THE EFFECTS OF PRIOR KNOWLEDGE ON MNEMONIC DISCRIMINATION IN YOUNG AND OLDER ADULTS, AND IN HIPPOCAMPAL AMNESIA

SARA PISHDADIAN

A THESIS SUBMITTED TO

THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE

OF MASTER OF ARTS

GRADUATE PROGRAM IN PSYCHOLOGY
YORK UNIVERSITY
TORONTO, ONTARIO

August, 2018

© Sara Pishdadian, 2018

Abstract

The hippocampus is critical to discriminating between newly learned, highly similar stimuli; less clear is its role in discriminating representations based on prior knowledge. In this study, young adults, older adults divided by performance on a cognitive screening measure, and people with hippocampal amnesia were asked to discriminate between pairs of real-world familiar landmarks and well-known animals using the metrics of geographical distance and size. Results showed all participants had lower accuracy for judgments with more similar item pairs. Low-performing older adults showed selectively worse performance on judgments with more similar item pairs. Amnesic individuals' performance appeared to depend on lesion location. Only patient BL, who has selective bilateral dentate gyrus lesions, had difficulty on the landmark task when judging between highly similar distances. These results reinforce the importance of investigating representation similarity, even for well-established representations, and offer insight into mnemonic discrimination across the lifespan and within amnesia.

Acknowledgements

I would like to thank my supervisor, Dr. Shayna Rosenbaum, for her continuous encouragement, support, and guidance over these past two years. I feel extremely fortunate to have a scientific mentor whom I admire, and I look forward to continuing to learn from her. I would also like to thank, Dr. Morris Moscovitch, for his scientific acumen, patience, and encouragement over the years. I feel very fortunate to have joined his laboratory as an undergraduate student years ago. I also would like to thank my thesis committee members, Drs. Dale Stevens, and Lauren Sergio for their helpful comments and questions. I have been very lucky to have received great support, advice, friendship, and had many valuable theoretical discussions from current and former members of the Rosenbaum Memory Lab.

I would like to thank Amanda D'Avanzo for her tireless effort with participant recruitment and screening and Dr. Eva Svodoba for her administration, scoring, and sharing of patient JD's neuropsychological testing findings. Thank you to Katherine Herdman for her assistance in administering neuropsychological tests to JD. Thank you to Dr. Rob Cribbie and Graham McCreath for assisting with data analysis.

I am grateful of all participants' who gave time to this research, especially B.L., D.A., and J.D. This work was supported by an NSERC grant awarded to R.S.R. and to a CIHR grant awarded to M.M. and R.S.R. S.P. acknowledges support from a Canadian Institutes of Health Research (CIHR) Master's Award and Ontario Graduate Scholarship (OGS) award.

Thank you to Fernando Monge-Loria, who has offered me immeasurable support, motivation, and unconditional love during my pursuit of this degree. I would also like to thank my parents, Hamed Pishdadian and Carmela Papandrea, for their unwavering belief in me and for always inspiring me to pursue my ambitions.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Introduction

The hippocampus, a brain region located in the medial temporal lobe (MTL), is involved in episodic memory. Neuroimaging and patient research that have used both laboratory stimuli, such as word lists, and naturalistic stimuli, such as film clips and autobiographical events, have demonstrated that the hippocampus is critical to episodic memory, whether the episodes were experienced recently or in the remote past (Moscovitch et al., 2016). Indeed, the more detail recollected from episodic memory and the greater the recollective re-experiencing, the higher the likelihood of increased hippocampal activation (Moscovitch et al., 2016). This role of the hippocampus in episodic re-experiencing appears to differ from its more temporary role in supporting at least some types of semantic memories, including general knowledge. Patients with hippocampal amnesia and corresponding episodic memory impairments are known to have relatively intact remote semantic memory (e.g., Westmacott & Moscovitch, 2001; evidence against from Manns et al., 2003). Research has shown that patients with extensive adult-onset hippocampal damage are able to retain knowledge of famous names and vocabulary words learned long ago, with additional evidence of postmorbid semantic learning (Tulving, Hayman, & Macdonald, 1991; Westmacott & Moscovitch, 2001). Work with patients with hippocampal amnesia, Alzheimer's Disease (AD), and Semantic Dementia suggests that knowledge of concepts can consist of non-contextual semantic components and sometimes an autobiographical, episodic component (Westmacott et al., 2003; Renoult et al., 2012). This research highlights how semantic knowledge may be influenced by episodic processes via the hippocampus, and the intertwined nature of semantic and episodic memory. The differential role of the hippocampus in episodic versus semantic memory appears to also apply to remote spatial memory: more detailed representations of places navigated long ago depend on the hippocampus, whereas more schematic or gist-like representations of the same environments do not (Herdman et al., 2015).

The hippocampus is required for yet another process that may or may not be orthogonal to the other forms of memory mentioned: mnemonic discrimination, the ability to discriminate between similar items or events in memory. This project aimed to better understand whether mnemonic discrimination operates on prior knowledge previously encoded, specifically, spatial and semantic memory representations. To examine this relationship, this thesis studied

mnemonic discrimination processes on semantic memories of well-known environments and common animals.

Hippocampus and Spatial Memory

Past studies indicate a necessary role for the hippocampus in some types of spatial memory. According to the Cognitive Map Theory (CMT), the hippocampus is necessary for supporting an allocentric mental representation of the external world (O'Keefe, 1990; right hippocampus Burgess et al., 2002). Allocentric mental representations are not dependent on the subject's location in space; instead the representations contain the locations of objects or landmarks in relation to one other. In contrast, egocentric representations vary based on the perspective of the viewer in relation to objects in space, and engage the parietal cortex (Burgess et al., 2002). While predictions of this theory appear to be supported by findings of hippocampal involvement in recent spatial memories for newly encountered environments, CMT cannot fully account for findings of spared remote allocentric spatial memories of environments learned long ago in patients with hippocampal damage (Herdman et al., 2015; Rosenbaum et al., 2000, 2005).

Evidence for the involvement of the hippocampus in distance judgments in humans comes from multiple sources. In one study, participants with a minimum of a year experience with their university campus viewed photos of prominent landmarks in an fMRI scanner and pressed a button when they identified each landmark (Morgan et al., 2011). Landmarks were repeated across different photos. The results showed that when landmarks were repeated, there was an attenuation in fMRI response in the parahippocampal place area and retrosplenial cortex, as well as adaptation in the left superior lingual gyrus and left medial retrosplenial region (Morgan et al., 2011). Further analyses showed that participants' subjective distance judgments (which were highly correlated with the objective distances) were related to activity in the left anterior hippocampus. The authors proposed that the hippocampus is automatically involved in distance-related effects since participants were not given a specific navigational task. The authors interpreted the results as demonstrating a response of the hippocampus to the 'mismatch' between spatial locations of presented landmarks (Morgan et al., 2011). In our task, participants were asked to make distance judgments in a familiar environment between pairs of landmarks to a cue, which theoretically should also invoke the hippocampus if the hippocampus codes distances between landmarks. Interestingly, previous work with vector mapping has found that amnesic patients K.C. and D.A. were intact compared to controls (Herdman et al., 2015).

