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by

Riikka Hess

Benjamin Hampstead
Adviser

Neuroscience and Behavioral Biology

Benjamin Hampstead

Adviser

Matthew Weinschenk

Committee Member

Krish Sathian

Committee Member

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An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
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Abstract

Navigational Memory in Amnestic Mild Cognitive Impairment

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Objective: Patients with amnestic mild cognitive impairment (aMCI) demonstrate impaired explicit memory due to medial temporal lobe dysfunction but relatively preserved implicit memory, which is more broadly mediated within the brain. Many patients have difficulty with navigation in both familiar and unfamiliar environments. Therefore, we assessed the relative contributions of explicit and implicit memory in aMCI and healthy elderly controls (HEC) on a virtual spatial navigation task using the process-dissociation procedure. We expected to find that explicit memory is impaired in aMCI while implicit memory is preserved, as compared to HEC. In navigation, explicit and implicit memory contributions are influenced by practice, such that there is a greater contribution of explicit memory for retrieval of novel mazes and a greater contribution of implicit memory in retrieval of well-learned mazes, with navigational demands held constant.

Participants and Methods: Five HEC and 5 aMCI were trained on 15 virtual T-mazes such that they became well-learned. Following a short delay, participants completed a retrieval task of well-learned mazes. Participants then viewed videos depicting navigation of 15 novel and 15 well-learned mazes. Following a 15 minute-delay, participants navigated the well-learned and novel mazes under both include and exclude conditions. During the include condition, participants were instructed to navigate to the correct exit. In contrast, during the exclude condition, participants were told to navigate to the incorrect exit. This procedure (i.e. the process dissociation approach) provides a method for assessing the relative contributions of explicit and implicit memory.

Results: Given the small sample sizes, the effect sizes for memory contributions are likely better indicators of meaningful differences than the inferential statistics are (none of which reached statistical significance). Considering explicit contributions, there were very large effect sizes for maze type (novel < well-learned) and for the interaction between maze type and diagnosis in explicit memory. Specifically, the contribution of explicit memory in aMCI was comparable to HEC for well-learned mazes but not for novel ones. Implicit contributions were comparable between HEC and aMCI regardless of maze type; however, implicit memory contributed more to navigation of well-learned mazes than novel ones.

Discussion: The results support our prediction that implicit memory is preserved in aMCI and appears to play a major role in the navigation of well-known environments. Conversely, explicit memory deficits in aMCI impede the learning of novel environments. These findings support the development of rehabilitation techniques that encourage greater reliance on implicit spatial

memory processes in aMCI. Our conclusions are based on extremely small sample sizes, however, the magnitude of the effects warrants additional study.

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INTRODUCTION

Spatial navigation is a fundamental yet complex function of everyday life. From learning and remembering novel routes to travelling well-learned ones, navigation presents a variety of demands on the brain's ability to encode, retrieve, integrate and manipulate spatial information. Our capacity to do so relies on two distinct yet interactive memory systems: explicit memory and implicit memory.

Explicit memory is the conscious and flexible retrieval of information (Squire & Zola, 1996; Bird & Burgess, 2008; Voss & Paller, 2008). In contrast, implicit memory is the inflexible retrieval of information without conscious awareness (Squire & Zola, 1996; Bird & Burgess, 2008; Voss & Paller, 2008), and is measured via changes in performance. For example, during the first week on campus, a college freshman may have to actively assess the relative locations of his classes and the distances between campus buildings in order to develop routes from one class to another. For the first few days in his new, unfamiliar college world, he will consciously evaluate every choice point in order to determine which path or direction to take. This process is dependent on explicit memory. Eventually however, he will navigate from one class to another by automatically following these well-learned inflexible routes; a process primarily mediated by implicit memory. As alluded to above, explicit memory supports flexible representations of the environment and adaptive navigation such as when encountering detours or developing novel routes. Conversely, implicit memory mediates navigation of fixed routes and is presumably guided by perceptual cues (Wolbers & Hegarty, 2010).

The Hippocampus and Explicit Memory

There is strong evidence to suggest that explicit memory depends upon the hippocampus in particular. The classical example in support of this is the patient H.M., who became densely amnesic after bilateral hippocampectomy (Scoville & Milner, 1957). Although it was eventually discovered that H. M. had additional lesions to neighboring medial temporal lobe structures that may have influenced his memory deficits, a number of studies on human hippocampal lesions have largely corroborated the involvement of the hippocampus in explicit memory (Moscovitch et al, 2006). Neuroimaging in healthy individuals also support these findings; tasks designed to engage the explicit memory system, such as retrieval of remote autobiographical memories, elicit activity in the hippocampus during explicit memory retrieval but not during baseline activities (Rekkas & Constable, 2005; Ryan et al, 2001; Gilboa et al, 2004).

One specific function of hippocampally-mediated explicit memory is the flexible use of spatial memory. In 1971, O'Keefe and Dostrovsky discovered 'place' cells in rodent hippocampi that signaled the spatial location of self and automatically updated with movement. This led to the "cognitive map" theory, which proposed that the hippocampus supports mental representations of the environment and one's location within that environment (O'Keefe & Dostrovsky, 1971; O'Keefe & Nadel, 1978). Existence of place cells in monkeys and humans was confirmed soon after (see Bird and Burgess, 2008 for a review). Interestingly, this relationship may be independent of vision. Functionality of place cells in blind rats is comparable to that in seeing rats (Save et al, 1998). In humans, Fortin et al (2008) demonstrated that blind individuals have significantly larger hippocampi and make fewer mistakes during navigation as compared to blindfolded seeing individuals. These results support the role of the hippocampus in spatial memory.

These studies and others have also suggested that the hippocampus plays a critical role in navigation (Burgess, Maguire & O'Keefe, 2002). More specifically, the hippocampus appears to be particularly important to the initial development and navigation of routes. Functional imaging during human virtual navigation demonstrates greater activity in the anterior hippocampus during early route encoding and posterior hippocampal activity throughout learning (Cornwell et al, 2008; Xu et al, 2010). Similarly, a series of experiments using virtual navigation and neuroimaging demonstrated increased hippocampal activity in London taxi drivers during initial route planning (Maguire et al, 1998; Spiers & Maguire, 2006). In addition, posterior hippocampal volume was enhanced in taxi drivers relative to control subjects and bus drivers, considered controls for navigational experience (Maguire et al, 2000; Maguire, Woollett & Spiers, 2006). This volumetric distinction also correlated with years of experience as a taxi driver (i.e. years of experience in route development). These results further implicate hippocampal involvement in navigational memory and suggest a specific function in early route development and encoding.

