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MEDIAL TEMPORAL LOBE AND PREFRONTAL CORTEX CONTRIBUTIONS TO
MEMORY EXPRESSED ON SHORT TIMESCALES

BY

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DISSERTATION

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ABSTRACT

Oftentimes, adaptive behavior relies on using memory for past events to guide upcoming decisions. To achieve this, memory structures in the brain interact with structures that exert cognitive control over the expression of such memories. This thesis investigated such interactions – the use of memory representations recently formed to guide adaptive behavior in the moment.

The medial temporal lobe (MTL) is critical for human memory. Its role in memory at long delays is well-established, while its contribution to memory at short delays had not been appreciated until recently, when studies specifically targeted the kind of processing it has come to be known for – binding of arbitrary relations among items in scenes or events into relational memory representations. In contrast, the role of the prefrontal cortex (PFC) in memory on this timescale has been well studied. One consequence of new insights about the role of MTL in memory under short delays is the question of how PFC fits into the picture. The framework for the work performed here is that the PFC exerts cognitive control over relational memory representations supported by the MTL.

The first experiment further shortened the delay, and investigated the role of the hippocampus in relational binding when there was no imposed delay. Using a restricted viewing paradigm, it was found that the hippocampus was critical for binding sequential glimpses into a coherent representation to guide exploration of a scene. The result demonstrated that, through its role in relational binding, the hippocampus contributes to task performance regardless of delays. The second experiment followed up on this finding, and investigated control processes carried out by the PFC that interact with MTL-based relational representations during ongoing behavior.

Using fMRI, PFC-MTL interactions were studied using a search task that required frequent updates of cue-outcome relations. It was found that both the PFC and the hippocampus were involved during ongoing task performance but they displayed different activity profiles. Negatively correlated activity between the PFC and the hippocampus further suggested that the two regions were important for different aspects of the task. The third experiment focused on one type of cognitive control exerted by the PFC – interference resolution. In an fMRI experiment, it was found that the inferior frontal gyrus was active during interference resolution caused by recently studied object-location relations. Taken together, experiments in this thesis underscore the role of the hippocampus in relational binding, and demonstrate that the MTL and the PFC interact closely to guide adaptive behavior online.

To Dad and Mom

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Chapter 1

General Introduction

Memory and on-going behavior

Memory plays an important role in guiding optimal behavior during the course of many cognitive tasks. For example, in various card games, optimal play depends on accurate evaluation of the cards held by your opponents, which in turn relies on the ability to remember their play history. How do we use memory representations just acquired online to guide our on-going behavior? There are two aspects to the answer of this question – the memory representations that support performance under this timescale, and the control of their expression. This dissertation investigated both. In particular, emphasis will be placed on memory for arbitrary relations that guide performance under short timescales, and its cognitive control. For example, in the card-game scenario, how do we remember which card is played by whom at which point of the game, how do we use this memory to guide our decisions, and how do we navigate through similar card-player representations without being interfered?

Patient H.M.

In 1953, a young man named H.M. underwent a radical surgical procedure to have his medial temporal lobes removed bilaterally in the hope of curing epilepsy that was irresponsive to any conventional drug treatment. Unbeknownst to H.M., and the doctor who performed the surgery, William Scoville, the surgery had grave consequences on H.M. and made him the most famous neuropsychological patient in the world. Although the surgery was successful in ameliorating H.M.’s intractable epilepsy, it left him with severe amnesia that lasted for the rest of

his life. H.M. could not remember events that had happened up to 11 years prior to his surgery (Sagar, Cohen, Corkin, & Growdon, 1985) (retrograde amnesia), nor learn new facts and events that occurred after his surgery (complete anterograde amnesia). The following are but a few examples that illustrate the extent of his severe anterograde amnesia. He read newspapers and magazines but completely forgot their contents immediately after. His family moved to a new house after his surgery but he was unable to remember his new address and was discouraged from going out by himself (Scoville, 1968). He could not remember a single food item he had during lunch a half hour ago (Scoville & Milner, 1957). His memory impairment was in stark contrast to his preserved cognitive abilities, indicated by comparable IQ scores pre- and post-operation (Scoville & Milner, 1957). H.M.'s case marked the beginning of an era of memory research that strives to understand the role of the medial temporal lobe in memory.

Characteristics of impaired and spared memory abilities in H.M.

Extensive testing on H.M. showed that he was impaired in some domains of learning and memory but preserved in others. As mentioned above, his remote memories were intact up until 11 years before his ill-fated surgery. Also, he was able to maintain and manipulate short lists of information like letters, words, or digits in immediate memory as long as he was not distracted (Milner, 1972; Wickelgren, 1968). However, once the information load exceeded his immediate memory span or he was distracted, the information he just learned was gone forever. Therefore, his deficits were selective for the formation of new long-lasting memories. His memory deficit was global, in that the types of information affected include all modalities, including shapes, patterns, faces, names, public and personal events, etc (Eichenbaum & Cohen, 2001).

Moreover, there was a further selectivity within his deficits in lasting memories – a distinction between “knowing how” and “knowing that”. When asked to trace a star-shaped object by looking at its mirrored image, his drawing speed improved upon repetitions although he did not remember any prior drawing episodes (Milner, Corkin, & Teuber, 1968). When he learned to read texts that were mirror-reversed, his reading speed improved over sessions, although he did not show an extra boost in reading speed for words that were repeated across sessions like healthy participants did, nor did he remember the prior experiment sessions (Cohen & Squire, 1980). These observations showed that H.M. did have memory for these experiences. However, the kind of memory he had is not what we generally think of as “memory” – reminiscences that we can tell others about, e.g., “I remember reading the word ‘elephant’ in reverse”. The kind of memory H.M. had was expressed through changes in behavior upon encountering the same stimuli again, e.g., becoming faster at reading texts in reverse because he had seen them in this manner before. As such, a distinction between “knowing how” and “knowing that” was observed – although H.M. was unable to declare what he learned (impaired declarative memory), previous experience biased his responses in the future (preserved procedural memory).

Relational memory theory

To characterize the nature of declarative memory, the relational memory theory was proposed (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001). According to this theory, the hippocampus and the surrounding parahippocampal region, which consists of the perirhinal cortex, the parahippocampal cortex, and the entorhinal cortex, constitute the hippocampal memory system to support declarative memory. The role of the hippocampus is to bind together

all manner of arbitrary relations among elements of scenes or events and to support the flexible use of such representations. Information from the neocortex is projected to the parahippocampal region before reaching the hippocampus; object (“what”) information projects to the perirhinal cortex, while spatial (“where”) information projects to the parahippocampal cortex. The two information types are then projected to the entorhinal cortex where they remain segregated. From the entorhinal cortex, they are projected to the hippocampus where they finally converge. Therefore, the hippocampus is located in an ideal anatomical location for relational binding to occur.

The relational memory theory receives support from multiple converging lines of evidence. Neuropsychological studies on patients with hippocampal lesions found that memory for relations between items is impaired (Giovanello, Verfaellie, & Keane, 2003; Holdstock, Mayes, Gong, Roberts, & Kapur, 2005; Turriziani, Fadda, Caltagirone, & Carlesimo, 2004). fMRI studies found that the encoding (Davachi, Mitchell, & Wagner, 2003; Ranganath et al., 2004), as well as retrieval (Giovanello, Schnyer, & Verfaellie, 2004) of relational information activate the hippocampus. Immediate early gene imaging found that hippocampal neurons are activated by novel arrangements of familiar objects, thus showing memory for the relations among objects (Wan, Aggleton, & Brown, 1999).

Role of the MTL in short-delay memory tasks

As the relational nature of declarative memory was gradually made clear with more research, there was rekindled interest in the issue of MTL involvement in short-delay tasks. Remember from the above that H.M. was found to be able to remember simple stimuli for a short period of time, in contrast with his profound impairment in forming lasting memories. Since then,

similar observations of intact performance at short delays have been reported in other patients with MTL lesions (Cave & Squire, 1992; Warrington & Baddeley, 1974). Together with patients with perisylvian lesions who were impaired in short but not long delays (Shallice & Warrington, 1970), this double dissociation has been considered strong evidence for distinct short- and long-term memory systems.

In retrospect, however, the materials that were used to test memory at short delays, and from which intact STM was observed, were not relational. For example, in Cave & Squire (1992), participants were asked to remember the location of a dot, the deflection of an angle, or a visual pattern in separate experiments. Stimuli like these might not have tapped into the particular processing requirements of the hippocampus. Therefore, questions remained as to whether impairments could be observed at short delays when the right kind of material, i.e., stimuli that require relational binding, was used. Indeed, neuropsychological and fMRI studies that burgeoned in the past decade confirmed MTL involvement in short delay tasks when relational processing was emphasized. Memory for novel, complex objects whose processing benefits from relational binding was found to be impaired in MTL patients (Holdstock, Gutnikov, Gaffan, & Mayes, 2000; Nichols, Kao, Verfaellie, & Gabrieli, 2006). In parallel, fMRI studies found increased MTL activity during the maintenance of novel scenes (Stern, Sherman, Kirchhoff, & Hasselmo, 2001) and faces (Nichols et al., 2006) in delayed match-to-sample tasks. Directly contrasting memory for relations and memory for items in the same experiment, disproportionate impairment in relational memory was found in MTL patients at delays of seconds (Finke et al., 2008; Hannula, Tranel, & Cohen, 2006; Hartley et al., 2007; Olson, Page, Moore, Chatterjee, & Verfaellie, 2006). Furthermore, fMRI studies found increased hippocampal activity when spatial relations of objects had to be held in mind briefly and manipulated (Hannula & Ranganath, 2008).

These studies challenge the classic notion that MTL damage selectively impairs performance at long delays, and instead suggest that MTL contributes to short delay performance through its role in relational binding. By this logic, the MTL is critical for task performance whenever relational binding is required, even when there is no delay, that is, during in-the-moment, “online” processing. Experiment 1 investigated this possibility. Together with other recent evidence (Voss et al., 2011; Voss, Gonsalves, Federmeier, Tranel, & Cohen, 2011; Warren, Duff, Tranel, & Cohen, 2011), this prediction was borne out.

PFC and memory at short delays

One consequence of new insights about the role of MTL in memory under short delays is the question of how PFC fits into the picture. The role of PFC in memory on this timescale has been well studied. In the early 1970s, cell recording studies in monkeys showed persistent activity during the delay period in delayed response tasks (Fuster & Alexander, 1971; Kubota & Niki, 1971), providing the first evidence of active maintenance of information in the absence of sensory input. Subsequently, a large body of fMRI studies in the 1990s have shown PFC activity during short-term maintenance and manipulation of information (for review, see Fletcher & Henson, 2001). Although it is undisputed that the PFC plays an important role in short-delay memory, the PFC is not typically regarded as a “memory structure”, much less for a structure exclusively important for memory at short delays. First, lesions to the PFC do not selectively impair memory performance. Instead, a wide range of cognitive functions is affected, including attention, emotion regulation, decision making, etc. Second, within the memory domain, the PFC is not exclusively important for memory at short delays. fMRI studies have found PFC activities during the encoding and retrieval of long-term memory (for review, see Fletcher & Henson,

2001). Third, lesions to the PFC do not always result in impairment in short-delay tasks, at least when simple maintenance of information is concerned (D'Esposito, Cooney, Gazzaley, Gibbs, & Postle, 2006). So, how should PFC activity during short-delay memory tasks be interpreted?

PFC as a structure for cognitive control

To generalize the role of the PFC across all cognitive domains that it is important for, Miller & Cohen (2001) proposed a framework of PFC function. According to this framework, the PFC is important when top-down control is required; that is, when behavior cannot be guided by automatic or well-learned tendencies. The patterns of PFC activity represent goals or rules of a task, and the PFC achieves cognitive control by exerting biasing signals on other cortical processors to guide processing that is not pre-programmed.

The concept of PFC as a structure for cognitive control is consistent with memory deficits seen following frontal lobe lesions. Damage to the PFC results in memory deficits that are distinct from those observed following MTL damage. The memory impairments in PFC patients are more subtle and are best characterized as deficits in the control processes that allow the efficient formation and retrieval of memory (Moscovitch, 1992; Shimamura, 2000). For example, PFC patients are impaired in free recall tasks, where the demand on strategic organization is high (Gershberg & Shimamura, 1995; Janowsky, Shimamura, & Squire, 1989). It was found that providing organization cues at study or test could bring up the performance of PFC patients, suggesting that their impairment lies in spontaneously organizing information to aid memory formation and retrieval (Dellarocchetta & Milner, 1993; Gershberg & Shimamura, 1995). Another prominent feature of PFC patients' memory impairment is that they are highly susceptible to interference. For example, using a paired-associate paradigm, Shimamura et al.

(1995) showed that PFC patients were impaired in learning the association between word-pairs (e.g., A-C) when the same cue word had been paired with another word in a previously studied word list (e.g., A-B). Besides free-recall and cued-recall, PFC patients are also found to be impaired in recognition, when the distractors are similar to the to-be-retrieved information (Curran, Schacter, Norman, & Galluccio, 1997; Swick & Knight, 1999). In addition to tasks that use long delays, PFC patients also appear to have deficits in tasks that use short delays, when the tasks require manipulating and updating information (Petrides & Milner, 1982). In summary, the core deficit that underlies a wide range of impairment observed across different paradigms is a deficit in exerting strategic control over memory representations, regardless of retention intervals.

From the perspective of cognitive control, PFC activities during the delay period of short delay memory tasks can be thought of as sustained attention to task relevant representations, maintenance of task goal, mediation of interference, etc, rather than storage of representations in short-term memory (Postle, 2006). Indeed, the same interpretations can be applied to PFC activities seen during memory tasks at any timescale, for any type of memory (item or relational). By extension, for the current investigations of relational memory expression during on-going task performance, it is expected that the PFC contributes by exerting cognitive control over the formation and retrieval of relational representations supported by the MTL.

Current work

The current set of experiments explores the contributions of the MTL and PFC to short-delay as well as in-the-moment task performance. From the review above, it is expected that the MTL is responsible for relational binding, while the PFC is responsible for cognitive control. Experiment 1 investigated the acquisition of object-location relations across successive glimpses

in amnesic patients with hippocampal damage, and measured performance both across delays of minutes as well as in real time. Impaired performance across short delays replicated similar previous findings. Interestingly, amnesic patients were impaired in binding sequential glimpses into a coherent representation online. This result converges with recent findings from our lab on the role of the hippocampus in real-time processing. Building on this result, Experiment 2 investigated the network of brain regions that work together with the hippocampus during a task that uses newly acquired relational representations to guide behavior online. Being exploratory in nature, Experiment 2 did not manipulate PFC control processes that contribute to task performance. Experiment 3 was designed to focus on one cognitive control process governed by the PFC – interference resolution – to examine the PFC’s control of relational representations under short delays.

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Chapter 2

The hippocampus binds information across sequential glimpses to create coherent representations

Introduction

The mammalian hippocampus is critical for creating long-lasting representations of scenes, events, and their constituent elements (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001). Damage to the human hippocampus results in severe impairment in processing the arbitrary relationships among individual items that, bound together, form scenes and events. Impaired relationships following hippocampal damage include co-occurrence relations between arbitrary words (Giovanello, Verfaellie, & Keane, 2003), spatial relations between objects and their locations in scenes (Crane & Milner, 2005; Hannula, Tranel, & Cohen, 2006), and temporal relations describing the order of events (Konkel, Warren, Duff, Tranel, & Cohen, 2008). Likewise, brain-imaging studies show activity in the hippocampus during the encoding (Davachi, Mitchell, & Wagner, 2003; Ranganath et al., 2004) and retrieval (Giovanello, Schnyer, & Verfaellie, 2004) of relations. However, one fundamental type of relational processing has traditionally been considered outside the purview of hippocampal function. Discrete samples of sensory information, such as glimpses of the visual world, must be bound together across space and time to create coherent representations of the relationships between items in the environment (Brockmole & Irwin, 2005). Does the hippocampus play an immediate role in forming these relationships as they are being observed?

Recent studies have implicated the hippocampus in short-delay relational memory tasks. However, compared to the deficits observed under long-delay conditions, those observed at short

delays have been modest (Hannula et al., 2006; Olson, Page, Moore, Chatterjee, & Verfaellie, 2006; Ryan & Cohen, 2004), suggesting a limited hippocampal role in the real-time integration of discrete sensory samples. However, it is possible that other brain structures which are intact in amnesia can support relational processing in some circumstances, such as when the memoranda, both the individual items and the relations between them, are available for study at the same time (Verfaellie, Martin, Page, Parks, & Keane, 2006). If this were the case, then deficits due to hippocampal damage would be expected primarily when the appreciation of relationships between items unfolds over time, thus requiring integration of discrete sensory samples. Indeed, it has long been theorized that the hippocampus might bind pieces of information presented at discrete moments into coherent representations. An early study found that the extent of hippocampal damage correlated with impairments in the recall of complex figures that were studied piecemeal—that is, for which information fragments needed to be bound across space and/or time during study (Jones-Gotman, 1986). Likewise, hippocampal activity during encoding predicts subsequent relational memory for information presented piecemeal (Staresina & Davachi, 2009).

In studies that have examined memory for items within complex scenes, amnesic patients have unsurprisingly shown impairments in direct memory tests that probed memory for relations among items (Hannula et al., 2006). However, additional and more fundamental deficits were uncovered by examining the patterns of eye movements made by amnesic patients while they studied those same complex scenes. Even without a study-test delay, amnesics exhibited eye movement patterns different from those of comparison participants (Ryan & Cohen, 2004). If these deficits had been observed in a traditional memory paradigm, a straightforward interpretation would be that amnesia disrupts long-term relational memory. However, the deficits

were observed during the initial visual exploration of a scene, implying that amnesia impairs relational processing that occurs from moment-to-moment. While the gist of a scene can be acquired within a quick glance (Biederman, Rabinowitz, Glass, & Stacy, 1974), the relations among the many items that make up a rich scene can only be appreciated via repeated fixations to discrete locations. The reported impairments may thus arise from the inability to bridge these moment-to-moment percepts into a coherent scene.

In the current experiment, we sought to investigate hippocampal involvement in binding separate percepts into coherent relational representations over time. Scenes containing only two objects were viewed through a “restricted viewing” window that moved based on input provided by subjects via a joystick. That is, each scene was covered almost entirely by a black mask (Fig. 2.1a), and moment-to-moment control of the viewing window provided piecemeal viewing of the scene, one small region at a time. Each trial began with the viewing window positioned on one of the two objects (the “start”), and subjects attempted to locate the second object (the “goal”). Upon finding the goal, participants returned the viewing window to the start object using the most direct route possible (Fig. 2.1b). This paradigm provides an experimental analog to real-world visual scene exploration—in both cases, only a restricted region of space is under scrutiny at any moment. Therefore, relationships among objects and other scene features could only be appreciated via integration across multiple, successive glimpses.

Each scene was explored in this way on six discrete trials, with each trial separated by two intervening search-and-return trials for other scenes containing different objects. This design allowed both search and return performance for each scene to be assessed both across trials and within trials, thus, with and without interposed trials. We focused on two within-trial performance measures: (1) return performance from the goal object to the start object, which

indicated the retention of the start location from the beginning of the trial to the end of the trial, and (2) search efficiency during the first search attempt. The latter performance measure was intended to capture the role of the hippocampus in integration of scene information across successive glimpses, given that efficient search requires planning future search locations based on moment-to-moment assessment of the current location and the history of previously searched locations. All performance measures therefore involved integrating and/or maintaining information across short periods of time, but varied in terms of whether learning occurred across multiple trials versus within a trial.

Materials & Methods

Participants

Four amnesic patients with hippocampal damage (three male and one female) and six neurologically intact comparison participants each matched to one of the patients in terms of age, gender, handedness, and education, took part in the study. The amnesic patients were selected from the Patient Registry of the Division of Cognitive Neuroscience at the University of Iowa. The comparison participants were recruited from the Champaign-Urbana community. All procedures were approved by the institutional review boards at the University of Illinois and the University of Iowa. Informed consent was obtained from each participant before testing began.

For all of the patients, amnesia was secondary to an anoxic/hypoxic episode, due either to an episode of seizures leading to status epilepticus (in one patient), or to cardiac or cardiopulmonary arrest (in three patients). Structural MRI scans, performed on three of the patients, confirmed bilateral damage that was restricted in large part to the hippocampus compared to a gender- and age-matched comparison group (Allen, Tranel, Bruss, & Damasio,

2006). One of the patients wears a pacemaker, and was therefore not eligible to undergo MRI scanning, but based on etiology of anoxia it is assumed that damage is limited to the hippocampus (Hopkins, Gale, Johnson, & Anderson, 1995; Rempel-Clower, Zola, Squire, & Amaral, 1996; Zola-Morgan, Squire, & Amaral, 1986). The studentized residual differences in hippocampal and parahippocampal volume (i.e. z-scores) with reference to a matched comparison group are presented in Table 1 (for more detailed information about the imaging protocol and volumetric data see Allen et al. (2006)). The studentized hippocampal volume was more than two standard deviations below the comparison group for each patient. Patient 2363 had additional volume reduction in overall cerebrum gray matter and parietal gray matter. His parahippocampal gray matter volume appeared to be significantly reduced. However, closer inspection of his MRI scan suggests that his parahippocampal region was intact and that the apparent volume reduction was due to a small brain (as shown by reduced overall cerebrum gray matter). Patient 1606 had additional volume reduction in temporal gray matter, and he is the only patient for whom perirhinal damage could not be ruled out confidently. None of the patients had significant volume reduction in the frontal lobe.

All of the patients had severe memory impairments that interfered with daily life and prevented them from returning to their former employment since the onset of their amnesia. Thorough neuropsychological testing of each patient confirmed that their memory impairment was disproportionate to any impairment in general cognitive function. The General Memory Index score, obtained from the Wechsler Memory Scale-III, was two standard deviations lower than the mean Full Scale IQ score obtained from each patient on the Wechsler Adult Intelligence Scale-III. Each patient was also severely impaired in delayed recall tests such as the Complex Figure Task, with a mean performance of 6.4 out of 36. In contrast, their performance on several

standardized working memory tests that assessed working memory for items was normal, a result that is consistent with well-established findings that performance under short-delay conditions is intact when memory for simple items is tested (Cave & Squire, 1992). Details on the amnesic patients' performance in neuropsychological tests are provided in Table 1.

Procedure

Instructions and practice were given before testing began. The stimuli were 48 computer-rendered scenes a resolution of 1600 x 1200 pixels created using Bryce 5.0 software. Each scene had a colored background with distinct top and bottom parts (Fig. 2.1a). It was notionally divided into 24 (6 x 4) cells of equal size, of which two were occupied by scene-unique novel objects ("start" and "goal") sized 128 x 128 pixels. Throughout a trial, the scene was masked in black except for a small viewing window that was smaller than the objects. The viewing window occupied 2.4° of visual angle, and expanded to 4.8° of visual angle when it was enlarged to show the objects fully. The placement of this viewing window was controlled by the participants, who manipulated a joystick to move it to the area they wished to inspect. Each trial consisted of two phases, search and return (Fig. 2.1b). The trial began with the viewing window centered on the start object. The viewing window was then enlarged for 2s to reveal the start object fully. When the viewing window returned to its original size, the search phase began. Participants then navigated the scene in search of the goal. Upon locating it, the viewing window was again enlarged for 2s to reveal the goal fully, and when the window returned to its original size the return phase began. Upon returning to the start object, the viewing window was once again enlarged for 2s to signal the end of the trial.

Participants were given unlimited time to search for and return from the goal; however, for repetitions of the same scene (Presentations 2-6), a beep was sounded if the length of the search path was more than 80% of that in the previous presentation, unless it was within 130% of the optimal search path length. The purpose of the beep was to encourage participants to use knowledge obtained from previous presentation(s), if any, to guide their search. During return, no beep would sound. Participants were told to search and return as quickly as they could if they thought they had seen a scene before and knew where the goal was. Instructions and practice were given before testing began.

There were two conditions in the experiment: in the same-start condition, all three start objects in a block occupied the same location; in the different-start condition, they occupied different locations. All three goals occupied different locations in both conditions. Statistical tests revealed no significant difference in performance between the two conditions. Therefore, all analyses were performed on data collapsed across the two conditions.

The 48 scenes were grouped into 16 blocks of three. Each block was shown six times consecutively, and the presentation order of scenes within a block remained the same across repetitions. Across participants, each scene was seen equally often in each condition. For both conditions, each of the 24 cells was used equally often as the start and goal locations across participants. Within each block, each scene was seen equally often as the first, second, and third trial across participants.

