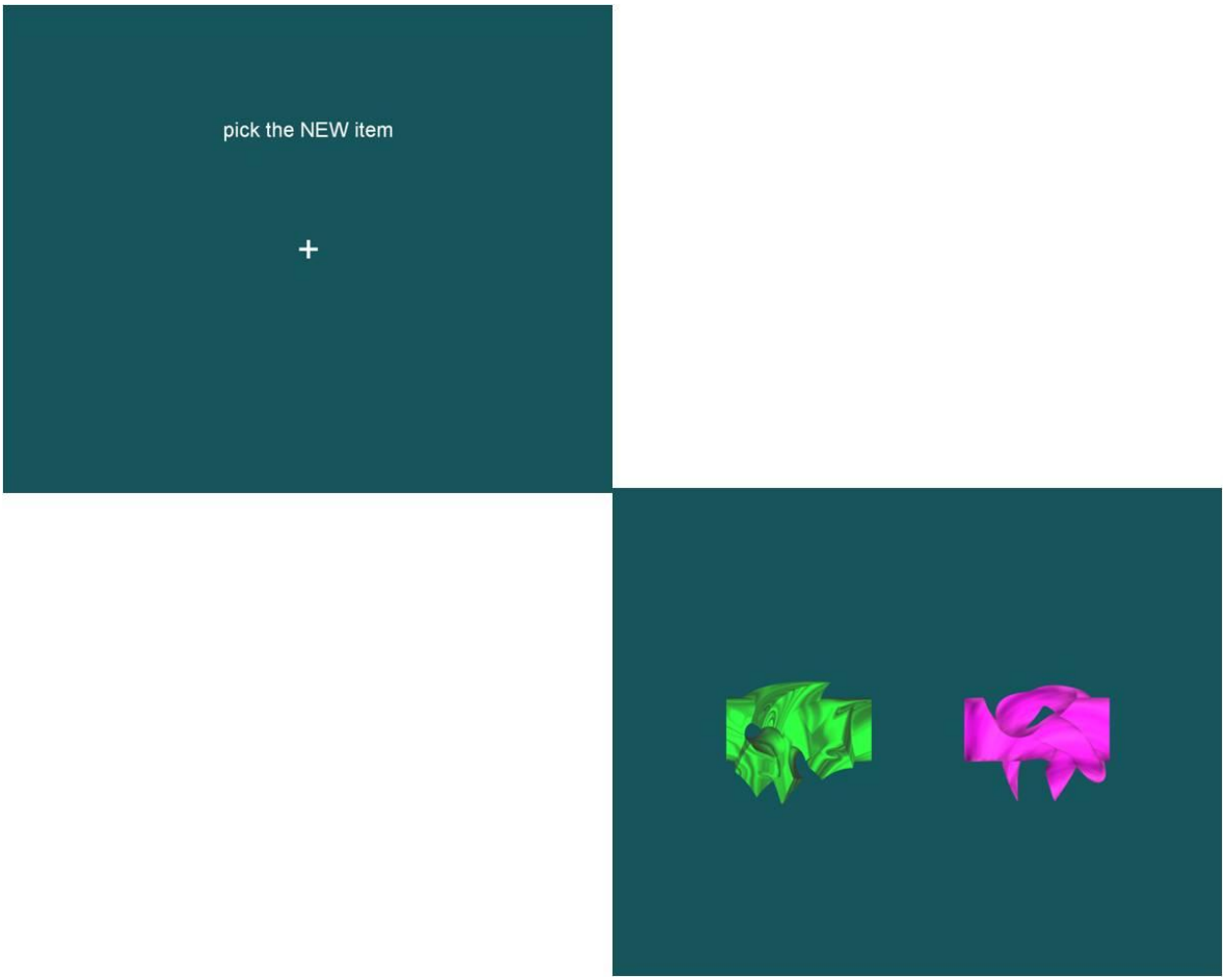

Figure 3.3. A long-term memory test trial with novelty instruction (LTMN) corresponding to the study trial in figure 2. The correct response would be to press the left button. The timing is the same as the second half of a WM trial, or 3 and 4 seconds for the two displays, respectively.

Participants completed 40 of each of the four trial types. Each trial type began with an instruction to remember the following items presented for two seconds, followed by two study items presented for three seconds. As an additional cue that the items were to-be-remembered, they were presented at the top and bottom of the computer screen (to contrast with test displays, described below). On short delay trials, the study items were followed by a three second delay consisting of a fixation cross and an orientation instruction. Familiarity trials had an instruction to 'pick the old item', referring to an item that had just been studied, consistent with the DMS paradigm. Novelty trials had an instruction to 'pick the new item', referring to an item that had never been studied, consistent with the DNMS paradigm. The delay period was followed by the test display, which consisted of one of the two study items and one novel item; the items were presented on the left and right sides of the screen for four seconds. Participants chose an item by clicking the left or right mouse button to correspond to the item on the left or right side of the screen.

LTM study trials differed from WM trials in that the instruction screen contained only a fixation cross and the test display was simply a blank screen; however, the same timing was used. After 160 trials (40 of each of the 4 trial types), participants received the tests for the LTM trials. The tests consisted of instruction and test displays identical to the working memory trials; a familiarity or novelty instruction was presented with a fixation cross for three seconds followed by a four second test display.

Due to the small number of participants, no attempt was made to counterbalance the stimuli. Instead one experiment order was created and each participant went through that order; thus each participant was subject to any potential item or trial order effects. Either the top or bottom study item could appear at test, and this item could be placed on the left or right side of the test display; these two variables were counterbalanced with the four trial types such that there were equal numbers of trials in each of the 16 (4 x 2 x 2) conditions. Trial order was randomized with the constraint that no more than three of the same trial type could be presented in a row.

3.3.5. Procedure

Participants were given a verbal description of the task in general and then led through a practice phase by the experimenter. Participants were shown the study instruction screen and a study display and told that the two items were to be remembered and that the instruction screen and the items presented on the top and bottom of the screen were markers of the study portion of a trial. They were told that items should be remembered for both the short and long term since they would not know if a test would come immediately afterward or later in the experiment. Next they were shown the delay phase with a familiarity orientation instruction and told that the instruction would tell them which item to choose, in this case referring to one of the two items just studied. Next they were shown a test display and told that test displays would always present items on the left and right sides of the screen. The participant was asked to press the left button if the 'old' item was on the left side or the right button if the old item was on the right. The experiment was paused on each screen while the experiment was described and the participants asked questions if they had any. Participants were then walked through a novelty working memory trial, noting the different instruction. They were then shown a long-term memory trial. They were told that seeing only a fixation cross without an instruction was a sign that they would be tested on those items later. Participants then completed three WM and one LTM trials at experiment speed for practice. Participants were encouraged to make their behavioral response while the test display was on-screen, although responses were recorded after the trial had moved on.

After the practice phase participants were asked if they had any questions, then settled into the chin rest. The eye tracker was calibrated so that it could determine the participant's point of gaze (see apparatus section) and the participant was told that the calibration screen would occur periodically

throughout the experiment to check the eye tracker as well as offer the opportunity for a break. The calibration screen was presented every 20 trials; participants were recalibrated if the experimenter felt it necessary. If the participant asked for a break or leaned back from the chin rest the eye tracker was always recalibrated. After 160 trials (80 WM and 80 LTM study trials) participants were told that the remaining trials would be only the tests for the items that had not been tested. The 80 LTM instruction and test displays were presented, again with breaks for calibration every 20 trials.

3.4. Analysis and Results

All statistical tests were considered significant with an alpha of .05. Unless otherwise stated, all p values come from the likelihood ratio test comparing a model including the effect being tested to a model that does not include that effect (e.g., if a three-way interaction is significant the p value comes from comparing the model with that three-way interaction to a model with all two-way interactions and main effects but not the three-way interaction). If a test is described as non-significant but no p-value is listed, p was at least .10.

Behavioral data. As mentioned previously, responses were still recorded if the button was pressed after the test display offset. Output files were checked by hand for such responses. If no response was made on a particular trial but a response was made within the first three seconds of the subsequent trial (during the study instruction display), the response was taken to be a late response. All late responses were given a response time of 4 seconds, corresponding to the length of the test display. This occurred on 64 trials (out of 1120 across the seven participants, or less than 6% of the time). Participants could respond multiple times during a trial; their last response was taken as their intended response. Trials with no response were removed from the behavioral analysis; this occurred for 36 trials (about 3% of trials).

Due to the request to make responses while the test display was on-screen, the distribution of response times was fairly normal and not improved by log-transform. Statistical analysis on response times were thus carried out on the raw times. The initial analysis was a mixed effects hierarchical linear regression using participant as a random effect and group (patient or comparison), test delay (LTM or WM), and retrieval orientation (familiarity or novelty) as fixed effects. The three-way interaction was not significant so it was removed from the model; two significant two-way interactions were found suggesting that patients took longer to respond than the comparison participants on the WM trials relative to the LTM trials ($p<.0001$) and additionally that patients took longer under novelty instructions relative to familiarity instructions ($p<.005$) than did comparison participants. The mean response times for each group on the four trial types are presented in table 3.1. As can be seen in the table, comparison participants took the same amount of time regardless of instruction (albeit longer on LTM than WM trials,

p<.0001). Patients, on the other hand, took roughly the same amount of time regardless of test delay (thus leading to the test delay interaction) but were slower to respond under novelty instructions (leading to the orientation interaction). These effects can also be seen in figure 3.4.

Trial Type	WMF	WMN	LTMF	LTMN
patient	2353	2709	2598	2741
comparison	2002	1970	2854	2788

Table 3.1. Mean response time on working (WM) and long term memory (LTM) trials under familiarity (F) and novelty instruction (N) for the patients and comparison participants.

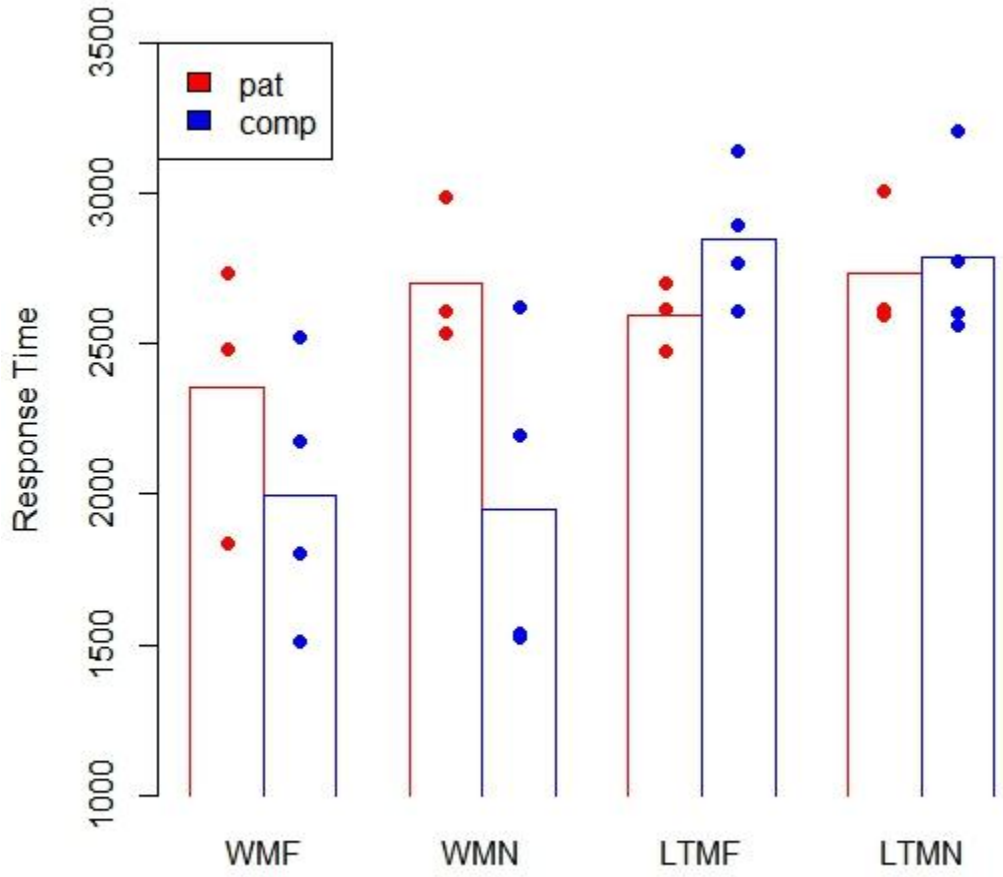

Figure 3.4. Mean response time on working (WM) and long term memory (LTM) trials under familiarity (F) and novelty instruction (N) for the patients and comparison participants, illustrating the values in table 1.