However, the hippocampus does appear to be needed for representing spatial details contained within well-known environments when recounting well-traveled routes verbally or when drawing maps (Herdman et al., 2015). The Multiple Trace theory (MTT) suggests that the hippocampus is required whenever detailed representations are needed in memory, whether spatial or episodic in nature (Moscovitch et al., 2005; Moscovitch et al., 2006). In remote spatial memory, basic knowledge of maps, which appears to be sufficient for navigation, is conceptualized as schematic or semantic-like, and does not appear to depend on the hippocampus for retrieval. By contrast, fine-grained details contained within well-known environments, such as the identity of landmarks or visual features incidental to navigation, always depend on the hippocampus (Rosenbaum et al., 2001).

Another influential theory of the role of hippocampus in spatial memory, derived from CMT, is the Scene Construction Theory. According to this theory, the hippocampus is involved in the construction of scene representations and plays a larger role in creating models of the environment (Zeidman & Maguire, 2016). The medial anterior hippocampus and the subiculum are viewed as particularly necessary when remote spatial knowledge is required, as this region is believed to integrate information from various regions of cortex (Zeidman & Maguire, 2016). This theory has been criticized for its lack of specificity in describing what constitutes a scene and for neglecting to elaborate on how these scene constructions relate to allocentric spatial representations as initially proposed in CMT (Ekstrom & Raganath, 2017). As an alternative, Ekstrom and Raganath have proposed that the hippocampus represents stable, regular information within its 4-D spatiotemporal framework and then revises this framework according to environmental demands. This theory differs from the CMT as it proposes that the hippocampus prioritizes spatial and temporal processing and that additional information is integrated depending on what is needed in the moment.

All the above theories propose that the hippocampus is playing a critical role in spatial memory and, as such, can help account for changes in strategy use in typical aging, which involves a shift from reliance on allocentric strategies to greater use of egocentric strategies, which are non-hippocampally based (Colombo et al., 2017). This age-related pattern has been attributed to changes in hippocampal structure and function, as well as declines in executive function that affect the ability to switch between hippocampal-based strategies (Colombo et al. 2017). Proponents of the above theoretical frameworks would likely predict that aging would be

associated with spatial representations that are lacking in either detail in their construction or spatiotemporal specificity. This project helps elaborate on how older adults' representations of well-known spatial environments may differ from younger adults' representations.

Mnemonic Discrimination

In a literature that has developed largely independently of the CMT literature, the hippocampus is also implicated in pattern separation. Pattern separation, expressed behaviourally as mnemonic discrimination, is the ability to discriminate between overlapping or similar items and events as they are encoded. At a neural level, projections from the entorhinal cortex reach the granule cells in the dentate gyrus (DG) via this perforant pathway and in turn, the granule cells also project to the CA3 cells via mossy fibers (Rolls, 2016). Mossy fibers are unmyelinated axon cells with large boutons which are related to collaterals within the polymorphic layer of the DG before entering the CA3 (Amaral et al., 2008). Projections begin in the DG and project to the CA3 via the mossy fibers; the Schaffer collaterals then project from the CA3 to the CA1 (Van Strien et al., 2009). The perforant pathway links the entorhinal cortex with the hippocampus, with the strongest projections reaching the DG of the hippocampus and weaker projections to the CA1 and CA2 subfields and subiculum (Kivisaari et al., 2013). In Rolls' theory of hippocampal function, it is proposed that the relatively small number of mossy fiber connections into CA3 creates a sparse signal and a randomizing effect on CA3 representations, physically separating representations (Rolls, 2016). These unstructured, separated CA3 representations are proposed to allow for the storage of many memories in the CA3 and allow for interference between representations to be kept to a minimum (Rolls, 2016). The sparse signal produced through DG mossy fiber connections to the CA3 is hypothesized to allow for this process of pattern separation or mnemonic discrimination (also named orthogonalization), whereby similar memories or representations are differentiated from one another (Rolls, 2016).

The Mnemonic Similarity Task

A staple behavioural test of pattern separation (mnemonic discrimination) in humans is the Mnemonic Similarity Task (MST; Bakker al., 2008). The MST has been tested across multiple task variations and has shown to be reliable (Stark et al., 2015). In this task, participants first engage in incidental encoding of everyday objects on a computer. Participants are then presented with new objects that resemble studied objects (i.e., "lures"), previously studied objects (i.e., "targets"), and novel objects that differ from studied objects (i.e., "foils").

Behaviourally, participants have the greatest difficulty discriminating lures from studied targets, a finding that is heightened in healthy older adults relative to younger adults, and even more so in individuals diagnosed with amnestic Mild Cognitive Impairment (aMCI) and AD (Yassa & Stark., 2011). This pattern of performance is reflected in greater activation within the DG and CA3 in an fMRI study of young adults (Bakker et al. 2008). This finding received direct support in a recent human lesion study, in which a patient with selective lesions to his DG showed impaired pattern separation relative to age-matched controls on the MST (Baker et al., 2016).

In a review of the role of the hippocampus in pattern separation, Yassa and Stark (2011) concluded that aging is associated with a shift from a bias for pattern separation to a bias for pattern completion. This bias is linked to elevated firing in the CA3 and thought to result in a preference for previous associations, favoring the associative network of pattern completion (Yassa & Stark, 2011). Experimental evidence using the MST shows declines in pattern separation in healthy adults across the lifespan, from 20 years to 89 years (Stark et al., 2013). In healthy adults over the age of 60, performance on the MST and measures of episodic memory are positively correlated (Stark et al., 2013). These findings are consistent with well-established age-related declines in memory linked to hippocampal dysfunction (Small, 2001). There is evidence that drug treatments reducing hippocampal hyperactivity in the CA3 and DG in patients with MCI (a condition which often progresses to AD) are associated with improvements in cognition and improvements on the MST (Bakker et al., 2012). To investigate age-related effects on pattern separation within prior knowledge we recruited participants across the lifespan and tested all participants on the MST.

Mnemonic Discrimination and Episodic Memory

The role of the hippocampal subfields CA_3 and DG in pattern separation has figured in experiments on episodic memory. In one fMRI study, participants recalled recent (2-3 weeks prior) and remote (10 years prior) autobiographical memories (Bonnici et al., 2013). Critically, the recent and remote memories analyzed were matched on features that would be associated with recollective, episodic re-experiencing (i.e., ease of recall, vividness, amount of detail). Results showed that remote autobiographical memories were significantly better classified in the CA_3 and DG (Bonnici et al., 2013). The study supports the involvement of the hippocampal subfields in vivid re-experiencing of autobiographical events, even within remote memories (Bonnici et al., 2013).

Recent work has also shown that DG/$CA_{2/3}$ volumes are positively correlated with remote and recent real-world episodic memories (Palombo et al., 2017). The authors used the Autobiographical Memory Interview and found that internal details of autobiographical memories, which are synonymous with episodic re-experiencing, were positively correlated with subiculum as well as DG/$CA_{2/3}$ volume (Palombo et al., 2017). Both studies support the idea that rich detail in remote episodic memories may be represented in the CA_3/DG regions, but neither study examined mnemonic discrimination within these memories. Using film clips with overlapping events and contexts, Chadwick et al. (2014) found that CA_3 volume predicted participants' subjective feelings of confusion and CA_3 neural interference or voxel overlap. This work supports the involvement of the CA_3 in the process of mnemonic discrimination (pattern separation) and pattern completion for rich, episodic-like stimuli (Chadwick et al., 2014).