Three of the patients (2363, 2563, and 1846) completed a second session of the experiment on different counterbalancing orders in order to achieve full counterbalancing. The two sessions were separated in time by several months.

Data Analysis

Cumulative Error

Originally developed by Gallagher, Burwell, & Burchinal (1993) to measure rats' performance in the Morris Water Maze task, cumulative error was used in this study to measure deviation from the optimal path between the start object and the goal. Cumulative error was calculated by sampling the path taken to navigate between the start object and the goal at a rate of 60 Hz, then measuring the distance from the goal at each sampling point, and then adding them together. This measure took proximity to the goal location into account, hence offering an advantage over traditional measures of performance that did not (e.g., total path length; see Gallagher et al. (1993) for comparisons between different kinds of measurements). The distribution of cumulative error deviated significantly from normality, and therefore a log transformation was applied to the raw data before statistical analyses were performed.

Initial Heading Error

Another performance measure, initial heading error, was used to assess retention of start and goal locations based on viewing window movements. Initial heading error was calculated as the deviation from the optimal heading between the start object and the goal, i.e., it was the angle between the initial and the optimal heading. To calculate the initial heading, instantaneous movement vectors were obtained from the first 60 samples (first second of navigation). Each movement vector was calculated from successive sampling points, e.g., (x_1-x_0, y_1-y_0) for the first movement vector. Then, the movement vectors were averaged to give the initial heading. In essence, the initial heading indicated the average direction the joystick moved during the first second of navigation. Because the central tendency of its distribution was significantly different

from zero, the absolute value of each initial heading was taken and the result was then log transformed to produce a distribution that conformed to the assumptions of parametric analyses. All statistical analyses were then performed on the transformed data.

Percent Coverage

Exploration efficiency was measured using percent coverage, calculated for each initial search attempt. Percent-coverage scores were obtained by creating a graphical depiction of the portion of the background image that was uncovered by the viewing window for the trial (i.e., a static image of the total the area viewed via the entire search path for the trial). A tight bounding rectangle was drawn around this viewed area, and percent-coverage was calculated as the fraction of the total area of the bounding rectangle that was viewed via the search path. All calculations were performed via a computer script, and the accuracy of the bounding-rectangle creation, etc. was checked via visual inspection.

Behaviors that would be unhelpful for finding the target (e.g., revisiting previously searched areas, "crossing" the path that has already been traversed, etc.) contribute negatively to percent-coverage, whereas behaviors helpful for finding the target (e.g., exploring each area only once, using an orderly pattern so that no back-tracking is necessary to uncover all areas, etc.) contribute positively to percent-coverage. Furthermore, the use of the bounding rectangle to constrain the overall search space accounts for the fact that trials differed in overall duration, and hence the amount of the background image that could have been covered in the given time, given that the viewing window moved with fixed velocity (although amnesic vs. control comparisons were also made for trials matched in overall search duration, see Results). Furthermore, the measure of percent-coverage does not penalize for overall little movement or activity, as the size

of the bounding rectangle is not increased with inactivity. Trials lasting less than 10 s were excluded because these generally comprised straight-line paths or very simple paths, indicating that the subject uncovered the target without considerable search effort. These trials therefore do not capture the search behavior.

Statistical Tests

To examine across-trial learning, a mixed-model repeated measures ANOVA with between-subject factor group (amnesics, comparison participants), within-subject factors phase (search, return) and trial (trial 1, 2, ..., 6), was performed. After finding a significant group x phase x trial interaction (cumulative error: $F(5,40)=26.8, p<0.001, \varepsilon = 0.30$; initial heading error: $F(5,40)=11.8, p=0.001, \varepsilon = 0.36$), separate 2-way mixed model repeated measures ANOVAs were performed for each phase, with between-subject factor group and within-subject factor trial. T-tests were performed for post-hoc comparisons. They were Bonferroni corrected for multiple comparisons, with overall alpha held at 0.05 and individual alpha at 0.01.

Results

Across-trial search performance

We first sought to assess how well amnesics and comparisons learned the locations of start objects and goal objects across the six trials for each scene. Similar results were obtained for the initial heading error and the cumulative error measures so they are reported together in the following. Amnesics exhibited impaired learning relative to controls (Fig. 2.2c, 2.3a). Error scores differed significantly between these groups across the six trials, indicating different learning rates (group- by-trial interaction: heading error: $F(5,40)=19.7, p<0.001, \varepsilon = 0.29$;

cumulative error: ($F(5,40)=65.0, p<0.001, \varepsilon = 0.33$). As expected, the two groups showed similar error for the first trial, when performance could not be guided by learning (heading error: $t(8)=0.83, p>0.4$; cumulative error: $t(8)=1.36, p>0.2$). Errors were significantly greater for amnesics by the second trial (heading error: $t(8)=5.49, p=0.001$; cumulative error: $t(8)=6.79, p<0.001$; Fig. 2.2c, 2.3a), leading to an overall higher level of error for amnesics (heading error: $F(1,8)=69.8, p<0.001$; cumulative error: $F(1,8)=96.6, p<0.001$).

To better assess learning rate, difference scores were calculated between the first trial and the n^{th} trial for each scene. Of particular interest were the difference scores between the first and second and the first and sixth presentations; that is, (1) did one-trial learning differ and (2) was there any overall difference in learning across the six trials? For amnesics, error levels for the second trial versus the first were not significantly different from zero (heading error: $t(3)=1.53, p>0.2$; cumulative error: $t(3)=1.83, p>0.1$), indicating no learning. In contrast, error levels were significantly less for comparisons' second trial versus first (heading error: $t(5)=5.70, p=0.002$; cumulative error: $t(5)=10.9, p<0.001$), indicating single-trial learning. Importantly, the first-trial vs. second-trial difference scores were significantly lower for amnesics compared to comparisons (heading error: $t(8)=3.50, p<0.01$; cumulative error: $t(8)=5.80, p<0.001$), showing reliable impairment in single-trial learning.

Comparing difference scores between the first and sixth scene presentations indicated that amnesics showed no learning across all trials (heading error measure ($t(3)=3.32, p=0.05$); cumulative error measure ($t(3)=2.26, p>0.1$)). On the other hand, comparisons showed difference scores markedly greater than zero (heading error: $t(5)=8.54, p<0.001$; cumulative error: $t(5)=19.9, p<0.001$), although this learning effect essentially began at the second trial, as indicated above. Amnesics were markedly impaired relative to comparisons by the sixth search attempt, as the

first-trial vs. sixth-trial difference scores were significantly lower for amnesics compared to comparisons (heading error: $t(8)=5.69, p<0.001$; cumulative error: $t(8)=10.4, p<0.001$). Visual inspection of the distribution of initial heading error supports these statistical conclusions (Fig. 2.2a).

Within-trial return performance

Amnesics were far less impaired in returning to the start location from the goal location at the end of each search trial, measured both within one trial and across the six trials. The same metrics of heading error and cumulative error were calculated for the trajectory taken from the goal back to the start object during the return phase of the trial. The two metrics again showed very similar results. Although amnesics' error was larger for the six trials overall than for comparisons (heading error: $F(1,8)=11.9, p<0.01$; cumulative error: $F(1,8)=15.6, p<0.01$), amnesics' return heading errors were substantially less than search heading errors collapsed across trials (heading error: $t(3)=9.90, p<0.01$; cumulative error: $t(3)=13.0, p=0.001$; Fig. 2.2d, 2.3b). The distribution of errors was also markedly different from that during search (Fig. 2.2b). Thus, amnesics were able to maintain the location of the start object for the duration of search, and therefore were only minimally impaired at this aspect of learning.

We therefore infer a dissociation between within- and across-trial learning in amnesics, whereby intact within-trial retention of start locations was coupled with impaired across-trial retention of goal locations. Amnesic impairments therefore only emerged with delay, and it is therefore important to determine the extent to which overall differences in delay between amnesics and comparisons contributed to this dissociation. That is, because amnesics showed significantly impaired search learning, it also took them longer than controls to search for the

goal object for all trials after the first. Therefore, there was a greater average delay for amnesics between successive trials for the same scene (105.1s vs. 37.7s, $t(8)=5.41$, $p=0.001$). Increased delay could thus have contributed to impaired across-trial learning for amnesics, and it remains to be determined if controls would show similar performance levels if similar delays were introduced. However, search duration was approximately equivalent for the first trial (105.7s vs. 89.7s, $t(8)=1.11$, $p>0.2$) and, therefore, the delay was approximately matched for amnesics versus comparisons for the first presentation of a trial to its second presentation. Comparisons showed robust learning by the second trial, whereas amnesics did not, despite similar delay (first vs second trial difference score: heading error: $t(8)=3.50$, $p<0.01$; cumulative error: $t(8)=5.80$, $p<0.001$). Nonetheless, delay could have been a factor that contributed to overall impaired learning for amnesics across subsequent trials. It is nonetheless striking that amnesics never showed learning between any consecutive scene presentations comparable to the learning evident for comparisons after the very first scene presentation.

Within-trial search efficiency

We next sought to assess the role of the hippocampus in the integration of scene information across successive glimpses within a single trial; that is, in real-time processing that occurs with no interposed study-test delay. We therefore examined the efficiency of search attempts, given that efficient search requires integrating information concerning the current viewing location, previous viewing locations, and intended future locations. Analyses were restricted to the searches made during the first presentation of each scene, such that differences in learning rates across scene repetitions would not confound comparisons between amnesics

(minimal learning across repetitions) and comparison participants (substantial learning across repetitions).

To quantify search efficacy, search patterns that would produce a high likelihood of uncovering the goal were considered highly effective, whereas search patterns that could result in failures to find the goal were considered less effective. If a subject were to adopt a highly regular pattern of viewing, then a relatively large percentage of the total space traversed in a given time would have been viewed, and therefore the goal likely would have been found. In contrast, if a subject were to search with an irregular pattern, then a relatively low percentage of the total space traversed would have been viewed, and the goal might therefore have been missed. This method for quantifying efficacy (Fig. 2.4a) produces measures of percent-coverage for each search attempt, with higher values indicating more effective search. Trials with overall search durations less than 10 s were excluded, as these searches were essentially straight-line paths unsuitable for the assessment of search effectiveness.

Considering searches of all durations (≥ 10 s), percent-coverage values were lower for each amnesic patient versus his/her comparison subject(s) (44% vs. 63% for patient 1606 vs. comparison; 38% vs. 44% for patient 1846 vs. comparison; 50% vs. 54% for patient 2363 vs. comparison; and 47% vs 51% for patient 2563 vs. comparison; mean values across subjects provided in Fig. 2.4b). We also grouped trials based on search duration into short (10-20 s), medium (21-50 s), and long (50+ s) searches (Fig. 2.4c). A marginally significant main effect of group (patient vs. control, $F(1,3)=7.9, p=0.06$) but nonsignificant group-by-duration interaction ($F(2,6)=2.5, p=0.2$) indicated that searches were less effective for amnesics vs. controls for all search durations, without significant variation across durations.

The aforementioned analyses utilized all trials, and a tighter comparison between amnesic and comparison search efficiency was achieved by analysis of trials with matched search duration for amnesics and controls. Each amnesic trial was paired with a randomly selected trial from his/her control that matched for the overall duration of search, and therefore both trials were equivalent in the maximum percent-coverage value that could have been obtained (given that the viewing window was of fixed area and moved with fixed velocity). The Appendix shows the path traversed by each amnesic subject, side-by-side with the corresponding matched control trial. For these search-duration-matched trials, percent-coverage was significantly lower for each patient relative to the matched comparison ($P<0.05$; Appendix).

One of our patients (1606) had additional damage in parahippocampal cortex and also the lowest coverage score of all amnesic participants. It is therefore possible that parahippocampal cortex also contributed to disorganized search behavior. However, all other amnesics with damage limited to hippocampus each had a significantly lower coverage score compared to his matched comparison, suggesting that hippocampal damage alone was sufficient to elicit the impairment.

Discussion

Amnesics demonstrated the ability to retain the start location for the duration of scene exploration during one trial. This retained functionality was in stark contrast to amnesics' severe impairment in retaining goal locations across successive presentations of the same object-scene configuration. This selective impairment for delayed retention is consistent with a long history of findings showing relatively worse performance for long retention intervals relative to brief retention intervals following hippocampal damage (Buffalo, Reber, & Squire, 1998; Cohen &

Eichenbaum, 1993; Eichenbaum & Cohen, 2001; Holdstock et al., 2000; Holdstock, Gutnikov, Gaffan, & Mayes, 2000; Owen, Sahakian, Semple, Polkey, & Robbins, 1995). Notably, a very similar deficit to that observed here was recently found in humans with transient global amnesia using a modified version of the Morris water maze (Bartsch et al., 2010). Selective deficits for delayed retention in our experiment may have resulted from amnesics' poor representations of the absolute spatial location of the goal, of the location of the goal within each scene, of the spatial relationship between the start object, the goal, and the scene, or any combination of representation qualities. Therefore, relatively impaired across-trial learning in this paradigm supports the notion that the hippocampus is more involved in long-term than short-term memory representation, and not that the hippocampus is specifically important for one particular type of representation.

In contrast, assessment of the exploration behavior of amnesics during the search attempt provided direct evidence for hippocampal contributions to very short-term processing of relational representations. Amnesics showed disorganized and ineffective search during the very first search attempt with no retention interval. Because this deficit was expressed on the very first search trial, differences in learning across successive trials for controls versus amnesics could not have been responsible for the amnesic deficit. Furthermore, amnesics successfully retained the start location during the entire search attempt, as indicated by successful return performance after the goal was identified, and therefore disorganized search occurred on a timescale briefer than that for which scene location memory was preserved (confounding factors such as reduced motivation during search, general confusion regarding the task, or rapid memory decay can therefore be dismissed). Amnesics thus displayed ineffective search behavior qua behavior that

was not secondary to object-location memory deficits, indicating a real-time deficit in the use of scene knowledge to guide behavior.

We interpret amnesic deficits in search efficiency as reflecting impairment in the integration and relational binding of successive scene glimpses into coherent scene representations. Effective search requires that individuals establish a coherent representation of the scene based on recent viewing and their current location such that this representation can be used to plan the upcoming exploratory movement. Notably, our amnesic subjects have no impairments that would suggest failures to appreciate or plan effective exploration strategies. They have no reliable impairments in executive function, as indicated by neuropsychological test scores and prefrontal cortex integrity (Konkel et al., 2008), and therefore no gross deficits in planning or strategic thinking, as these capabilities are commonly attributed to frontal cortical function. The most effective search path (i.e., that which produces the highest coverage and therefore rarely results in overlooking a target) involves a simple “snaking” exploration pattern with tight turns made at the edges of the computer screen. Indeed, inspection of scan paths (Appendix 1) indicates that this strategy was adopted frequently by comparison subjects, but very infrequently by amnesics. However, occasional adoption of this strategy by amnesics indicates no fundamental inability to devise or execute such a strategy.

We therefore suggest that amnesic’s disorganized exploration behavior was not caused by poor executive planning capability, but was due instead to poor scene representation brought about by failure to integrate and relate scene information across successive glimpses during exploration. In essence, we propose that a failure to integrate scene glimpses into coherent scene representations caused amnesic subjects to “get lost” during exploration, including during periods when they were attempting to execute effective search using the snaking strategy

(Appendix 1), therefore disrupting effective search strategies. Interestingly, some reports have suggested that rats with hippocampal lesions show abnormal exploratory behaviors (Faraji, Lehmann, Metz, & Sutherland, 2008; Packard, Hirsh, & White, 1989; Riedel et al., 1999) that are similar in some ways to those we see here in amnesia, although these deficits have rarely been quantified in the animal literature. For instance, rats with hippocampal inactivation persistently used an ineffective thigmotaxic search strategy (wall-hugging) during training in the Morris water maze (Riedel et al., 1999). Some aspects of our paradigm might have served to emphasize these deficits. Notably, our use of novel scenes eliminated amnesics' ability to rely on knowledge regarding the normal structured organization of environments that could be used to aid navigation in familiar real-world environments. Furthermore, the restricted viewing window eliminated peripheral information that could be used to facilitate scene representation, thus requiring that any knowledge regarding the scene be acquired via integration across sequential glimpses.

Impaired search behavior in amnesics suggests that the hippocampus plays a critical role in executing strategic behaviors in real-time. This is consistent with the proposal that the hippocampus translates learning into adaptive behavior rapidly (Bast, 2007; Bast, Wilson, Witter, & Morris, 2009). It is important to consider that the anatomical connectivity of the hippocampus (Lavenex & Amaral, 2000; Squire & Zola-Morgan, 1991) shows that it is the ultimate convergence zone for many of the brain's functionally distinct information-processing pathways. We thus speculate that the hippocampus may be critical for binding the output of distinct functional systems in the real-time service of behavior, such as when search strategies must be integrated with representations of locations traversed moments ago, with motor plans for arriving at future locations, etc., to enable systematic search. This proposal is consistent with recent

evidence that the memory performance of hippocampal amnesics is not improved by providing them with strategic control over their study behaviors, which significantly improves memory in healthy individuals (Voss, Gonsalves, Federmeier, Tranel, & Cohen, 2011), and that part of this lack of ability to benefit from control derives from their lack of implementing effective strategies when given control (Voss et al., 2011). Notably, in these studies the hippocampus was associated with strategic control through its participation with prefrontal and other cortical regions more closely aligned with executive/strategic planning. Deficits in moment-to-moment hippocampal relational binding and the impacts that these deficits have on the ability to execute effective behavior could thus be a primary cause of the long-term memory deficits observed in amnesia. The current results provide an example of this, as ineffective and disorganized search behavior can easily be appreciated as a factor in the impaired across-trial goal-location learning.

In conclusion, by providing an experimental analog of the way in which the world is normally perceived, glimpse-by-glimpse, we were able to show that the role of the hippocampus is far more immediate than would be suggested by previous findings of impaired long-term relational memory. Our results indicate that the hippocampus is needed to integrate the information sampled from moment to moment, and that hippocampal damage can therefore result in disorganized and ineffective behavior in the moment. Additional research will be needed to determine whether the role of the hippocampus in online relational binding occurs in addition to its role in long-term memory formation, or whether this is the primary function of the hippocampus.

Tables & Figures

Table 2.1: Amnesic Subject Characteristics

Patient	Handedness	HC Residual	PHC Residual		WMS-III GMI	CFT	WAIS-III			Working Memory			
			gray	white			VIQ	PIQ	FSIQ	WMI	DS	Arith	Sent Rept
1606	R	-3.99	-2.46	-2.36	66	11	94	89	91	76	7	9	8
1846	R	-4.23	-1.28	-2.19	57	6	89	79	84	85	10	7	11
2363	R	-2.64	-2.26	-0.37	73	5	112	83	98	88	8	11	10
2563	L	NA	NA	NA	75	7	98	105	102	99	14	6	13

HC Residual: Bilateral studentized residuals (z-scores) of hippocampal volume relative to a group of 43 comparison participants (see Allen et al., 2006). PHC Residual: Bilateral studentized residuals (z-scores) of the parahippocampal region (gray matter and white matter) volume relative to a group of 43 comparison participants. WMS-III, Wechsler Memory Scale-III (GMI, General Memory Index); CFT, Complex Figure Test (delayed recall raw score); WAIS-III, Wechsler Adult Intelligence Scale-III (VIQ, Verbal IQ; PIQ, Performance IQ; FSIQ, Full Scale IQ); WMI, Working Memory Index; DS, Digit Span subtest; Arith, Arithmetic subtest; Sent Rept, Sentence Repetition subtest. WMS-III and WAIS-III yield mean scores in the normal population of 100 with a standard deviation of 15.

Figure 2.1. Example trial.

(a) A representative background image is shown (left) along with the same background image covered by the mask that was used to restrict viewing (right). (b) Each trial began with the viewing window centered on the start object. Participants moved the viewing window with a joystick to search for the goal. When they reached the goal, they returned to the start object to terminate the trial.

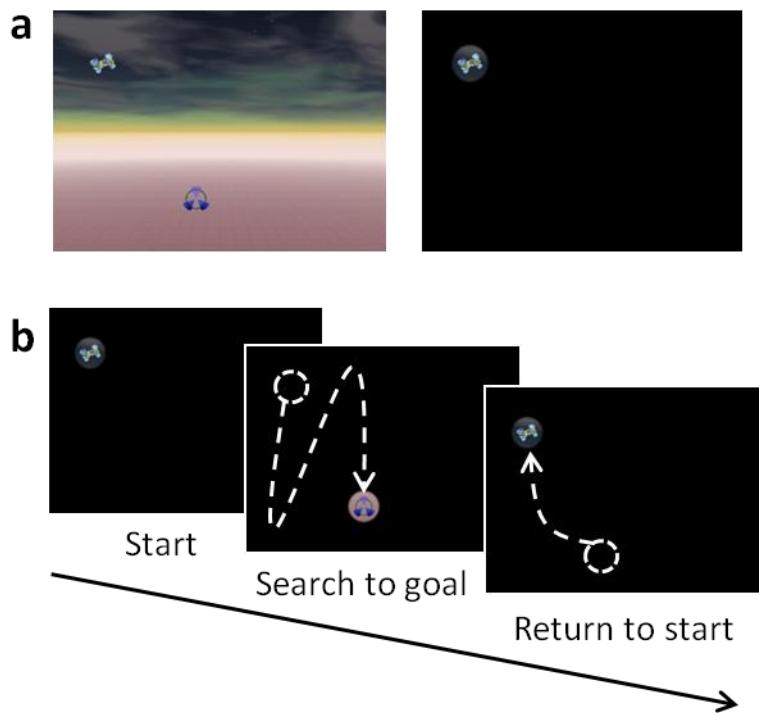


Figure 2.2. Amnesia disrupts across-trial search performance more than within-trial return performance.

(a,b) Distribution (shown by both radial and traditional histograms) and frequency (shown by traditional histograms only) of initial error angle of all trials pooled across participants from each group during search (a) and return (b) across six presentations. Black mark above each radial histogram indicates the correct heading direction; each line in the radial histogram indicates the actual heading of a single trial. (c,d) Log-transformed initial error angle of amnesics (black) and comparison participants (red), during search (c) and return (d) across six presentations. Error bars indicate *SE*.

Figure 2.2 (cont.)

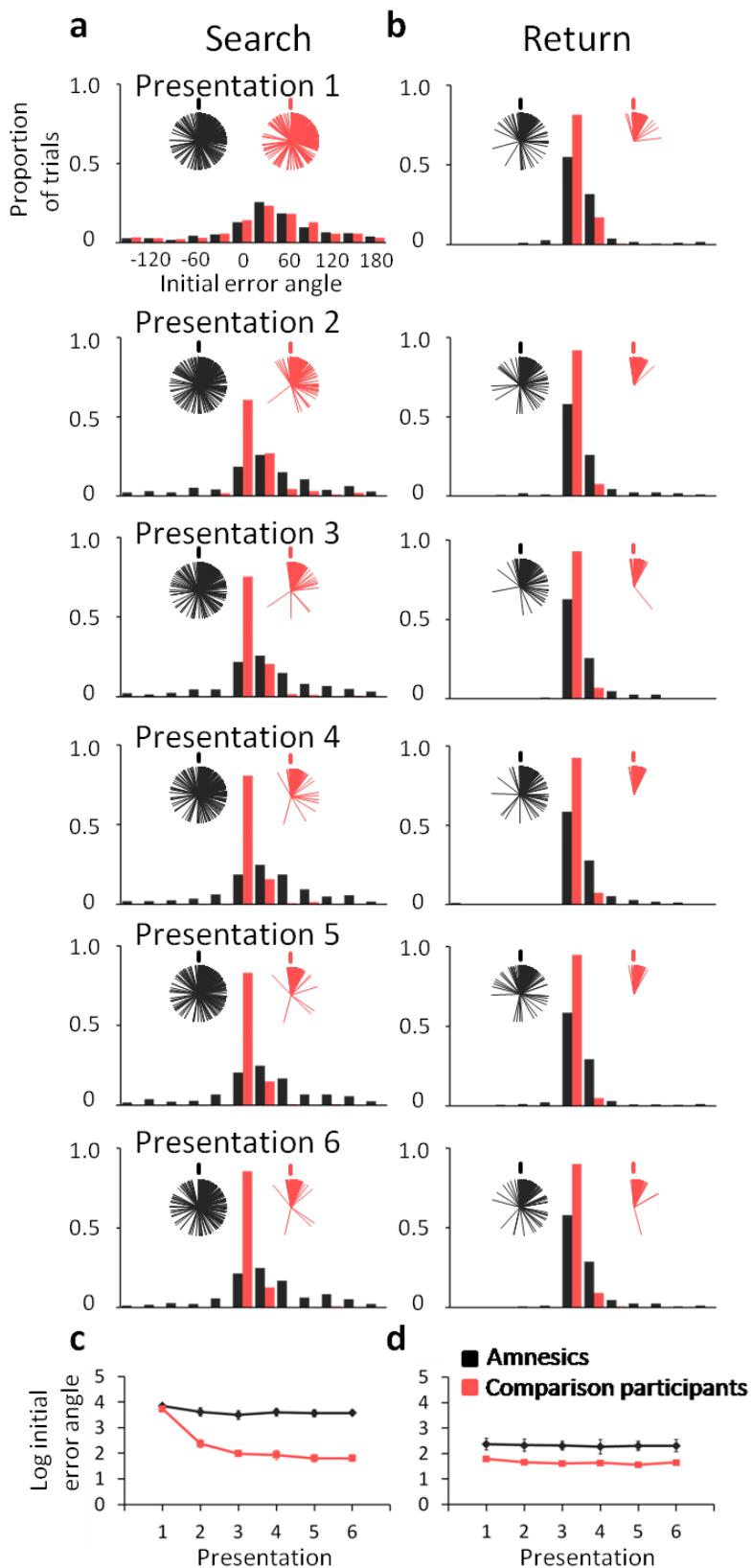


Figure 2.3. Cumulative error scores show the same pattern of relatively more impairment in across-trial search versus within-trial return performance for amnesics relative to controls.