Response accuracy was analyzed with a similar model but using a logistic generalized linear regression. While the response times were normally distributed, correct responses are binomially distributed at the trial level (can only take the values 0 or 1). The mean percent correct for each group in each condition is presented in table 3.2 and shown in figure 3.5.

Trial Type	WMF	WMN	LTMF	LTMN
patient	82.9%	59.8%	54.9%	47.4%
comparison	82.3%	85.3%	67.5%	65.7%

Table 3.2. Mean percent correct on WM and LTM trials under familiarity and novelty instruction for the patient and comparison participants.

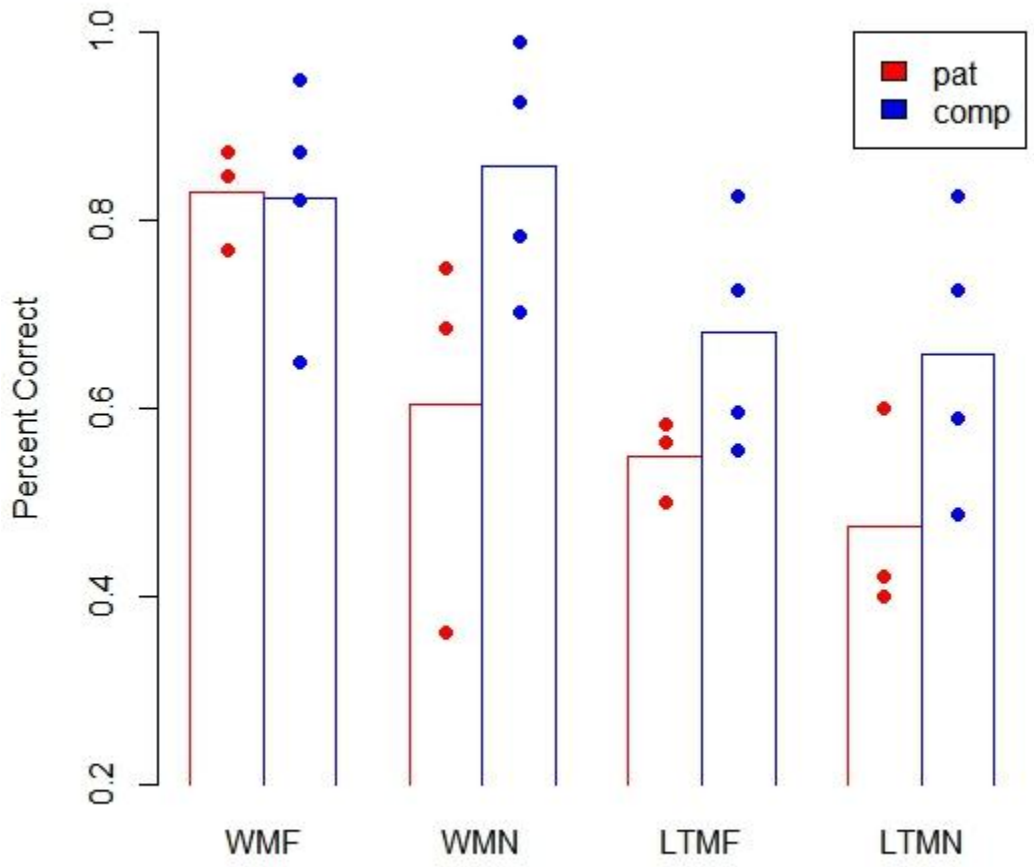

Figure 3.5. Mean percent correct on WM and LTM trials under familiarity and novelty instruction for the patient and comparison participants, reporting the values seen in table 2.

The model found a significant three-way interaction suggesting that patients performed worse on WM trials under novelty instructions. This effect appears to be driven by one patient who performed far below chance (36.1%) on that trial type (the other two patients performed with 68.4 and 75% accuracy; see table 3.3). If it is assumed that many of these responses were a failure to press the correct button, as opposed to failures of memory, then that data cell would be much closer to comparison performance. In that case, both patients and comparison participants would perform worse on the LTM trials than the WM trials, and the patients would perform worse than comparison participants on LTM trials (p=.04). These results would be expected given the traditional views of forgetting and amnesia. However, a speed-accuracy trade-off is possible since the patients responded more slowly than the comparison participants. Alternatively, the poor-performing patient also performed the worst on the other three trial types but at comparable levels to the other two patients (table 3.3); he did not consistently ignore the orientation instruction. So it is possible that his performance was indeed at chance (although numerically below), but, as is further explained below, we believe that the poor performance is due to a failure to follow instructions and not poor memory.

Trial Type:	WMF	WMN	LTMF	LTMN
1846	84.6%	68.4%	56.4%	60%
2363	76.9%	36.1%	50%	40%
2308	87.2%	75%	58.3%	42.1%

Table 3.3. Mean percent correct for each amnesic patient on WM and LTM trials under novelty (N) and familiarity (F) instructions. Note that patient 2363 is an outlier only on WMN trials.

Eye data. Three kinds of eye data variables were analyzed: fixation durations, number of transitions, and proportion of viewing. (Hannula et al, 2011).

The first analysis considered first fixations to an item on a test trial. Many viewing effects are apparent very early, even on the first fixation (e.g. Ryan et al, 2007). Fixation durations were strongly skewed, so analyses were conducted on the log transformed values. A mixed effects hierarchical linear model treating participant and trial number as random effects and test delay (LTM or WM), orientation (familiarity or novelty), group (patient or comparison), and item fixated (the proper target or not) was fit to the data. A significant three-way interaction (p=.02) between test type, orientation, and item fixated was found. The data were separated by test delay and tested with similar models to investigate this effect. On WM trials, the only significant predictor of first fixation duration was item fixated; fixations to the correct item were longer than fixations to the incorrect item regardless of group or orientation. In contrast, on LTM trials there was a trend (p=.1) for patients to spend more time fixating the correct item

under novelty instructions. Disregarding that trend, there was a significant two-way interaction (p=.02) for the correct item to elicit longer fixations than the incorrect item under novelty instructions but not familiarity instructions. To illustrate these effects difference scores were created by subtracting the average fixation duration to the incorrect item from the average fixation duration to the correct item for each participant. This difference is presented for each group in each trial type in table 3.4. In general, greater viewing to the correct item was larger for WM trials than LTM trials. This may reflect the stronger representation for the items at short delay compared to long delay.

Trial Type	WMF	WMN	LTMF	LTMN
Patient	32	25	-14	61
Comparison	65	22	5	10

Table 3.4. Mean difference in first fixation duration by group and trial type. Positive values indicate that the correct item evoked longer fixations than the incorrect item.

The number of transitions was examined next. The number of transitions was defined as the number of times the item being fixated changed; if only one item was fixated on a trial, then zero transitions occurred. Transitions were only counted before a response was made; before a response is made the participant is presumably extracting information from the display and comparing the items, but it is unclear what a participant is doing after a response is made. Transitions were analyzed with a mixed effects hierarchical generalized linear model using the Poisson distribution to account for their status as a counting variable. Participant was treated as a random effect while test type (LTM or WM), group (patient or comparison), orientation (novelty or familiarity) and accuracy (if the trial received the correct response or not) were treated as fixed effects. There was a significant two-way interaction (p=.007) between test type and accuracy; participants made the same number of transitions on LTM trials regardless of accuracy whereas they made more transitions on incorrect WM trials. This is likely an indication of uncertainty on WM trials; memory was generally good so more transitions could be a sign that the participant was uncertain and needed to compare the two items more. Memory was weak on LTM trials and so the participant was relatively equally uncertain whether they were correct or not. Again, this effect did not differ depending on group or orientation.

Finally, proportion of viewing time was examined. The total viewing on a trial was defined as the total amount of time spent fixating the two items on-screen. The proportion of viewing to a given item was defined as the total amount of time spent fixating that item divided by the total viewing time on that trial. Proportion of viewing can also be calculated within time bins (e.g. Hannula et al, 2007) to produce a picture of how viewing changes over the course of a trial. Each trial is divided up into 500

millisecond bins relative to the onset of the test display (i.e. 0 to 500 milliseconds, 500 to 1000 milliseconds, etc.). Fixations are assigned to bins, and any fixation that spans two bins is divided (e.g. a fixation from 400 to 600 milliseconds would add 100 milliseconds to the 0-500 bin and 100 milliseconds to the 500-1000 bin). The data were analyzed with a mixed effects hierarchical generalized linear model using the binomial distribution since the data were proportions. As before, participant and trial were treated as random effects while orientation, test type, group, and time bin were treated as fixed effects. The highest-order model did not converge, but visual inspection suggested that the groups may have responded differently and thus the data set was divided by group and analyzed separately. The timecourses are shown for the patient and comparison groups in figures 3.6 and 3.7.

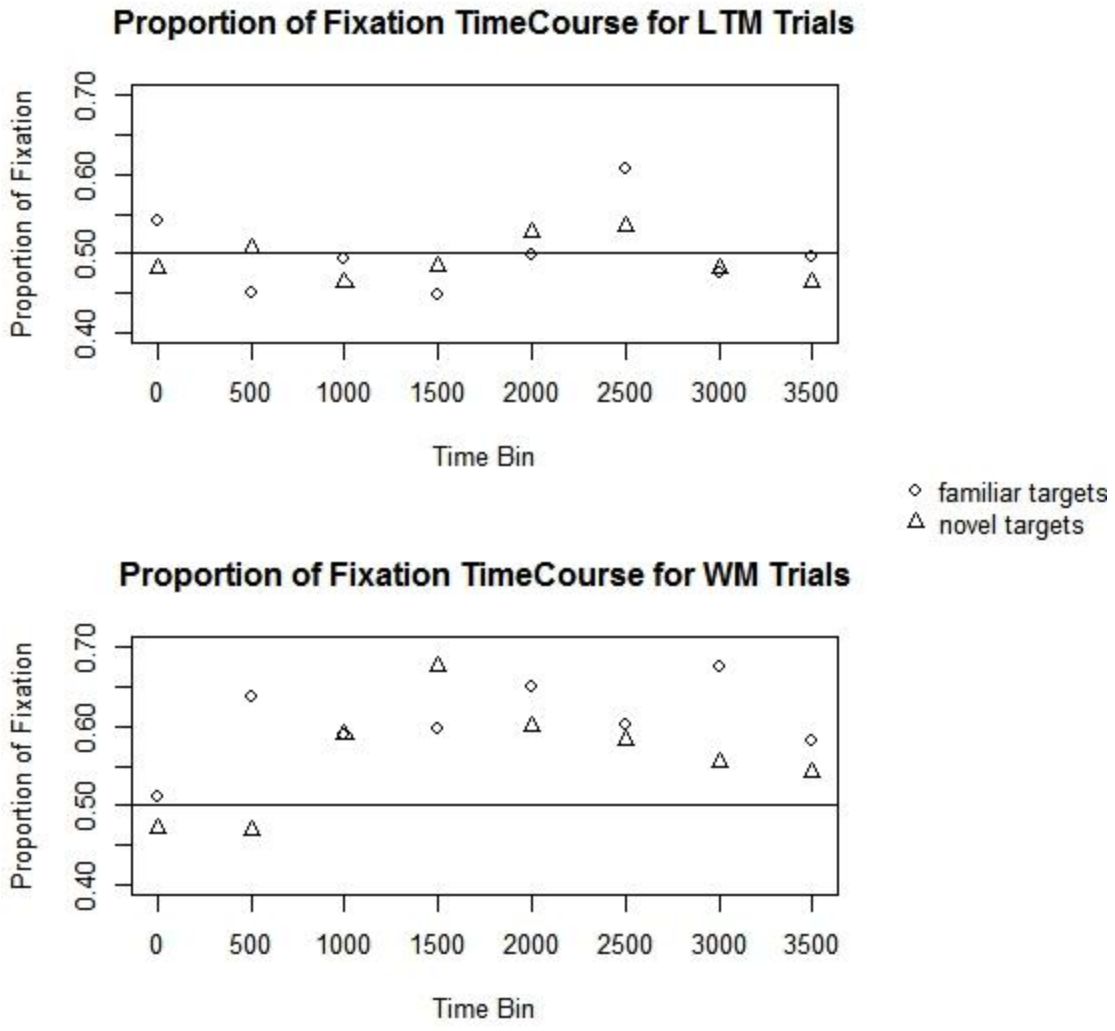

Figure 3.6. The proportion of fixation to the correct item timecourse for patients separated by test type and orientation. Circles represent familiarity orientation and triangles represent novelty orientation. The horizontal line is set at .5 or chance viewing of the correct item.