Taken together, this research bridges the episodic memory and mnemonic discrimination literatures under their shared neural substrate of the DG/CA_3. How specifically mnemonic discrimination is implicated in these processes, however, remains speculative. One possibility is that it is needed to represent detailed episodic memories with overlapping elements to reduce interference among them.

One study aimed to investigate how overlapping context may influence the involvement of the hippocampus. Participants learned artificial city environments differing in the degree of overlapping spatial context, which was manipulated by shared or unique geometry and store locations (Kyle et al., 2015). Results showed that participants were more likely to become confused learning the city with the most overlap with store locations and making errors to the similar cities (Kyle et al., 2015). Pattern classification through a searchlight classifier throughout the MTL found a cluster in the left CA3/DG and CA1 of the hippocampus which classified city identity above chance for all but the city highest in interference. Results showed that the interference city was often misclassified as one of the two similar cities, consistent with behavioural findings of confusion. These results are consistent with a pattern separation explanation of the findings, as this city did not have distinct representation from the other cities (Kyle et al., 2015). This study offers support that the DG/CA_3 is involved in separating out similar representations for spatial information in healthy young adults.

In summary, there is substantial evidence for the importance of hippocampal subregions in representing fine-grained details, but not schematic or gist-like information, in remote spatial

and episodic memory. Additionally, the hippocampus, including the DG/CA_3, has been implicated in the process of mnemonic discrimination or pattern separation in multiple paradigms. These functions may interact with one another, as indicated by a recent finding that these subregions' volumes are correlated with level of episodic memory detail in autobiographical memories (Palomba et al., 2017). One possibility is that the DG is critical when mnemonic discrimination operates on detailed information, even if the information is part of one's prior knowledge within remote semantic memory.

Current Study

In this study, we hypothesize that the ability to discriminate between highly similar representations, even within otherwise preserved remote spatial or semantic memory, will be impaired with hippocampal damage to the DG/$CA_{2/3}$ when the process of pattern separation (mnemonic discrimination) is required to discriminate highly similar stimuli. Likewise, older adults, who, on average, show an age-related shift in bias from pattern separation towards pattern completion, are predicted to have greater difficulty than younger adults in mnemonic discrimination within remote memory. Given the preservation of remote spatial memory and semantic knowledge within aging, we predict that a subset of our older adults showing potential cognitive impairment may show this effect.

To address these hypotheses, we will investigate remote spatial memory and semantic knowledge with a task that involves mnemonic discrimination in neurotypical younger and older adults, older adults identified as "at-risk" of developing AD or other dementias (defined below), and individuals with amnesia likely due to hippocampal damage, including a patient with selective lesions to the DG. The remote spatial memory task is a distance discrimination task or vector mapping task, in which participants are asked to judge the proximity of pairs of well-known Toronto landmarks, with distances between one pair closer or farther apart from those of another pair. For example, participants are asked to decide whether Toronto Eaton Centre or the Art Gallery of Ontario is closer in distance to the CN Tower. For those familiar with the city, this would be a more difficult judgment than deciding whether the Toronto Eaton Centre or Bata Shoe Museum is closer to the CN Tower. We hypothesize that this task tests one's mnemonic discrimination abilities in remote spatial memory.

To investigate whether mnemonic discrimination operates within prior knowledge beyond spatial information, we used animal stimuli in a similar manner to landmark stimuli.

Animal knowledge is a commonly measured aspect of semantic memory that is known to be impacted by Semantic Dementia and other conditions which impact conceptual knowledge (Patterson et al., 2007; Binder et a., 2009). Animals offer a good contrast to landmark stimuli, as they are visually rich, have associated functions, and are well-known. In this study, participants were asked to decide which of two well-known animals is closer in size to a target animal. Using animal judgments in a similar manner to landmark judgments, with size as a metric instead of distance, allows us to see if the pattern of performance differs based on stimulus type. We predict that if there is a high similarity in size between the two cues and the target, there will be a greater requirement for mnemonic discrimination, and therefore lower performance accuracy. Given the relative lack of hippocampal involvement in semantic memory and its general preservation in aging, we would predict that these judgments will not be as difficult as the landmark judgments and amnesic patients should not be impaired relative to controls. We predict that at-risk older adults will show impairments on the highly similar judgments given the potential for abnormal aging (defined below) and therefore impaired semantic knowledge (Patterson et al., 2007).

We predict that at-risk older adults and amnesic cases, including an individual with DG lesions, will show impairments on high similarity trials compared to healthy younger adults. We predict that healthy older adults and healthy young adults will show similar performance on the task for judgments that rely on schematic, gist-like knowledge and do not require mnemonic discrimination. This prediction stems from previous work showing intact semantic and gist-like knowledge in older adult participants for spatial information (Rosenbaum et al., 2004). However, for judgments with highly similar information, older adults should show worse performance, specifically on the landmark remote spatial memory task, which we hypothesize involves the hippocampus to a greater degree than the other tasks. If at-risk older adults show decreased performance on high-similarity trials compared to the healthy older adults, we propose that these results would reflect the activation of DG/CA_3 when mnemonic discrimination is required, even in remote spatial memory or knowledge of visual stimuli.

BL, an individual with selective bilateral DG lesions, will provide insight into the causal nature of the DG in remote memory when pattern separation is required. BL has been described previously in the literature and shows impaired pattern separation on the MST, as would be predicted in a person with hippocampal damage selective to the DG (Baker et al., 2016). Two additional amnesic patients will offer insight into how damage to the episodic memory system

more broadly impacts mnemonic discrimination abilities. This is an important consideration given previous work that has investigated mnemonic discrimination in AD and proposes that the hippocampus drives impairments in performance (Yassa & Stark, 2011).

The results will have implications for theories of hippocampal function and may help to refine and unify them. For example, if people at-risk of developing dementia, and amnesic patients including a person with DG lesions, have difficulties on tests of remote spatial and non-spatial memory only when pattern separation is necessary, it would suggest that the role of the hippocampus is not specific to spatial representations, not fully consistent with predictions of the CMT. These results would also offer insight into how mnemonic discrimination in prior knowledge (spatial and semantic) differs compared to mnemonic discrimination for newly learned information (specifically using the MST). Given the testing of participants experiencing potentially abnormal aging and people with amnesia, these results also have implications for theories of mnemonic discrimination and theories explaining memory difficulties in AD. If the hypothesized results are confirmed, they would also support the involvement of the DG/$CA_{2/3}$ pathway in mnemonic discrimination beyond the visual discrimination of objects within newly formed representations or even details of rich episodes, in well-represented semantic and spatial information.

Methods

Participants

The study received approval from the University of Toronto, Baycrest Hospital, and York University research ethics boards. Participants were recruited from the University of Toronto, Baycrest, and York University communities. All participants gave informed consent for participation, were debriefed, and compensated for their time.

Three groups of participants were recruited for this study, healthy young participants between the ages of 18 and 35 years, older participants, between the ages of 60 and 90 years, and 3 patients with amnesia and their respective control participants. All participants had normal or corrected-to-normal vision and no history of neurological or psychological diagnoses. Participants were tested individually, and an experimenter was present during testing to review task instructions and answer any questions that might arise.