Log-transformed cumulative error of amnesics (black) and comparison participants (red), during search (a) and return (b) phases across six presentations. Error bars indicate *SE*.

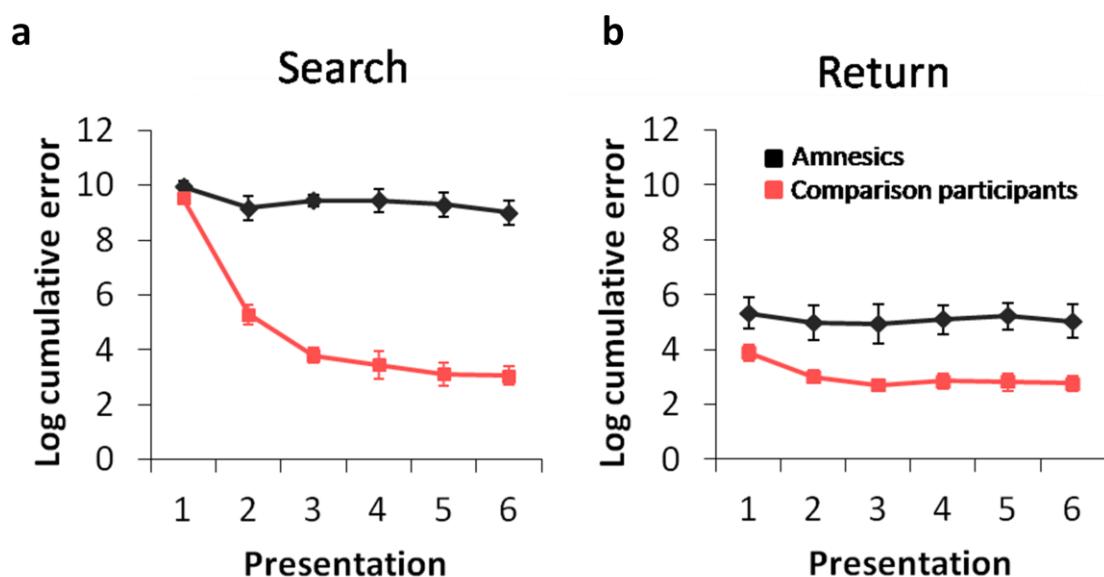
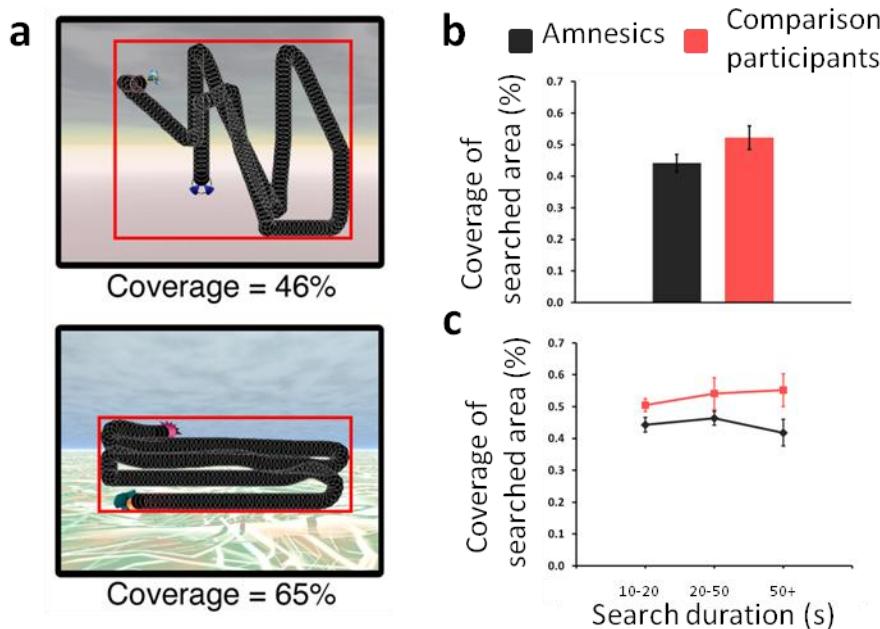


Figure 2.4. Real-time exploration deficit in amnesia shown by analysis of search paths.

(a) Search paths are illustrated as black lines superimposed over representative background images. Coverage was calculated as the percentage of the total space traversed in a given time (bounded by a red square for illustration). A less efficient search path (top) revealed less of the total space traversed, resulting in a lower percent-coverage value than the bottom path. (b) Coverage of searched area in amnesics and comparison participants. (c) Coverage of searched area subdivided into short (10-20 s), medium (21-50 s), and long (50+ s) search duration in amnesics and comparison participants. Error bars indicate *SE*.



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Chapter 3

Use of relational memory in real time to guide task performance

Introduction

In recent years, increasing evidence has accumulated to suggest a critical role of the hippocampus in supporting memory under short timescales of minutes or seconds, in addition to its well-established role in forming long-lasting memories. Pushing on the time limit, recent studies have found that the hippocampus is critical even when there is no imposed delay, during online, in-the-moment task performance. Using a restricted viewing paradigm, it was found that in amnesic patients who sustained damage to the hippocampus, online exploration of a scene is abnormal when sequential glimpses need to be bound into a coherent representation (Yee et al., submitted). In a visual search task, it was found that representations degrade faster in the absence of hippocampal support, and result in abnormal eye movement patterns during the search for a constantly present target amongst a large array of highly similar distractors (Warren, Duff, Tranel, & Cohen, 2011).

The hippocampus does not act alone during the process of online task performance. fMRI studies have revealed a network of brain regions functionally connected to the hippocampus, including the PFC and the cerebellum, in coordinating adaptive behavior during online processing (Voss et al., 2011; Voss, Gonsalves, Federmeier, Tranel, & Cohen, 2011). In these two fMRI studies, subjects studied an array of objects presented on a grid. The entire display was masked except for a small transparent viewing window. Subjects inspected one object at a time through this small viewing window, either by using a joystick to manipulate the position of the window (active self exploration that allowed subjects to determine which object to inspect and

for how long), or by viewing passively the active exploration path of a yoked subject (no control over object inspection). It was found that active self exploration confers an advantage to subsequent memory, and this advantage is driven by a network of regions centered on the hippocampus, including the PFC and the cerebellum. Furthermore, the pattern of exploration was found to be different in neurologically intact participants and amnesics. In neurologically intact participants, there was back-and-forth inspections between objects (e.g., A-B-A, or A-B-C-B-A), a behavior known as “revisitation”. The amount of revisit was positively correlated with hippocampal activity and subsequent memory. Together, these two studies suggest that the hippocampus plays a role in optimizing the acquisition of information online that leads to better memory subsequently. A proposed mechanism through which this occurs is that the hippocampus communicates with the PFC about the quality of the representations. If the representations are not well-established, revisits are initiated. As a result, better representations are formed hence better performance on memory tests. Being in the passive mode does not confer this advantage as the revisits were not based on the subject's own representational state. The interplay between the PFC and the hippocampus thus reflects the optimization of information seeking based on representational state.

The above studies showed that during online processing, the hippocampus forms memory representations and use them to guide adaptive behavior in real time via interaction with the PFC. One common feature across these paradigms is that the information remains relatively “static” throughout the course of the task, in that the stimuli in these paradigms only change their status once during the course of the task, when they go from unstudied to studied, unrevealed to revealed. An unexplored area was that, what would happen if the status of the stimuli changed dynamically during the course of a task, e.g., changing from relevant to irrelevant from moment

to moment? Such task demands might produce a high degree of interference and require heightened MTL-PFC interactions. Such task demands are present in self-order memory tasks, such as the one used in Owen, Sahakian, Semple, Polkey, & Robbins (1995). In the non-spatial variant of this task, subjects inspected an array of n objects one by one until they found a target hidden behind one of them. Then, in a new round of search, subjects initiated the inspection process again and looked for a new target. During this subsequent round, the search space decreased by one, as subjects were told that the object that had been associated with a target in the previous round would not contain the target. That is, the new target could be in any of the n-1 objects. The task continued where the search space decreased by one on each subsequent round until all n targets were found. Optimal behavior in the task was to avoid revisits to stimuli previously associated with targets on previous rounds, as well as to avoid revisits to stimuli already examined on the current round (which were not associated with the target).

In contrast to the studies reviewed above, in this paradigm, information acquired online needed to be updated continuously as object-status relations kept changing. E.g., a stimulus could change its status from “chosen in current round” to “target in current round”, or from “chosen in previous round” to “non-chosen in current round”. In a new round, chosen objects in the previous round became “fresh” objects again (except for the target objects). Optimal task performance was to select objects based on their previous outcome, which changed dynamically as the task progressed. Similar to the active learning study, memory representations just established were to be used instantly to guide choices in this paradigm. However, an additional aspect was that object-status representations changed in a dynamic manner and required constant updating.

This self-order memory paradigm was suitable for investigating MTL and PFC interactions, because it had both mnemonic and strategic requirements, which had been demonstrated to depend on the hippocampus and the PFC respectively. Self order memory paradigms were developed based on work on the radial arm maze, which is a widely used paradigm for testing memory in rats. In a seminal study by Olton & Papas (1979), rats with fornix lesions were found to be impaired in a variant of the task where arms were to be visited once and only once. Petrides & Milner (1982) modified this task to be used in humans. In one of the experiments in that study, twelve abstract stimuli were presented and subjects had to select them one by one without repetition. The locations of the stimuli were rearranged between selections. It was observed that patients with right temporal lobe lesions that included the hippocampus, and frontal lobe patients were impaired in this task, in that they made more revisit errors than controls. A positron emission tomography (PET) study using the same paradigm found that the mid-dorsolateral PFC (area 46) is active during task performance (Petrides, Alivisatos, Evans, & Meyer, 1993). This task was further developed in subsequent years and made multi-round, where subjects had to repeat the search in multiple rounds, and find targets in stimuli that had not been associated with targets yet in previous rounds (Feigenbaum, Polkey, & Morris, 1996; Owen et al., 1995; Owen, Downes, Sahakian, Polkey, & Robbins, 1990; van Asselen et al., 2006). Both frontal (Owen et al., 1995; Owen et al., 1990; van Asselen et al., 2006) and temporal lobe patients with damage that included the hippocampus (Feigenbaum et al., 1996; Owen et al., 1995; van Asselen et al., 2006) were found to be impaired in this task, but the nature of impairment is different. Impairment in frontal patients was attributable to poor strategy, while impairment in hippocampal patients was mnemonic in nature. Therefore, this task had been shown to have both a strategic and a mnemonic component and was suitable for current

investigations of MTL-PFC interactions. The addition of the multi-round component placed demand on the updating of representations that we were interested in.

To my knowledge, no fMRI studies have been performed using this paradigm to investigate MTL-PFC interactions. Owen, Evans, & Petrides (1996) did a PET study using this paradigm and found activations in the right mid-dorsolateral frontal cortex (areas 46 and 9), right frontopolar cortex (area 10), and ventrolateral frontal cortex (area 47). However, there were yet unanswered questions. First, the Owen study used a “spatial” version of the self order paradigm. Stimuli consisted of identical boxes arranged in random locations. Between selections, the boxes remained in the same locations. Therefore, a strategy would be to follow a certain spatial sequence, e.g., always inspect the top row first. By contrast, in the “non-spatial” version of this paradigm, unique stimuli were used and they were rearranged between selections, necessitating memory for the stimuli themselves rather than following a spatial sequence. This latter design, as explained above, was more suitable for investigating MTL-PFC interactions during online processing. Second, blocked design in PET studies did not permit the investigation of brain activity related to individual choice selections. In the current study, a mixed block / event-related design was used to target both sustained effects that extended over the entire task period and transient effects related to individual choice selections. Such a design could potentially reveal different response profiles in different brain regions and better inform their contributions to task performance.

Based on previous neuropsychological findings, it was predicted that this task would engage both the hippocampus and the PFC. Functional connectivity analyses were performed to investigate MTL-PFC interactions during online task performance. The sign of the correlation

revealed the nature of their interaction, whether it was cooperative or antagonistic, and informed theories of PFC cognitive control over relational memory representations.

Methods

Subjects

Twenty-one right-handed college-aged adults (seven male) with no known history of neurologic or psychiatric disorders gave informed consent to participate in the study. All procedures were approved by the institutional review board of the University of Illinois at Urbana-Champaign. Participants received \$15 per hour for their participation. Four participants were excluded, one due to poor behavioral performance (see definition below), one due to abnormal brain anatomy, and two due to excessive head motion, resulting in 17 participants total.

Design

Subjects performed two tasks in the scanner in two sessions on different days. The two tasks were referred to as “memory” and “no memory” (the control condition), and were identical to each other except for the use of colors to eliminate memory demands in the control condition. The entire experiment consisted of 10 runs. Each run was made up of three trials of the same task, with task type alternating between runs. Stimuli were 240 minimalist visual shapes called “squiggles”, which were created by random hand-deformation of a square, circle, or triangle (Groh-Bordin, Zimmer, & Ecker, 2006), and were presented in white on a black background, housed inside white square boxes. The stimuli were presented on a computer monitor, which was projected onto a screen and viewed through a mirror attached to the head coil.

Each trial began with a familiarization phase of 20s, during which the eight stimuli to be used in the trial were presented side by side simultaneously (Fig. 3.1a). The trial consisted of eight discrete rounds. In each round, a target grey circle was hidden behind one of the eight squiggles. Subjects used a joystick to move around the screen and clicked on squiggles until they found the target. Upon a click on a squiggle, subjects either saw an “X”, which indicated that the target was not hidden behind the squiggle just selected (Fig. 3.1b), or a grey circle, which indicated the target had been found (Fig. 3.1f). Subjects were allowed to click on any squiggles until they found the target or until a maximum of 20 clicks, upon which the screen displayed the words “You lost!” and signaled an early abortion of the trial. Subjects were given unlimited time to make their decision on each click, although they were encouraged to solve the task as quickly as they could without sacrificing accuracy. After a box was selected, an “X” or a grey circle appeared for 1.5 seconds, followed by a blank black screen until the next TR onset, upon which the stimuli were shown again and the task continued. The stimuli were presented at non-overlapping random locations on the screen, and their positions were rearranged between selections (Fig. 3.1d). The purpose of rearranging and randomizing stimuli presentation locations was to minimize the use of a spatial strategy in remembering which stimuli had already been selected and necessitated the use of memory for the squiggles themselves to guide choices. In the control condition, within each round, squares containing squiggles that had already been selected during that round (but did not contain the target) were highlighted in yellow during all subsequent choices (Fig. 3.1d). In addition, in each subsequent round, squares containing squiggles that were found to be associated with targets in previous rounds were highlighted in magenta (Fig. 3.1g). The use of colors removed the need to remember the squiggles that had

already been selected during the current round and the squiggles that were associated with targets in previous rounds.

Targets were “found” after a predetermined number of unique squiggles selected, rather than tied to a specific squiggle. The reason was for control purposes: had the target been associated with a specific squiggle, some subjects would have found it early and some would have found it late, resulting in unequal memory load across subjects. Although arguably, memory load might still differ between subjects because they make different number of mistakes along the way, which results in different degrees of interference, and reaction times differ, which results in different retention intervals, this approach at least controlled for the number of relevant items that need to be maintained. The predetermined number for each round varied across trials to introduce variability so that the task appeared more naturalistic. In rounds 1-3, the number of predetermined selections varied between 4-6; in round 4 between 3-5, in round 5 between 2-4, in round 6 between 1-3, in round 7 between 1-2, and in round 8 only one (as only one non-target object is left by then). Due to this variability, there were three levels of required search length within each round (short, medium, long), except for round 7, where there were only two levels, and round 8, where there was only one remaining unique squiggle, hence one single level. The predetermined number was on the long end to allow for a longer time window to observe memory in use.

The inter-round interval was 20 sec, during which subjects made odd/even judgment to numbers randomly selected between 0 and 100. Numbers were presented at a rate of four seconds each. Each number was displayed for 1.5 sec and subjects were encouraged to make a response as quickly as possible. The inter-trial interval was 30 sec, during which subjects also performed odd/even judgment on numbers. Subjects responded by pressing buttons on the

joystick using their right thumb and index finger. Odd/even number assignment to response finger was counterbalanced across subjects.

A different set of eight squiggles was used for each trial. Within a trial, between rounds, the same stimuli were used. Each stimulus was seen equally often in each condition across subjects. In addition, squiggles used in a particular trial were randomly drawn from the stimuli pool.

fMRI Procedures

Whole brain imaging was performed on a 3 T Siemens Trio scanner. T2*-weighted functional images were acquired using a gradient-echo echo-planar sequence (TR = 2s, TE = 25 ms, flip angle = 90°, field of view = 240 mm, 38 axial slices, voxel size = 2.5mm x 2.5mm x 3mm). The number of volumes of each run was variable and was determined by the time the subject finished the behavioral task. High-resolution T1-weighted (MPRAGE) anatomical images (TR = 1900 ms, TE = 2.32 ms, flip angle = 9°, slice thickness = 0.9 mm) were collected for visualization. Head motion was minimized using foam padding that surrounded the head and stabilizers that pushed on earphones to minimize left-right translational movements. Stimuli were projected onto a screen and viewed through a mirror attached to a standard 12-channel head coil.

Data were preprocessed using Analysis of Functional NeuroImages (AFNI) software (Cox, 1996). Functional data were first phase shifted using Fourier transformation to correct for differences in slice acquisition time, and then realigned to the third volume of the run closest in time to the acquisition of the anatomical images to correct for motion, using a rigid body transformation algorithm with six parameters. Subjects with more than 3mm movement in any direction of translation or rotation in any functional run were excluded from analysis. After

realignment, a mean functional volume was computed for the functional run closest in time to the acquisition of the anatomical volume, and this mean functional volume was coregistered to the anatomical volume. Functional and structural data were then spatially normalized to the MNI template, an approximation of Talairach space, using a 12-parameter affine transformation. Images were spatially smoothed with a 6 mm full width half maximum isotropic Gaussian kernel. Finally, all voxels were normalized to have a mean signal of 100 to reflect percent signal change. These resulting images were then submitted to statistical analyses.

Behavioral Analyses

Errors were counted and characterized as “between errors” and “within errors”. Between errors are revisits to squiggles that had been found to contain targets in previous rounds. Within errors are revisits to squiggles that had already been found in the current round to contain an X. Average reaction time for each choice was calculated for each condition.

fMRI Analyses

Voxel-based multiple regression analysis was performed in AFNI using the general linear model. First, subject-level analysis was performed using a fixed effects model. Parameter estimates of brain activity related to regressors of interest were obtained via a deconvolution approach. The experiment was modeled as a mixed-block / event-related design. Block-shaped regressors modeled the entire duration of memory and control rounds to investigate sustained effects in each condition. Transient effects were coded as events that were time-locked to the onset of each stimulus display. A median split by response latency was performed on the correct events in each condition to categorize them into four event types: memory long, memory short,

control long, and control short. A separate regressor modeled events where errors were made. The unmodeled time points, i.e., inter-round and inter-trial intervals where subjects performed odd/even judgment on numbers, defined the baseline. The six motion parameters were included in the model as covariates of no interest. Additional covariates of no interest included regressors that modeled linear and polynomial trends.

These parameter estimates were then entered into a second-level group analysis treating subjects as a random effect. Here, individual subjects' images of parameter estimates for each contrast of interest were entered into a one sample t-test against zero. The resulting statistical map was thresholded at $p < 0.001$ for individual voxels to identify regions of significant activation. In a Monte Carlo simulation by the program 3dClustSim within the AFNI software package, it was determined that a minimum of 37 contiguous suprathreshold individual voxels (579 mm^3) were required to reach the experiment-wise threshold of $p < 0.05$. All results were corrected for multiple comparisons unless otherwise noted.

Functional connectivity analysis

To explore changes in connectivity between the hippocampus and other regions of the brain during the memory task, functional connectivity analysis was conducted using the psychophysiological interaction (PPI) method (Friston et al., 1997). PPI measures context-dependent connectivity and explains activity of a brain region in terms of an interaction between the activity of another seed region (hippocampus here) and a psychological context (memory condition here). To perform PPI analysis, two additional regressors were added to the original regression model. The first was the time series of the hippocampal seed region, identified by the memory versus control block contrast that showed hippocampal deactivation. The time series of

the signal in the seed region was averaged spatially over the entire seed region. The second additional regressor represented the interaction between the seed time series and the task context. To create this regressor, the time series of activity in the seed region was extracted and deconvolved into its neural function. The deconvolved time series was multiplied with a vector that coded time points where the memory and control tasks occurred as +1 and -1, and all other time points as zero. The result was then reconvolved with a canonical hemodynamic response. This interaction regressor identified brain regions that increased or decreased connectivity with the hippocampus based on task context (memory or control). Clusters that showed a significant difference in correlation with the hippocampus for the memory versus the control condition were identified in a second-order analysis across subjects.

Results

Behavioral Results

Subjects performed very well in the task, making an average of 2.37 ± 1.51 (mean \pm s.d.) between errors and 1.99 ± 1.50 (mean \pm s.d.) within errors on each trial in the memory condition. As expected, subjects made almost no errors in the control condition (between errors: 0.01 ± 0.02 ; within errors: 0). In the memory condition, there is a significant positive correlation between the two types of errors ($r = 0.69, p < 0.005$), indicating that worse subjects performed worse overall and made more errors of both kinds. Two of the subjects lost one memory trial out of a total of 15. Subjects also performed well in the odd/even number judgment task, with a proportion correct of 0.96 ± 0.03 (mean \pm s.d.). Reaction time was longer in the memory condition (memory: 4.34s; control: 2.23s, $p < 0.05$).

Further analyses were conducted to investigate the distribution of between / within errors as a function of how many rounds ago those items were found to contain the target / last selected on the current round. Visual inspection suggested that for between errors, in each round, subjects were equally likely to revisit items that were recently or remotely found to contain the target circle (Fig. 3.2a). A similar pattern was observed for the within errors. In each round, subjects were equally likely to revisit items that were recently selected versus those that were selected earlier in the round (Fig. 3.2b).

Next, performance as a function of required search length was analyzed. The number of extra selections beyond the required search length was counted for each length level (short, medium, long) at each round and compared to chance performance. Chance performance was the number of selections one would make before finding the target if one were to select at random, minus the required search length. It is derived as follows. For a particular search length, each discovery of a unique squiggle is associated with a waiting time. For example, on the third round, two squiggles were already associated with a target on the previous two rounds. The probability of the first selection to result in a unique squiggle is therefore 6/8, therefore the waiting time is 8/6, meaning that an average of 1.33 selections were needed before finding the first unique squiggle in the third round. Summing up the expected waiting time for all the n squiggles required for a round results in the chance number of selections for that round.