Finally, these findings are echoed in human lesion studies. Moscovitch and colleagues' review (2006) of hippocampal lesions in humans noted deficits in spatial memory. A meta-analysis by Kessels et al (2001) on maze learning, spatial working memory and object-location memory after hippocampal lesions in humans consistently found significant impairments in each of these categories. Interestingly, a comparison of patients with unilateral lesions displayed greater impairments on maze learning, object location memory and positional memory in individuals with right hippocampal damage. These results support the importance of the hippocampus in spatial processing and navigational memory in humans.

The Striatum and Implicit Memory

As described earlier, implicit memory is the "influence of past experiences [on] subsequent task performance – unintentionally and without conscious recollection of a learning episode" (Schacter, Chui & Ochsner, 1993). These responses are exhibited through improved performances and do not require use of explicit memory.

The striatum, which mediates inflexible, "automatic" responses to perceptual environmental stimuli, has been implicated in implicit memory (Poldrack et al, 2001). This function of the striatum appears to be particularly important in the navigation of inflexible, well-learned routes (Squire & Zola, 1996, Iaria et al, 2003, Hartley et al, 2003). In fact, Hartley and Burgess (2005) claim that "the caudate is crucial for the acquisition of 'habits' – stereotypical responses to repeatedly reinforced situations, such as learning to turn right at a particular point in a route."

Striatal mediation of implicit spatial memory can be seen in rodents during win-stay and win-shift Morris water maze tests. Rats with striatal lesions are severely impaired at learning the stimulus-response relationship in the win-stay condition (implicit memory) yet show no impairment in the win-shift condition (explicit memory) (Packard & Knowlton, 2002). Conversely, glutamate injections in the caudate nucleus enhanced the use of striatally-mediated response strategy while injections in the hippocampus enhanced the use of hippocampally-mediated spatial strategy in a cross maze navigational task (Packard, 1999). These findings support the striatal mediation of implicit spatial memory.

In humans, damage to the striatum in patients with Parkinson's disease also impairs tests of implicit memory (Moody et al, 2010), as evidenced by diminished performance on a concurrent discrimination task. In addition, striatal damage in Parkinson's disease and Huntington's disease impairs probabilistic classification learning on the weather prediction test (Packard & Knowlton, 2002). The weather prediction test is considered one of the primary tests of implicit memory, as use of explicit memory generally does not enhance performance.

Human studies also confirm striatal mediation of implicit spatial memory processes. A virtual navigation task in which healthy participants learned to navigate to a target location found that enhanced bilateral activity in the striatum correlated with successful retrieval of location after the target was removed (Baumann, Chan & Mattingley, 2010). These findings indicate that implicit memory contributions to spatial navigation are supported by the striatum.

Competitive Interactions Between Memory Systems:

Although research provides strong evidence for hippocampal involvement in explicit memory and striatal involvement in implicit memory, these memory processes are not mutually exclusive and may, in fact, be quite interactive. For example, the college freshman could be following the same invariant route but think ahead to determine whether he will be walking past the cafeteria. However, Poldrack and Packard (2003) proposed that these two neural systems are competitive in nature such that a lesion to one system facilitates processes mediated by the other. This theory is supported by a number of studies that found reciprocal activation between the striatum and hippocampus during a variety of learning tasks, such that activity in one structure was correlated with negative signal change in the other (Poldrack & Rodriguez, 2004). For example, increased hippocampal activity was found during an implicit habit learning tasks in patients with Parkinson's disease (whose striatum are dysfunctional) (Moody et al, 2004).

Notably, reciprocal interactions between the striatum and the hippocampus also appear influence spatial navigational memory. As noted above, explicit memory is critical for the initial formation of a cognitive map and developing routes from one location to another. As routes become invariant and well-learned with practice, navigation is increasingly supported by implicit memory processes (Poldrack & Packard, 2003). This can be seen in virtual navigation tasks in humans in which enhanced hippocampal activity correlated with use of a spatial strategy in early navigation yet additional practice corresponded with reduced hippocampal activity and increased striatal activity (Iaria et al, 2003; Bohbot et al, 2007). Switching from a spatial strategy to a nonspatial strategy or constant use of a nonspatial strategy was also associated with improved performance and enhanced caudate activity. There is strong evidence demonstrating that individuals who are able to switch between spatial and procedural strategies in accordance with task demands are the most successful navigators (Hartley et al, 2003; Bohbot et al, 2007; Etchamendy & Bohbot, 2007). These findings from spatial navigation studies showing variability in hippocampal or striatal activity lend further support to their distinct yet interactive involvement in navigational memory.

Spatial Navigation in HEC & aMCI

Navigational memory is sensitive to the effects of aging (see Moffat 2009 for a review). In addition, degeneration of the hippocampus and associated explicit memory deficits are evident early in the course of Alzheimer's disease. Amnestic mild cognitive impairment (aMCI) is considered a clinical precursor of Alzheimer's disease (AD) (Petersen, 2004). Importantly, early hippocampal atrophy is also characteristic of aMCI and may be used a measure of disease progression (Leung et al, 2010; Morra et al, 2009; Whitwell et al, 2007). However, the structure, integrity and function of striatum remain relatively preserved in aMCI (Madsen et al, 2010, Agosta et al, 2010). These pathological findings are supported by changes in performance since neuropsychological testing shows an early decline in explicit memory but intact implicit memory in AD (Klimkowicz-Mrowiec et al, 2008, Golby et al, 2004). Patients with aMCI also consistently perform worse than healthy elderly controls yet better than patients with early AD on numerous spatial memory tasks, such as self-orientation, route drawing and spatial location (Cushman, Stein and Duffy, 2008). These impairments may impose restrictions on independent living for aMCI such as increasing their risk of getting lost when taking a detour or navigating to an unknown location.