Participants over the age of 50 were administered the Montreal Cognitive Assessment (MoCA) to characterize cognitive status. Participants who received a score of 26 or above on the MoCA were included in the "healthy aging" sample, whereas those who score 25 or below were considered "at-risk" for developing dementia, following previous practices in research studies looking at group-based differences based on MoCA performance (see Newsome et al., 2015 and Fidalgo et al., 2016). Data on other factors associated with the risk of developing dementia, such as genetic, physiological, and cognitive were not considered in assigning group status, as per previous practices (Newsome et al., 2015; Fidalgo et al., 2016). Recent work has advocated for a standard cut-off of 23 when using the MoCA clinically, as this appears to be more sensitive to cognitive dysfunction in the general population (Luis et al., 2009; Rossetti et al., 2011; Carson et al., 2017). To this end, a cut-off of 23 was also considered in the analyses.

Younger Adults

23 younger adult participants were recruited to participate in this study. Three participants were excluded due to insufficient landmark familiarity (see supplemental methods for more information), and an additional participant was excluded due to an inability to complete the task. The remaining sample consists of 19 participants. Two participants reported a history of anxiety but were not currently being treated with medication or other interventions and remained in the sample. Demographic information is provided in Table 1.

Older Adults

46 participants over the age of 50 participated in this experiment, including participants recruited as controls for the amnesic cases. Twelve participants were excluded from analyses due to not meeting enrollment criteria, lack of familiarity with landmarks, inability to complete task within the allotted time. Additionally, a further participant withdrew from the experiment. A final sample of 33 participants were included in the analyses. Demographic information for the older adults is presented in Table 1. Eighteen of the older participants scored at or above 26 on the MoCA and were included in the healthy older adult group and fifteen participants scored at or below 25 and were placed into the "at-risk" group. Controls matched to the three amnesic cases are identified in Table 2.

Amnesic Cases

Three adult men with documented memory impairment were also recruited. These patients have diverse etiologies and differ in their degree of memory impairment.

Patient DA is a 66-year-old man with 17 years of education in mathematics and finance who has been described previously (Rosenbaum et al., 2008; Kwan et al., 2015). He is a right-handed male and native English speaker. In 1993, he contracted viral encephalitis, which resulted in substantial MTL damage (see Figure 3, adapted from Kwan et al., 2013). His MTL damage is bilateral, with more severe damage in his right hemisphere than left hemisphere. In addition, he has volume reductions in the posterior temporal, ventral frontal, occipital regions, anterior cingulate, and posterior thalamus (Kwan et al., 2013).

Patient BL is a 57-year-old man with 13 years of education who has been described previously. He is right-handed and native English speaker. In 1985, he experienced a hypoxic-ischemic brain injury following an electrical accident and cardiac arrest (Kwan et al., 2015). BL has bilateral loss of the DG/ CA_3 of his hippocampus (See Figure 2; Baker et al., 2016). In addition to this loss, he has also has left hemisphere volume loss relative to controls in the superior parietal lobule as well as right hemisphere loss in the precuneus (Baker et al., 2016). Prior work has shown that BL is selectively impaired on the MST lure discrimination relative to controls, consistent with his DG lesion (Baker et al., 2016).

Patient JD is a 65-year-old man with 19 years of education in mathematics and engineering. His case has not been previously documented in the literature. He is left-handed and is a native English speaker. JD suffered a severe anoxic brain injury secondary to cardiac arrest in 2013. There are no MRIs available for JD due to contraindications. Within the year following his injury, JD underwent neuropsychological testing (Table 3). JD's most prominent deficits appeared on tests of memory, consistent with subjective report, as well as on tests of verbal fluency and processing speed (symbol search). JD has experienced difficulties writing and forming a fist since his injury, which may be suggestive of damage beyond the MTL or nerve damage outside the central nervous system. These issues may also relate to an earlier injury involving dislocation of his left shoulder years prior. He also exhibited minor facial paralysis, but the source is unclear.

Procedure & Materials

Procedure

Because participants have different experience navigating in different portions of the downtown core, the stimuli used for the landmark condition were necessarily tailored to the individual. Prior to participation, all participants completed a survey either online or over the telephone where they were asked to indicate their familiarity with 54 landmarks in downtown Toronto on a Likert scale ranging from 1-5, with 5 indicating high familiarity and 1 indicating no familiarity. Participants were only recruited to participate if they gave a rating of 4 or 5 on a clear majority of landmarks. Because distances between landmarks was a key manipulation, participants were required to be highly familiar with landmarks in different areas of the city and not just a single area of the downtown core. Participants were required to have a minimum of 3 years' experience living or navigating frequently in the city, with most participants having 10 years' or more experience. Given the variability in experience with the city, years' experience was included as a predictor in the analyses.

All participants began the experiment by giving informed consent for participation, and then filling out demographic questionnaires. Participants then completed the MST described above (See Supplemental Methods for how missing MST data was handled). The MST takes place over 2 phases, first an incidental encoding task for images of objects followed by a forced choice recognition task where participants indicate whether presented objects are old (previously presented), similar (similar to but different from a previously presented image), or (new) newly presented. Afterwards, participants were administered the main experimental task, the Similarity Judgment Task, which consisted of two practice runs and at least 6 test runs [1], with 32 trials in each run. For each of the landmark, animal, and number conditions, trial runs involved presentation of a target on the screen. Two seconds later, 2 additional cues appeared below the target on the screen. Participants were asked to choose which of the 2 bottom choice stimuli was closer in distance, size, or value to the target stimulus (see Figure 1 for a visual depiction of the task). Participants were then asked to rate on a 7-point likert scale the vividness (ability to visualize in the mind's eye) of the landmarks and animals or the ease of judgment for the numbers. Participants completed two trials during each run where they counted the number of

[2]Some participants in the young adult group completed 7 runs.

vowels in landmark stimuli. This was included to replicate an fMRI version of the task, which required a low-level control condition but that is not meaningful behaviourally. For this reason, the vowel counting condition was not analyzed in the current study. The results of the number task are also not reported here.

After completing the Similarity Judgment Task, participants were questioned about the strategies they used to complete the task. Participants also completed a brief visual working memory task, the results of which are not reported here, for brevity. The scoring procedure of the participants' strategies is included in Supplemental Methods.

Materials

Landmark condition

Twenty landmarks rated as most familiar (with rating ≥ 4 on the prescreening survey) were selected for each participant. The distance between all possible pairs of landmarks was calculated using Google-map walking distance. Next, we chose 100 sets of 3 landmarks (one designated as the starting location and the other two as targets) such that the differential distances, i.e., the distance between the starting location and Target 1 minus the distance between the starting location and Target 2, were equally grouped into 5 distance bins (0 m – 249 m, 250 m – 499 m, 500 m –749 m, 750 m – 999 m, 1000 m – 1249 m). For example, the walking distance from the CN Tower (start location) to City Hall (Target 1) is 1300 m and from the CN tower (start location) to Union Station (Target 2) was 750 m, with a stimulus distance value of 1300 m-750 m = 650m. This trial was included in bin level 3 (moderate stimulus distance). To counterbalance the left/right response choice, we randomly presented half of the closer targets (i.e., the correct response) on the left side of the screen within each bin. The stimuli were prepared using an Excel Visual Basic script.