The number of extra selections (Fig. 3.3a) was by far fewer than if selections were made randomly (Fig. 3.3b), at each round and at each search length, providing evidence for the use of memory during task performance. Performance level at each round and search length was then scaled by its respective chance level to assess performance controlled for differential chance levels. The conversion formula is given by (1-actual number of selections / number of selections

if performance is at chance) / (1 – number of selections if performance was perfect / number of selections if performance is at chance). This adjusted score ranges from zero (chance performance) to one (perfect performance). A 3x6 repeated measures ANOVA with factors search length (short / medium / long) and round was performed on the first six rounds. Rounds 7 and 8 were not included in the statistical analysis because they had fewer search length levels. There was no main effect of search length ($p > 0.1$) or interaction between search length and round ($p > 0.1$). The main effect of round was significant ($p < 0.02$), although follow up t-tests suggest that it was driven by worse performance on Round 3 only, instead of systematic changes in performance as a function of round (Fig. 3.3c).

fMRI Results

Sustained effects

A number of regions showed sustained activity in response to each task. Of particular interest, three clusters in the PFC showed sustained activation in the memory condition compared to the control condition (all $p < 0.05$, corrected; Fig. 3.4a): two of them were located in the DLPFC at the medial frontal gyrus (MFG), at an anterior site (BA 10) and bilaterally at a more lateral site (BA 9/46), and one at the superior aspect of the medial PFC (mPFC). The reverse contrast revealed that the hippocampus was more active during the control task than the memory task ($p < 0.05$, corrected; Fig. 3.4b). Follow-up analyses were conducted to investigate this hippocampal deactivation relative to baseline. Both memory and control conditions elicited significant deactivations in the hippocampus, but there was greater deactivation in the memory condition. A list of clusters significantly different in the memory and control conditions at $p < 0.05$, corrected, can be found in Table 1.

Transient effects

To reveal activity that reflects the use of memory to guide decisions, events (choice selections) were time-locked to the onset of the stimulus display. For modeling purposes (so that the BOLD signal could be deconvolved), correct events in each condition were median-split by reaction time (from onset of stimulus display to when a choice was made) into short and long events. Both memory long and short events elicited greater hippocampal activity compared to their respective control events. Because the interaction of response time (long / short) and task (memory / control) was not significant ($p > 0.05$), the analysis was collapsed across response time. The hippocampus activation cluster that resulted from this main effect is shown in Fig. 3.4c ($p < 0.001$, exceeds an extent-threshold of 20 voxels). A list of clusters significantly different in the memory and control conditions at $p < 0.05$, corrected, can be found in Table 2.

Relationship between hippocampal sustained deactivation and transient activation

It was further observed that across subjects, the amount of sustained hippocampal deactivation correlated positively with the amount of transient activation ($r = 0.68, p < 0.01$; Fig. 3.5). That is, subjects who showed more sustained deactivation during the memory task showed more transient activation in response to the display onset. The hippocampal activation / deactivation clusters overlapped with each other, with the deactivation cluster being larger to encompass the entire activation cluster. Analysis was performed by averaging activity over the entire deactivation cluster subject-by-subject, and correlated this value with average activation in the smaller cluster. The same result was obtained when deactivation was averaged over the subset of voxels that showed the transient activation effect. To rule out the possibility that the

correlation was driven by a lower variability in the BOLD signal in subjects with more deactivation, standard deviation of the signal in the memory condition withinin the hippocampal activation cluster was correlated with the amount of deactivation it exhibited. No such correlation was found ($r = 0.04$, $p > 0.1$); confirming the positive correlation between sustained deactivation and transient activation.

Functional connectivity analysis

Using the hippocampus deactivation cluster as a seed region, a context-dependent correlation analysis was performed to determine areas in which activity correlated with the observed decrease in sustained hippocampal activity during the memory condition. The hippocampus was positively correlated with the inferior parietal lobule, but was negatively correlated with the precuneus, caudate, DLPFC, and orbitofrontal cortex (OFC) (Fig. 3.6). The DLPFC region revealed by this analysis was located within the middle frontal gyrus where sustained activation was observed during the memory task. A list of clusters showing significant correlation with the hippocampus at $p < 0.05$, corrected, can be found in Table 3.

Discussion

The current experiment investigated MTL and PFC contributions to online task performance using a paradigm that emphasized heavily on the update and creation of relational representations as the task unfolded. Our mixed block / event-related design permitted us to observe both sustained effects throughout the task period and transient effects associated with individual choice selections. Bilateral MFG, SFS, and the medial PFC showed sustained activation throughout the memory task. In the hippocampus, the response profile was different.

There were both sustained deactivation during the memory task and transient activation in response to stimulus onset, and the amount of sustained deactivation was positively correlated with the amount of transient activation across subjects. Functional connectivity analysis revealed that activities in the hippocampus and the DLPFC were negatively correlated during task performance. Our results highlight the important role of the hippocampus in online processing. The different response profiles in the PFC and the hippocampus suggest they play different roles during performance, and the negative correlation further suggests an antagonistic relationship between them for this kind of online processing.

The DLPFC contributes to both WM and LTM by implementing control processes that monitors and organizes information held online. In fMRI studies of WM, the DLPFC is activated in tasks that require organization of items, for example, when items need to be arranged in alphabetical order (Postle, Berger, & D'Esposito, 1999), or when chunks need to be formed (Bor, Duncan, Wiseman, & Owen, 2003). Through comparison and organization, the DLPFC contributes to LTM encoding by promoting the formation of relational links (Blumenfeld & Ranganath, 2006). During LTM retrieval, it holds the retrieved content in mind for further processing (Israel, Seibert, Black, & Brewer, 2010). Our sustained MFG activation is consistent with such a monitoring account. The kind of monitoring performed by the MFG in this task can be appreciated by comparing our design with another task that also found sustained MFG activation. In a PET study (Owen et al., 1996), subjects searched through an array of circles in a random fashion on multiple rounds to discover targets. Unlike our design where eight unique stimuli were used in each trial, in that study, all the stimuli were the same (red circles), and each circle remained in the same spatial location across successive choices without being rearranged. Despite these differences, common activation was found in the MFG, suggesting that this region

is involved in processes common to both tasks, e.g., monitoring how many rounds have been done, organizing stimuli into sub-groups (already searched, already contained targets).

Additional PFC activation was found in the anterior PFC (BA 10). This region is consistently activated in n-back WM studies (Owen, McMillan, Laird, & Bullmore, 2005) and may be governing additional control demands in our task that were not present in the Owen et al. (1996) study. Because the stimuli in our task were unique and they appeared in different locations from one selection to the next, additional control might be needed to keep track of the identity of the stimuli and their new locations in the next display. These additional control demands are similar to those in n-back working memory tasks in a number of ways. In the n-back task, one is required to simultaneously monitor a stream of stimuli, update memory representations for the currently relevant items, and compare these items with incoming information. Similarly, in our task, a number of cognitive processes take place at the same time, as one is required to concurrently monitor multiple squiggles, make selections based on memory representations, and update their status regarding the action performed and outcome. Indeed, more generally speaking, the anterior PFC is proposed to be important when more than one rule needs to be maintained in order to achieve the task goal. In these instances, it coordinates the multiple control processes needed for task performance (Ramnani & Owen, 2004).

Additional sustained activation was found in the dorsal medial PFC. Its involvement in the current task can be appreciated through its role in predicting action outcomes (Alexander & Brown, 2011; Forster & Brown, 2011). More specifically, its role in prediction has been proposed to have close links to memory-guided adaptive behavior through interactions with the hippocampus (Voss et al., 2011). In that study, activity in both the medial PFC and the hippocampus correlated positively with the amount of back-tracking when subjects studied an

array of objects for a later memory test, in the condition where one had volitional control over which objects to study and for how long. Back-tracking means revisits to recently inspected items, for example, A-B-A, or A-B-C-B-A, and was proposed to involve an interaction between the medial PFC and the hippocampus, where the medial PFC queries the quality of memory representations from the hippocampus to generate predictions about possible outcomes before they were made, thereby controlling whether such actions should be taken or not. Similar mechanisms might be in play in the current task. Based on memory for previous selection outcomes, predictions might be generated for the selection of a squiggle before it was actually chosen. For example, if one remembered the squiggle had been associated with a target before, the prediction would be seeing an X if it was chosen, and so one should avoid it. However, if one remembered the squiggle had not been found to contain targets in a few consecutive rounds, the chance that it contained the target now was high, and so one might generate a prediction of seeing a target and this led to its actual selection. The prediction could be wrong, especially since unbeknownst to the subjects, whether a squiggle contained the target was based on a predetermined number of unique items chosen, not with its own selection history. The prediction error would then engage mPFC error detection mechanisms to refine its prediction and adjust for future behavior, for example, by not always choosing items that were remembered to have been empty for a long time, or some other strategy.

The PFC control mechanisms discussed above act on memory representations of stimulus-status associations. We predicted the processing of such associations would involve the hippocampus because they were arbitrary in nature. Another way to conceptualize the retrieval of these associations is that it was context-dependent – each stimulus was associated with multiple statuses as the trial progressed (selected in round n, found to contain a target in round n, etc), and

the overlapping relations need to be disambiguated for correct retrieval. Such context-dependent retrieval has been shown to involve the hippocampus (Brown, Ross, Tobe, & Stern, 2012).

In addition to sustained effects throughout the memory task period, our mixed design permitted us to isolate activities associated with individual selections. We found a different response profile in the hippocampus than that seen in the PFC – activation when individual selections were to be made that happened in a background of sustained deactivation. In our analysis, event onset was time-locked to the onset of the stimuli display, and so the transient hippocampal activation might reflect the retrieval of memory representations and the use of them to guide the up-coming choice. The reactivated relational memory representations of the cue-status relationship (e.g., it contained a target before, or, it has been visited in the current round, etc) can be queried by the mPFC to generate a prediction of what happens if it is selected. This is broadly consistent with an emerging emphasis on the role of the hippocampus in prediction and future thinking (Buckner, 2010). In cell recording studies, the hippocampus has been found to show prospective coding for upcoming behavioral choices (Johnson & Redish, 2007). In hippocampal amnesic patients, the ability to imagine future events is impaired (Hassabis, Kumaran, Vann, & Maguire, 2007). It is possible that the hippocampal activity observed here reflects prediction of future selection outcomes in addition to retrieval of past memories.

Surprisingly, activation in the hippocampus in response to stimulus onset happened in a background of sustained deactivation in the same hippocampal region throughout the memory task. Such deactivation was not driven by particular rounds of the task, but was consistently present in all rounds and in all subjects. Although less reported in the fMRI literature, deactivation of the hippocampus has been found before, in tasks that would have been expected to involve the hippocampus, e.g., transverse patterning (Astur & Constable, 2004), source

memory (Duarte, Henson, & Graham, 2011), autobiographical memory retrieval (Rekkas et al., 2005) and pair-associate retrieval (Israel et al., 2010; Reas, Gimbel, Hales, & Brewer, 2011). An interpretation of hippocampal deactivation during memory retrieval is that it reflects the direction of mental resources away from processes like incidental encoding that the hippocampus is tonically engaged in so that mental efforts can be devoted to retrieval (Reas et al., 2011). This could be one of the reasons that we saw hippocampal deactivation in our task. As the hippocampus binds relations obligatorily, encoding irrelevant relations could potentially interfere with task performance. For example, as an associative mismatch detector (Kumaran & Maguire, 2007), the hippocampus is sensitive to changes in spatial relations when stimuli are rearranged between selections. However, this information might be harmful to task performance, as the task requirement was not about where stimuli went but the outcome they were associated with. With much information to handle, it might be beneficial to suppress the hippocampus so that irrelevant relations are prevented from being encoded. Alternatively, if irrelevant relations are encoded obligatorily, i.e., it is impossible to deliberately encode stimuli-outcome associations without encoding their spatial relations simultaneously, hippocampal deactivation might reflect active suppression of their retrieval. In some ways this is similar to the think / no-think task, where hippocampal deactivation was seen when subjects actively suppressed learned associations from coming to mind (Anderson et al., 2004).

Not limited to memory tasks with long delays, hippocampal deactivation has also been observed under short delays like in the current study, in n-back working memory tasks (Cousijn, Rijpkema, Qin, van Wingen, & Fernandez, 2012; Stretton et al., 2012). The interpretation is that dampening the activity level in the hippocampus might be a way to reduce interference from multiple simultaneous processes (encoding, update, retrieval) to optimize performance. This

could be another potential explanation for deactivation in our task, as it also required these processes concurrently. Furthermore, hippocampal deactivation was observed in a virtual radial-arm maze task (Astur et al., 2005), which was similar to our design except that it did not have the multi-round feature. In summary, our finding fits with a body of literature that found hippocampal deactivation during both long and short delay memory tasks, and such deactivation may reflect suppression of incidental encoding, suppression of irrelevant retrieval, and/or reduction of interference.

Before accepting hippocampal deactivation as evidence for suppression of irrelevant memory representations in order to facilitate performance, alternative explanations must be considered. Because fMRI is a relative measure, activation and deactivation must be considered with regard to the comparison condition used. In the control condition, colors were used to identify already chosen items to remove memory demands. An unintended consequence was that the control task was noticeably less engaging than the memory task. At debriefing, most subjects reported mind-wandering during the control task. They reported that they paid very little attention to the task as they clicked through the stimuli. As such, the control task might have been comparable to a “resting” baseline, where the hippocampus is known to be active (Stark & Squire, 2001), as it is part of the default mode network (Greicius, Srivastava, Reiss, & Menon, 2004). Therefore, deactivation in the memory condition might have been driven by the hippocampus being even more active during the control condition. A comparison with the baseline during which simple odd/even number judgment was performed is therefore informative. Both tasks elicited significant deactivations in the hippocampus compared to the odd/even baseline, and there was significantly more deactivation in the memory than the control condition. In other words, deactivation was still observed when the memory condition was contrasted with

an arguably more appropriate baseline. Therefore, hippocampal activity was truly dampened in our memory task. We noted that the odd/even baseline might not have been homogenous – odd/even judgment was performed during inter-round intervals in the memory and control conditions, as well as inter-trial intervals. During inter-round intervals in the memory task, subjects might have been performing further processing of the stimuli and relations learned in the task phase, and so activity level in the hippocampus might have been different from those in the control inter-round intervals and inter-trial intervals. In a follow-up analysis we modeled the memory and control inter-round intervals and contrasted them with the inter-trial interval as baseline. No significant differences were found in the hippocampus when the inter-round intervals were compared to each other, or when they were compared to the inter-trial interval, permitting us to collapse all odd/even time points together and used them as a baseline.

The site of sustained hippocampal deactivation overlapped completely with that of transient activation. Interestingly, across subjects, more sustained deactivation was associated with more transient activation. This is consistent with the interpretation that hippocampal deactivation reflects a suppression mechanism. The relationship between sustained deactivation and transient activation can be interpreted from either an encoding or retrieval perspective. From a retrieval perspective, it could mean that when memory representations are more suppressed, the hippocampus has to work harder in order to bring them back online for the current choice. From an encoding perspective, it could mean that when more sustained effort is spent on preventing encoding of irrelevant information, the hippocampus responds more to encode the relevant stimulus-outcome relation at each choice point.

Functional connectivity analysis revealed that activity in the DLPFC (MFG), where sustained activation was found in the memory condition, correlated negatively with activity in

the hippocampus. Similar negative coupling between the DLPFC and the hippocampus, where the hippocampus showed task-induced deactivation, has been found in a pair-associate retrieval study where memory retrieval was followed by living / non-living classification (Israel et al., 2010). The interpretation was that once the hippocampus retrieves the information needed, it is suppressed so that PFC can work on the retrieved information without further intrusion from the hippocampus. A similar interpretation may be applicable here. Our finding shows that hippocampus-PFC anti-coupling can be seen for memory retrieval during ongoing processing, in addition to during retrieval of representations learned a longer time ago. Therefore, such anti-coupling may be a general mechanism through which the PFC exerts control over MTL relational representations, regardless of delays, when there is a large amount of interference.

Negative correlation with the hippocampus was also found in the caudate and the orbitofrontal cortex. The negative coupling between the caudate and the hippocampus perhaps can be understood as competition between the striatum and the hippocampus which belong to different memory systems (Poldrack & Packard, 2003). It might reflect that learning occurred in both systems simultaneously, and while the hippocampus was suppressed by the DLPFC, the caudate gained dominance. The caudate and the hippocampus are not directly connected, but each of them has connections to the orbitofrontal cortex (Arikuni & Kubota, 1986; Lavenex, Suzuki, & Amaral, 2002). Perhaps the negative correlation seen in the OFC reflects that it was mediating activities in the caudate and the hippocampus. This is highly speculative because the correlational nature of the analysis does not allow for inference of directionality. On top of that, caution should be exercised in interpreting the negative coupling found here because both the caudate and the orbitofrontal cortex showed sustained deactivation during the memory task compared to the control task (as well as when the memory task was compared to the baseline).

In summary, the current study showed that the PFC and the hippocampus are part of a functional network that supports ongoing task performance when continual update of stimulus-outcome relational representations is required. Their interaction appears to be antagonistic in nature, as sustained activation in the DLPFC was associated to sustained deactivation in the hippocampus. In addition, the hippocampus is active when memory representations are to be used to guide decisions at individual selection points. Our results highlight the important role of the hippocampus in online processing that has begun to emerge in the literature, and show that it accomplishes this goal together with the PFC.

Tables & Figures

Table 3.1. Clusters significant ($p < 0.05$) for the block effect of memory versus control

Region	Hemisphere	MNI coordinates			BA	t^*	Volume (mm ³)
		X	Y	Z			
<i>Memory > Control</i>							
Middle occipital gyrus	Left	-32	-82	-6	18	5.68	28672
Middle occipital gyrus	Right	39	-73	-6	18	5.41	19406
Precuneus	Right	2	-64	46	7	5.01	15531
Middle frontal gyrus	Left	-45	15	32	9	4.92	8063
Middle frontal gyrus	Right	45	21	31	9/46	5.03	6219
Medial frontal gyrus	Right	1	24	48	8	4.97	3172
Middle frontal gyrus	Left	-39	57	10	10	4.66	1531
Insula	Right	33	26	-1	13	5.35	1484
Insula	Left	-31	24	-1	13	5.51	1375
Cerebellum	Left	-7	-77	-25	NA	4.76	953
Pulvinar	Right	2	-29	-4	NA	4.6	703
Cerebellum	Right	12	-76	-24	NA	5.57	625
<i>Control > Memory</i>							
Anterior cingulate	NA	0	47	7	32	-5.32	47969
Inferior temporal gyrus	Left	-59	-12	-19	20	-5.03	8609
Inferior parietal lobule	Right	64	-27	32	40	-4.98	8359
Angular gyrus	Left	-47	-65	29	39	-4.71	7297
Inferior parietal lobule	Left	-64	-35	30	40	-4.79	4922
Cingulate gyrus	Right	2	-25	46	31	-5.06	3594
Inferior temporal gyrus	Right	60	-12	-25	20	-4.82	3313
Angular gyrus	Right	50	-71	33	39	-4.98	2359
Precuneus	Left	-3	-50	31	31	-4.86	1984
Hippocampus	Left	-24	-20	-15	34	-5.28	1531
Middle temporal gyrus	Right	66	-48	6	22	-4.63	1422
Superior temporal gyrus	Right	61	10	4	22	-4.59	1078
Superior temporal gyrus	Left	-36	20	-38	38	-4.58	859
Inferior parietal lobule	Right	61	-49	47	40	-4.55	672

BA, Brodmann area; NA, not applicable; MNI, MNI coordinates of cluster centroid.

* t statistic averaged over the cluster.

Table 3.2. Clusters significant ($p < 0.05$) for memory versus control events

Region	Hemisphere	MNI coordinates					Volume (mm ³)
		X	Y	Z	BA	t*	
<i>Memory > Control</i>							
Cuneus	Right	4	-82	20	18	4.87	11422
Caudate	Right	6	17	-5	NA	4.77	1875
Lingual gyrus	Left	-8	-64	-3	19	4.71	1250
Inferior temporal gyrus	Left	-62	-6	-20	21	4.64	1234
Angular gyrus	Left	-41	-63	26	39	4.55	1172
Angular gyrus	Left	-49	-56	34	40	4.34	578
§hippocampus	Left	-22	-20	-12	34	5.14	406
<i>Control > Memory</i>							
Middle occipital gyrus	Left	-29	-90	-7	18	-4.85	6313
Superior parietal lobule	Right	29	-65	49	7	-5.05	5922
Fusiform gyrus	Left	-33	-56	-15	37	-4.73	1938
Middle occipital gyrus	Right	37	-82	-2	18	-4.47	1234
Middle frontal gyrus	Right	49	32	29	46	-4.71	1219
Insula	Right	34	26	-1	13	-4.94	1031
Middle occipital gyrus	Right	45	-59	-10	19	-4.78	906
Putamen	Right	29	6	3	NA	-4.54	844
Fusiform gyrus	Right	33	-49	-15	37	-4.83	766
Insula	Left	-33	22	-2	13	-4.99	656
Putamen	Left	-26	2	5	NA	-4.52	656

BA, Brodmann area; NA, not applicable; MNI, MNI coordinates of cluster centroid.

*t statistic averaged over the cluster.

§ Because of our *a priori* prediction, a combined voxel ($p < 0.001$) and cluster-extent (10 voxels) threshold was used for multiple-comparison correction in the hippocampus instead of the more stringent whole-brain correction criteria.

Table 3.3. Clusters that show significant correlation ($p < 0.05$, corrected) with the hippocampal deactivation seed

Region	Hemisphere	MNI coordinates					
		X	Y	Z	BA	t^*	Volume (mm ³)
<i>Positive correlation</i>							
Inferior parietal lobule	Left	-62	-40	44	40	4.46	922
Inferior parietal lobule	Right	65	-36	36	40	4.53	734
<i>Negative correlation</i>							
Precuneus	Left	-1	-56	27	31	-5.49	20422
Mid orbital gyrus	Right	1	45	-7	11	-5.08	14719
Superior frontal gyrus	Right	1	58	17	10	-4.48	2594
Superior parietal lobule	Left	-37	-80	40	7	-4.54	2594
Middle frontal gyrus	Left	-44	22	25	46	-4.57	1094
Middle frontal gyrus	Left	-23	68	11	10	-4.49	938
Middle temporal gyrus	Left	-63	-10	-14	21	-4.62	859

BA, Brodmann area; MNI, MNI coordinates of cluster centroid.

* t statistic averaged over the cluster.

Figure 3.1. Example trial sequence in the control condition.

(a) Trial began with a 20 s preview of the eight stimuli used in that trial. (b) Round 1 began. Stimuli were presented at random locations and awaited the first selection. (c) A click on the upper left stimulus revealed that it contained an “X” (target not present). (d) Round 1 continued. Stimuli locations were rearranged. The stimulus selected previously was highlighted in yellow. (e) Three stimuli had been selected in Round 1 and the 4th selection was pending. (f) Grey circle target was found. Round 1 ended and was followed by a 20 s inter-round interval filled with odd/even number judgment. (g) Round 2 began. The stimulus that contained the Round 1 target was highlighted in magenta. (h) Four stimuli had been selected in Round 2 and the target was found on the 5th selection. (i) Trial ended when all eight targets had been found.

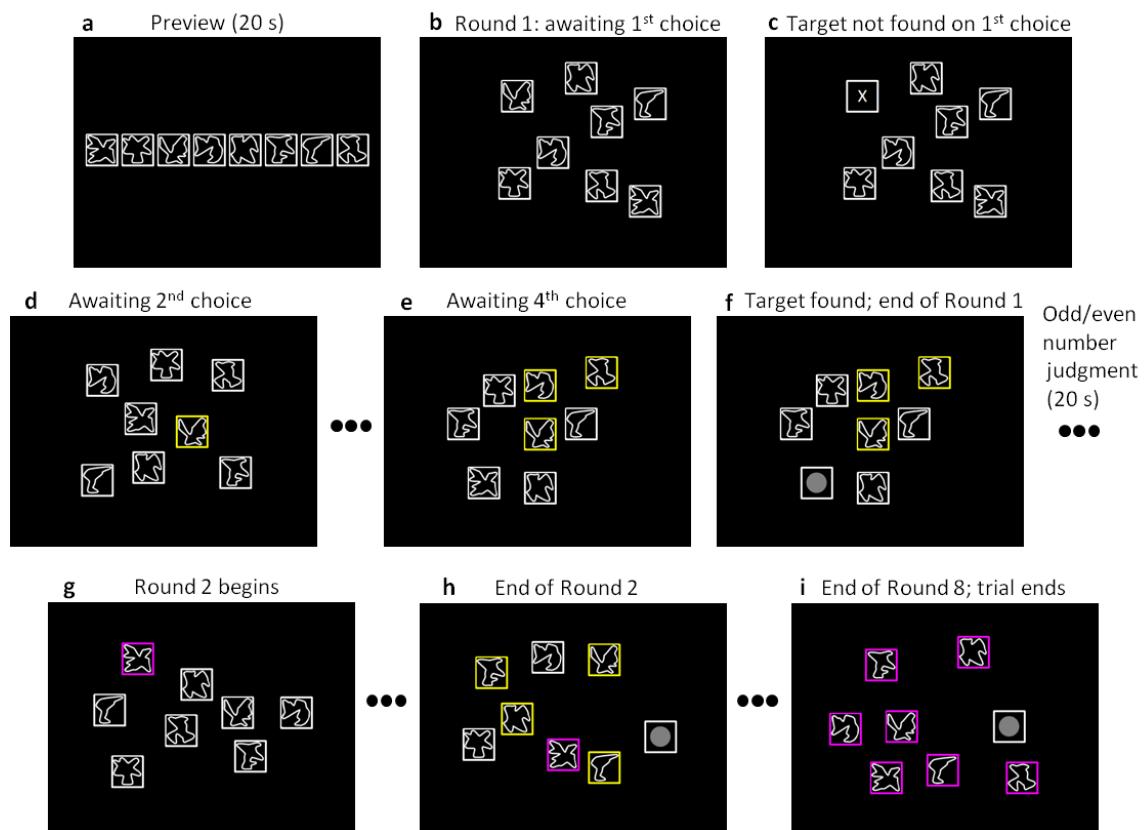


Figure 3.2. Between and within errors were made equally often to remote or recent target stimuli / selected stimuli.