There was a significant three-way interaction ($p<.00001$) for the patient group between time bin, test type, and orientation. On LTM trials the correct item was not viewed above chance under either orientation except for the 2500 to 3000 millisecond time bin when studied items under familiarity instructions drew more viewing than new items under novelty instructions. In contrast the correct item was viewed above chance quickly on WM trials, with studied targets rising above chance after 500 milliseconds and novel targets after 1000 milliseconds. The correct item was then viewed at above-chance levels throughout the rest of the trial. The comparison group (three-way interaction also significant, $p<.00001$) showed a similar pattern on LTM trials, with viewing rarely deviating from chance levels, as well as WM trials, with studied items receiving above-chance viewing in the second time bin

and novel items in the third. The comparison group differed somewhat on WM trials in that viewing of the correct item dipped back closer to chance after the initial rise.

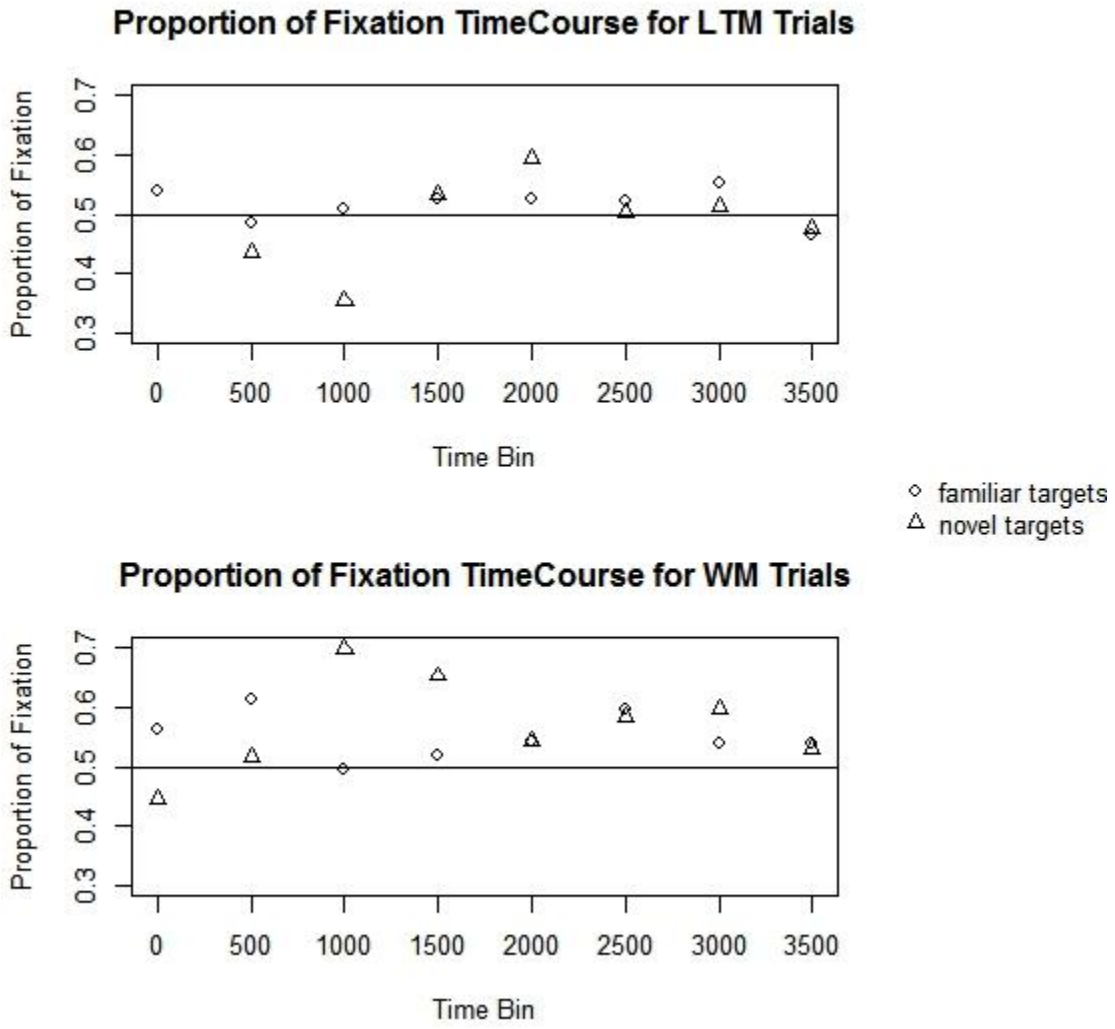

Figure 3.7. The proportion of fixation to the correct item timecourse for comparison participants separated by test type and orientation. Circles represent familiarity orientation and triangles represent novelty orientation. The horizontal line is set at .5 or chance viewing of the correct item.

The response-locked timecourse for proportion of viewing was also analyzed (e.g. Hannula et al, 2007). While the timecourse analysis above provides a view of how quickly differences can arise after stimulus onset, they are complicated to interpret as a whole because of the influence of making a response (discussed in the transitions analysis). In a response-locked analysis, the 0 time point is set at whenever a participant responded on a certain trial instead of stimulus onset and bins are defined relative to that point. If, for example, the participant responded after 2750 milliseconds on one trial, the -500 to 0 bin would

cover from 2250 to 2750 ms post-stimulus onset on that trial; if the response time on another trial was 950, the same bin would cover from 450 to 950 ms. Trials on which no response was made were discarded. Some bins had few fixations and could not be reliably analyzed; for example, the earliest possible time bin could only be filled if the participant responded at the very end of the trial and fixated an item at the very beginning of a trial whereas the latest time bin could only be filled on trials where a response occurred very early but an item was still fixated at the end of the test phase. Therefore to enable more reliable analysis and give a tighter picture of how participants responded, only fixations from -2000 to 1000 (two seconds before response to one second after response) were included.

The timecourses for the patient and comparison groups can be seen in figures 3.8 and 3.9. The four-way interaction between group, time bin, test type, and orientation was significant. Supporting the results from the initial LTM timecourse analysis, viewing of the correct item stayed near chance levels for the patients throughout the response-locked timecourse. Viewing did appear to rise numerically above chance for novel items under novelty instructions within the second before response, but it returned to chance just after the response was made. In contrast, viewing to both novel and familiar targets rose above chance 1500 milliseconds before the response was made on WM trials. For the comparison group, viewing of the novel items rose above chance in the half second before a response was made on LTM trials but viewing of studied targets remained at chance throughout. The reverse seemed to be true on WM trials as viewing rose above chance 1500 milliseconds before the response for studied targets but stayed at chance for novel targets until 500 milliseconds before the response.

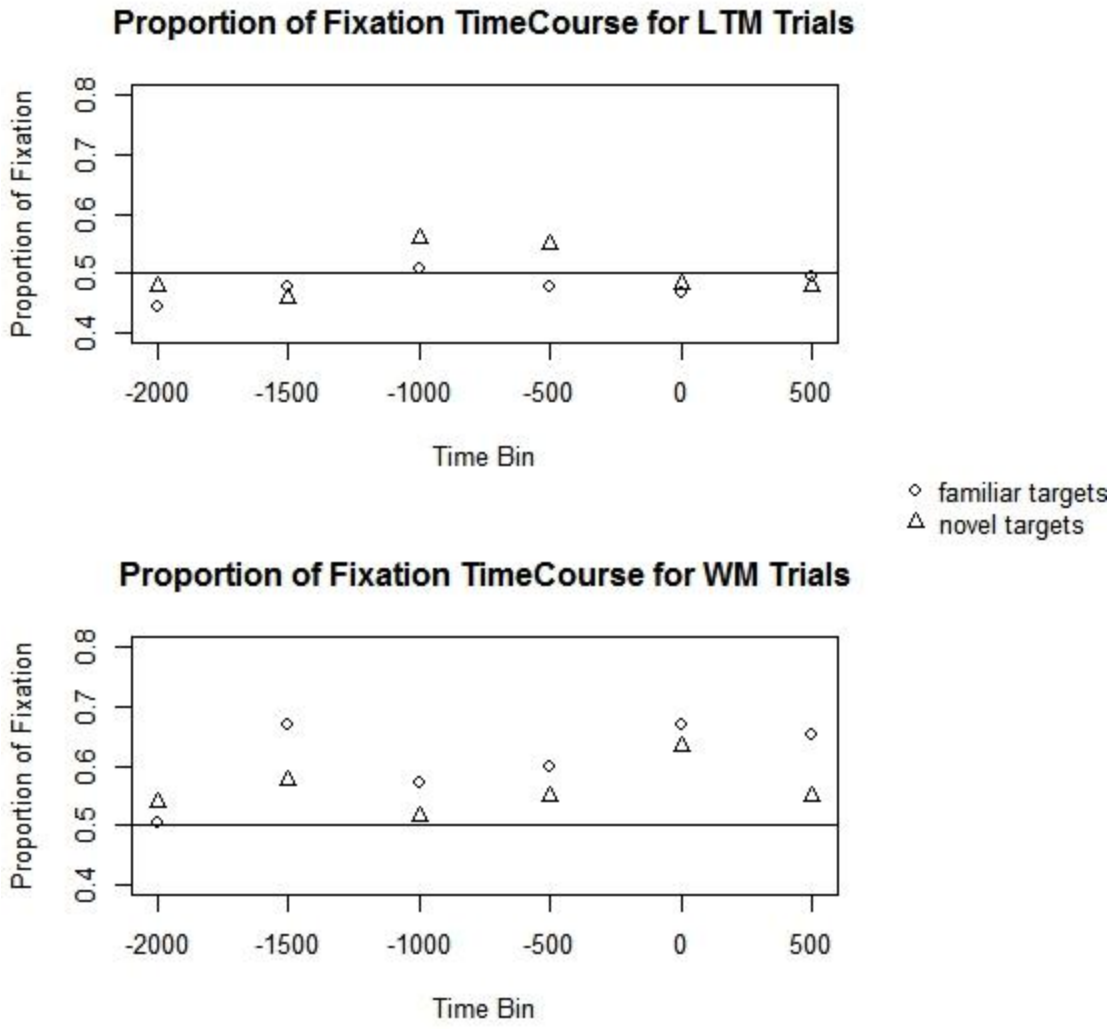

Figure 3.8. The proportion of fixation to the correct item response-locked timecourse for patients separated by test type and orientation. Circles represent familiarity orientation and triangles represent novelty orientation. The horizontal line is set at .5 or chance viewing of the correct item.

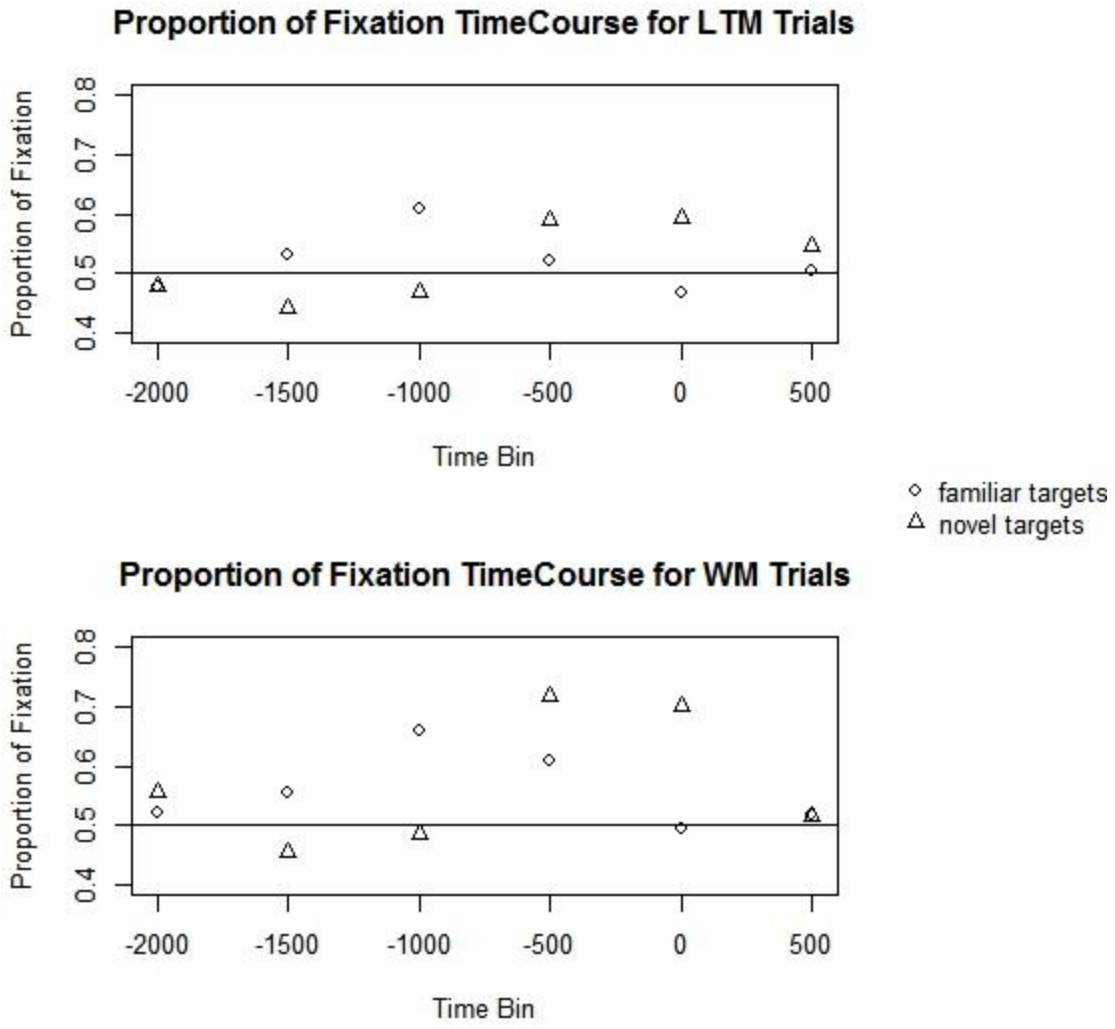

Figure 3.9. The proportion of fixation to the correct item response-locked timecourse for comparison participants separated by test type and orientation. Circles represent familiarity orientation and triangles represent novelty orientation. The horizontal line is set at .5 or chance viewing of the correct item.