Landmarks for patients BL and DA differed from those of other participants, as both patients were not sufficiently familiar with downtown Toronto. Both patients' environments were municipalities located outside of the downtown core and, as such, shared commonalities in terms of more residential houses and fewer landmarks overall. BL's environment allowed for the creation of bins identical to those of control participants in terms of range of differential distances. DA's environment differed from that of control participants, and his bin 5 landmarks

exceeded the maximum 1249 metres used for controls and extended to 5700 metres. His other bins (1-4) were identical.

Animal condition

Twenty familiar animals were used for all participants, and the ranking of the animal sizes was guided by a seminal publication (Moyer, 1973). Like the landmark condition, 100 sets of 3 animals were selected such that the differential size could be equally distributed into five bins. Here, the differential size was calculated using animal rankings (from 1-10), with the minimum size differential set at 1 and maximum set at 5. For example, if the starting animal had a size ranking of 7 (e.g., lynx), and Target 1 had a ranking of 1 (e.g., flea), and Target 2 had a ranking of 8 (e.g., bear), then the differential ranking would be [(7-1)-(8-7)] = 5. This trial would be placed in bin 5, as it is relatively large. The left and right correct responses were also counterbalanced within bins. With this method of stimulus creation, stimulus distance was largely manipulated by varying the size of the two targets, such that the differential distance and the intra-target distance (the difference in size between the targets) were highly correlated (r = .99).

Stimulus Presentation

During each trial of the landmark and animal condition (Figure 1), participants were first shown the name of a target landmark for 2 seconds. Then, two different cues were presented, and participants were asked to determine which of the landmarks represented by the cues is closer to the presented target. For the landmarks, ‘closer’ was closest geographic distance and for animals, this was overall size. All stimuli remained on the screen for 6 seconds. After responding, participants were given 4 seconds to provide a vividness rating from 1–7, where a higher rating indicated stronger vividness of the judgment. Patient DA and his wife (included as a control participant for him) had an additional 2 seconds (total of 8 seconds) to respond to the task, since DA struggled to successfully complete the practice within the allotted 6 seconds.

Data Analyses

To investigate task performance on the MST across participant groups, analysis of variances was used followed by pairwise comparisons. To investigate performance on the similarity judgment task, generalized hierarchical logistic regressions were used. Logistic regression was chosen as it predicts performance for a binary variable, in this experiment accuracy. Accurate responses were coded as 1 and inaccurate responses were coded as 0. Demographic and experience covariates were included in the model if they were relevant to predicting task performance and were not highly correlated with one another. Pairwise comparisons were completed to test the difference in accuracy across the stimulus bins holding all predictors constant. Patients' performance on all conditions was compared to that of controls using Crawford and Garthwaite's (2002) modified t-test procedure. All t-tests' p-values are reported with one-tailed probability.

Results

Mnemonic Similarity Task (MST)

MST results are presented in figures 4 and 5. Figure 4 shows recognition accuracy across the old, similar, and new conditions across younger adults, healthy older adults, and 'at-risk' older adult participants. Figure 5 shows the Lure Discrimination Index (LDI) scores for each of the participant groups. The LDI has been used in the MST task as a measure of pattern separation (Stark et al., 2013; Baker et al., 2016). The LDI is the difference between the rate of "Similar" responses given by participants to lure stimuli minus the rate of "Similar" responses given to foil items (Stark et al., 2015).

There were no significant differences in accuracy in the Old and New conditions between younger adults, healthy older adults, and 'at-risk' older adults (Old: $F(2,44) = 0.058$, $p = 0.94$; New: $F(2,44) = 0.15$, $p = 0.86$). However, there was a significant difference in the Similar Condition [$F(2,44) = 21.42$, $p < .001$]. To investigate these differences in a more detailed manner, LDI scores were analyzed. 'At-risk' older adults had numerically but not significantly lower LDI scores than healthy older adults ($t(29) = (-1.46)$, $p = 0.16$), healthy older adults had a significantly lower MST LDI scores than young adults ($t(32) = 2.81$, $p = 0.01$), and 'at-risk' older adults had significantly lower MST LDI scores than young adults ($t(27) = 4.75$, $p < .001$).

Patient DA had an LDI score of 29.03. His accuracy for correctly identifying targets (indicating old) was 89%, correctly identifying lures (indicating similar) was 31%, and correctly identifying foils (indicating new) was 97%. Patient JD had an LDI score of 14.09. His accuracy for correctly identifying targets (indicating old) was 65%, correctly identifying lures (indicating similar) was 16% and correct identifying foils (indicating new) was 95%. Patient BL's performance on the MST has been documented previously in the literature (Baker et al., 2016). BL's LDI score across two sessions of testing was 0.84. His accuracy for correctly identifying targets (indicating old) was 81%, correctly identifying lures (indicating similar) was 15% and correctly identifying foils (indicating new) was 72.79%.

Similarity Judgment Task

Young Adults

Landmarks

A generalized hierarchical logistic regression was used to predict landmark accuracy from differential distance bins, with MST LDI Score, years living in Toronto, frequency navigating in downtown Toronto, years of education, and intra-target distance held constant. MST score and age were excluded from the model due to the high collinearity with MST LDI Score and years of education, respectively. Regression coefficients are shown in Table 9. Frequency navigating in downtown Toronto had significant partial effects in the null model. Separate models were run to test whether bin type and frequency downtown are significant contributors, both of which were significantly different (see Table 9).

Pairwise comparisons were conducted to test the difference in accuracy across the differential distance bins, holding the aforementioned predictors constant. Accuracy across the bins is shown in Table 5, which demonstrates accuracy increases over the differential distance bins. Bin 1 was found to be significantly different from bins 3, 4, and 5 (Bin 3: $Z = 2.13$, $p = .03$; Bin 4: $Z = 2.53$, $p = .01$; Bin 5: $Z = 5.21$, $p < .001$). Bin 2 was significantly different from Bin 5 ($Z = 4.65$, $p < .001$). Bin 3 was significantly different Bin 5 ($Z = 3.38$, $p < .001$]. Bin 4 was significantly different from Bin 1 [($Z = (-2.53)$, $\underline{p} = 0.01$)] and Bin 5 [($Z = 2.96$, $\underline{p} = 0.003$)].

Animals

A generalized hierarchical regression was used to predict animal accuracy from differential distance bins, with MST LDI Score, age, and years of education held constant. MST score and age were excluded from the model due to the high collinearity with MST LDI Score and years of education, respectively. Regression coefficients are presented in Table 10. Age had significant partial effects (.05 level) in the null model. To test whether bin is a significant predictor of accuracy in the model, an identical model was run without bin as a predictor and compared to the original model, and results showed the model containing bins was significantly different (see Table 10).

Pairwise comparisons were completed to test the difference in accuracy across the differential distance bins holding the aforementioned predictors constant. Accuracy was found to increase with increasing bin level (see Table 5 for means). Bin 1 was found to be significantly different from bins 3, 4, and 5 (Bin 3: $Z = 3.17$, $p = .002$ .01; Bin 4: 4.67, $p < .001$; Bin 5: $Z = 4.45$, $p < .001$). Bin 2 was significantly different from Bins 4 and 5 (Bin 4: $Z = 3.59$, $p < .001$; Bin 5: $Z = 3.27$, $p = .001$). Bin 3 was significantly different from Bins 1, 4, and 5 [Bin 1: $Z = (-3.17)$, $p = .002$; Bin 4: 2.68, $p = .007$; Bin 5: $Z = 2.27$, $p = .02$]. Bin 4 was significantly different from Bins 1, 2, and 3 [Bin 1: $Z = -4.66$, $p < .001$; Bin 2: $Z = (-3.59)$, $p < .001$; Bin 3: $Z = (-2.68)$; $p = .007$].