(a,b) Average number of between errors (a) and within errors (b) made on a memory trial as a function of round. For between errors, at each round, the errors are broken down by how many rounds back those objects were found to contain targets. For within errors, the errors are broken down by how many selections back those objects had last been selected. Darker color indicates errors made to more recent target objects (between errors) / non-target objects that had been selected on the current round (within errors).

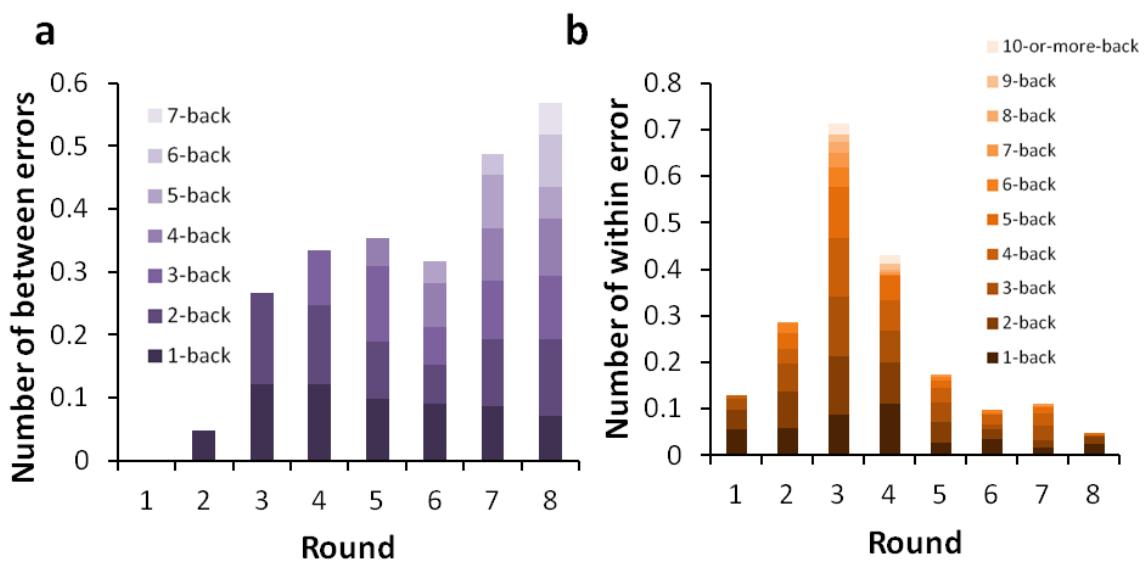


Figure 3.3. Memory was used to guide task performance but there was no effect of search length on number of errors made.

(a) Extra selections beyond the required search length subjects made before reaching the target, at each round and at each search length. (b) Extra selections beyond the required search length if selections were made at random. (c) Actual performance corrected for differential chance levels. Note that Rounds 7 and 8 did not have all three levels of search length hence labeling is arbitrary.

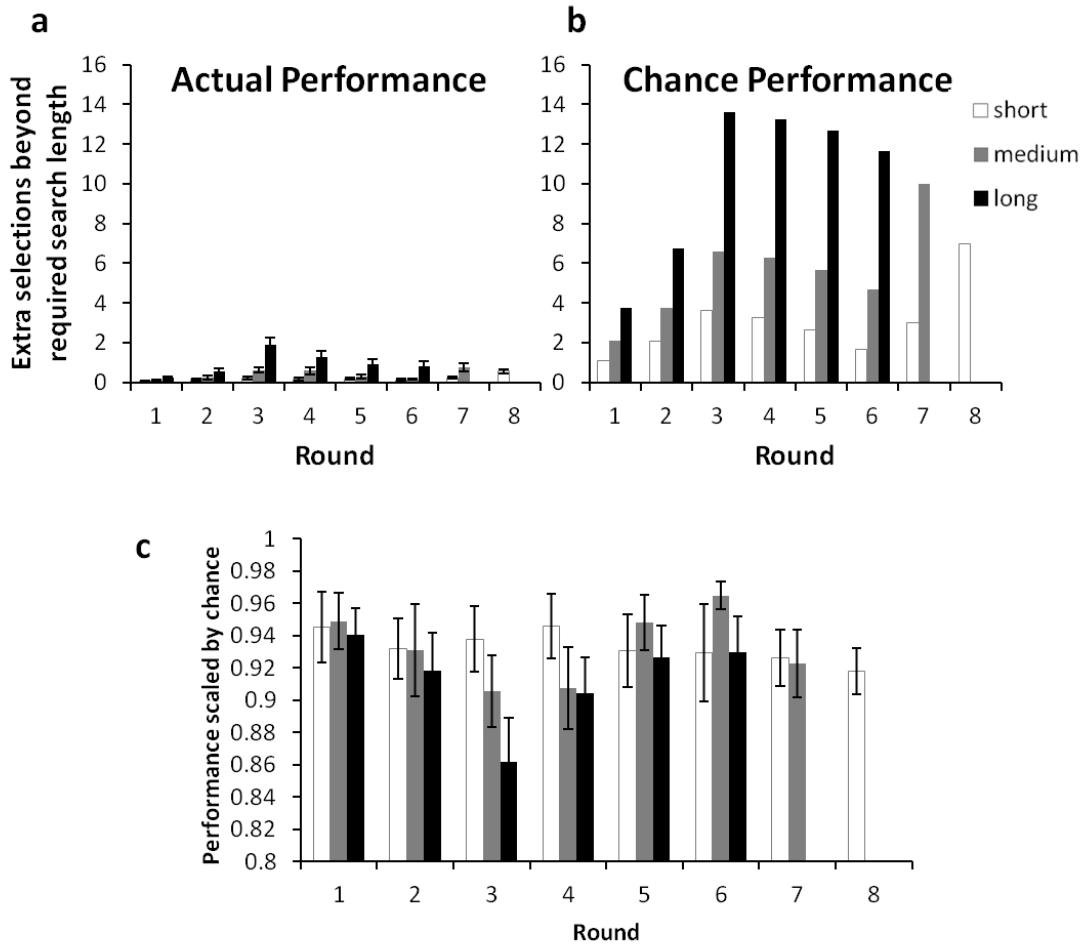


Figure 3.4. Memory versus control sustained effects (a: memory > control; b: control > memory) and transient effect (c: memory > control).

Orange / blue coloration indicates clusters showing significantly greater activity during the memory / control condition. Regions discussed in text are highlighted in red circles for emphasis (top row: left – MFG, middle – mPFC, right – SFS; bottom row: hippocampus). Maps are displayed on an MNI template brain.

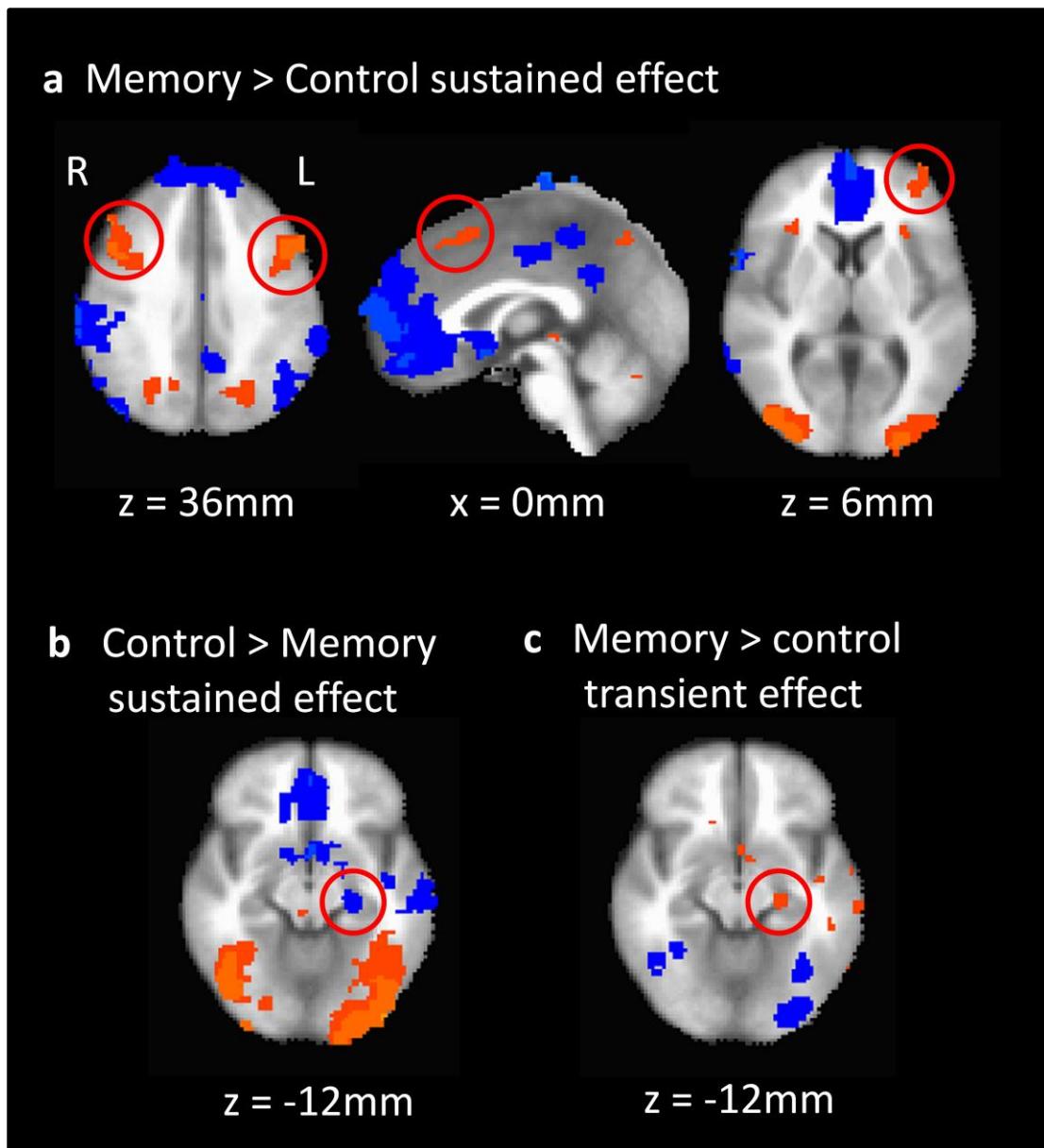


Figure 3.5. In the memory condition, across subjects, greater sustained deactivation in the hippocampus was associated with greater transient activation.

Each data point represents value from one subject. For each subject, parameter estimate of transient activation was averaged over the cluster identified by the transient memory > control contrast. Similarly, parameter estimate of sustained deactivation was averaged over the cluster identified by the sustained memory > control contrast.

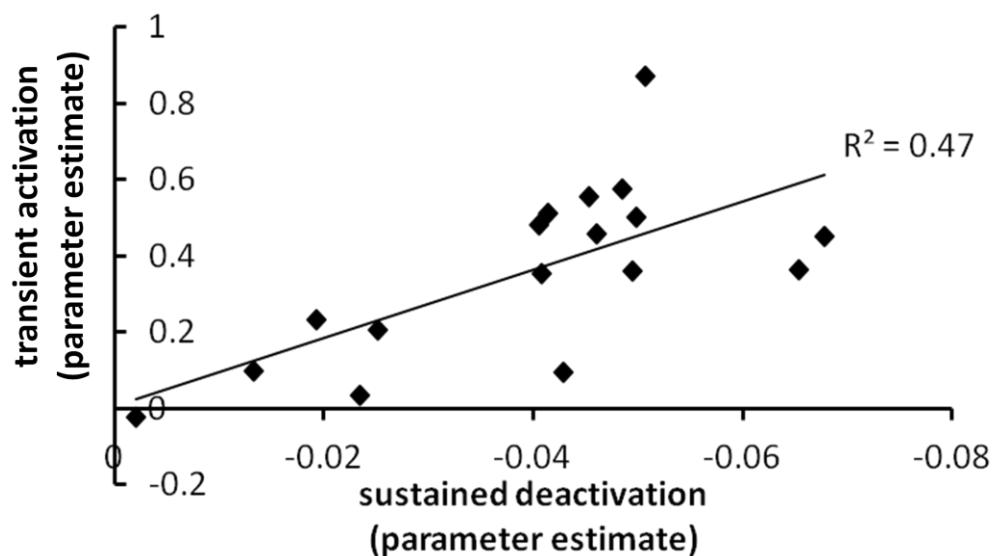
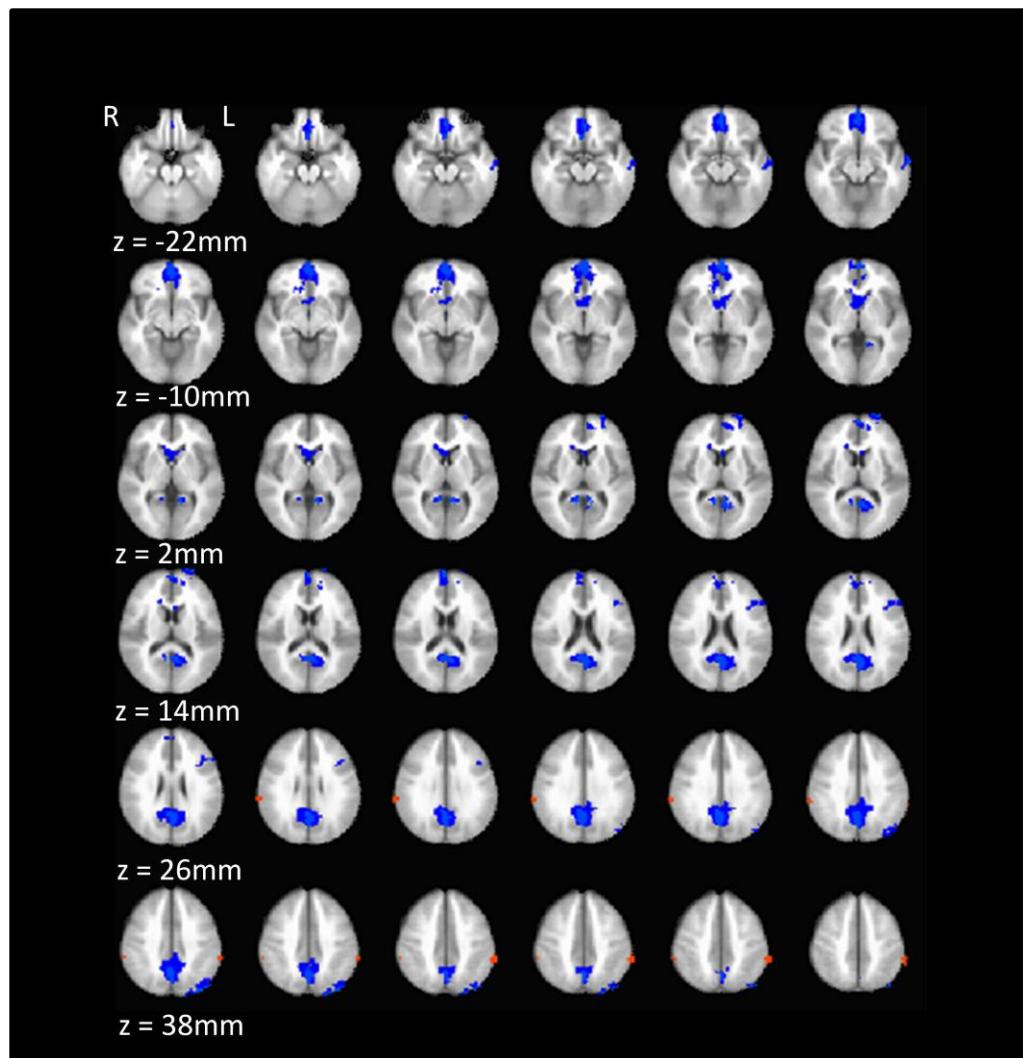


Figure 3.6. Functional connectivity with the hippocampal seed that showed sustained deactivation during the memory task.

Regions that showed significantly greater / less correlated activity with the hippocampus for the memory condition than for the control condition ($p < 0.05$, corrected) are shown in orange / blue, overlaid on transverse slices from an MNI template brain. The MNI z-coordinate of each successive slice increases by 2 mm.



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Chapter 4

Relational memory retrieval at short delays under interference from recently encountered associations

Introduction

The ability to inhibit prepotent responses to salient but irrelevant stimuli is one of the most important aspects of cognitive control. In the domain of memory, cognitive control is required during both encoding and retrieval. At retrieval, one situation that heightens the demand for cognitive control is when multiple representations are activated by the retrieval cue but only one is relevant for the current context. Interference is said to have occurred. In a laboratory setting, interference is studied using paradigms like the recent probe paradigm (Jonides & Nee, 2006; Monsell, 1978). In this paradigm, on each trial, subjects first study a set of stimuli (e.g., letters, words). After a brief delay, subjects receive a probe consisted of one stimulus and decide whether it belongs to the set of stimuli just studied. Critically, there are two types of negative (mismatch) probes, recent and non-recent. Recent negatives are probes that do not belong to the current study set (and thus should receive a negative response). However, they belong to the study set on the previous trial. Proactive interference has been observed in recent negative trials, in that the error rate is higher, and reaction time is longer for trials correctly rejected. One interpretation is that recent negative probes are interfering because of familiarity built up from the previous trial that biases for a positive response. It has been proposed that, in order to correctly reject recent negatives, one must successfully attribute that familiarity as irrelevant (D'Esposito, Postle, Jonies, & Smith, 1999; Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998; Nelson, Reuter-Lorenz, Sylvester, Jonides, & Smith, 2003). Neuroimaging studies

have consistently found activations in the left VLPFC during the probe period in recent negative trials and this activation has been thought to reflect the role of the VLPFC in selecting among competing representations (Badre & Wagner, 2005; Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2001; D'Esposito et al., 1999; Jonides et al., 1998; Jonides et al., 2000; Nelson et al., 2003; Postle & Brush, 2004). Using a recent probe paradigm, neuropsychological studies on VLPFC lesioned patients (Thompson-Schill et al., 2002) and TMS studies that target the VLPFC (Feredoes, Tononi, & Postle, 2006) provide converging evidence and imply a critical role of this region in resolving interference.

Although much has been studied about how the VLPFC resolves interference at the item level, that is, when interference arises from competing item representations, less is known about how interference that come from competing relational representations are resolved. Relational representations are bindings of arbitrary relations between two or more individual items, e.g., the association between an object and its location in a scene. A real-life example is remembering where you parked your car in the parking lot today. Because there are likely many parking instances that give rise to multiple item-location associations between your car and the parking spots, in order to specifically retrieve where it is parked *today*, your brain needs to hone in to the relevant information, most likely by inhibiting irrelevant associations from previous parking instances and/or retrieve additional information from today's parking episode to help bring that information to mind. Behaviorally, using word-pairs, it has been shown that when a cue is paired with multiple associates, the time it takes to retrieve a particular associate increases (Anderson, 1974). This phenomenon is known as the fan effect and a possible mechanism is interference due to competing associations, i.e., relational representations. A few fMRI studies have been conducted as well - increased PFC activations (anterior PFC, VLPFC, and DLPFC) have been

observed during the retrieval of items that are less distinct because multiple items are associated with the same cue/context (Bunge, Burrows, & Wagner, 2004; Henson, Shallice, Josephs, & Dolan, 2002; Herrmann et al., 2001; Sohn, Goode, Stenger, Carter, & Anderson, 2003)(but see Bunge for *increased* VLPFC activation for stronger associations, which presumably are less interfering). Not limited to semantic associations between words, similar results have been obtained between competing object-person associations in a virtual reality task (King, Hartley, Spiers, Maguire, & Burgess, 2005).

Although the above studies established a critical role of the VLPFC in resolving interference at the item level, and a few studies have investigated interference arising from long-term associations, less is known about whether and how the VLPFC mediates the resolution of relational interference arising from associations that are recently acquired about half a minute ago. This investigation will further our understanding of the cognitive control of relational representations under a short timescale.

Methods

Subjects

Thirty-three right-handed, native English speakers (number female; aged number – number years) gave informed consent to participate in the study. All procedures were approved by the institutional review board of the University of California, Berkeley. Participants received \$12 per hour of participation. Ten participants were excluded: five due to failure to complete study, two due to falling asleep in the scanner, one due to poor behavioral performance (two

standard deviations below mean), one due to excessive head motion, and one due to abnormal brain anatomy, resulting in 23 participants total.

Design

Subjects performed 12 blocks of a delayed-match-to-sample task in the scanner across two days. The stimuli were 16 experimentally novel objects created using the software Bryce. The trial sequence is shown in Fig. 4.1a. Each trial began with a cue phase of 2.5s, during which four objects from the set were presented at the top, bottom, left, and right relative to a central fixation cross. The size of each object was number visual angle and the entire display was number visual angle. A variable delay of 5.5s, 7.5s, or 9.5s consisted of a central fixation cross followed. Then, a probe was presented at one of the locations for 2s. Participants were instructed to respond ‘yes’ if the probe was one of the four objects studied at the same location in the cue phase of the current trial, and ‘no’ otherwise. Responses were made via button press (left and right thumbs, yes/no mapping counterbalanced across participants). Participants were instructed to respond as quickly as they could without sacrificing accuracy. A variable inter-trial interval of 4s, 6s, 8s, or 10s consisted of a central fixation cross occurred before the next trial began. Each block consisted of 25 trials. Participants completed the experiment in two sessions on different days.

There were six probe conditions, classified along two dimensions: 1) match / mismatch (M / NM), which refers to whether the probe was one of the four objects studied in the same location during the cue phase of the current trial, and 2) whether the probe had been studied in the previous (n-1) trial, and if so, whether it had been studied in the same location on both trials. In ‘n-1 not cued’ (N) trials, the current probe was not presented as a study item during the cue

phase of the previous trial (Fig. 4.1b). In ‘n-1 same cue-location’ (S) trials, the current probe was studied at the same location in trials n and n-1, during the cue phase (Fig. 4.1b). In ‘n-1 different cue-location’ (D) trials, the current probe was studied at different locations in trials n and n-1, during the cue phase (Fig. 4.1b). Of primary interest were the mismatch conditions. In n-1 different cue-location mismatch (DNM) trials, relational interference was expected, because the object-location binding in the previous trial was identical to the current probe, making it harder to reject the current probe as a mismatch. In n-1 same cue-location mismatch (SNM) trials, no relational interference was expected, because the cue-location binding in the previous trial was different from the current probe. Importantly, in both DNM and SNM trials, the current probe was cued on both trials n-1 and n, and required the same ‘no’ response. In other words, response requirement was controlled, and interference could not be attributed to item interference alone. In n-1 not cued mismatch (NNM) trials, no relational interference was expected because the probe did not appear in trial n-1.

The experiment consisted of 12 blocks of 25 trials each. Each block began with a dummy trial that established the recency for the following trial and was excluded from analysis. The actual 24 trials consisted of four trials from each of the six conditions, resulting in 48 trials per condition across the entire experiment.