Given the large amount of data and analyses presented, a summary is appropriate. Behaviorally, the amnesic patients performed with the same accuracy as the comparison group on short delay (WM) trials but worse on long delay (LTM) trials; neither group demonstrated an effect of retrieval orientation (novelty or familiarity instruction). The comparison group provided consistent response time data, taking longer on long delay trials. Patients, on the other hand, took relatively longer on short delay trials and under novelty instructions (regardless of delay). This suggests that perhaps there was some manner of speed-accuracy trade-off that allowed the patients to perform well at short delays and under novelty instructions.

Analysis of first fixations (table 3.4) showed that both groups knew what the target was even on their first view of the item; novel items elicited longer fixations under novelty instructions while studied items elicited longer fixations under familiarity instructions. This effect was stronger on short delay trials when the memory trace may have been stronger. Additionally, the correct item elicited longer first fixations under novelty instructions than familiarity instructions on long delay trials; this effect appeared to be driven by the patient group. This may be evidence that as memory for the studied items fades, it is easier to search for a completely novel item than to look for what has been seen before.

The transitions data generally confirmed the behavioral results. Before a response was made, an equal number of transitions were made on correct and incorrect long delay trials, whereas fewer transitions were made on correct short delay trials. This suggests that participants were able to find the correct item quickly when memory was strong but had difficulty and needed to make more comparisons when memory was weak. Notably this effect did not differ by group or retrieval orientation.

Proportion of viewing time was analyzed with timecourses created relative to both stimulus onset and response. Neither group demonstrated much preferential viewing of the correct item on long delay trials, but both groups quickly viewed the correct item on short delay trials with a tendency for studied targets to evoke above-chance viewing more quickly than novel targets. The response-locked analysis confirmed these results, with viewing on long delay trials rarely rising above chance even at the time of response but rising above chance before the response on short delay trials.

3.5. Discussion

This experiment examined whether participants act differently when their goal is to search for novelty as opposed to when they are searching for familiar stimuli. Further, we tested patients with damage to the hippocampus because the previous literature has commonly found the hippocampus to be important to novelty processing. The results touch on a number of issues in the novelty and hippocampus literatures, which will be discussed in turn.

Novelty as a goal: As discussed in the introduction, novelty processing is seen as a critical ability. However, little research has focused on people's ability to actually exert control over novelty processing, i.e. by treating it as a goal. The current experiment found evidence that when asked to search for novelty, participants may in fact still search for familiar stimuli and use that to make their decision. On short delay trials, eye tracking data showed that familiar stimuli attracted more fixations when participants were looking for old items than novel stimuli attracted when participants were looking for new items. This difference occurred early, as much as a second and a half before a response was made. Only closer to response time did novel targets begin to gather more fixations. Supporting evidence for this claim was

found in the transition data; if participants were inherently searching for the familiar item regardless of instruction, then more transitions should occur if they happened to initially fixate the novel item, since they would then want to transition to the familiar item to confirm their memory. This prediction was confirmed numerically although not statistically (p=.11); participants made more transitions when they initially fixated the novel item, regardless of instruction, than when they initially fixated the familiar item. If people prefer to search for novelty by finding a familiar object, it casts some doubt on the claim that novelty processing is a critical, inherent ability of organisms. Instead, perhaps an automatic memory judgment is made, focused on the familiarity of the object, and this provides the basis for novelty-related phenomena in the literature.

The function of the hippocampus: Despite the strong connection between the hippocampus and novelty, novelty processing is rarely listed as a putative function of the hippocampus. Instead, the hippocampus is often described as supporting relational memory (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001). Relational memory is memory for the associations between arbitrary elements of the environment, such as the spatial location that an item occupies or which two words were studied together in a word pair experiment. Importantly, in many cases the hippocampal connection with novelty has been found under conditions in which one would expect relational memory to be important (Kumaran & Maguire, 2006, 2007; Köhler et al., 2005). It has even been suggested that the hippocampal novelty response in fMRI could be used as a kind of adaptation signal to help further delineate the exact processes supported by the hippocampus (Kumaran & Maguire, 2009). This perspective raises an interesting parallel between novelty processing in the hippocampus and priming responses found in other brain regions. For example, reduced fMRI activity for repeated stimuli of different types (e.g. different objects of the same type, the same object presented in a different size or a different viewpoint) has been used in an effort to map out the visual system (e.g. Grill-Spector et al., 1999). But this neural response in the visual system is considered priming or adaptation, not a novelty response (Habib, 2001). Kumaran and Maguire (2009) similarly argue that the commonly found novelty activation in the hippocampus may just be a similar sign of the actual kind of processing that the hippocampus supports. This would not be novelty processing, but relational memory or some other memory-based function.

The current experiment supports this view in two ways. First, hippocampal damage had no effect on performance under a novelty goal. If the hippocampus supported novelty processing in some manner, one would have predicted that hippocampal damage would impair patients' ability to search for novelty, but that was not the case. There is a concern behaviorally that the patients performed worse than the comparison group on the novelty trials at short delay. However, we argued that one patient drove that result and likely was not following directions, given how far below chance he performed. Additionally,

that patient was faster to respond on incorrect trials in that condition than correct trials, reversing the pattern exhibited by each other patient as well as himself in other conditions. Thus the patients performed similarly to the comparison group both behaviorally and in terms of their eye movements at short delay (this issue will be discussed further in the next section). Second, the current experiment had no relational component, and thus would not be expected to have produced any deficit in performance under extant theories of hippocampal function. Participants were required only to encode two independent items into memory and to remember them, separately, for a later test. While the stimuli used in this experiment are broadly similar to each other, and amnesic patients have demonstrated impairment on similar materials (Duff et al., 2011; Holdstock et al., 2002), that was unlikely to be a concern here. The two stimuli presented on any given trial could be readily identified and maintained over the delay by their primary color or pattern; the items in figure 3.1 could be remembered as 'the neon one' and 'the purple one', for example. This strategy would work a large proportion of the time for the short delay trials, and only provide difficulties on the long delay trials when multiple purple items have been studied. This is exactly the pattern of results found.

The hippocampus at short delay: The hippocampus has long been viewed as supporting long-term memory, commonly based on evidence that amnesic patients could retain information only for a short period of time (e.g. Warrington & Baddeley, 1974). However, the distinction between short and long-term memory has been questioned as of late (Ranganath & Blumenfeld, 2005) and an increasing number of fMRI (Barense, Henson, & Graham, 2011; Gazzaley et al., 2007; Hannula & Ranganath, 2008; Oztekin, McElree, Staresina, & Davachi, 2009; Ranganath & D'Esposito, 2001; Voss, Galvan, & Gonsalves, 2011; Voss, Gonsalves, et al., 2011) and patient (Crane & Milner, 2005; Duff et al., 2011; Hannula, Tranel, & Cohen, 2006; Olson, Moore, et al., 2006; Olson, Page, et al., 2006; Voss, Galvan, et al., 2011; Voss, Gonsalves, et al., 2011; Warren, Duff, Jensen, et al., 2011; Warren et al., 2010; Warren, Duff, Tranel, et al., 2011) studies have found connections between the hippocampus and performance on short-delay and even no-delay tasks (see also Graham, Barense, & Lee, 2010). These results have led to the idea that the hippocampus (and, indeed, any brain region) should be viewed in terms of its information processing abilities or the representations that it supports as opposed to in regards to time scale. This viewpoint is bolstered by the finding that hippocampal involvement is typically found in short-delay tasks with a relational binding component (Crane & Milner, 2005; Hannula & Ranganath, 2008; Hannula, Baym, Warren, & Cohen, 2012; Hannula et al., 2006; Olson, Page, et al., 2006; Warren, Duff, Tranel, et al., 2011). If the hippocampus is critical for supporting the representations that underlie relational binding, it would be necessary to support performance at any time scale so long as relational memory were important to the task. That would be true of the long delay test in the current experiment, but not the

short delay test. As discussed above, performance on the short delay test could easily be supported by verbal rehearsal across the delay. However, as more items were seen and these labels became insufficient, the hippocampus would be needed to help support memory after a long delay. At this point, the amnesic patients performed at chance while the comparison group performed above chance, albeit worse than after a short delay.

Conclusions and future directions: In summary, the results of the current experiment fit well with the current view of hippocampal function as it relates to pattern separation and relational binding. They are less consistent with a strong view of novelty processing as an independent psychological function; instead, novelty processing may consist of a constellation of other processes, such as retrieval (as part of evaluating the novelty of a stimulus), goals (organisms may default to emphasizing novelty exploration if no other goal is pressing), attention (focus is aimed at novel stimuli over familiar stimuli), and encoding (novel stimuli need to be entered into memory) amongst others. However, it is possible that a novelty difference could be found under other circumstances. For example, Freed and Corkin (1988) found that amnesic patient H.M. was able to demonstrate normal memory for pictures six months after having studied them, provided that he was tested with novelty-focused recognition. While the long delay in this experiment was much shorter (on the order of ten minutes), it is possible that the study time allowed was insufficient for these materials and thus the patients tested here simply could not perform above chance under any circumstances. The plausibility of this claim is mitigated somewhat, however, by the fact that the patients performed equally well under novelty and familiarity-focused tests after a short delay but were not near ceiling; if a preference for one instruction over the other were present, it should have been noticeable in that condition but none was found.

Another possibility is that another brain region aside from the hippocampus supports novelty processing. One contender from the literature is the prefrontal cortex (for review see Ranganath & Rainer, 2003). Like the hippocampus, the prefrontal cortex has been implicated in a variety of novelty experiments; it is typically more active for novel than familiar stimuli (Kirchhoff et al., 2000; Tulving et al., 1996), prefrontal lesions reduce the novelty P3 ERP component (Knight, 1984; Lovstad et al., 2011), and prefrontal lesions reduce the von Restorff effect (Kishiyama, Yonelinas, & Knight, 2009). Future research could examine the role of prefrontal lesions on novelty in the way that hippocampal lesions were tested here. However, since much of the same evidence for the hippocampus applies to the prefrontal cortex, it is questionable what result should be expected.

4. The Effects of Novelty Processing on Recognition Memory

4.1. Abstract

Novel stimuli are known to evoke different responses than familiar stimuli. Unexpected stimuli, such as oddballs in the novelty oddball task, elicit an orienting response. Similarly contextually odd items are also better remembered on later memory tests, as in the von Restorff paradigm. However, there is little research on the mnemonic effects of searching for novel stimuli. It is possible that a novelty orientation would benefit all items, treating them as if they were novel stimuli. In contrast, we hypothesized that a novelty orientation would lead participants to limit the retrieval strategies they might otherwise use, leading to poorer memory. We adapted the Jacoby, Shimizu, Daniels, & Rhodes (2005) memory for foils paradigm to investigate if participants search their memory differently under a novelty goal compared to typical recognition. Using a between-subjects design, half of the participants completed the test under typical recognition instructions, replicating the Jacoby et al. (2005) effect. The other half completed the second phase of the experiment, when retrieval constraint occurs, under novelty instructions. The novelty group showed a reduced depth of processing effect compared to the 'familiarity' group but was not significantly different in their memory for foils. It appears that a novelty orientation does not impart the same benefits seen in other areas of novelty research, and may have some costs for memory.

4.2. Introduction

Determining whether a particular element of the environment is novel or not is an important ability for survival; a novel creature, object, or location needs to be further investigated to determine if it is a threat, is useful, could provide shelter, etc. Thus it makes intuitive sense that novel stimuli should evoke a response that leads to additional processing. Research on novelty detection or novelty processing has thus proceeded in a number of different arenas, perhaps most commonly in the novelty oddball paradigm with event-related potentials (ERPs).