Interestingly, no studies have examined the relative contributions of explicit and implicit memory contributions for navigational memory. One potentially useful method for determining such contributions is the process-dissociation procedure (Jacoby, 1991; Jacoby, Toth & Yonelinas, 1993). The process dissociation approach has been applied to a number of tests of explicit and implicit memory processes, including a famous name judgment task (Wippich, 1994), memory search tasks

(Yonelinas & Jacoby, 1995) and variations of the word-stem completion test (Toth, Reingold & Jacoby, 1994; Adam et al, 2005). It has also been successfully employed in patients with AD (Knight, 1997; Smith & Knight, 2002; Kessels, Feijen & Postma, 2005) and early AD (Koivisto, Portin & Rinne, 1998). This procedure could be particularly useful for determining the extent to which navigational memory deficits are mediated by explicit versus implicit memory in aMCI. Given the documented deficits in aMCI, quantifying the preservation and use of explicit and implicit memory system in navigation may have possible ramifications for designing rehabilitative strategies that promote functional independence in daily life.

In the current study we examined the relative contributions of explicit and implicit memory to spatial navigation in aMCI and healthy elderly controls (HEC). Participants navigated a series of virtual T-mazes until they were well-learned, confirmed by a memory test after a short delay. Participants then viewed videos of navigation through novel and well-learned mazes. Later, the process dissociation procedure was used to assess the explicit and implicit contributions to memory for the novel and well-learned mazes. We expected to see a greater contribution of explicit memory in the HEC for novel mazes, in accordance with the early involvement of explicit memory processes in navigation. In navigation of well-learned mazes, we expected the increased practice to elicit a greater contribution of implicit memory in the HEC. In contrast, we expected early impairments in hippocampal function and explicit memory in the aMCI to support the use of implicit memory. That is, we expected to see comparable or enhanced contributions of implicit memory but impaired explicit memory on both well-learned and novel mazes in the aMCI relative to the HEC.

METHODS

Participants

Six healthy elderly controls (HEC) and eight patients with amnestic mild cognitive impairment (aMCI) were recruited from the Emory University Alzheimer's Disease Research Center (ADRC) and the Atlanta VAMC. HEC were independent in daily living activities and free of subjective and objective memory impairments. Diagnoses of aMCI were made according to Petersen's criteria during a consensus conference attended by neurologists, neuropsychologists and other essential clinical staff (Petersen, 2004). The Institutional Review Boards of Emory University and the Atlanta Veterans Affairs Medical Center (VAMC) approved the study and all participants gave informed consent prior to enrollment.

All HEC and aMCI underwent a brief neuropsychological screening to ensure that the HEC did not demonstrate any memory impairments and the aMCI had not progressed to Alzheimer's disease or reverted to normal. General exclusion criteria included a history of neurological disease or injury, psychiatric disorders, learning or attentional disorders, and current or past alcohol or drug abuse.

We excluded one HEC and three MCI from analyses of the data. The HEC individual failed to learn any of the 15 well-learned mazes during the training portion of the study (defined as less than 80% correct on the last 5 of 15 total training trials given for each maze). Two of the excluded aMCI were reportedly diagnosed with aMCI, but were unable to provide any medical records to warrant such a diagnosis. Additionally, they did not demonstrate any memory deficits on the neuropsychological screening tests. Finally, the third excluded aMCI patient repeatedly fell asleep during the hour of scanning despite repeated attempts to awaken him and restart the task. Thus, a total of 5 HEC and 5 aMCI were included in the analyses.

HEC and aMCI were comparable in terms of demographics and neuropsychological variables, except for immediate and delayed memory (as expected) and education. Demographics and test performances are provided in Table 1.

Experimental Stimuli

The T-maze is commonly accepted in scientific literature as a measure of navigational memory (Poldrack and Packard, 2003; Paul, Magda & Abel, 2009). Additionally, the simple nature of the maze was thought to be appropriate for HEC and aMCI patients. Therefore, we made minor modifications to a standard T-maze to facilitate navigation and restrict participants from seeing the correct exit prior to making a choice (see Appendix A for a maze blueprint). Unique photographs of landscapes were superimposed onto the walls of thirty mazes in order to create realistic immersive environments. Examples of mazes used in the spatial navigation task are shown in Figure 1.

Participants navigated the mazes using a Logitech Attack™ 3 Joystick. The correct exit in each maze was indicated by a green stoplight. Similarly, the incorrect exit was indicated by a red stoplight. We segregated mazes into two lists based on similar features (e.g. geographical landscape, environmental features, color scheme and geometric composition). After completion of the current study, we confirmed that there were no significant differences in training on any of the mazes. MazeSuite software (www.mazesuite.com) was used for maze design, navigational testing, and data collection.

Procedure

After consenting to the study, maze navigation was explained to all participants using a standard set of instructions. We also provided a blueprint of the maze, sample images and a brief written explanation of the task to supplement the verbal instructions (Appendix A). Participants then learned to use a joystick to navigate through two sample mazes during a practice session that simulated the experimental tasks. The practice session ended when participants consistently navigated to the correct exit within approximately 8 seconds. All participants successfully completed the practice session within 25 minutes and reported being ready to begin the training portion of the task.

Participants were trained on one of two lists of mazes that were presented in a counterbalanced manner. Each list was comprised of 15 total mazes, but training was performed on only 3 mazes at a time to facilitate learning, as supported by pilot testing. Participants received a total of 15 trials on each of these 15 mazes (Figure 2), referred to hereafter as the *well-learned mazes* (WL). The other list of mazes is referred to as the *novel mazes*. A 15-minute delay followed the completion of training. After the delay, participants performed a single-trial *short-delay* memory test wherein they were instructed to navigate to the exit in each of the well-learned mazes.

Next, participants viewed 5 pre-recorded videos that depicted navigation through all 30 mazes (i.e. both the well-learned and the novel mazes) (Figure 3). Only navigation to the correct exit was shown during these videos in order to promote learning. Each of the 5 videos contained a total of 6 - 30 second active blocks (3 novel mazes; 3 well-learned mazes) that were separated by 20-second rest blocks (Figure 3). The sequences of active blocks and the orders of mazes within each block were initially randomized in all videos. The order in which videos were presented was also randomized across participants. Although the current study only focuses on the behavioral aspects of the study, 3 HEC and 5 aMCI underwent fMRI scanning while viewing the videos. Those who were unable to undergo fMRI scanning experienced the same procedure in a quiet office. As they viewed the videos, participants were required to indicate the direction traveled within each maze shown (i.e. left or right) either by button press (in the scanner) or using paper and pencil (in the office) to ensure that they were attending to the videos.