The ordering of trials was random but the appearance of each of the 16 object stimuli followed the following constraints. Each object was cued no more than 12 times within a block. Each location was probed equally often in each condition within a block. Each trial consisted of two repeating items from the previous trial. For the n-1 not cued conditions, the current probe was never cued nor probed in recent trials up to and including trial n-3. For the n-1 same / different cue-location conditions, the current probe was never cued in trial n-2 and was never

probed in recent trials up to and including trial n-2. For all conditions, the current probe never occupied the probe location in trial n-1 to eliminate possible response interference. None of the cued stimuli in the current trial had been studied for more than four consecutive trials. Once probed, an object did not appear in the upcoming two trials.

fMRI Procedures

Whole brain imaging was performed on a 3 T Siemens Trio scanner. T2*-weighted functional images were acquired using a gradient-echo echo-planar sequence (TR = 2s, TE = 25 ms, 34 axial slices, 3.1mm x 3.1mm x 3.6mm, 249 volumes per run). High-resolution T1-weighted (MPRAGE) anatomical images were collected for visualization. Head motion was minimized using foam padding that surrounded the head. Stimuli were projected onto a screen and viewed through a mirror attached to a standard 32-channel head coil.

Data were preprocessed using Analysis of Functional NeuroImages (AFNI) software (Cox, 1996). Functional data were first phase shifted using Fourier transformation to correct for differences in slice acquisition time, and then realigned to the third volume of the run closest in time to the acquisition of the anatomical images using a rigid body transformation algorithm with six parameters to correct for motion. Subjects with more than 1.5mm movement in any direction of translation or rotation in any functional run were excluded from analysis. Using the slice-by-slice variability output from the “tsdiffana” tool in SPM as a guide, raw functional images were censored for drastic movements that were visible to the human eye. A covariate for inclusion/exclusion of timepoints was set up where timepoints with quick sudden movements were censored from statistical analyses. After realignment, a mean functional volume was computed for the functional run closest in time to the acquisition of the anatomical volume, and

this mean functional volume was coregistered to the anatomical volume. Functional and structural data were spatially normalized to the MNI template, an approximation of Talairach space, using a 12-parameter affine transformation. Images were resampled to 2 mm cubic voxels and spatially smoothed with a 6 mm full width half maximum isotropic Gaussian kernel. Finally, all voxels were normalized to have a mean signal of 100 to reflect percent signal change. These resulting images were then submitted to statistical analyses.

Behavioral Analyses

Reaction time (RT) and accuracy (proportion correct) were calculated for each subject. 3x2 repeated measures ANOVAs, with condition (n-1 different cue-location, n-1 same cue-location, and n-1 not cued) and probe type (match / mismatch) as within-subject factors, were performed on the reaction time (RT) and proportion correct data. Due to possible violations of the homogeneity of variance assumption when binary data are summarized as proportions, an arcsine transformation was applied to the proportion correct data before statistical tests were carried out. Furthermore, to improve the equality of variance, proportions of one (perfect performance) was computed as $(n-1/4)/n$, where n is the total number of trials, before the arcsine transformation was applied. RT analysis was restricted to correct trials only.

In order to assess performance independent of individual subjects' response criterion, a d' score was calculated from the hit rate and the false alarm rate for each condition. Hits were defined as correctly identifying match as a match, whereas false alarms were defined as incorrectly endorsing a mismatch as a match. A one-way ANOVA was performed on the d' scores.

fMRI Analyses

Voxel-based multiple regression analysis was performed in AFNI using the general linear model. Parameter estimates of brain activity related to the cue / delay period and the six probe conditions for each subject were obtained via a deconvolution approach. Trial events were modeled as two components, cue / delay and probe. Because encoding of stimuli and the maintenance of them during delay were identical across experimental conditions, the cue / delay period was modeled as a single covariate irrespective of probe conditions. Specifically, cue and delay were modeled as boxcar events spanning the entire duration of the cue and delay period. A finite impulse response model was constructed for each subject to estimate the observed event-related hemodynamic responses for each of the six probe conditions — n-1 not cued match / mismatch, n-1 same cue-location match / mismatch, and n-1 different cue-location match / mismatch — without making assumptions about the shape of the hemodynamic responses. For the model, seven time points were used (two seconds each), starting at the probe onset and ending 12 seconds later. All incorrect trials were modeled separately and were not included in the analysis. The unmodeled time points, i.e., inter-trial intervals, defined the baseline. The six motion parameters were included in the model as covariates of no interest.

Parameter estimates for the cue /delay period and the six probe conditions were obtained for each subject using a fixed-effects model. These parameter estimates were then entered into a second-level group analysis treating subjects as a random effect. Here, for each contrast, individual subjects' images of parameter estimates were entered into a one sample t-test, in which the mean estimate across subjects at each voxel was tested against zero. The resulting statistical map was thresholded at $p<0.005$ for individual voxels to identify regions of significant activation. Because of our a priori prediction of left IFG involvement in interference resolution,

instead of correcting the whole brain for multiple comparisons, a small volume correction was applied to the left IFG. The left IFG mask used for this small volume correction was obtained from the Harvard-Oxford Cortical Structural Atlas, and included all three sub-regions of the IFG (opercularis, triangularis, and orbitalis). In a Monte Carlo simulation by the program AlphaSim within the AFNI software package, it was determined that a minimum of 32 contiguous suprathreshold voxels were required to reach the experiment-wise threshold of $p < 0.05$.

Results

Behavioral Performance

Proportion Correct

Accuracy differed among probe conditions ($F(2,44) = 14.0, p < 0.001$), and was marginally lower in match (0.89 ± 0.02) than mismatch (0.90 ± 0.02) trials ($F(1,22) = 3.82, p > 0.06$), but condition and probe type did not interact ($F(2,44) = 2.64, p > 0.08$) (Fig. 4.2). Collapsed across match / mismatch, pairwise comparisons among probe conditions indicated that accuracy was lowest in n-1 different cue-location trials (0.87 ± 0.02), followed by n-1 not cued trials (0.90 ± 0.02), then by n-1 same cue-location trials (0.91 ± 0.01 , all $t(22) \geq 5.28$, all $p's < 0.001$). Interference was thus seen in both match and mismatch trials: when an item was studied in two consecutive trials at different locations, more errors were made during its retrieval at the probe phase.

Reaction time

Subjects were slower on mismatch (1362.4 ± 90.0 ms) compared to match (1238.0 ± 72.2 ms) trials ($F(1,22) = 31.6, p < 0.001$), and RT differed among probe conditions ($F(2,44) = 4.98,$

$p < 0.02$), but condition and probe type did not interact ($F(2,44) = 1.57, p > 0.2$) (Fig. 4.2). Collapsed across match / mismatch, pairwise comparisons among probe conditions revealed that RT was slower in n-1 different cue-location trials (1325.8 ± 86.0 ms), compared to n-1 same cue-location trials (1287.4 ± 78.6 ms, $t(22) = 2.50, p < 0.05$), and n-1 not cued trials (1287.4 ± 78.1 ms, $t(22) = 2.40, p < 0.05$). RT did not differ between n-1 same cue-location and n-1 not cued trials ($t(22) = 0, p > 0.1$). Again, interference was evident by the RT measure in both match and mismatch trials – when an item was studied in two consecutive trials at different locations, its retrieval took longer.

d' measure

d' differed among conditions ($F(2,44) = 12.6, p < 0.001$) (Fig. 4.2). Pairwise comparisons indicated that d' was lower in the n-1 different cue-location condition, compared to the n-1 same cue-location condition ($t(22) = 5.09, p < 0.001$), and to the n-1 not cued condition ($t(22) = 3.45, p < 0.001$), demonstrating behavioral interference. Subjects who displayed behavioral interference in d' , RT, or both were entered into the fMRI analysis (22 of 23).

fMRI Results

Match trials vs. Mismatch trials

Collapsed across probe conditions, the left hippocampus (MNI coordinates: -22, -22, -16) was more activated during match than mismatch trials (Fig. 4.3). This finding is consistent with studies that observed a match enhancement effect during the probe period of relational memory tasks (Duncan, Curtis, & Davachi, 2009; Hannula & Ranganath, 2008).

Relational Interference Effects

Although the main effect of probe condition coupled with the lack of an interaction between probe type and condition suggests that interference occurred in both match and mismatch trials and that trials should be collapsed across the match / mismatch dimension, we approached the fMRI data separately for match and mismatch trials for two reasons. First, reaction time was faster in match trials, suggesting that different response related processes would have been mixed together had we combined match and mismatch trials. Second, previous studies on item interference focused on mismatch trials only. Analyzing match and mismatch trials separately thus offered a more direct comparison with previous findings. In mismatch trials, the contrast DNM and SNM revealed greater activity in the left IFG (-50, 30, -4) in the DNM condition (Fig. 4.4). This finding is consistent with previous reports of higher left IFG activity during resolution of item interference. In match trials, the contrast DM and SM did not yield any significant activations.

Discussion

In the current study, relational interference was introduced by manipulating a probe item's study history in the current trial and the trial immediately preceding it. Specifically, when a probe item had been studied in different locations in the current trial and the immediately preceding trial, interference was observed behaviorally as a decrease in accuracy and an increase in reaction time, for both match and mismatch probes. Different from the behavioral results, an interference effect was observed in the brain for mismatch probes only, where the left IFG showed greater activity when the mismatch probe was studied at different locations in the current

and the previous trial, compared to when it was studied at the same location in two consecutive trials.

One important difference between the current relational design and its item counterpart is the control condition to which performance in interfering trials was compared. In the item version, conclusions about interference were drawn from comparing recent with non-recent trials. However, in the current relational version, such a comparison ($n-1$ different cue-location trials vs. $n-1$ not cued trials) would not allow item effects to be disentangled from relational effects, because these two conditions differed both in terms of the presence of the probe item in the preceding trial and the item-location relation. Instead, an additional recent condition was designed – the $n-1$ same cue-location trials. In this condition, the probe item was studied in the same location in both trials. Item exposure is therefore controlled for, and no relational interference was expected because item-location relation remained constant, making this an appropriate control condition.

The behavioral results are not in complete alignment with the fMRI results. While behavioral interference was found for both match and mismatch trials in the $n-1$ different cue-location condition, the left IFG was responsive to mismatch trials only. The selective activation of the IFG for mismatch trials may mean that it is only engaged when the lure is identical to the interfering representation it is trying to overcome. In our design, the mismatch probe in the DNM condition was presented at the location where it was studied in trial $n-1$. We reasoned that this would produce the maximum degree of interference. Although behaviorally there were no differences between matches and mismatches, perhaps the mismatch trials were found to be more interfering by the brain because they required a mismatch response *and* the lure was highly salient due to its recent appearance in the same location. In the match (DM) trials, perhaps the

brain found it less interfering because the probe was not physically in the n-1 cue location and visually reminding the brain of the interfering representation. Follow-up studies that include a mismatch condition where the probe is presented at a third location other than the study locations in trials n and n-1 will be informative. If there is behavioral interference but the IFG is not activated for this kind of mismatch, it will suggest that the IFG does not respond to mismatches per se, but only when a mismatch is identical to the recent representation it is trying to resolve. If the IFG is activated for this kind of mismatch, it will suggest that the IFG respond whenever mismatch responses are to be made in the face of interference. Nonetheless, our finding is consistent with the well-established role of the left IFG in resolving interference caused by recently seen items, as demonstrated by a line of research investigating item interference resolution using the recent probe paradigm. Importantly, our finding extends this region's role in interference resolution to encompass relational representations, providing support for its general role in interference resolution.

Behaviorally, it was somewhat surprising to find that having studied the same item twice in a row in the same location produced little facilitation in performance, as seen in the comparison between n-1 same cue-location trials and n-1 not cued trials (although the proportion correct in n-1 same cue-location trials was higher, the effect was not significant in the d' measure, therefore evidence for facilitation in terms of accuracy is rather weak). One potential explanation is that, in n-1 same cue-location trials, even though the probe item was studied in the same location on trial n-1, its representation on the two trials are interfering to some extent due to the different temporal contexts and the different items it is seen with on two trials. This interference might have been offset by the identical item-location binding on two trials, resulting in the same level of performance as non-recent n-1 not cued trials.

The left IFG site activated in the current study is more rostral than those reported in studies of item-level interference. A speculation is that there might be a functional topography within the IFG, where more rostral regions are responsible for the cognitive control of more abstract representations, in this case, relational representations. This idea fits well with the proposal that the PFC is organized in a hierarchical manner, such that more rostral regions respond to increasingly abstract information (Badre, 2008).

Results obtained in the current study shed light on the interference resolution mechanisms at retrieval. An interesting question is, whether interference occurred at the cue phase, and if so, the brain mechanisms involved for the encoding of a competing relational representation. Our design did not permit us to answer this question, because items with different viewing history were presented during the cue phase and so brain activity could not be attributed specifically to the encoding of the interfering item. Future studies with different designs are needed to understand interference effects at encoding.

Retrieval of match probes activated the hippocampus to a greater extent than retrieval of mismatch probes. This is consistent with a match enhancement effect often observed during memory retrieval (Dudukovic, Preston, Archie, Glover, & Wagner, 2011; Duncan et al., 2009; Hannula & Ranganath, 2008), and may reflect increased attention to the probe when the probe matches retrieval goal (Duncan et al., 2009), or pattern completion to other contextual details about the probe (Dudukovic et al., 2011). Mismatch enhancement has also been reported often in the hippocampus (Kumaran & Maguire, 2006; Kumaran & Maguire, 2007) and such activity has been suggested to reflect prediction errors and the encoding of the unexpected events. In our paradigm, because the small set of stimuli repeated in the same locations often, the associative

novelty was subtle. Therefore, it is not surprising that we did not observe a mismatch-enhancement effect.

In conclusion, using a modified recent probe paradigm, interference was found to occur among relational representations across successive trials. fMRI results showed that the left IFG is active during resolution of relational interference. Together with previous findings in item-level interference resolution, the current results show that the left IFG plays a general role in interference resolution.

Figures

Figure 4.1. Trial structure and the six different probe conditions.

(a) Schematics of two consecutive trials with the same trial sequence. Of interest is the probe on trial n, which belonged to any one of the six conditions illustrated in (b). (The probe on trial n was an actual object like that in trial n-1. The boxes are for illustrative purposes only.) Probe conditions were classified along two dimensions: match / mismatch with the cue on the current trial, and relationship between cue locations on trials n and n-1, which could be different, same, or not cued in n-1. Italic letters below the probes in (b) refer to their abbreviations used in the main text.

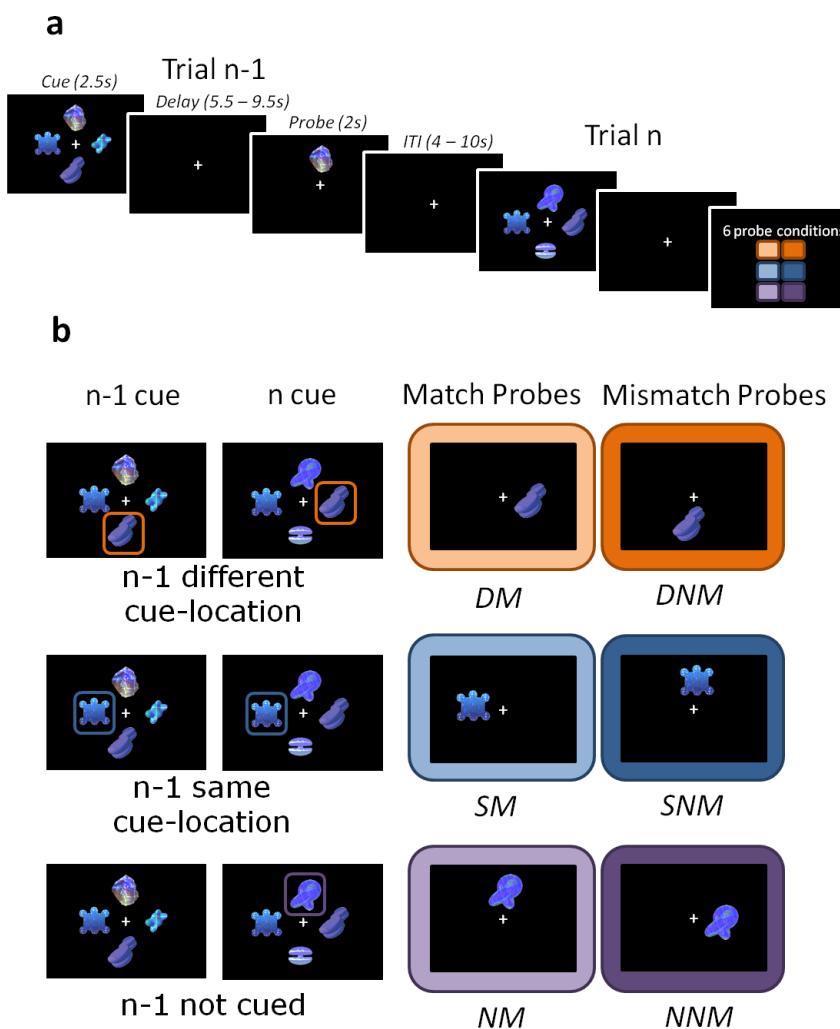


Figure 4.2. Behavioral reaction time, proportion correct, and d' .

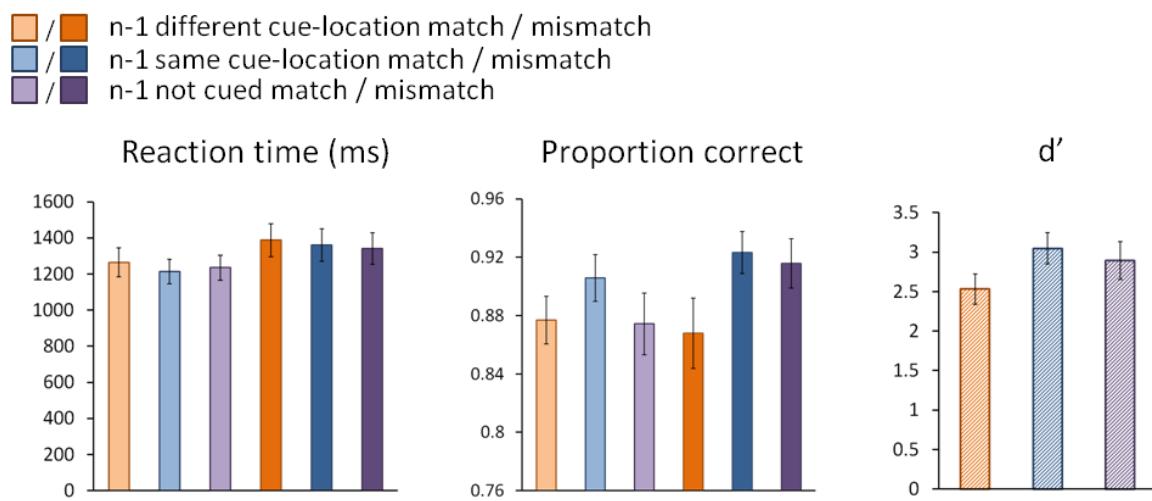


Figure 4.3. Hippocampus showing a match enhancement effect.

The contrast between all match probes and all mismatch probes, shown on an average brain of all participants ($p < 0.05$, small volume correction).

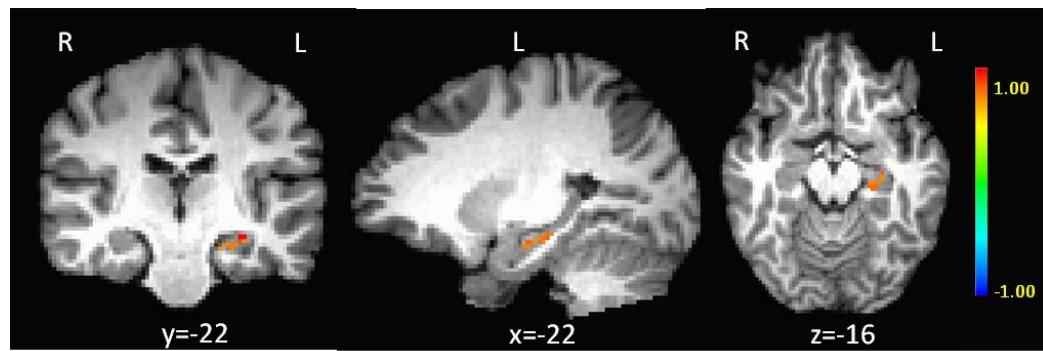
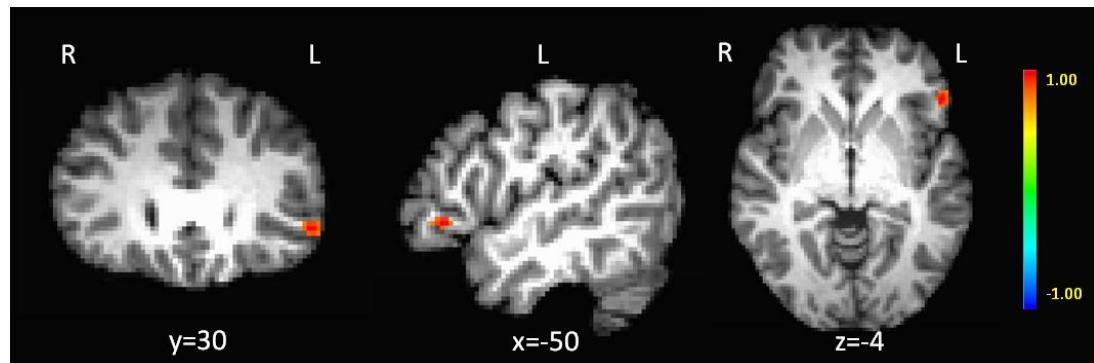


Figure 4.4. Greater left IFG activity observed during resolution of relational interference.

The contrast between n-1 different cue-location mismatch probes and n-1 same cue-location mismatch probes, shown on an average brain of all participants ($p < 0.05$, small volume correction).



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Chapter 5

General Discussion

In three experiments, this dissertation examined PFC and MTL contributions to relational memory and the control of it on short timescales. Experiment 1 revealed a critical role of the hippocampus in integrating information acquired over discrete moments in time and space to guide optimal behavior. Experiment 2 found that the PFC was functionally connected to the hippocampus during ongoing task performance, when decisions relied on continuous updates of relational representations. Experiment 3 focused on one type of control process governed by the PFC – interference resolution – and found that the IFG resolved interference among competing relational representations. What have we learned from the three experiments about the nature of processing that critically depends on the MTL? What differential roles do the MTL and the PFC play in ongoing behavior? What can we conclude about the nature of PFC-MTL interaction that supports online performance?

Experiment 1 was particularly informative on the nature of hippocampal processing. It reinforced the view that the hippocampus is critical for relational binding, regardless of delays. In most experiments, the pieces of information to be bound are naturally separated in space and/or time. This is true for Experiment 1 as well, as individual glimpses were by definition separated in space and time. This leads to the question of whether instantaneous binding of relations requires the hippocampus. The prediction based on the relational memory theory (Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001) is yes. Indeed, in experiments where within-item binding occurs, e.g., when word-font relations are encoded (Prince, Daselaar, & Cabeza, 2005), the hippocampus is active. This is a close approximation to instantaneous binding

as the word is presented at the fovea. Note that different kinds of representations can be formed from a glimpse of a word. The kind of flexible word-font representation is different from a unitized representation of word-in-a-font, which does not rely on the hippocampus for its processing (Cohen, Poldrack, & Eichenbaum, 1997). The former is flexible in the sense that the word and the font retain their individuality, but the latter is a single inseparable representation (a relational versus item distinction, see Hannula, Tranel, & Cohen, 2006; Konkel, Warren, Duff, Tranel, & Cohen, 2008; Ryan, Althoff, Whitlow, & Cohen, 2000). The relational memory theory predicts that creating the former kind of representation from a glimpse requires the hippocampus.

Together with other results of hippocampal recruitment at short delays or no delays, these studies bring up questions about the characterization of hippocampal function. For a long time impaired performance at long delays and intact performance at short delays have been used as evidence for a dissociation between long-term and short-term memory (e.g., Cave & Squire, 1992). But if the dissociation is non-existent (see similar idea in Ranganath & Blumenfeld, 2005), are there frameworks that can accommodate these recent findings? The answer is yes. One such framework is the embedded-process model proposed by Cowan (1995, 2005). Instead of postulating dissociable long-term and short-term memory, this model posits that all memories belong to a unitary store, where they are compartmentalized into three pools that are nested within each other – the focus of attention, which is a subset of an activated memory store, which in turn is a subset of a long-term memory store. Activation weights of memories residing in each pool differ. Representations in the focus of attention are most active, while those in the long-term store are least active. Without postulating separate stores for long-term and short-term memory, frameworks like this avoid the problem of having to categorize representations in a binary fashion, and instead allow the hippocampus to contribute to representations of all activation

weights. The model further posits that incoming information is integrated with existing representations in the focus of attention by control processes and that relational links are formed there. The hippocampus likely acts at the focus of attention to bind incoming information with representations that are in the activated store or long-term store. The focus of attention is capacity limited. It is likely that by forming relational links, more information can be kept in this limited store because the size of each item/chunk is larger, and as a result, loss caused by temporal decay or interference is slowed down.