The novelty oddball paradigm (e.g. Knight, 1996)involves presenting participants with a stream of stimuli, typically auditory, and asking them to respond to a certain subset of those stimuli. These are called targets and are presented infrequently; participants might be asked to press a button any time they hear a 2000 Hz pure tone, for example. Participants are also told about 'standard' stimuli, which are presented frequently but require no response; an example might be a 1500 Hz tone. However, a third class of stimuli are also presented during the experiment without the participant being informed beforehand; these 'oddballs' are typically very different from the targets and standards (e.g. environmental noises like car horns and dog barks) and also occur infrequently. These oddball stimuli are novel due to their unexpectedness, infrequent occurrence, and inherent characteristics (i.e. being of a

different sort than the targets and standards). They evoke a particular ERP component called the novelty P3 or P3a which responds just as one might predict an orienting response would. For example, the response habituates after a few oddballs have been presented and become less unexpected (Knight, 1996; see Yamaguchi et al., 2004 for the fMRI equivalent), but habituation only occurs if the oddballs are unexpected; participants who know about them demonstrate a reduced novelty P3 response from the start (Cycowicz & Friedman, 1999).

This novelty response has additional cognitive benefits. In the realm of memory, contextually novel stimuli are usually tested in the von Restorff paradigm (R. R. Hunt, 1995). In this paradigm, some stimuli in a list are made contextually novel by being of a different class than the rest of the memoranda; words could be presented in a larger or smaller text size or a different font (e.g. Karis et al., 1984) or line drawings could be presented in a different color (Kishiyama & Yonelinas, 2003). These novel stimuli stand out and are better remembered on a subsequent memory test. A similar result was found by Tulving & Kroll (1995) using what might be called stimulus novelty (Kumaran & Maguire, 2007; Nyberg, 2005; Ranganath & Rainer, 2003). Participants were initially familiarized with one set of words by making repeated living/non-living judgments as well as taking an old-item only recognition test. This was followed by a 'critical phase' in which half of the familiarized words were presented along with new words; participants were told to specifically remember this list for a later test. On the final test participants saw familiarized and 'novel' words from the critical list along with non-critical familiarized words and completely novel lures; only words from the critical phase were to be endorsed. Tulving and Kroll (1995) found that critical novel words were more often endorsed than critical familiarized words and novel lures were more often rejected than familiarized lures. This was taken as evidence in support of the novelty/encoding hypothesis (see also Tulving et al., 1996), which states that novelty assessment is a necessary but not sufficient condition for encoding. In short, novel stimuli have a memory advantage, even when novelty is defined in different ways.

While there is a large literature on the mnemonic consequences of detecting a novel stimulus, there is much less research on the consequences of intentionally searching for novel stimuli; that is, having a novelty goal or orientation. Given the importance of novelty detection in general, one might expect that searching for novelty is a distinct process or ability than searching for known or familiar materials. If this is true, then one might predict that searching for novelty could lead to generally better memory than searching for familiarity (e.g., working under typical recognition instructions). Support for this idea comes from a study by Dudukovic & Wagner (2007). Participants first studied a list of words, then were presented with three-alternative forced choice test trials consisting of two studied and one novel word. Before each test trial participants were cued to either choose the more recently studied word

(recency judgment trials) or to choose the unstudied word (novelty judgment trials). Having found brain activity differences between the two test types with fMRI, Dudukovic and Wagner (2007) then conducted a follow-up behavioral study using the same paradigm but followed by a second recognition test. This test contained novel words from recency and novelty judgment trials as well as completely novel lures; participants were asked to endorse any word seen earlier in the experiment. Participants endorsed more novel words from novelty judgment trials than recency judgment trials, which the authors took as evidence that those novel words drew more attention and thus more encoding.

The current experiment aims to expand on the novelty literature by investigating 1) if a novelty orientation differs from a familiarity orientation, and 2) if so, what the mnemonic consequences of searching for novelty are. To do so, we adapted the source constraint paradigm used by Jacoby et al. (2005, experiment 1). That experiment consisted of three phases. In the first phase, participants studied two lists of words under a depth of processing manipulation: one list was incidentally encoded while participants made a pleasantness judgment while a second was incidentally encoded while participants made a perceptual (vowel detection) judgment. The second phase consisted of two recognition tests, one for each of the previously studied lists. Critically, participants were told that all of the old words on a test came from a particular list, deeply processed words on one test and shallowly processed words on the other. Jacoby et al (2005) believed this would allow participants to constrain their memory search to a particular source, and if so they would reinstantiate the processing from study. In this case, if participants believed that words may have come from the pleasantness task list, they would perform deep processing at test (and similarly for the shallow list test). To test this, the third phase consisted of a recognition test for lures; participants saw lures from the deep and shallow tests in phase two as well as completely novel lures and were asked to endorse any word seen earlier in the experiment. Consistent with their prediction, participants endorsed more deep test lures than shallow test lures (called the memory for foils effect), suggesting that a depth of processing effect occurred at test due to source-constrained retrieval and thus reinstatement of encoding processes even on novel lures.

In order to test the potential differences between novelty and familiarity processing, we used the same paradigm but added a between-subjects manipulation during phase two. One group of participants received typical recognition instructions (familiarity orientation) and thus replicated the Jacoby et al (2005) paradigm. The second group of participants was told to look for and respond positively to new words (novelty orientation). If a novelty orientation leads to different retrieval strategies than a familiarity orientation, then participants in this condition should demonstrate differences in performance. We predicted that while participants in the familiarity group would engage in typical source-constrained retrieval, participants in the novelty group would perform a more low-level evaluation of test words.

More specifically, since they need only determine if a word is new, the novelty group would be less likely to constrain their memory search and may be less likely to engage in effortful retrieval processes like recollection (Yonelinas, 2002). If this is true, the memory for foils effect should be reduced in the novelty orientation group compared to the familiarity orientation group.

4.3. Methods

4.3.1. Participants

Participants for experiment 1a were 82 undergraduates from the University of Illinois; there were 93 participants in experiment 1b for a total of 175 participants. Experiment 1b was run subsequent to experiment 1a, but no one participated in both experiments. One participant in each experiment was removed for failure to follow instructions, leaving 173 for analysis. Participants received either $8 or partial credit toward fulfillment of course requirements. Testing was carried out under the guidelines of the University of Illinois Human Subjects Committee and Institutional Review Board.

4.3.2. Materials

Separate lists of 5 and 6 letter words were collected from an online database (http://www.psy.uwa.edu.au/MRCDataBase/uwa_mrc.htm). All words were nouns with a Kucera-Francis written frequency of at least 1 and a familiarity rating between 505 and 615; these values were chosen simply to control the number of words obtained (265 five letter words and 241 six letter words) while choosing words known by most people. Both word lists were randomly divided into six lists of 40 words each and matched for frequency and familiarity; the remaining 26 words were removed from the word pool. The five and six letter lists were then combined to form six lists of 80 words each containing 50% five letter and 50% six letter words. These six lists did not differ significantly in terms of frequency or familiarity (p value for each ANOVA >.69). The word lists were randomly assigned to conditions for each participant; presentation order within a condition was random as well.

4.3.3. Task and Design

The experimental design follows Jacoby et al's (2005a) experiment 1 but slightly changes the first phase and adds a between-subjects manipulation during the second phase. Phase 1 was the study phase and began a depth of processing (DOP) manipulation. All participants studied two lists of words (80 words each) under incidental encoding conditions. One list was presented with instructions to press one button (k) if the word was six letters long and another button (d) if the word was five letters long; this list will be referred to as the shallow list due to its role in the DOP framework. The other list was presented with instructions to press one button (k) if the word was pleasant and another button (d) if the word was unpleasant. This list will be referred to as the deep list. The order of list presentation was counterbalanced across participants. Participants had as much time as needed to respond.

Phase 2 was the first test phase. As in Jacoby et al (2005a) there were two separate tests. In the deep test, participants were told that all old or familiar words were from the pleasant study list. In the shallow test, they were told that all old words were from the letter length study list. For each word, participants were to indicate if it was previously seen or not. The order of test presentation was counterbalanced across participants. Each test list consisted of the earlier presented list (deep or shallow) and an equivalent number of previously unseen lures for a total of 160 words on each test. Orthogonal to study and test order, retrieval orientation was also manipulated and counterbalanced across participants. Half of the participants received typical recognition test instructions and thus served as a theoretical replication of Jacoby et al (2005a) experiment 1. They pressed the right-side key (k) for old words and the left-side key (d) for new words to match with typical handedness. The other half of the participants received novelty orientation instructions. They were asked to look for new words that had not been seen before, and to indicate that a word was new by pressing the right-side key (k) or previously seen by pressing the left-side key (d). Participants had two seconds to make a response; they were told their time was limited and that they should be quick yet accurate. The time limitation was instituted to ensure that words were seen for equal amounts of time by the familiarity and the novelty retrieval orientation (RO) groups in the event that they differed on response time. Even if one group responded faster than the other on average, words would be available for encoding for the same amount of time.

Phase 3 was the final test. All participants performed the final test under typical recognition memory instructions, such that they pressed one button (k) to indicate that a word had been seen before and another button (d) to indicate that it was new. The target words consisted of the 80 deep and 80 shallow lures from phase two; that is, the words that should have been labeled 'new' on the deep and shallow tests. An equal number (160) of lures were presented during the test. Participants were told to consider any word seen anywhere earlier in the experiment as old and had as much time as needed to respond.

Experiments 1a and 1b were identical except for the final test phase. Instead of making an old/new response, participants in experiment 1b made a one-step old/new and confidence judgment. The rating scale ranged from 1 meaning "sure new" to 6 meaning "sure old". This change was made to allow for a more sensitive signal detection theory (SDT) analysis to be performed. The participants in experiment 1b will be referred to as the rating group while the participants in 1a will be referred to as the ON (for 'old/new') group.

4.3.4. Procedure

Participants were tested in groups of two to five but on individual computers in separate rooms. After obtaining informed consent, participants were directed to a room and told that the instructions for

the experiment would be presented on screen. They were also told that the experimenter would answer any questions during the experiment. Participants then paced themselves through the three phases of the experiment described above. Breaks were only available between phases; participants had to wait a fixed amount of time to read instruction screens but were then able to press a button to begin a phase whenever he/she was ready. Instructions were presented prior to each of the deep and shallow study lists, each of the deep and shallow test lists, and the final test. A reminder of the task was always present at the top of the screen during each phase of the experiment; for example, participants in the novelty RO condition saw the phrase "Is it new?" during each test trial in phase two. The response buttons (d and k) and their meaning (yes or no) were also presented on each test trial. Words were always presented in the center of the screen in Arial size 60 font. Trials in each phase of the experiment contained an inter-trial interval of 500 milliseconds during which a blank screen was presented. At the end of the experiment a screen informed participants that they had finished and they were then debriefed by the experimenter.

4.4. Analysis and Results

Despite the similarity of the two experiments, all analyses were run with experiment (1a or 1b) as a factor to check if performance differed in the two groups of participants. Response time data were collected, but due to the differences in response contingency across RO groups during phase two (right hand – new for novel and right hand – old for familiarity) they were not analyzed. Most analyses were conducted via a mixed effects hierarchical regression model; unless otherwise described, all effects were tested via the Wald test and considered significant at alpha=.05. Other statistical tests were also considered significant at alpha=.05. Phases 2 and 3 were also analyzed with a second hierarchical generalized linear model. This model converts responses to d' measures (Macmillan and Creelman, 2005) via the binomial distribution with a probit link function (the other analyses used the typical logistic link). These models allow for trial-level information like word identity, frequency, familiarity, and length to be added as sources of variability. The results of the d' regressions were qualitatively similar to the logistic regressions, so only the logistic results are presented. The data from phases 2 and 3 were also analyzed after hit rate and false alarm rate values for each participant were converted to d' (MacMillan and Creelman, 2005), but again the results corresponded with the logistic regression analyses presented.

Phase 1: While the pleasantness of a word is a subjective opinion, the length of a word can be objectively evaluated. As such, accuracy on the shallow study portion of phase 1 was analyzed to ensure that participants were paying attention and able to follow instructions, and that the randomly assigned RO groups did not differ in this ability (note that RO had not yet appeared in the experiment, so it should not affect performance). The novelty group had an average accuracy of 97.1% and the familiarity group had an average accuracy of 97.6% in identifying the number of letters in the presented word. A mixed effects

logistic regression model was fit to the trial-by-trial accuracy data with the length, frequency, and familiarity rating of the word as covariates of no interest; retrieval orientation and group as fixed effects; and participant ID, word, and list as random effects. As expected, neither retrieval orientation nor group had significant effects on accuracy nor did they interact (all $p > .55$).