Healthy Older Adults Task Performance

Landmarks

A generalized hierarchical regression was used to predict distance accuracy from differential distance bins, with MST LDI Score, MoCA Executive Functions subscale, MoCA memory subscale, years living in Toronto, age, years of education, and intra-target distance held constant. MST score and age were excluded from the model due to the high collinearity with MST LDI Score and years of education, respectively. Regression coefficients are presented in Table 11. MST LDI Score had significant partial effects ($p = .03$) in the null model. To test whether bin is a significant predictor of accuracy in the model, an identical model was run without bin as a predictor and compared to the original model, and results showed the model containing bins was significantly different (Table 11). A model with frequency navigating in Toronto was compared to the original model and found not to be significant (Table 11).

Pairwise comparisons were completed to test the difference in accuracy across the differential distance bins, with the aforementioned predictors held constant. Mean accuracy increased over the differential bins (see Table 6). Bin 1 was found to be significantly different from bins 3, 4, and 5 (Bin 3: $Z = 2.24$, $p = .02$; Bin 4: 3.73, $p < .001$; Bin 5: $Z = 4.93$, $p < .001$). Bin 2 was significantly different than Bins 4 and 5 (Bin 4: $Z = 3.13$, $p = .001$; Bin 5: $Z = 4.42$, $p < .001$). Bin 3 significant different from Bins 1 and 5 [Bin 1: $Z = (-2.24)$, $p = .02$; Bin 5: $Z = 3.03$, p = .003]. Bin 4 was significantly different from Bins 1 and 2 [Bin 1: ($Z = (-3.73)$, $p < .001$); Bin2: $Z = (-3.13)$; $p = .002$].

Animals

A generalized hierarchical regression was used to predict distance accuracy from differential distance bins holding MST LDI Score, MoCA Executive Functions subscale, MoCA memory subscale, Years living in Toronto, downtown frequency, age, years of education and intracue distance constant. MST score was excluded from the model due to the high collinearity with MST LDI Score. Age had significant partial effects in the null model. Regression coefficients are shown in Table 12.

Pairwise comparisons were completed to test the difference in accuracy across the differential distance bins holding the aforementioned predictors constant. Accuracy increases over the differential bins (see Table 6). Bin 1 was found to be significantly different to bin 3 (Bin 3: $Z = 2.76$, $p = .006$). Bin 2 was not found to be significantly different from any other bins. Bin 3 significant different from Bin 1 [Bin 1: $Z = (-2.76)$, $p = .006$]. Bin 4 was not found to be significantly different from any other bins.

‘At-risk’ Older Adult Task Performance

Landmarks

A generalized hierarchical regression was used to predict landmark accuracy from differential distance bins holding MST LDI Score, MoCA Executive Functions subscale, MoCA Memory subscale, years living in Toronto, downtown frequency, age, years of education, and intracue distance constant. Regression coefficients are shown in Table 13 for all but the bin condition. Age had significant partial effects (.05 level) in the null model. To test whether bin is a significant predictor of accuracy in the model, an identical model was run without bin as a

predictor and compared to the original model. Results showed the model containing bins was significantly different (Table 13). To test whether downtown frequency is significant predictor of accuracy in the model, an identical model was run without frequency as a predictor and results showed the model containing downtown frequency was not significantly different (Table 13).

Pairwise comparisons were completed to test the difference in accuracy across the differential distance bins holding the aforementioned predictors constant. Accuracy increases over the differential bins (see Figure 6). Bin 1 was found to be significantly different to bin all bins (Bin 2: $Z = 2.28$, $p = .02$; Bin 3: $Z = 2.99$, $p = .003$; Bin 4: $Z = 3.19$, $p = .001$; Bin 5: $Z = 5.82$, $p < .001$). Bin 2 was found to be significantly different from Bin 1 and Bin 5 [Bin 1: Z = (-2.28), $p = .02$; Bin 5: $Z = 3.90$, $p = < .001$]. Bin 3 was found to be significantly different from Bin 1 and Bin 5 [Bin 1: $Z = (-2.99)$, p = .003; Bin 5: $Z = 3.14$, $p = .002$]. Bin 4 was significantly different from Bins 1 and 5 [Bin 1: ($Z = (-3.19)$, $p = .001$); Bin 5: Z= (2.88); $p = .004$].

Animals

A generalized hierarchical regression was used to predict animal accuracy from differential distance bins holding MST LDI Score, MoCA Executive Functions subscale, MoCA memory subscale, age and years of education constant. Regression coefficients are shown in Table 14. MoCA memory score had significant partial effects in the null model. To test whether bin is a significant predictor of accuracy in the model, an identical model was run without bin as a predictor and compared to the original model and results showed the model containing bins was significantly different (Table 14).

Pairwise comparisons were completed to test the difference in accuracy across the differential distance bins holding the aforementioned predictors constant. Accuracy increases over the differential bins (see Figure 6). Bin 1 was found to be significantly different from bins 3, 4, and 5 (Bin 3: $Z = 3.22$, $p = .001$; Bin 4: $Z = 3.22$, $p = .001$; Bin 5: $Z = 3.65$, $p < .001$). Bin 2 was found to be significantly different from bin 5 (Bin 5: Z = 2.29, $p = .02$). Bin 3 was found to be significantly different from bin 1 [Bin 1: $Z = (-3.22)$, $p = .001$]. Bin 4 was found to be significantly different from bin 1 (Bin 1: $Z = (-3.22)$, $p = .001$].

Group Comparisons

Younger versus Healthy Older adults

Landmarks

A generalized hierarchical regression was used to predict landmark accuracy from differential distance bins for older and younger adults holding MST LDI score, Participant Group, Downtown Frequency, Years of Education, and intracue distance constant. Years living in Toronto was not included in the model as it was highly collinear with Participant Group. Regression coefficients are shown in Table 15. No partial coefficients were significant. To test whether bin is a significant predictor of accuracy in the model, an identical model was run without bin as a predictor and compared to the original model and results showed the model containing bins was significantly different (Table 15). A model with group removed was not significantly different from a model including group (Table 15).

Pairwise comparisons were completed to test the difference in accuracy across the differential distance bins holding the aforementioned predictors constant. Accuracy increases over the differential bins for both groups but there is not a difference in accuracy between older and younger adults (see Figure 6). Bin 1 was found to be significantly different from bins 3, 4, and 5 (Bin 3: $Z = 2.97$, $p = .003$; Bin 4: $Z = 4.34$, $p < .001$; Bin 5: $Z = 7.10$, $p < .001$). Bin 2 was found to be significantly different from bins 3, 4, and 5 (Bin 3: $Z = 2.18$, $p = .03$; Bin 4: $Z = 3.61$, $p < .001$; Bin 5: $Z = 6.50$, $p < .001$). Bin 3 was found to be significantly different from bin 1, 2, and 5 [Bin 1: $Z = (-2.97)$, $p = .003$; Bin 2: $Z = (-2.18)$, $p = .03$; Bin 5: $Z = (4.56)$, $p < .001$]. Bin 4 was found to be significantly different from bin 1, 2, and 5 [Bin 1: $Z = (-4.34)$, $p < .001$; Bin 2: $Z = (-3.61)$, $p < .001$; Bin 5: $Z = (3.11)$, $p = .002$].