Next, let us turn to the nature of MTL-PFC interaction exemplified by the three experiments. A broad overarching principle of PFC function is that it exerts top-down biasing signals to a brain region to influence its processing (Miller & Cohen, 2001). Different phenomena are seen based on the region that is being influenced. For example, the PFC has been shown to modulate activity in the fusiform face area and parahippocampal place area to influence the processing of faces and places (Gazzaley, Cooney, McEvoy, Knight, & D'Esposito, 2005). In that experiment, by selectively enhancing or suppressing the processing of faces and places, memory performance was modulated. In our case, relational memory governed by the MTL is of interest. As such, the effect of PFC on relational memory can be broadly understood as the PFC modulating activities in the MTL to influence the formation and/or retrieval of relational representations. To use the railway analogy by Miller & Cohen (2001), the MTL is responsible for laying down tracks between stimuli, i.e., providing relational links between them, while the PFC controls which railway tracks are to be used for the current goal. The mechanism of how control is accomplished, according to Miller & Cohen (2001), is that activity in the PFC reflects contingencies (if this stimulus then this response), or rules, of a task. Fuster proposed that contingencies of events separated in time are mediated by retrospective codes and prospective

codes in PFC neurons (Fuster, 2001). Now, let us turn to each experiment to discuss additional details of PFC-MTL interaction under this broad framework.

In Experiment 1, although testing was limited to patients with hippocampal damage, the results speak to PFC-MTL interactions when they are considered together with the revisit study (Voss et al., 2011) and Experiment 2. The common thread is that information learned online was integrated with existing representations and updated iteratively to guide behavior. From the revisit study a PFC-hippocampus-cerebellum network was proposed to be important for this process. This set of results suggests that the importance of PFC-MTL interaction goes beyond memory as it influences future behavior as well. Prospective codes generated by the MTL likely interact with monitoring and error detecting mechanisms in the PFC to optimize behavior as it unfolds. The interaction is likely to be two-way: strategy implementation may benefit from coherent representations, and vice versa; as we propose that the PFC and the MTL interact in an iterative manner, coherent representations may lead to the use of better strategies, which in turn lead to the formation of a stronger representation at the next update.

In Experiment 2, PFC-MTL interaction was directly examined by assessing the functional connectivity between them. Activity in the PFC and the hippocampus was negatively correlated with each other throughout the memory task. The anti-correlation shed light on potential interaction mechanisms between the PFC and the MTL. It shows that the PFC may achieve control by actively inhibiting MTL activity in some circumstances, like in the Gazzaley study (2005) the PFC could selectively suppress representations in the visual association cortex based on task demand. Although the direction of interaction cannot be concluded from the functional connectivity analysis that is correlational, based on the well-accepted view the PFC is a control

region, this direction of interaction is plausible. It could be that representations in the PFC and the MTL are overlapping and they interfere with each other, and a balance has to be maintained in order to achieve optimal performance. Activity in the PFC is proposed to represent an integration of response contingencies and task-relevant information. In this task, this would be the action to be performed on memory representations. Perhaps the amalgamation of cue-outcome-action representation in the PFC is similar to some of the cue-outcome associations in the MTL that are currently irrelevant. Once the PFC derives a plan for an upcoming action, the MTL representations do nothing more but interfere, and so they are suppressed. By the railroad metaphor, once the control room derives a track plan for the journey, e.g., A-B-C-D, it is probably more efficient to suppress knowledge on B's connections to other tracks because they are irrelevant for the current trip.

In Experiment 3, the same IFG region that was critical for resolving interference caused by item representations was recruited to resolve interference caused by relational representations. This finding reinforces the point that the function of the PFC is best characterized by the nature of the control processes it carries out. The same PFC region can be activated by a range of tasks and a variety of representations, but the nature of cognitive control it carries out is the same. For example, the IFG is active for interference resolution of different kinds of memory representations, items and relations. Furthermore, besides interference resolution, it is active for other memory tasks like semantic retrieval and contextual retrieval as well (see Badre & Wagner (2007) for a review). The common nature of control required across these tasks is that they all require selection among multiple representations. Returning to the railroad metaphor, the IFG is responsible for selecting which track to travel along when multiple tracks coincide. Our finding

also exemplifies another principle of PFC function: it is active when a task-relevant response needs to be selected against a prepotent but task-irrelevant response.

Overall, results from the three experiments are congruent with the idea that PFC-MTL interaction represents top-down control from the PFC on MTL relational representations. Their interaction can be antagonistic under some situations. Together, the two regions contribute to ongoing behavior in addition to their well-known role in memory.

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Appendix: individual search paths

Individual search paths are presented for amnesic and matched comparison subjects. Each image depicts the entire search path for one trial of the specified search duration.

Each amnesic search path was matched randomly to a search path from the corresponding comparison, such that the overall search duration was approximately matched for the amnesic path versus the comparison path. For search paths less than 50 seconds in duration, duration-matched pairs were only included if the difference between the amnesic search path duration and the control search path duration was less than 5 seconds. For search paths longer than 50 seconds, the closest match was included. Search paths less than 12 seconds in duration were excluded.

Search paths are presented separately for each amnesic patient and the corresponding comparison subject. Each page of search paths is divided into two large columns. In each column, the amnesic search path is shown on the left and the duration-matched comparison subject search path is shown on the right. Also provided for each amnesic/comparison set is the mean percent-coverage measure for all presented search paths and the corresponding statistics.

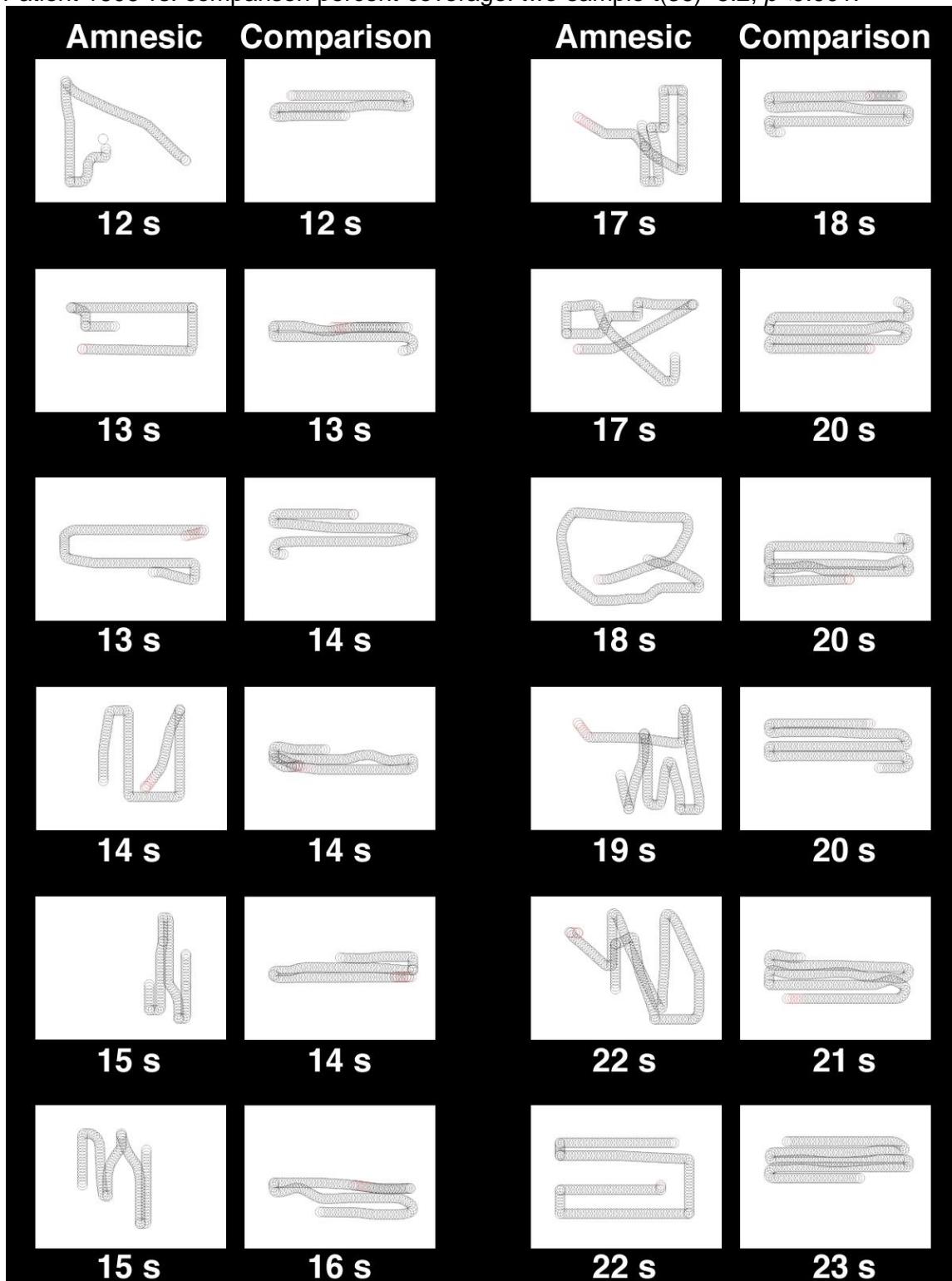
Search paths are depicted as circles corresponding to positions of the viewing window during search, sampled continuously at 60 Hz and down-sampled to 10 Hz for presentation purposes. Regions of increased circle density indicate repeated viewing of the same spatial location.

Patient 1606 versus comparison – Page 1 of 2

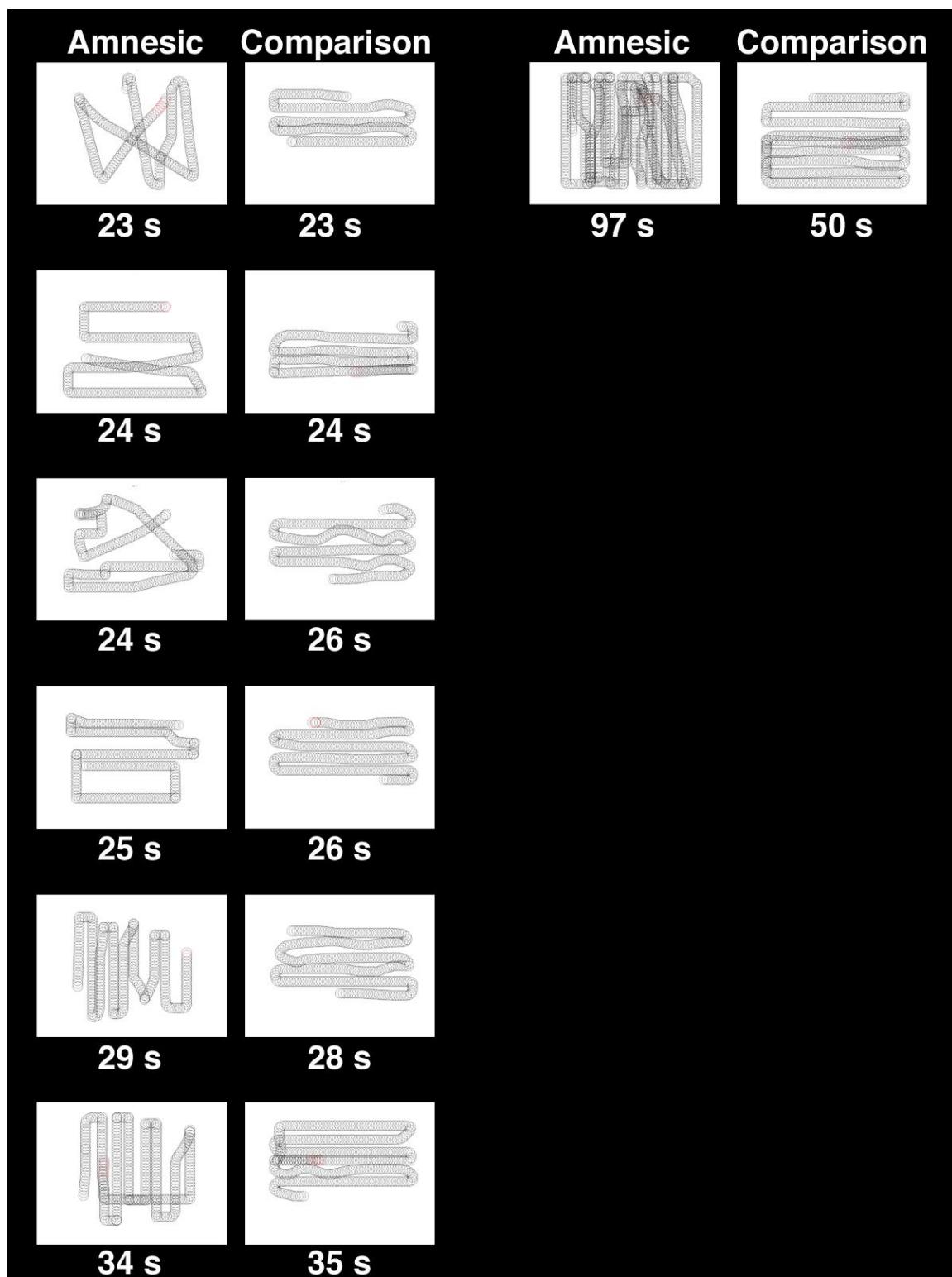
Patient 1606 mean percent-coverage: 46.4%

Comparison mean percent-coverage: 65.9%

Patient 1606 vs. comparison percent-coverage: two-sample $t(36)=5.2$, $p<0.001$.



Patient 1606 versus comparison – Page 2 of 2

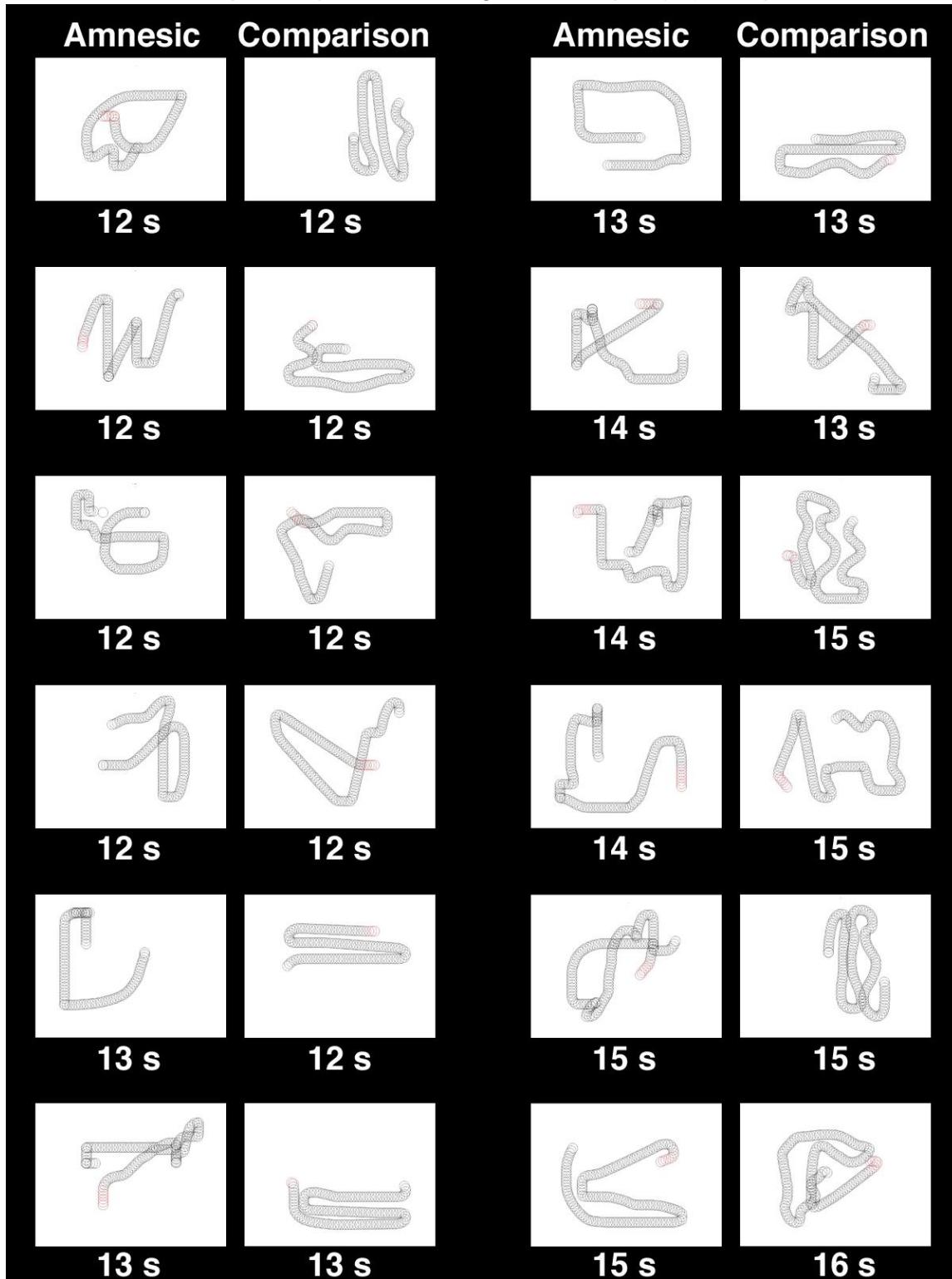


Patient 1846 versus comparison – Page 1 of 4

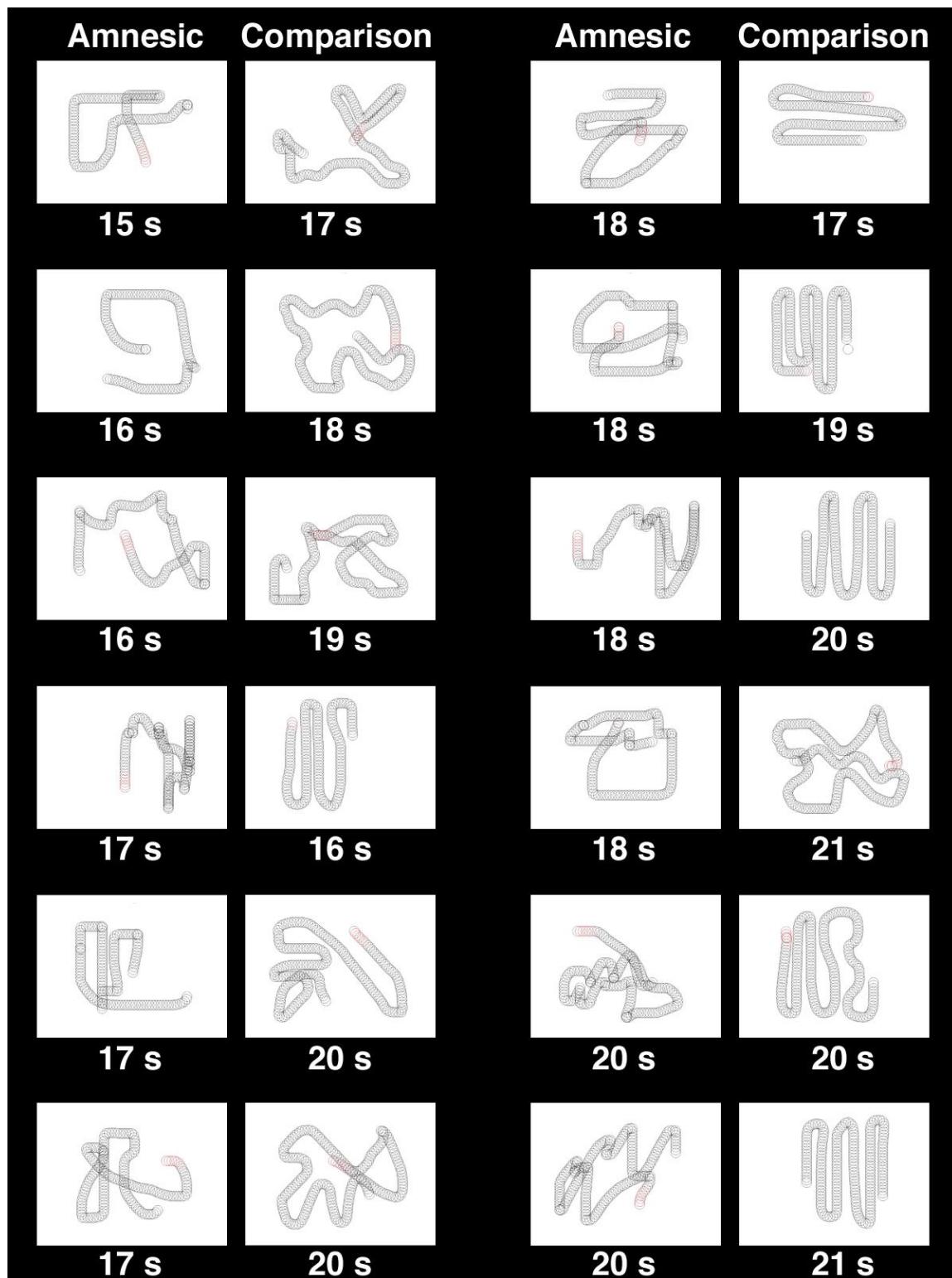
Patient 1846 mean percent-coverage: 43.2%

Comparison mean percent-coverage: 50.0%

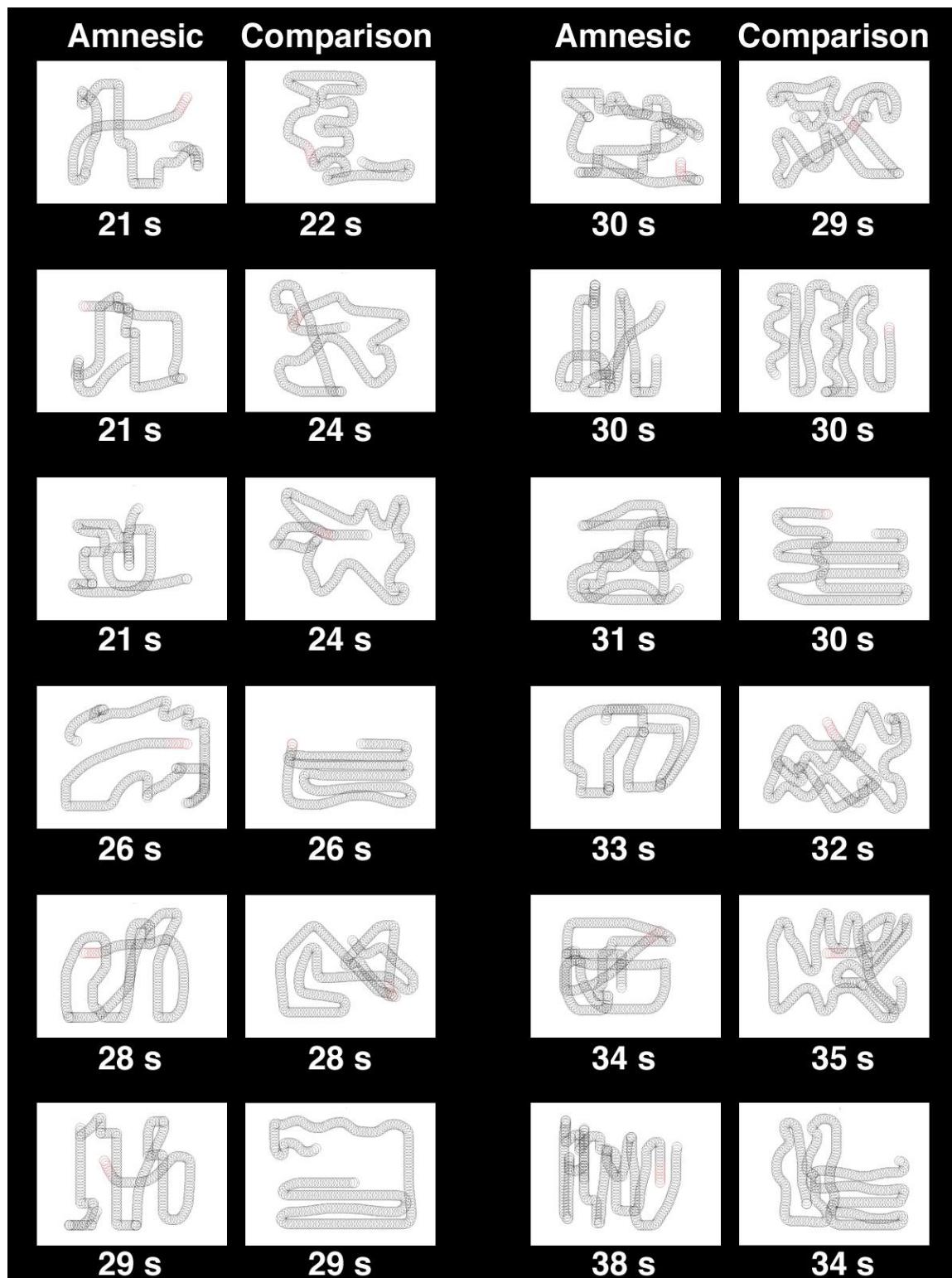
Patient 1846 vs. comparison percent-coverage: two-sample $t(80)=2.5$, $p=0.01$.