Phase 2: A model similar to that used to analyze phase 1 was fit to accuracy data in phase 2 as an initial search for potential effects. Across all participants, there were 2,277 trials (or 4.1% of trials) on which no response was given in the time allowed; these trials were removed from the analysis. The three-way interaction between retrieval orientation (novelty or familiarity), group (rating or old/new) and test (deep or shallow) was not significant ($p=.309$), so it was removed from the model. There were significant interactions between RO and test ($p<.0001$) as well as test and group ($p<.0001$). To further investigate these effects, the data were split by group and the model run again with RO and test as effects of interest. For the ON group, test and RO interacted significantly ($p=.002$) and there were significant main effects of RO ($p=.008$) and test ($p<.0001$). These effects can be described as a significant depth of processing effect with the novelty RO group showing a reduced effect. Proportion correct is plotted below (figure 4.1) and hit and false alarm rates are presented in table 4.1.

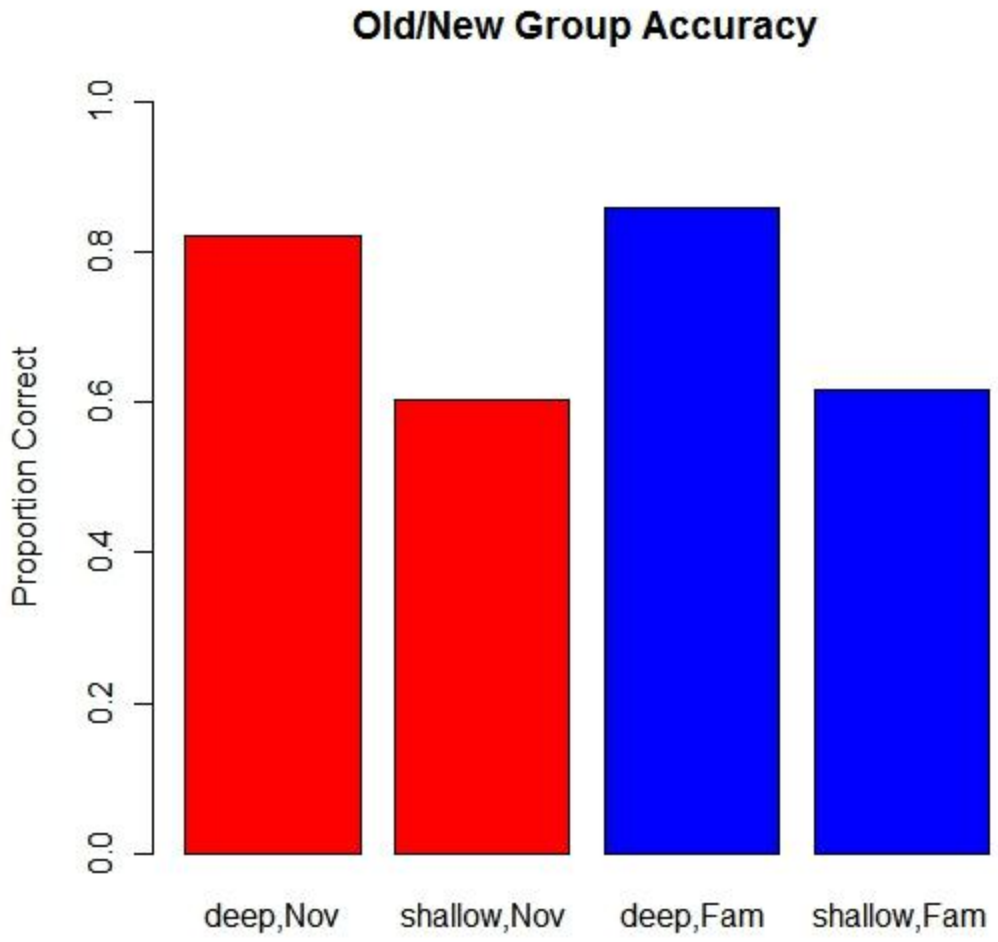

Figure 4.1. Proportion correct for the ON group under novelty and familiarity RO for the deep and shallow tests in phase 2.

	Novelty Orientation	Familiarity Orientation
Deep test hit rate	.834	.851
Deep test false alarm rate	.190	.133
Shallow test hit rate	.576	.496
Shallow test false alarm rate	.373	.263

Table 4.1. Hit and false alarm rates for the ON group under novelty and familiarity RO for the deep and shallow tests in phase 2.

The rating group demonstrated the same effects. Their proportion correct (figure 4.2) and hit and false alarm rates (table 4.2) are presented below.

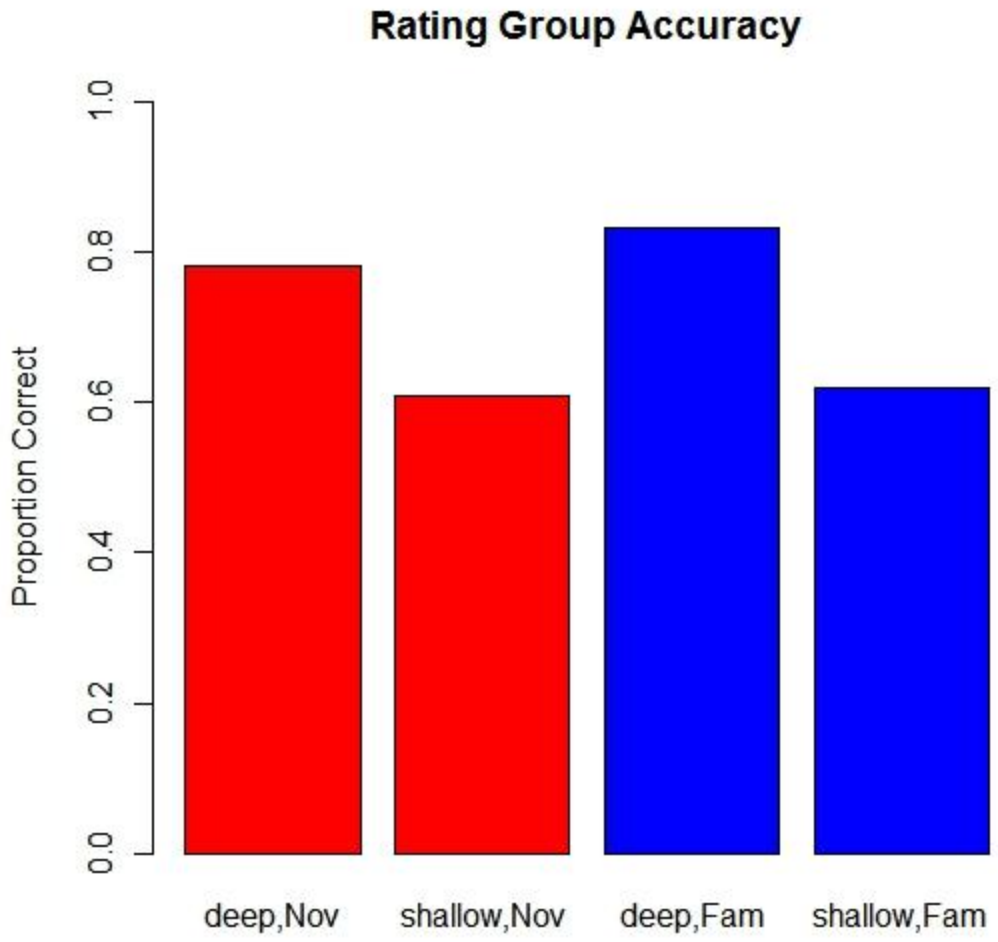

Figure 4.2. Proportion correct for the rating group under novelty and familiarity RO for the deep and shallow tests in phase 2.

	Novelty Orientation	Familiarity Orientation
Deep test hit rate	.824	.831
Deep test false alarm rate	.259	.162
Shallow test hit rate	.564	.541
Shallow test false alarm rate	.354	.304

Table 4.2. Hit and false alarm rates for the rating group under novelty and familiarity RO for the deep and shallow tests in phase 2.

In both groups and both retrieval orientation conditions, the main effect of test (DOP effect) is apparent; words encoded in the shallow condition were less likely to be correctly recognized. The main effect of retrieval orientation is due to generally better accuracy under typical recognition memory instructions (i.e. for participants in the familiarity condition). The test-RO interaction is due to the DOP effect being larger for participants in the familiarity condition. This interaction is shown more clearly in figure 4.3. Each bar represents the DOP effect by subtracting performance on the shallow test from performance on the deep test. Additionally, the DOP effect is larger for the ON group than the rating group.

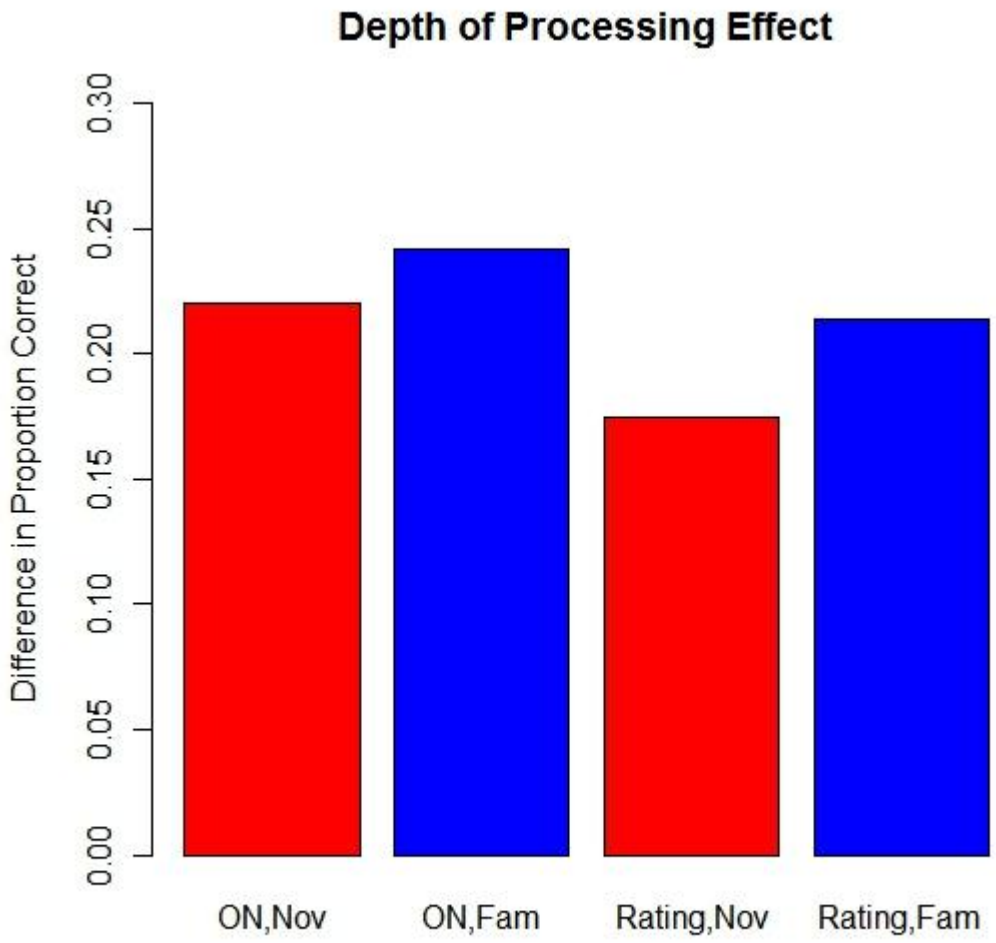

Figure 4.3. Depth of processing effect size for rating and ON groups under novelty and familiarity RO.

In summary, in phase 2 we found the expected DOP effect due to the study phase manipulation. In addition, we found that this effect significantly interacted with retrieval orientation; participants with the typical familiarity retrieval goal showed a larger DOP effect. This difference was driven by performance on the deep test; participants in the familiarity and novelty orientation groups performed similarly on the shallow test (hits minus false alarms ~ .21) but the familiarity group performed better on the deep test (hits minus false alarms = .692 versus .603 in the novelty group). Finally, the size of the DOP effect was also larger for participants in the ON group than those in the rating group. This final interaction was not expected since the final test response manipulation had not yet occurred; it would appear to be due to differences in the participant groups run at different times. The lack of a three-way interaction suggests that the DOP-RO interaction did not differ for the two groups.