Animals

A generalized hierarchical regression was used to predict animal accuracy from differential distance holding MST LDI Score and group constant for older and younger adults. Age was not included in the model as it was highly collinear with Group. Regression coefficients are shown in Table 16. To test whether bin is a significant predictor of accuracy in the model, an identical model was run without bin as a predictor and compared to the original model. The results showed the model containing bins was significantly different. The same procedure was

taking to test whether group was a significant predictor of accuracy, and these models were also significantly different.

Group means show that healthy older adults have higher accuracies than young adult participants across bins (Table 6). Pairwise comparisons were completed to test the difference in accuracy across the differential distance bins holding the aforementioned predictors constant. Bin 1 was found to be significantly different from all bins (Bin 2: $Z = 2.51$, $p = .01$; Bin 3: $Z = 4.26$, $p < .001$; Bin 4: $Z = 5.51$, $p < .01$; Bin 5: $Z = 5.46$, $p < .001$). Bin 2 was found to be significantly different from all bins (Bin 1: $Z = (-2.51)$, $p = .01$; Bin 3: $Z = 1.97$, $p = .05$; Bin 4: = 4.33, $p <$ .001; Bin 5: $Z = 5.46$, $p < .001$). Bin 3 was found to be significantly different from all bins [Bin 1: $Z = (-4.26)$), $p < .01$; Bin 2: $Z = (-1.967)$, $p = .05$; Bin 4: $Z = (-3.19)$, $p < .001$; Bin 5: $Z = 2.90$, $p < .001$]. Bin 4 was found to be significantly different from bins 1, 2, and 3 (Bin 1: $Z = (-3.19)$, $p = .001$; Bin 2: $Z = (-4.33)$, $p < .001$; Bin 3: $Z = (-5.51)$, $p < .001$]

Healthy older adults and 'At-risk' older adults

Distances

A generalized hierarchical regression was used to predict landmark accuracy from differential distance bins holding MST LDI score, MoCA Status, Downtown Frequency, Years of education, age, and intracue distance constant for all older adults. Regression coefficients are shown in Table 17. Significant null predictors of performance were MST LDI Score and Intracue Distance. To test whether bin is a significant predictor of accuracy in the model, an identical model was run without bin as a predictor and compared to the original model. Results showed the model containing bins was significantly different. A model with downtown frequency was not significantly different from a model. The same procedure was taken to test whether group was a significant predictor of accuracy, and these models were significantly different.

Bin 1 was found to be significantly different from all bins (Bin 2: $Z = 2.19$, $p = .03$; Bin 3: $Z = 3.68$, $p < .001$; Bin 4: $Z = 4.9$, $p < .001$; Bin 5: $Z = 7.62$, $p < .001$). Bin 2 was found to be significantly different from bins 1, 4, and 5 [Bin 1: Z = (-2.19), $p = .03$; Bin 4: Z = 2.97, p =.003; Bin 4: $Z = 4.9$, $p < .001$; Bin 5: $Z = 5.91$, $p < .001$]. Bin 3 was found to be significantly different from bins 1 and 5 [Bin 1: $Z = (-3.68)$, $p < .001$; Bin 5: $Z = 4.38$, $p < .001$). Bin 4 was found to be significantly different from bins 1, 2, and 5 [Bin 1: $Z = (-4.897)$, $p < .001$; Bin 2: $Z = (-2.97)$, p = .003; Bin 1: $Z = 3.00$, p =.003]

Animals

A generalized hierarchical regression was used to predict animal accuracy from differential distance holding MST LDI Score, MoCA status, years of education and age constant for all older adults. Regression coefficients are shown in Table 18. To test whether bin is a significant predictor of accuracy in the model, an identical model was run without bin as a predictor and compared to the original model and results showed the model containing bins was significantly different from its competitor. The same procedure was taken to test whether group was a significant predictor of accuracy, and these models were significantly different.

Pairwise comparisons were completed to test the difference in accuracy across the differential distance bins holding the aforementioned predictors constant. Mean Accuracy increases over the differential bins and differs depending on the bin (see Figure 6). Bin 1 was found to be significantly different from bins 2, 3, 4, and 5 (Bin 2: Z = 2.47, p = .01; Bin 3: *Z* = 2.47, p < .001; Bin 4: Z = 4.76, p < .001;Bin 5: Z = 4.85, p < .001). Bin 2 was found to be significantly different from all bins [(Bin 2: Z = (-2.52, p = .01; Bin3: Z = 2.23, p = .03; Bin 4: *Z* = 3.12, p < .001; Bin 5: *Z* = 3.54, *p* < .001). Bin 3 was found to be significantly different from bins 1 and 2 [Bin 1: *Z* = (-4.35), *p* < .001; Bin 2: *Z* = (-2.23), *p* = .03]. Bin 4 was found to be significantly different from bins 1 and 2 [Bin 1: *Z* = (-4.91), *p* < .001; Bin 2: *Z* = (-3.13), *p* = .002].

Defining Healthy and 'At-risk' Older Adults - MoCA cut-offs

Mean performance for 8 older adult participants scoring 24 and 25 on the MoCA was not significantly different from mean performance for the 7 older adults scoring 23 and lower on the MoCA in any bin for the landmark condition [Bin 1: *t*(13) = 0.25, *p* = 0.63; Bin2 : t(13) = (-1.0), p = 0.67; Bin 3: *t*(13) = (-0.10), *p* = 0.68; Bin 4: *t*(13) = 0.41, *p* = 0.78; Bin 5: *t*(13) = (-0.70) , *p* = 0.19]. In the animal condition there was a significant difference between the groups in Bin 4 [Bin 4: *t*(13) = 0.28 , *p* = 0.51] and no differences in the remaining bins [Bin 1: *t*(13) =(-0.77), *p* = 0.20 ; Bin 2: t(13)= (-1.61), p =0.24; Bin 3: *t*(13) = (-1.23), *p* = 0.03; Bin 5: *t*(13) = (-.070) , *p* = 0.59]. In the animal bin 4 condition, a single participant had an accuracy of 75% which offers some explanatory value for this significant difference.

Amnesic Patients

Patient JD

Patient JD was compared to 7 control participants (see Table 2). JD's performance on the landmark condition is comparable to that of his 7 controls for all bins (1 tailed tests; Bin 1: t = 0.29, p = 0.39; Bin 2: t = 0.18, p = 0.43; Bin3: t = 0.06, p = 0.48; Bin 4: t = 0.22, p = 0.42; Bin 5: t = 0.37, p = 0.36).

On the animal condition, JD showed impaired performance relative to controls for bins 3-5 [Bin 1: t = (-0.35), p = 0.37; Bin 2: t = (- 0.680), p = 0.26; Bin3: t = (-233.85), p = 0.00; Bin 4: t =-308.687, $p < .001$; Bin 5: t = -187.083 $p < .001$]. For a graphical presentation see Figure 8.