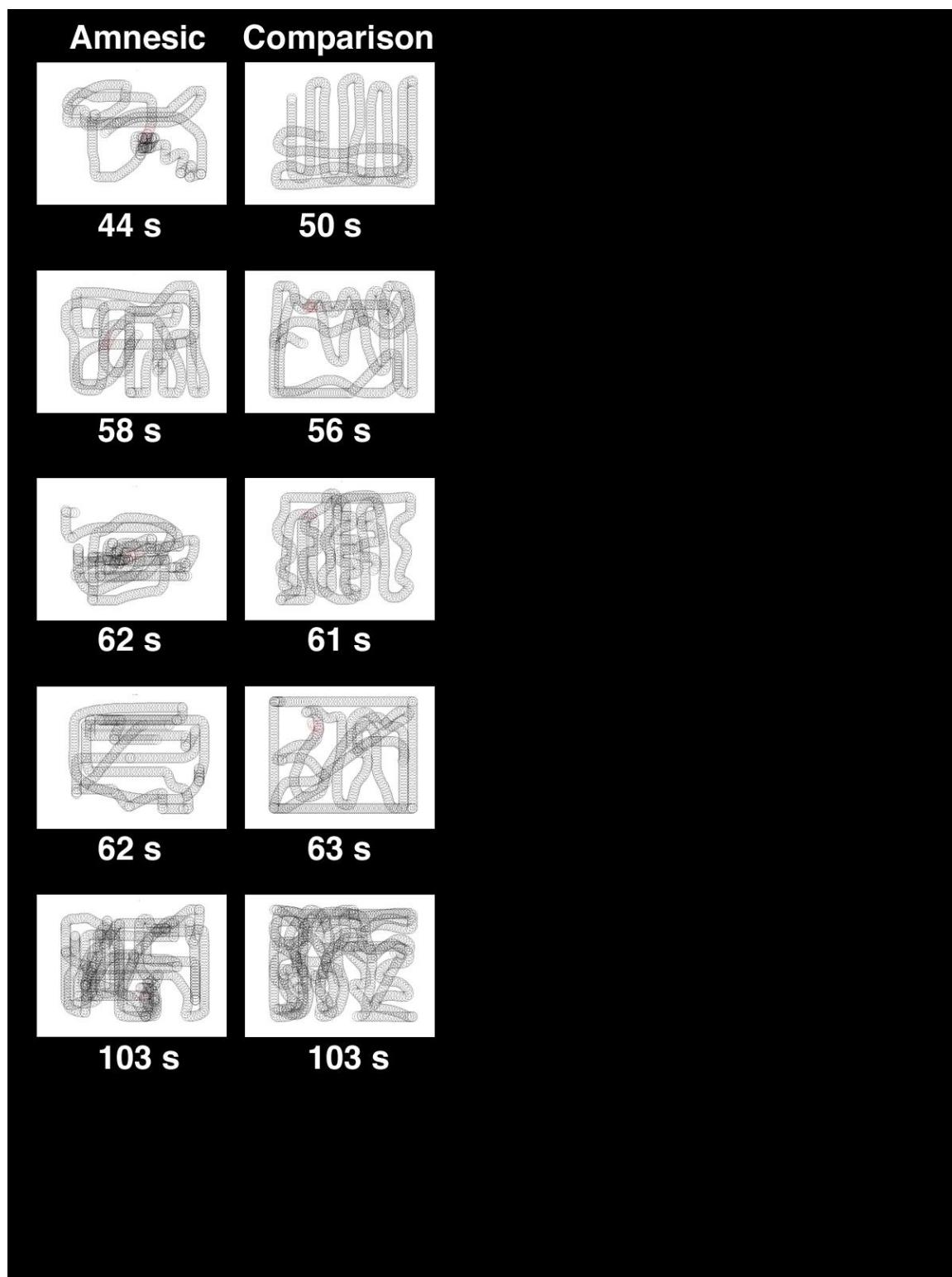
Patient 1846 versus comparison – Page 2 of 4



Patient 1846 versus comparison – Page 3 of 4



Patient 1846 versus comparison – Page 4 of 4

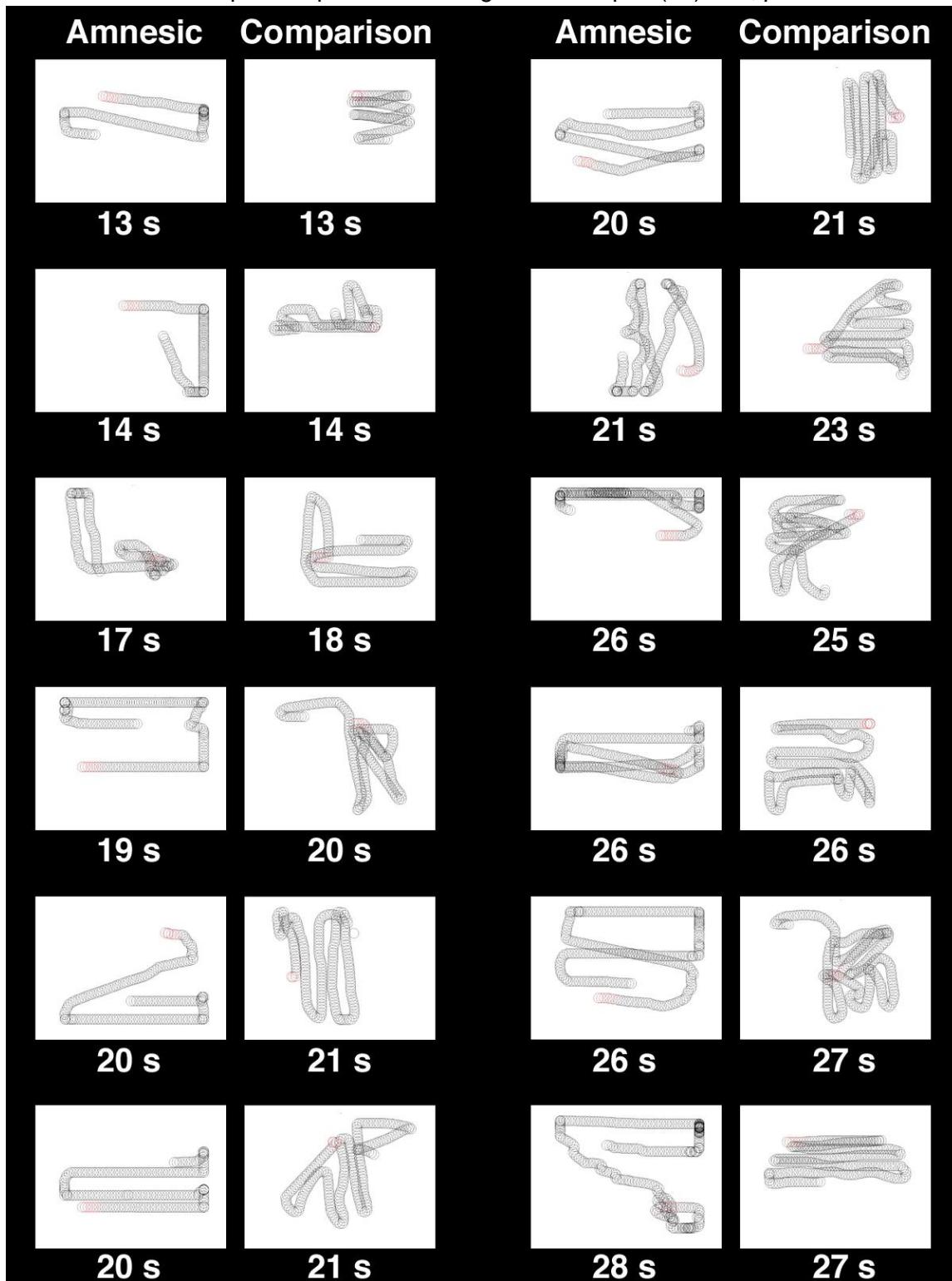


Patient 2363 versus comparison – Page 1 of 3

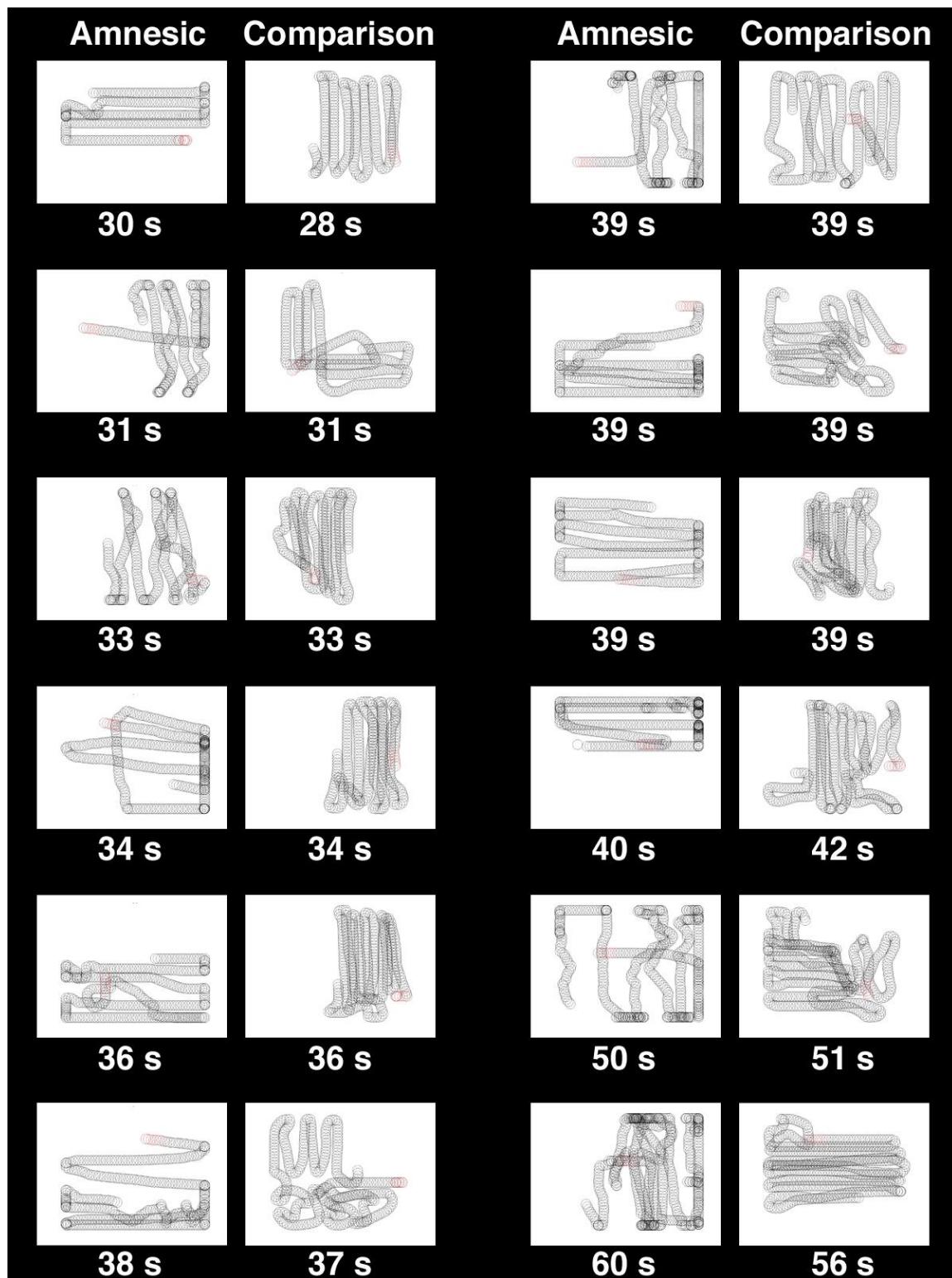
Patient 2363 mean percent-coverage: 50.6%

Comparison mean percent-coverage: 59.6%

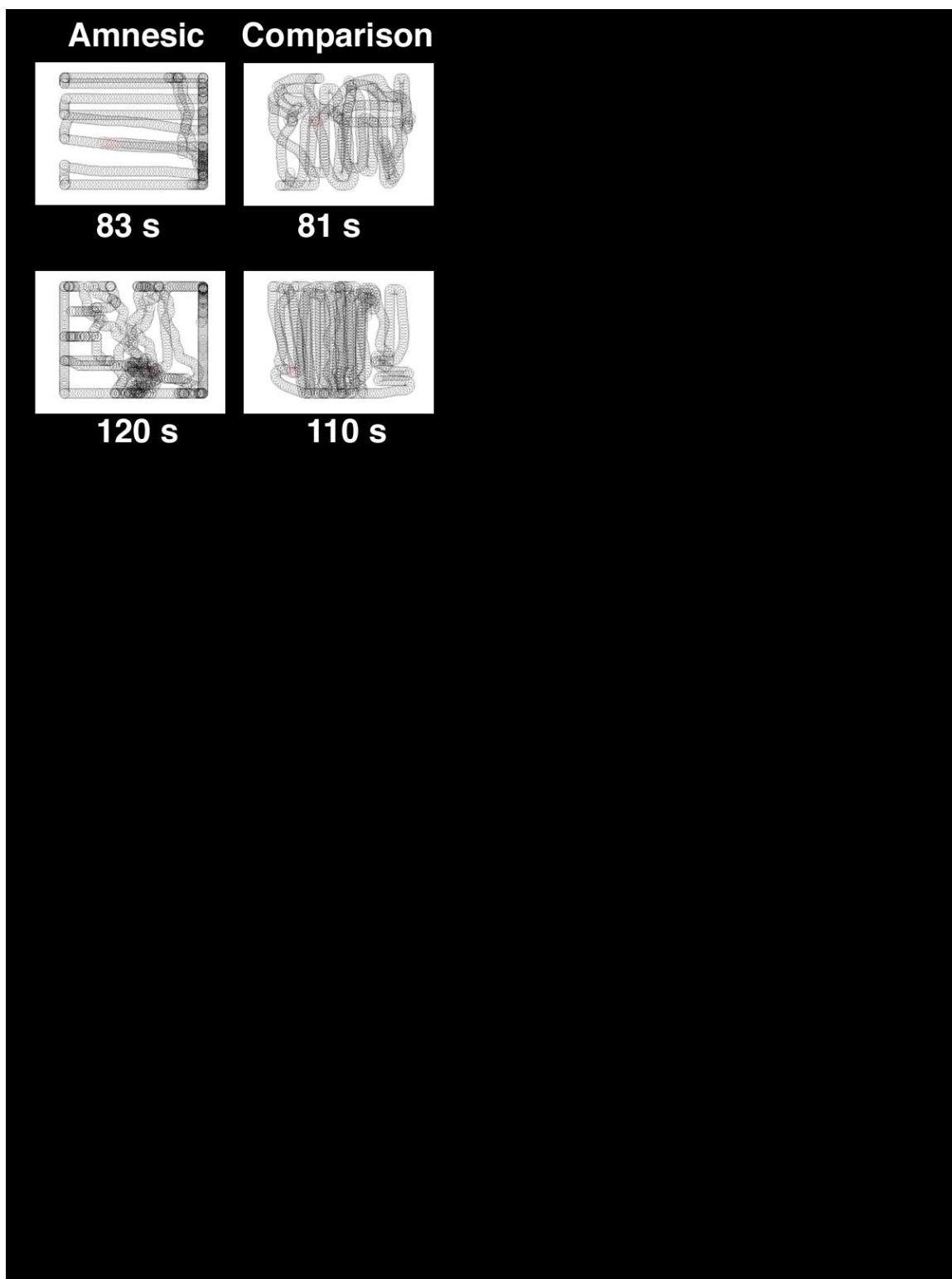
Patient 2363 vs. comparison percent-coverage: two-sample $t(50)=2.5$, $p=0.02$.



Patient 2363 versus comparison – Page 2 of 3



Patient 2363 versus comparison – Page 3 of 3

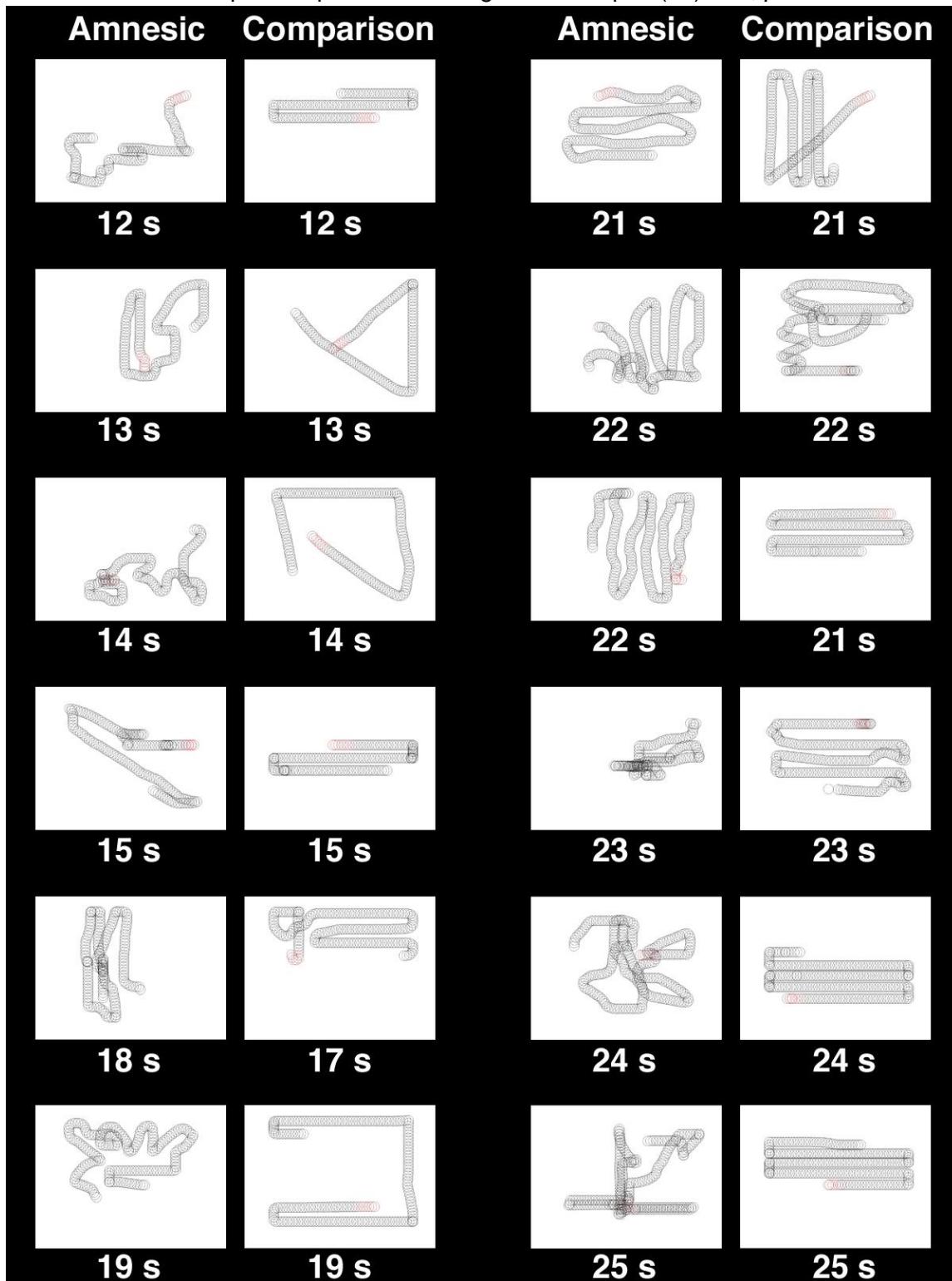


Patient 2563 versus comparison – Page 1 of 3

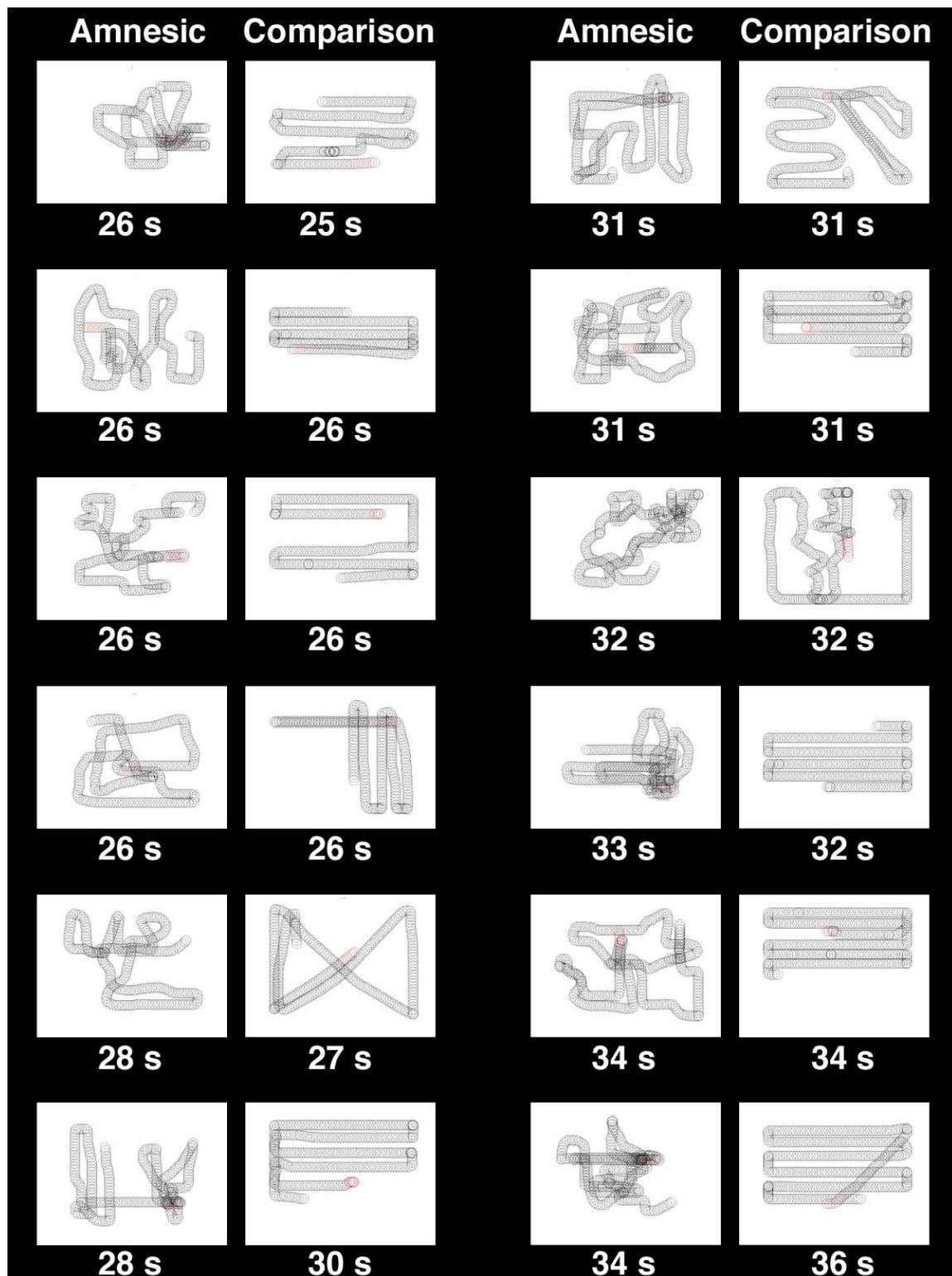
Patient 2563 mean percent-coverage: 46.4%

Comparison mean percent-coverage: 62.0%

Patient 2563 vs. comparison percent-coverage: two-sample $t(70)=5.2$, $p<0.001$.



Patient 2563 versus comparison – Page 2 of 3



Patient 2563 versus comparison – Page 3 of 3