Approximately 15 minutes after completion of fMRI scanning (or the behavioral equivalent if performed in an office), participants completed two *long-delay* memory tests for these stimuli in a quiet office. In accordance with the process dissociation procedure (Jacoby, Toth & Yonelinas, 1993), the two long-delay memory tests presented all 30 mazes (i.e. both the well-learned and the novel) in an *include* condition and an *exclude* condition, respectively. As mentioned above, in the include retrieval test, participants were instructed to navigate to the correct exit as they had done previously during training and the short-delay retrieval test. In exclude test, participants were instructed to navigate to the *incorrect* exit (i.e. the one containing the red light). The rationale for these tests is described further below. The overall study design is provided in Figure 4. Finally, we performed two repeated measures analyses of variance (ANOVAs) to compare the main and interaction effects of diagnosis (HEC or aMCI) and maze type (well-learned or novel) on explicit (R) and implicit memory (A) contribution.

Jacoby (1991) recognized that memory tests may not be "process-pure," meaning that tests of explicit memory may be "contaminated" by implicit memory and vice versa. The purpose of the process dissociation procedure, therefore, was to distinguish the true contribution of each memory system. The process dissociation procedure is constructed as follows. Explicit memory is designated as *R* (recollection) and implicit memory is designated as *A* (automatic retrieval) (Jacoby, 1991). In the *include* condition, participants were told to navigate to the correct exit, represented by a green stoplight. Participants navigated successfully if they explicitly remembered the correct exit (R) or if performance was guided by implicit memory (A). In the *exclude* condition, participants were instructed to navigate to the incorrect side, represented by a red stoplight. This required them to consciously recall the correct direction (via explicit memory) and intentionally chose the opposite. Navigation to the green stoplight (opposite of instructions) is considered the contribution of implicit memory to performance in the absence of negative feedback from the explicit memory system. A series of mathematical calculations are then performed using the performances on these two conditions to arrive at R and A values (see Table 4). Implicit memory performances could not be calculated for two participants (one HEC and one aMCI) due to missing data.

RESULTS

None of the following contrasts demonstrated statistical significance. This is hardly surprising, given the very small sample sizes. Therefore, we primarily consider effect sizes when discussing the results of the study, as these will be critical for constructing future studies. All included participants performed at 80% or better on the last 5 learning trials for at least 80% of the mazes. At the end of training, there was no difference between groups ($U = 12.0$, $p = 0.906$, $r = 0.04$) (see Table 6 for a comparison of effect sizes). After a 15 minute delay, a large effect size suggests that aMCI already tended to perform relatively worse than HEC ($U = 5.00$, $p = 0.12$, $r = 0.50$). Data from mazes that were not learned were excluded from analyses.

Explicit Memory (R)

For explicit memory, there was a large main effect of maze type (partial $\eta^2 = 0.431$), due to greater contribution of explicit memory on the well-learned than the novel mazes, and a medium main effect of group (partial $\eta^2 = 0.086$) where explicit memory was relatively greater in the HEC than the aMCI. The interaction effect size was large (partial $\eta^2 = 0.351$) such that the groups demonstrated comparable contributions of explicit memory to the well-learned mazes but a substantially reduced contribution of explicit memory in the aMCI for the novel mazes (Table 2; Figure 5). According to a power analysis (Table 7), 56 total participants would be required for the difference between groups in explicit memory contribution on well-learned mazes to reach significance. In contrast, only 20 total participants would be necessary for the difference in explicit memory contribution on novel mazes to reach statistical significance.

Implicit Memory (A)

For implicit memory, there was a large effect of maze type (partial $\eta^2 = 0.320$) with greater implicit contribution overall to well-learned mazes than to novel ones. However, there was no main effect of group (partial $\eta^2 = 0.004$) and no interaction effect (partial $\eta^2 = 0.002$). These findings indicate comparable contributions of implicit memory in both groups, the magnitude of which was reduced for novel relative to the well-learned mazes (Table 3; Figure 6). In support of this, a power analysis demonstrated that 62,774 total participants total participants would be required for implicit memory contributions to well-learned mazes to become statistically different between groups (Table 7). Likewise, 210 total participants would be required for implicit memory on novel mazes to become statistically different between groups.

Initial fMRI Data

Example fMRI images from one HEC and one aMCI are provided in Figures 7 and 8, respectively. As expected, hippocampal activity during video presentation of novel mazes was enhanced in the HEC but absent in the aMCI. In contrast, during the well-learned mazes, there was increased activity in the caudate nucleus (which is a major component of the striatum) of the aMCI but a lack of caudate activity in the HEC.

DISCUSSION

The purpose of the present study was to examine the relative contributions of implicit and explicit memory to navigation in aMCI and healthy aging. Given that hippocampally-mediated explicit memory is dominant early in navigation while striatally-mediated implicit memory becomes more influential as navigation of routes become invariant and well-learned, we expected to see this same trend in healthy aging. That is, explicit memory would contribute more to navigation of the novel mazes while implicit memory would contribute more navigation of the well-learned mazes in the HEC. However, as early deficits in explicit memory are characteristic of aMCI, we expected to see impaired explicit memory but comparable or enhanced contributions of implicit memory on both well-learned and novel mazes in the aMCI, relative to the HEC. Initial fMRI imaging is consistent with these distinctions (Figures 7 and 8).

Explicit Memory (R)

In the current study we found that explicit memory contributions were comparable between the HEC and the aMCI for well-learned mazes, but substantially diminished in the aMCI for novel mazes. The impaired explicit memory in the aMCI patients is consistent with previous studies demonstrating poor performance in aMCI on spatial memory tasks that are sensitive to explicit memory deficits (Cushman, Stein & Duffy, 2008). Considering that explicit memory processes are involved early in route encoding during navigation (Cornwell et al, 2008; for a review see Burgess, Maguire & O'Keefe, 2002), our finding of specific explicit memory impairment in aMCI for novel mazes is consistent with such previous work. This supports our prediction that explicit memory would be impaired in aMCI relative to controls as well as our distinction between maze types, such that novel mazes would promote greater use of explicit memory.