Phase 3: One participant in the ON group had three inappropriate (neither 'yes' nor 'no') responses; these were removed from the analysis. For the initial analysis of the final test phase, responses from the rating group were collapsed into 'old' (a response of 4, 5, or 6) and 'new' (1, 2, or 3) and combined with the ON group and a model similar to that from phase 2 was fit to the data. The model contained word familiarity, frequency, and length as covariates and participant, word, and list as random effects as before; the fixed effects of interest were RO, group, and word role. The possible word roles were novel lure (never seen before in the experiment and should be rejected), deep target (a lure seen on the phase 2 deep test), and shallow target (a lure seen on the phase 2 shallow test). The main effect of interest is to replicate the Jacoby et al (2005a) memory for foils effect, which would appear as a main effect of word role, and to determine if the size of the effect varies with retrieval orientation, which would appear as a word role – RO interaction. No significant interactions were found; when they were removed from the model the main effects of word role ($p<.0001$) and group ($p=.047$) were significant. Lures from the deep test were correctly identified more often than shallow lures, replicating the memory for lures effect, and participants in the rating task were more accurate overall. Critically, there was no significant effect of retrieval orientation on final test performance. The memory for foils effect is shown in figure 4.4 for the four group-by-RO conditions.

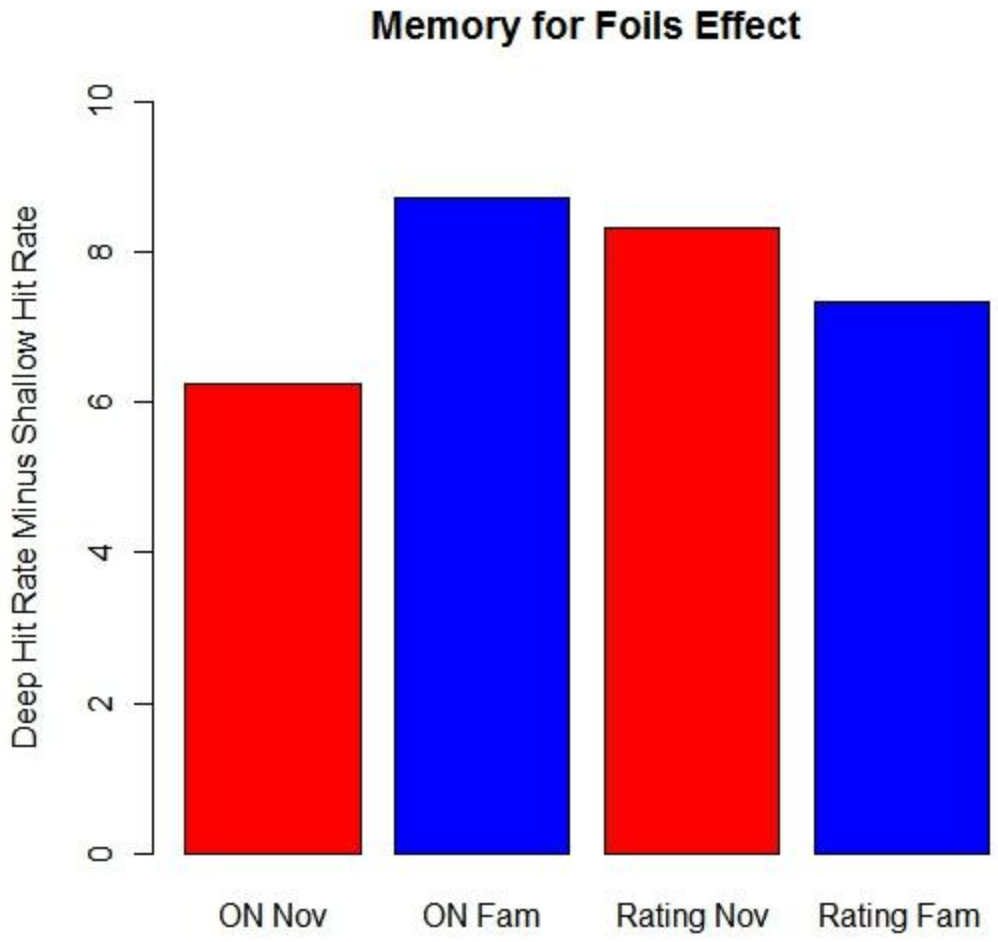

Figure 4.4. The memory for foils effect for group (rating and ON) and RO (novelty and familiarity) conditions. The effect is calculated as the difference in hit rate between deep targets and shallow targets, expressed as a percentage.

As a final analysis of the final test data, only participants from the rating group were examined. As opposed to collapsing their ratings to give old/new responses, their confidence ratings were fit with a maximum likelihood estimation program (Diaz, personal communication) to an unequal-variance SDT model. Unequal variances are typically found for the signal and noise distributions in recognition tasks (e.g. Glanzer, Kim, Hilford, & Adams, 1999), and a model of this type provides estimates of the multiple criteria points and d_a (d sub a, a measure of accuracy independent of response criteria; see Macmillan and Creelman, 2005) for each participant. The program was fit to each participant separately for deep and shallow targets, again using novel lures as the common 'noise' distribution, and thus each participant provided two accuracy values. The d_a values were analyzed with a linear mixed effects model as well as a

repeated measures ANOVA. Confirming the results of the previous regression analysis, the linear regression found only a significant effect of target, which was also confirmed by the repeated measures ANOVA. Thus the d_a analysis also shows that the memory for foils effect occurred, but did not differ with retrieval orientation.

Summary: The three phases of the experiment were examined with a series of mixed effects regression models. In phase 1, as expected, accuracy for determining the number of letters in a word did not differ for any of the groups or conditions manipulated later in the experiment. In phase 2, as expected, a significant depth of processing effect was elicited by the study phase manipulation. The effect was smaller for participants operating under novelty orientation instructions. This finding suggests that the novelty retrieval orientation did have an effect on participants' memory search. It is possible that the task was simply strange or more difficult for participants, but the significant interaction suggests that accuracy did not decrease evenly but in fact differed on the deep and shallow tests. Performance on the shallow test was above chance (two tailed t-test, $p<.0001$), so the interaction is not likely to be due to floor effects. Participants in the RO conditions did not differ during the study phase, so it is unlikely that the DOP difference is due to encoding effects.

Instead, the difference appears to be driven by lowered performance on the deep test, suggesting that perhaps novelty participants failed to properly constrain their memory search to look for detailed information in the same way that familiarity participants did. The two groups performed equivalently on the shallow test, presumably because memory judgments were made on the basis of a general familiarity or strength signal that was not affected by the retrieval instruction. However, this difference did not carry forward into the final test. In phase 3 a significant memory for foils effect was elicited but did not significantly differ with retrieval orientation. Assuming the null result is accurate, it suggests that while the novelty RO group was less likely to constrain their memory search in phase 2, they were able to perform a normal memory search in phase 3 under typical recognition memory instructions. Furthermore, their memory accuracy was not harmed despite the lowered overall performance and memory constraint during phase 2.

4.5. Discussion

The current experiment had two aims: to attempt to determine if searching for novelty appears to be a distinct process from searching for familiarity (i.e. recognition), and if so to look for possible effects on memory due to a novelty orientation. While a large amount of research has examined the effects of viewing a novel stimulus (such as different patterns of eye movements (Loftus & Mackworth, 1978) or better memory (R. R. Hunt, 1995)), much less is known about what happens when a person is attempting

to find novel stimuli. One potential outcome is better encoding; according to Tulving and Kroll's (1995) novelty/encoding hypothesis, novelty detection is a necessary condition for encoding. If novelty is a feature or characteristic of stimuli that can be searched for, a novelty orientation could emphasize that information and thus lead to increased or better encoding of even somewhat familiar stimuli. One might also predict that a novelty orientation is really just a familiarity orientation in masquerade; any particular stimulus is familiar to the extent that it isn't novel and vice versa (Habib, 2001). When asked to make a memory decision, whether it is aimed towards familiarity or aimed towards novelty, participants evaluate the memory content of the stimulus and then simply respond appropriately. In that case, null effects would be predicted throughout the experiment. Alternatively, we predicted that a novelty orientation would reduce memory performance due to a lowered reliance on recollection or source-constrained processing. Because participants would be focused on a simple familiar/not-familiar decision, they would be less likely to constrain their memory search or engage in more thorough retrieval processes.

While we predicted that the novelty orientation group would show a reduced memory for foils effect, there was no support for this in the data. There are a number of reasons this could have occurred. First, the second hypothesis from above could be correct and novelty orientation participants simply performed the exact same processes as the familiarity group, simply pressing a different button at the end of test trials. However, the orientation effects found during phase two argue against that interpretation. Novelty orientation participants demonstrated a reduced depth of processing effect; we believe this to be due to a focus on a simple strength-based evaluation of each stimulus as opposed to a deeper search for associated information. This hypothesis is supported by the observation that the reduced DOP effect comes from lower performance on the deep, but not the shallow, test. A similar pattern of results was found for older adults in the original memory for foils paradigm (Jacoby, Shimizu, Velanova, & Rhodes, 2005), who also do not appear to constrain their memory search. This reduced processing should cause the deep and shallow lures to be processed more similarly in the novelty group, leading to a reduced memory for foils effect. However, this result was not confirmed. One potential reason is that the orientation manipulation, while effective, was too subtle to carry through to the final test. The depth of processing difference between groups was on the order of only a few percentage points, and while statistically significant may not have been large enough to carry over. Another, not mutually exclusive reason could be due to extra encoding processes brought to bear on the lures by the novelty group. An important difference brought on by the orientation manipulation is that the phase two lures were targets for the novelty group while they were simply lures for the familiarity group. The previously-described experiment by Dudukovic and Wagner (2007) already found that novel lures appear to draw more attention and hence more encoding when they are retrieval targets than when participants are searching

for familiar targets. These encoding processes may have served to mask any memory for foils differences between the orientation groups that would have otherwise been observed.

Returning to the goals of the experiment, the evidence is mixed. We did demonstrate that a novelty orientation can evoke different processes than a familiarity orientation; the novelty group produced a reduced depth of processing effect during phase two of the experiment. However, there did not appear to be later consequences for memory; the novelty group produced a memory for foils effect (and overall memory performance) on par with the familiarity group. Further research is necessary to determine if these results are indeed due to extra encoding of novel lures at test time as hypothesized. However, it seems clear that the intent to search for novelty does not boost memory above levels found during typical recognition. Instead, it is possible that a novelty orientation impairs memory by reducing the likelihood of using recollection or a 'deep' retrieval strategy.

5. General Conclusions

5.1. Summary of Results

The hippocampus is a popular focus of research and, perhaps as a consequence, has seen its putative role in cognition expanded over the past decades. What began as essentially a general memory module, and stood for a long time as only necessary for long-term memory, has since been claimed to be involved in domains including working memory, perception, language, and imagination while its role in memory has been scaled back to 'only' relational memory. Few of these claims have gone unchallenged as researchers provide counter-evidence with their own patients or paradigms. This thesis has focused on one of these putative domains, novelty processing. Due primarily to the advent of neuroimaging techniques, the hippocampus has consistently been found to be involved in novelty processing (Knight & Nakada, 1998; Nyberg, 2005; Ranganath & Rainer, 2003). However, others (Graham et al., 2010; Konkel & Cohen, 2009; Kumaran & Maguire, 2007) have argued that hippocampal function should be defined by the kinds of representations that it creates/supports or the information processing role that it provides for the brain (even if the authors disagree on what those representations are). This viewpoint would dismiss much of the novelty literature by noting that the hippocampus would be expected to be involved in the examined paradigms due to its role in memory, perhaps particularly encoding relational information.

The data presented here aimed to address and expand the literature on novelty processing and how it may depend on the hippocampus. Instead of examining expected and unexpected stimuli, or more and less recently studied stimuli, participants were asked to treat novelty as a goal and explicitly search for novelty in the environment. A range of predictions could be made based on the novelty literature. Under the novelty/encoding hypothesis (Tulving & Kroll, 1995; Tulving et al., 1996), it is believed that novelty is a necessary component of encoding. If a person were in a novelty orientation, actively searching for novel information, perhaps they would be more likely to bring encoding processes to bear and memory would be enhanced. Given the central role of the hippocampus in the novelty processing network (Knight & Nakada, 1998) it would be expected that hippocampal lesions would reduce or eliminate novelty-related effects (Kishiyama et al., 2004; Knight, 1996). Or perhaps, consistent with the claim made by Freed and Corkin (1988), hippocampal lesions would actually lead to a novelty preference, such that amnesic patients would actually perform better on memory tests that emphasize novelty.

However, no such effects were found. Patients with hippocampal damage as well as matched comparison participants were tested on an eye tracking paradigm that has demonstrated both the automatic effects of memory as well as the influence of goals (Ryan et al., 2007). Stimuli of various levels of memory strength (or stimulus-based novelty) were used, namely famous and non-famous faces, as well as unexpected (or contextually novel) stimuli, namely non-studied famous faces. Hippocampal

damage had no effect on the ability to follow novelty instructions and patients treated the different levels of novelty in the same manner as comparison participants. The patients did, however, demonstrate reduced discriminability between the studied faces and novel lures, an indication of their memory deficit.