The similar contribution of explicit memory between well-learned and novel mazes in the HEC did not match our prediction that explicit memory would be relatively greater for novel mazes and reduced for well-learned mazes. In addition, the contribution of explicit memory was comparable between the HEC and the aMCI on well-learned mazes. However, these findings may be explained by the multiple trace theory (Nadel & Moscovitch, 1997), which states that memory acquisition and retrieval are dependent on the medial temporal lobe. Each time a memory is retrieved, the MTL supports the creation of a "memory trace." The addition of multiple memory traces strengthens the memory, such that repeated practice makes information become both more resistant to degradation and more accessible for retrieval by the explicit memory system. Thus, when directly requested to navigate to the correct side, HEC participants were able to explicitly recall the correct direction on both maze types while the aMCI were only able to do so on the well-learned mazes.

Implicit Memory (A)

Implicit memory contributions were comparable in the HEC and the aMCI for both maze types. This finding supports our prediction that the contribution of implicit memory to spatial navigation is equivalent between groups or greater in the aMCI. In addition, between maze types, implicit memory contributed more to well-learned mazes than novel ones in both groups. Here also our findings supported our prediction that retrieval of well-learned mazes would promote greater use of implicit memory, in accordance with the practice-enhanced involvement of striatally-mediated implicit memory processes in spatial navigation (Poldrack & Packard, 2003). Together, these findings also coincide with previous studies indicating that implicit memory supports spatial navigation (Baumann, Chan & Mattingley, 2010) and is preserved in aMCI (Klimkowicz-Mrowiec et al, 2008). In consideration of memory traces, it is possible that memories are ultimately represented in the cortex, thus allowing for access by both the striatally-mediated implicit memory system and hippocampally-mediated explicit memory system (Winocur, Moscovitch & Bontempi, 2010). In addition, the preservation of implicit memory in aMCI has important ramifications for designing potential rehabilitative strategies to overcome explicit memory deficits via use of the implicit memory system. In fact, neuroimaging studies in humans strongly indicate that individuals who are able to switch between explicit and implicit memory strategies are the most successful during navigation (Hartley et al, 2003; Bohbot et al, 2007; Etchamendy & Bohbot, 2007).

Limitations

As mentioned before, the greatest limitation to the current study was sample size, which necessitated our focus on effect sizes. However, the results provided important initial findings that warrant further exploration, as evidenced by the power analyses. It is also possible that a more complex environment would be more sensitive to existing navigational deficits. Other virtual navigation studies have overcome this obstacle by increasing choices and adding features that allow for more elaborate and realistic navigation tasks (Rosenbaum et al, 2004). However, we purposefully examined performance in a T-maze because it has a robust history in neuroscience and its simplicity allows patients to perform at a reasonably high level.

Future Directions

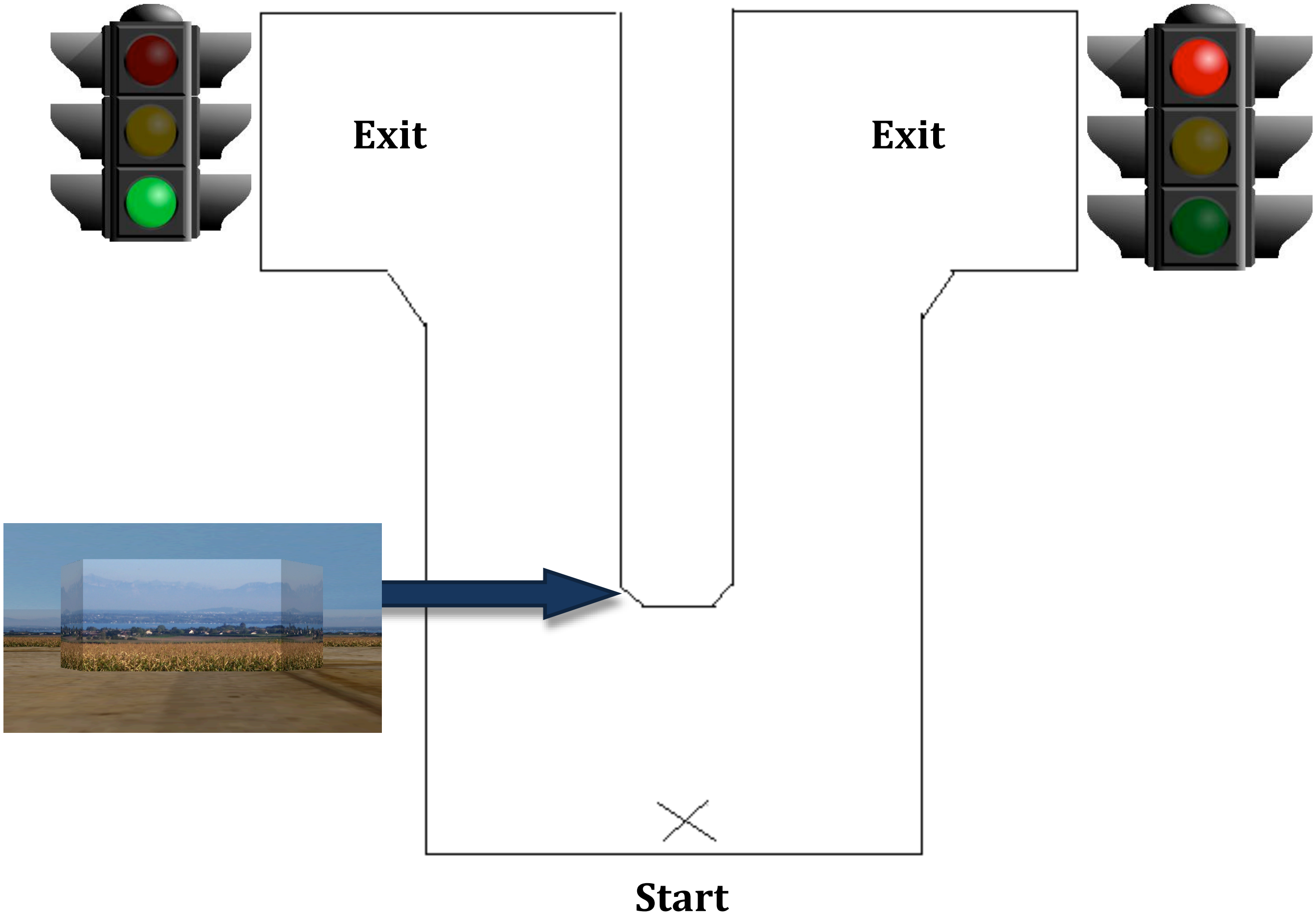
Additional studies may find it useful to compare three maze types using an experience-dependent model (i.e. novel, intermediate experience and well-learned mazes) to better capture the time-dependent interactions between processes mediated by the hippocampus and striatum in navigation. In addition, to reduce the high baseline chance of accurate performance in a T-maze, a multi-option maze, such as a radial arm maze or cross-maze may be useful. These mazes have been used successfully to test navigational memory in young healthy individuals (Bohbot et al, 2007) and in rodents (Packard, 1991), respectively. However, in light of the difficulties some of the participants had in the present study with only two choice options, these types of mazes may prove to be too difficult for HEC and aMCI. Another useful modification of this study could include virtual navigation (as opposed to attending to videos using button pressing) of well-learned and novel mazes during scanning. Alternatively, if the button presses cued the direction of maze navigation in the videos, this could achieve a similar benefit with minor adaptations to the navigation software. Finally, neuroimaging during encoding and retrieval would also allow for greater examination of neural substrates involved in navigation in healthy aging and aMCI.