The first experiment was meant to investigate multiple forms of novelty, with the manipulation of orientation occurring across blocks. The second experiment expanded on the results by using much more novel stimuli, adding a working memory test, and manipulating orientation at the trial level instead of the block level. If the hippocampus is an important part of the novelty processing network, perhaps a deficit would appear when that network was taxed by constantly changing demands and novel, unusual stimuli. However, across both behavioral and eye tracking measures, the amnesic patients performed similarly to the comparison participants regardless of if they were in a familiarity or a novelty orientation. The patients also performed normally on the working memory trials but were impaired on the long-term memory trials, consistent with their memory deficit. Indeed, the eye tracking data suggested that participants have a preference for familiarity even under novelty instructions, which seems problematic for strong accounts of novelty processing as an important function.

Finally, an experiment was conducted to determine what behavioral consequences might arise from instituting a novelty orientation. Novel stimuli seem to enjoy the benefit of grabbing attention and (presumably as a consequence) greater memorability; does this benefit extend to a novelty orientation? The third experiment adapted the Jacoby et al. (2005) source-constraint paradigm to determine if participants search their memory differently when looking for novelty as opposed to familiarity. Half of the participants replicated the original effects demonstrated by Jacoby et al. (2005) while following familiarity instructions. The other half followed novelty instructions during the initial test phase, examining whether the novelty orientation has an effect on retrieval as well as encoding. The novelty orientation did appear to influence retrieval as the novelty group demonstrated a reduced depth of processing effect. However, it did not affect the memory for foils effect. This null result may have been influenced by the fact that lures on the initial test were targets for the novelty group and as such likely received more attention than the familiarity group would have given them. If this occurred, then there must have been a deleterious effect of the novelty orientation that was then countered by the extra attention. In any event, there was no support for the idea that a novelty orientation provides any benefits beyond what is found under typical familiarity instructions, and there are actual costs.

In short, little evidence was found that a novelty process has an explanatory power beyond usual memory processes. Damage to the hippocampus, known to be critical to memory, had no effect on any novelty manipulation attempted in the first two experiments. This result would support the view held by

Habib (2001) and others that novelty and familiarity are 'opposite sides of the same cognitive coin'. Novelty retrieval orientation, however, may not be simply the complement of familiarity retrieval orientation, as the third experiment found differences in performance between groups of young adults under the two different goals.

Some caveats must be noted in this research. One is the constant battle of sample size fought by researchers using special populations. In this case there were only four patients available (three at any given time) for the two amnesic patient experiments, whose performance was compared to only four intact control participants. Using typical paradigms and analyses, this would be a greatly limiting problem. I circumvented the issue of small sample size in two ways: by using eye tracking and by analyzing the data using hierarchical generalized linear regression models. Eye tracking provides a much richer picture of behavioral than a single button press as well as more data in general. While behavioral responses provide two pieces of data per trial (the response and the time taken to made it), eye tracking data are collected at 1000 Hz providing potentially thousands of data points per trial. Even when summarized into fixation durations there are a number of fixations made per trial that can be analyzed in regards to where gaze was directed on-screen, when they occurred relative to stimulus onset, and when they occurred relative to when a response was made (if any was required).

Accompanied by this larger amount of data is an analysis approach that allows for data from each trial to be used instead of averaged at the participant level and used for statistical inference. The regression models not only allow for trial-level analysis but also improve on more typical statistical tests by nesting responses within the participant who made them and treating the data as coming from an appropriate distribution. Behavioral responses, for example, are typically averaged at the participant level and expressed as a proportion correct or difference of proportions such as hit rate minus false alarm rate. They are then typically analyzed with t-tests or ANOVA. Not only does this throw away a large amount of information (namely, what happened on each trial) but it is statistically inappropriate as proportions are rarely normally distributed, especially with such a small sample size. Generalized linear models treat trial-level data as coming from their appropriate distribution; binary (correct or incorrect) responses are analyzed with a binomial regression, count data (such as transitions) with a Poisson regression, and so on. These regressions provide more power by using more information and treating it in a statistically appropriate manner.

Another necessary caveat is that only one patient population was tested. That population was obviously critical, given that the novelty literature has focused on the hippocampus. However, brain damage is known to create some general deficits, such as cognitive slowing, almost regardless of the

location of the lesion. It is possible that such a general deficit could have created or contributed to the results found here. However, I would argue that it is unlikely that such a deficit would have led to the specific results found in the first two experiments, which align nicely with decades of research on amnesic patients. It is scant evidence, but one patient with a larger lesion (due to encephalitis) was tested in the second experiment, and his performance was similar to the two patients with restricted lesions. This suggests that hippocampal damage alone is sufficient to cause the results seen here. Even so, a stronger argument for the specific role of the hippocampus in these results could be made if a control group with lesions in a different brain region were also tested in future studies. An intriguing choice would be patients with lesions in the prefrontal cortex, which has also been implicated in novelty processing (Knight & Nakada, 1998; Ranganath & Rainer, 2003) and is known to be important for goals and retrieval strategies (Miller & Cohen, 2001). However, if patients with selective enough lesions could be found, their memory should be largely intact. With such a group I would predict a different pattern of results from what was found with the amnesic patients; memory performance would be at normal levels, perhaps even after a long delay, but the prefrontal patients would have difficulty instantiating a novelty orientation as instructed. They would likely be more influenced by the automatic aspects of memory (Ryan et al., 2007) and demonstrate the retrieval orientation differences that the amnesics failed to show.

5.2. Processing Versus Processes

The conclusions from the current experiments are largely based on null results; patients with hippocampal lesions failed to perform differently under novelty and familiarity orientations and intact young adults failed to show a different memory for foils effect under a novelty orientation. In such a case it is important to have a strong theoretical framework for predicting these null results as well as the differences that were found. I believe that the relational memory theory of hippocampal function (Cohen and Eichenbaum, 1993; Eichenbaum and Cohen, 2001) coupled with an information processing view of how relational binding occurs (the Complementary Learning Systems (CLS) approach (Norman, 2010; Norman & O'Reilly, 2003) provide a framework that not only explains the current results but most of the literature in general. The relational memory theory was described at a process level earlier; the hippocampus binds together items processed in regions of cortex that feed forward to it. However, this provides little in the way of how exactly the hippocampus might accomplish this.

A more mechanistic account is provided by a computational model based on the CLS approach. In this model, the MTL cortex (primarily perirhinal cortex) functions largely via a matching process; representations of previously seen items are stored in the cortex and when an item is presented it is compared to these representations. These representations are largely bundles of feature values that describe the items already in memory or currently being presented, and any particular item would activate

a number of nodes in the model, representing neurons in the cortex. The hippocampus, in contrast, stores representations via pattern separation due to sparse encoding. When representations come into the hippocampus from the perirhinal cortex they are not only bound together (multiple perirhinal nodes converge onto a single hippocampal node) but they are stored in a relatively small number of nodes compared to the cortex (sparse encoding). Thus inputs that share some features (thus overlapping in perirhinal cortex) but not others would be stored in separate hippocampal nodes (pattern separation). This allows even highly similar inputs to be distinguished by the hippocampus while they would be considered matches by the cortex. Furthermore, reflecting the hippocampus' unique recurrent connections, the system is able to take a partial input, recover the entire input (pattern completion), and compare it to what is actually seen in the environment. For example, if the system learned pairs of items A-B and C-D and was later presented with A-D, the cortex would likely call this an old combination due to its strong match to representations in memory. The hippocampus, on the other hand, would reject A-D because of the non-overlapping representations of A and D in separate pairs. Additionally, the hippocampus could recover the original study pair A-B using only A as an input. The predictions of the model have been supported by empirical research (Duff et al., 2011; Holdstock et al., 2002) and evidence of both pattern separation and pattern completion have been found in the hippocampus (Bakker, Kirwan, Miller, & Stark, 2008). As such, the model seems well-equipped to describe how the hippocampus accomplishes relational binding.

Focusing on the type of information processing the hippocampus performs and the types of representations it supports allows for reasoned predictions in a variety of experimental settings (Graham et al., 2010; Konkel & Cohen, 2009). The CLS model provides such a backbone. Accounts of hippocampal function based on putative psychological processes, on the other hand, are less likely to be informative and may lead to circular reasoning (e.g. hippocampal lesions impair long-term memory, therefore any deficit seen in amnesic patients is due to long-term memory being involved in that task). Importantly, as will be described next, the relational memory/CLS model provides an account of why the hippocampus appears to be involved in novelty processing.

5.3. The Hippocampus and Novelty

At a mechanistic level, the pattern completion portion of the CLS model relates to novelty as it provides the basis for a mismatch detector in the hippocampus (Kumaran & Maguire, 2007; Lisman, 1999; Lisman & Otmakhova, 2001). The assumption is that the hippocampus is typically in 'retrieval mode'. When a stimulus is experienced, sensory cortex processes it and the representations travel to the hippocampus. The hippocampus performs pattern completion, retrieving any additional information that might have previously been associated with that stimulus. For example, when walking into a restaurant it

might retrieve the names of people seen there before. This is a prediction, potentially calculated by hippocampal subregion CA3 (Lisman & Otmakhova, 2001). Subsequent experience will also be processed and sent to the hippocampus, providing an opportunity for the predictions to be compared to reality (perhaps in CA1). If the prediction and reality do not match, a mismatch is registered and the hippocampus switches to 'encoding mode' to create a new representation.

As discussed throughout, the claim that the hippocampus is important for novelty processing is based on two types of evidence: the hippocampus is more active during the presentation of relatively novel/unstudied stimuli (Kirchhoff et al., 2000; Stern et al., 1996; Tulving et al., 1996) and the hippocampus is more active for (Yamaguchi et al., 2004), or hippocampal damage eliminates effects based on (Knight, 1996), unexpected stimuli. However, both of these results are predicted by the relational memory theory/CLS model just described. It is natural to expect the hippocampus to be important for building contextual associations and expectations; it would bind together the presence of certain stimuli with the experimental context or task. This binding allows for an expectation to be created via pattern completion: as the experimental context continues, certain stimuli are predicted to occur. If an unusual stimulus is presented, such as an oddball in the novelty oddball paradigm, the expectation is broken and the stimulus-experiment binding needs to be updated. Thus the habituation found by Yamaguchi et al. (2004), and the absence of it in amnesic patients (Knight, 1996), is to be expected. After a number of similar unexpected events occur, they are no longer unexpected because the experimental context has been updated, or in the case of amnesics no experimental context exists to allow for predictions to be made and expectations to be violated. A similar argument can be made for relatively novel stimuli activating the hippocampus. To the extent that the hippocampus performs any binding on a stimulus, it will need to perform less binding if that stimulus occurs again (Kumaran and Maguire, 2009, make a similar argument). Assuming that mismatch detection drives the observed hippocampal responses, is it necessary to claim that the hippocampus additionally supports novelty processing?

The current work aimed to avoid these issues and the conflation of novelty effects with relational processing by examining novelty as a goal or retrieval orientation instead of as a stimulus property. A strong conclusion given the current empirical results as well as literature review would be that 'novelty processing' does not exist and instead familiarity and novelty are complements as claimed by Habib (2001). This may be true in regard to stimulus novelty, as discussed throughout. However, this may not be the case when applied to meta-mnemonic processes like retrieval strategy. While novelty effects do not appear to depend on the hippocampus, the third experiment did find evidence that behavior changes under a novelty orientation as compared to a familiarity orientation. The intention to find novel stimuli appears to reduce source-constrained retrieval, being sufficient to reduce the commonly found depth of

processing effect. Further research is necessary to validate the claim that a novelty orientation makes controlled retrieval and reinstatement of study processes less likely. Further arguments could then be made as to whether novelty processing exists as a kind of retrieval orientation or whether it is then simply a particular constellation of strategies; that is to say, the same effects could be brought about by the same underlying retrieval strategies via some other manipulation. However, that is beyond the scope of the current work. What has been shown here is that novelty processing may exist as a phenomenon, but not in the manner typically described in the literature, and it does not rely on the hippocampus.

5.4. Conclusion

Across three experiments novelty processing was tested as a goal or retrieval orientation. The first two experiments demonstrated that certain mnemonic processes, but not the ability to instantiate a novelty orientation, are dependent on the hippocampus despite its prominent role in the novelty literature. A third experiment demonstrated that a novelty orientation is not simply the complement of a familiarity orientation but that it does have its own effects on performance. The former results combined with other evidence from the literature suggest that many novelty-based results can be accounted for with existing mnemonic functions without requiring an additional novelty process. The latter result, in contrast, is a novel demonstration of a potential novelty-based retrieval strategy or process. Further research will be needed to better describe both the representations and the neural bases involved in the novelty and familiarity retrieval goals examined here.

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