CONCLUSION

The results of the current study are suggestive of important differences and similarities in HEC and aMCI, in terms of in memory contributions to spatial navigation, and warrant additional examination using larger group sample sizes. In accordance with our predictions and previous studies, explicit memory is impaired, particularly on novel mazes, in aMCI. Conversely, implicit memory for spatial navigation.is preserved in aMCI. These findings hold valuable implications designing rehabilitative strategies that promote greater use of implicit memory in aMCI during navigation. Finally, virtual navigation and the process dissociation procedure are useful methods for distinguishing between the concurrent explicit and implicit memory contributions to performance in HEC and aMCI.

Appendix A

****Note- the 'correct' side will vary, depending on the maze environment. I.e. some correct exits will be on the right-hand side***



Goal: Determine the 'correct side' associated with each maze environment

Correct = Green Light
Incorrect = Red Light

Each maze will be repeated multiple times so you can learn it.

You have 8 seconds per maze to make a decision to go to the left or right.

Figure 1. Immersive maze environments used for the spatial navigation

Figure 2.

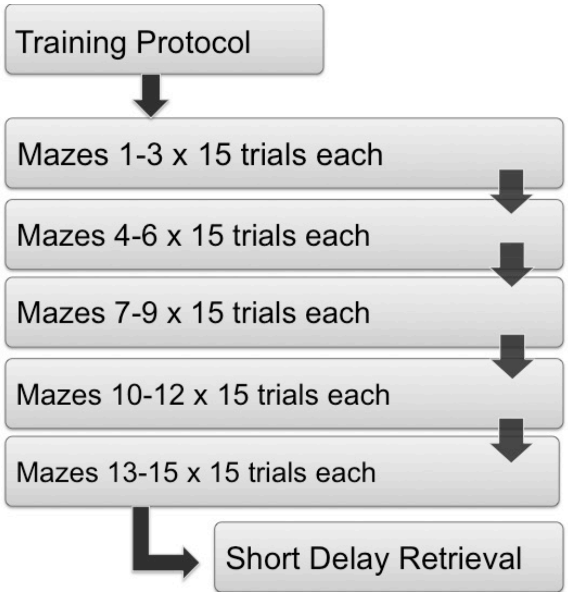

Training Protocol
Mazes 1-3 x 15 trials each
Mazes 4-6 x 15 trials each
Mazes 7-9 x 15 trials each
Mazes 10-12 x 15 trials each
Mazes 13-15 x 15 trials each
Short Delay Retrieval

Figure 3. Presentation of mazes during videos

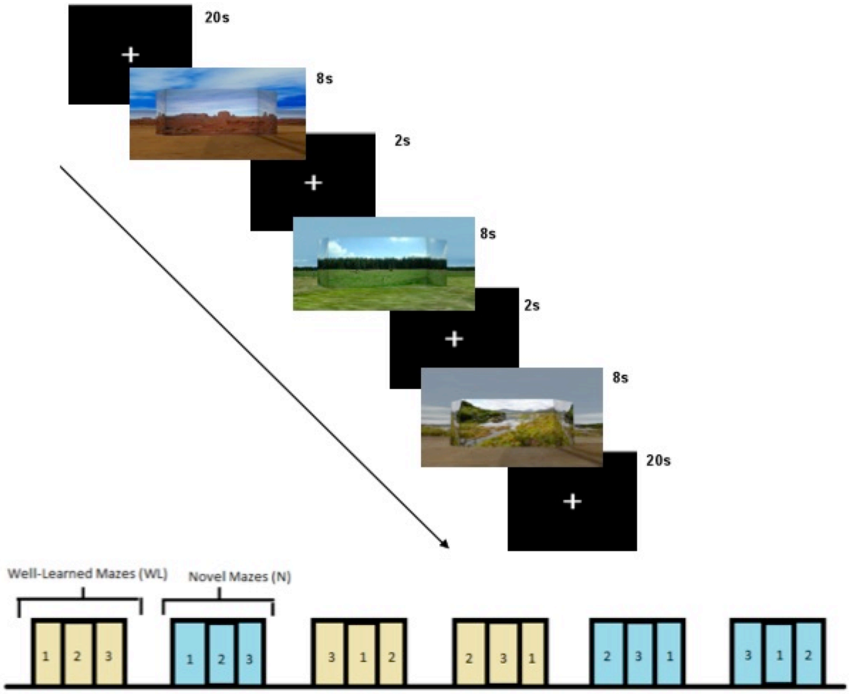


Figure 4. Sequence of tasks

Table 1. Demographic and neuropsychological data for HEC and aMCI. Standard deviations are given in parentheses. Significant differences on t-tests are indicated by *. MMSE = Mini-Mental State Exam, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, WCST = Wisconsin Card Sorting Task, GDS - Geriatric Depression Scale and FAQ = Functional Activities Questionnaire.

	HEC (n=5)	aMCI (n=5)	t(6)	p-value
Age	67.0 (4.7)	72.4 (8.2)	1.28	0.24
Education (years)*	16.6 (0.89)	18.8 (1.3)	3.11	<0.05
MMSE	29.8 (0.45)	28.8 (1.3)	1.62	0.17
WAIS-III Information Subtest	13.7 (1.5)	13.5 (0.58)	0.21	0.85
RBANS Indices (Standard Scores)				
Immediate Memory*	113.8 (6.1)	80.2 (20.8)	3.47	<0.01
Visuospatial/construction	101.4 (13.0)	106.2 (13.7)	-0.57	0.59
Language	98.8 (14.0)	94.0 (9.8)	0.63	0.55
Attention	108.4 (9.3)	96.4 (10.0)	1.96	0.09
Delayed Memory*	111.2 (13.7)	84.2 (10.9)	3.44	<0.01
Total Score*	108.6 (7.7)	88.4 (7.8)	4.11	<0.01
Trails A (T-score)	53.2 (9.1)	50.8 (9.5)	0.39	0.71
Trials B (T-score)	48.2 (8.1)	42.5 (5.8)	1.18	0.28
WCST - Number of Sorts Completed	4.20 (1.1)	4.50 (1.00)	-0.42	0.69
WCST - Total Number of Errors	16.4 (6.2)	15.8 (6.3)	0.16	0.88
WCST - Number of Perseverative Errors	3.80 (3.63)	4.25 (5.3)	-0.15	0.88
WCST - Number of Set Loss Errors	1.20 (0.45)	1.00(0.82)	0.47	0.65
GDS *	0.20 (0.45)	1.60 (1.1)	2.56	<0.05
FAQ	0.00 (0.0)	3.25 (4.0)	1.65	0.2

**Note - WAIS-III Information Subtest had 3 HEC and 4 MCI; Trails A & B, WCST, GDS and FAQ had 5 HEC and 4 MCI.*

Table 2. Explicit memory contributions in HEC and aMCI on well-learned and novel mazes

Explicit Memory	F(1,6)	p-value	Partial η^2
Maze Type	4.54	0.08	0.43
Diagnosis	0.57	0.48	0.09
Maze Type*Diagnosis	3.25	0.12	0.35

**HEC (n=4), aMCI (n=4)*

Table 3. Implicit memory contributions in HEC and aMCI on well-learned and novel mazes

Implicit Memory	F(1,6)	p-value	Partial η^2
Maze Type	2.81	0.14	0.32
Diagnosis	0.025	0.88	0.004
Maze Type*Diagnosis	0.012	0.92	0.002

**HEC (n=4), aMCI (n=4)*

Table 4. Process Dissociation Calculations

$$\text{Include} = R + A(1-R)$$

$$\text{Exclude} = A(1-R)$$

$$R = \text{Include} - \text{Exclude}$$

$$A = \text{Exclude}/(1-R)$$

Table 5. Mean contributions of memory in HEC and aMCI.

	HEC (n=4)	aMCI (n=4)
Explicit Memory (R)		
Well-Learned Mazes	0.525 (0.36)	0.615 (0.29)
Novel Mazes	0.483 (0.22)	0.117 (0.37)
Implicit Memory (A)		
Well-Learned Mazes	0.688 (0.28)	0.690 (0.25)
Novel Mazes	0.497 (0.06)	0.523 (0.11)

Figure 5.

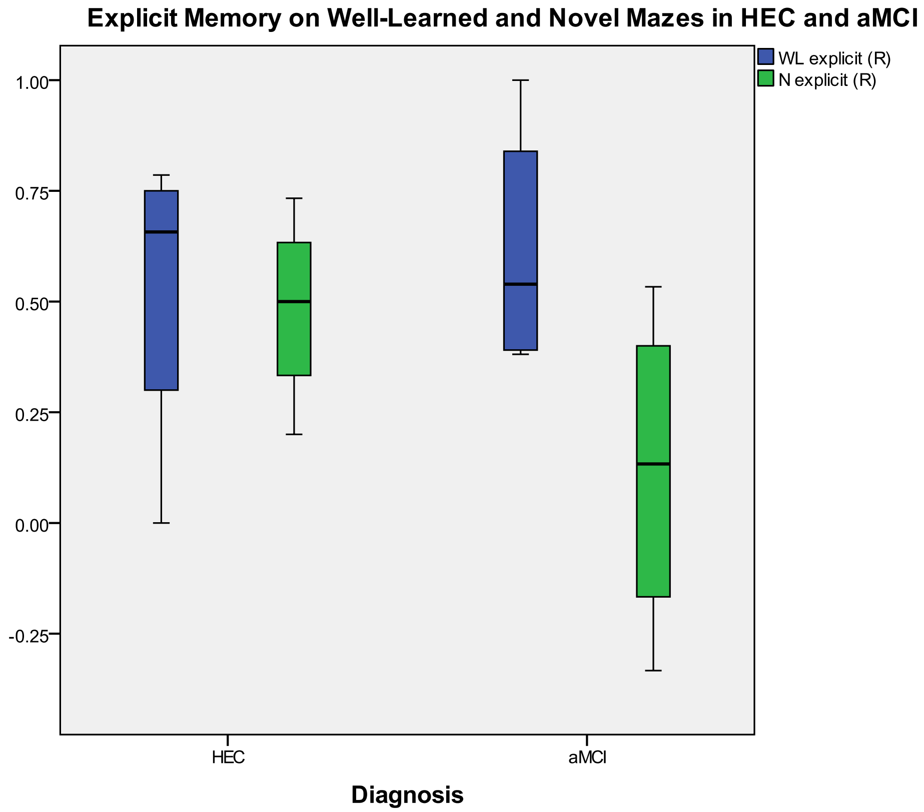

Explicit Memory on Well-Learned and Novel Mazes in HEC and aMCI
WL explicit (R)
N explicit (R)
1.00
0.75
0.50
0.25
0.00
-0.25
HEC
aMCI
Diagnosis

Figure 6.

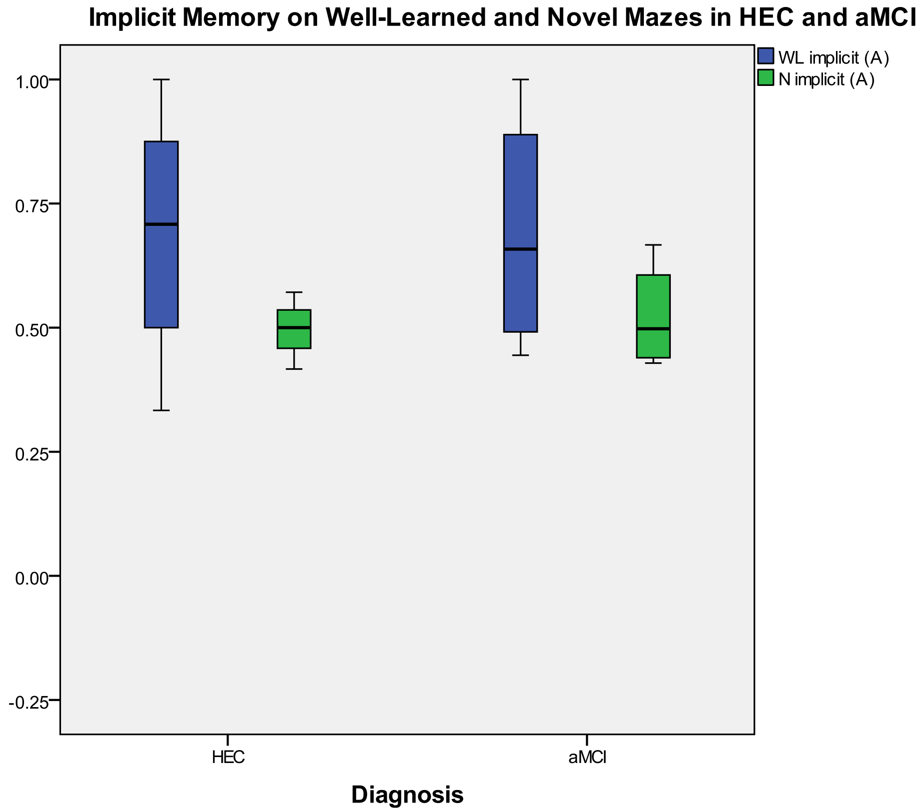

Implicit Memory on Well-Learned and Novel Mazes in HEC and aMCI
WL implicit (A)
N implicit (A)
1.00
0.75
0.50
0.25
0.00
-0.25
HEC
aMCI
Diagnosis

Table 6. A comparison of effect sizes according to Cohen (1988)

Effect Size	Cohen's d	Pearson's r	Partial η^2
Small	0.2	0.1	0.0099
Medium	0.5	0.243	0.0588
Large	0.8	0.371	0.1379

Figure 7. *Sample fMRI imaging from one HEC.* For the novel > well-learned maze type contrast, the hippocampus was active for novel mazes but not for well-learned ones. Activity in the striatum was absent for both novel and well-learned mazes. Warm colors indicated novel mazes and cool colors indicate well-learned mazes.

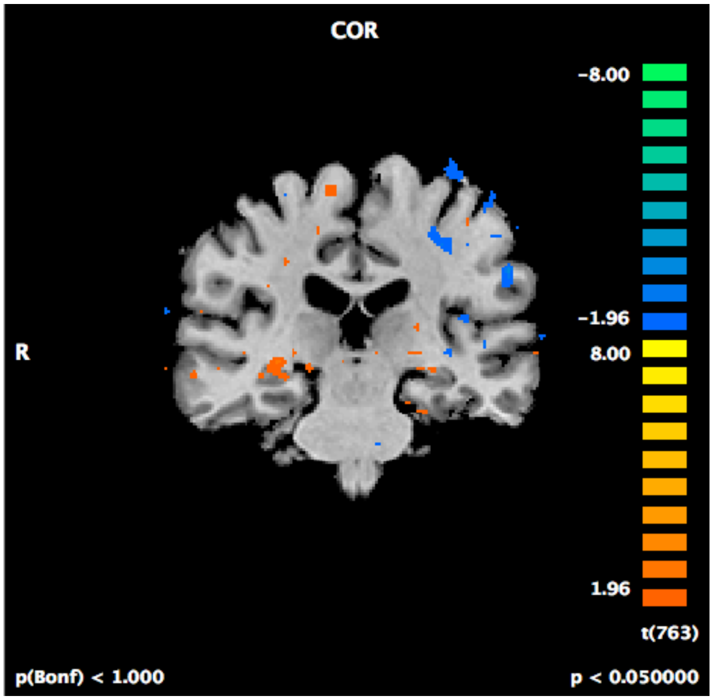


Figure 8. *Sample fMRI imaging from one aMCI.* For the novel > well-learned maze type contrast, the striatum, specifically the head of the caudate nucleus, was active for well-learned mazes but not for novel ones. Activity in the hippocampus was absent for both novel and well-learned mazes. Warm colors indicated novel mazes and cool colors indicate well-learned mazes.

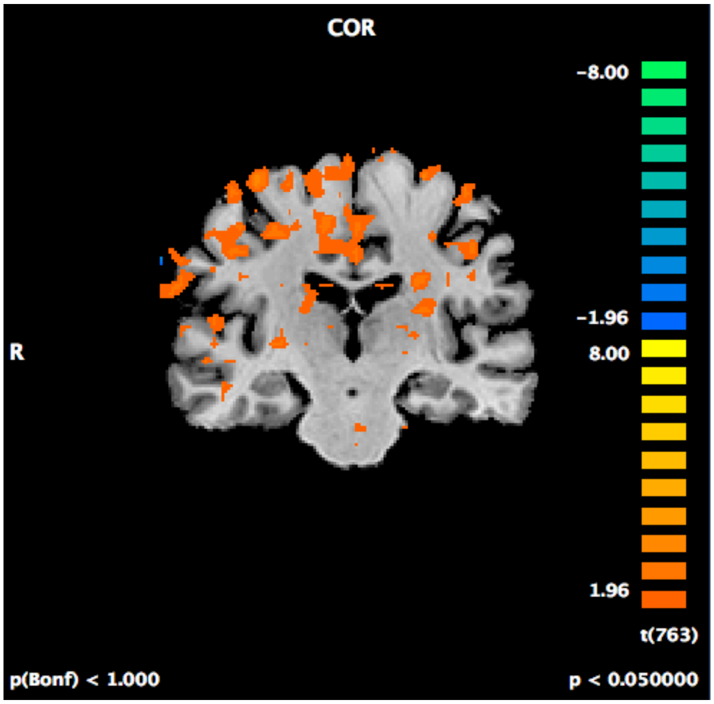


Table 7. A power analysis for the estimation of sample sizes required for statistical significance (p<.05) at a power of 0.8.

	Total N	Effect size F	Correlation Between Repeated Measures
Explicit Memory			
Well-Learned Mazes	56	0.147	-0.137
Novel Mazes	20	0.533	0.515
Implicit Memory			
Well-Learned Mazes	62,774	0.006	-0.006
Novel Mazes	210	0.154	0.498

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