To help interpret JD's results on the animal condition, further exploratory testing was conducted to investigate the integrity of his semantic knowledge of animals. Several weeks following testing, JD was asked to rank the twenty presented animals in terms of size (Figure 9). This was largely normal, with a few oddities. Specifically, he ranked a skunk as smaller than a dove and finch. He also ranked a tiger as smaller than a wolf and goat. Next, JD was asked to describe a feature, function, colour, as well as a similar sized everyday object to each animal. Interestingly, JD had many semantic-like stories for certain animals (for example, a family friend who had lyme disease, which originates from ticks), which he repeated (consistent with his memory impairment). Notably, some of these stories were repeated for different animals, showing interference for the underlying semantic representation of the animal. For example, JD shared the same story about goats and sheep eating grass at an old home, failing to discriminate between the two animals in memory. In addition, JD sometimes struggled to generate detailed descriptions of the visual properties for each animal and needed encouragement at times. He was, however, able to generate responses to every animal.

Patient DA

Patient DA's performance was compared to that of 8 control participants (see Table 2 for details). One control participant for DA is his wife whose landmark condition was based on the same geographic environment on which DA was tested and who also had the same additional 2 seconds to respond to the task as DA. For a graphical presentation see Figure 10.

Statistically, DA's performance in the landmark condition did not differ from control participants' for any bin (Bin 1: $t = 0.16$, $p = 0.44$; Bin 2: $t = 0.16$, $p = 0.44$; Bin 3: $t = 0.27$, $p = 0.40$; Bin 4: $t = -0.878$, $p = 0.20$; Bin 5: $t = 0.157$, $p = 0.44$). In the animal condition, DA's performance also did not differ from control participants' for any bin (Bin1: $t = 0.11$, $p = 0.46$; Bin 2: $t = 0.31$, $p = 0.38$; Bin 3: $t = 0.00$, $p = 0.50$; Bin 4: $t = 0.00$, $p = 0.50$; Bin 5: $t = 0.00$, $p = 0.50$).

Patient BL

Patient BL was compared to five control participants (see Table 2). With this sample size there are large variabilities in standard deviation. Control participants were tested in the downtown Toronto environment. For a graphical presentation see Figure 11.

BL's landmark performance was not statistically different from controls in any bin [Bin 1: $t = (-0.75)$, $p = 0.25$; Bin2: $t = 0.00$, $p = 0.50$; Bin 3: $t = (-0.34)$, $p = 0.38$; Bin 4: $t = (-0.34)$, $p = 0.38$; Bin 5: $t = (-0.47)$, $p = 0.33$]. As seen in Figure 10, BL's performance in bin 1 is well below chance at 25% and is numerically lower than control participants in bin 4 by 16% and in bin 5 by 17%. In the animal condition, BL is comparable to controls in all bins [Bin1: $t = -0.39$, $p = 0.36$; Bin 2: $t = -0.20$, $p = 0.42$; Bin 3: $t = 0.27$, $p = 0.40$; Bin 4: $t = (-1.22)$, $p = 0.15$; Bin 5: $t = 0.000$, $p = 0.50$].

Discussion

Overall Summary

This project aimed to determine whether mnemonic discrimination operates on prior knowledge previously encoded, specifically, remotely formed spatial and semantic memory representations. We investigated whether mnemonic discrimination operates on prior knowledge across the lifespan where hippocampal function is known to decline (Small, 2001) and within the face of potentially abnormal aging and amnesia. All participant groups showed decreased accuracy on higher similarity judgments for both landmark and animal stimuli, demonstrating how discriminating between overlapping representations within prior knowledge is more difficult than discriminating between less similar memory representations. Results showed that young adults and healthy older adults performed similarly on the task, suggesting preservation of this discrimination ability with age or a relative decrease in ability given older adults' higher familiarity with the city and overall higher knowledge. 'At-risk' older adults, who may have a

higher likelihood than healthy older adults for developing cognitive impairments, performed significantly worse than their healthy older adult counterparts on highly similar judgments in both landmark and animal judgments. Patients with amnesia (DA and JD) showed preservation on the landmark judgments relative to controls while patient BL, who has bilateral DG lesions, showed impairment in the highly similar judgments in the landmark condition. In the animal condition, patients DA and BL performed normally, while a patient, JD, showed impairment. Follow-up testing with JD found that his semantic representations were impoverished and sometimes dependent on personalized-semantic-like (Renoult et al. 2012) knowledge. These results suggest that with decreased hippocampal functioning, there are challenges with the ability to discriminate among similar representations that form part of one's prior knowledge. Our findings suggest that the ability to discriminate between these representations interacts with multiple other brain regions given intact performance in healthy older adults and some patients with amnesia. These results will be discussed in the context of the prior literature on spatial memory, semantic knowledge, and how it informs theories of mnemonic discrimination.

High Similarity Judgments for Spatial Information

Young & Older Adults

Healthy older adults performed similarly to younger adults in the landmark condition (see Table 6, Figure 6). These results are not consistent with our hypothesis that older adults would struggle on the most similar discrimination judgments due to findings of decreased hippocampal functioning occurring with age, age-related decrements in mnemonic discrimination, or based on their MST scores (Figure 4; Small, 2001; Yassa & Stark, 2011). It is worth noting the confound of years of experience in the city. Healthy older adults, on average, have 37 more years' experience with the city than younger adults. With the difference of experience in mind, healthy older adults' performance should probably be higher than younger adults' task performance if they are cognitively intact. However, in no condition does the performance significantly differ. Instead, these results are consistent with predictions that the landmark condition is relying on semantic-like, schematic knowledge of the remote environments, which is typically intact in aging as well as hippocampal amnesia (Rosenbaum et al., 2000; Rosenbaum et al., 2012; Herdman et al., 2015).

Unlike the current results, Holden et al. (2012) found that cognitively intact older adults over 65 years of age performed significantly worse than younger adults on a delayed match-to-sample task, and statistically controlling for delayed recall scores did not change this effect. Performance in both groups improved with increasing spatial separation between stimuli, but to a lesser extent in the older adults (Holden et al., 2012). The authors concluded, based on their findings and previous research, that spatial pattern separation may become less efficient with healthy aging (Holden et al., 2012; Holden & Gilbert, 2012). Our study does share the finding of improved performance with increasing separation between representations. However, our results contrast with these findings, as we do not see impaired performance in our older adult group. Given that our task does not involve new learning and the stimuli are within prior knowledge, we suggest that spatial pattern separation may decrease in aging when the stimuli are novel and the same may not be true for remote spatial information.

The 'at-risk' group of older adult participants performed worse than the healthy older adults in the highest similarity landmark condition, though their performance was numerically inferior in all similarity conditions. This group of heterogenous participants scored between 18 and 25 on the MoCA, meaning that some participants scored in the range of MCI (Carson et al., 2017). MST LDI scores for this 'at-risk' group were also comparable to patients diagnosed with aMCI (Stark et al., 2013). While neither the MoCA nor MST are diagnostically conclusive, the converging evidence suggests that these participants as a group are potentially showing cognitive changes that may put them 'at-risk' for further cognitive decline (Newsome et al., 2015).

Previous work has found that the hippocampus activity relates to images of landmarks which are geographically closer to one another (Morgan et al., 2011). Other evidence has found the entorhinal/subiculum regions are involved in coding goal proximity; specifically, a negative correlation between goal proximity and activity was found in this region using virtual navigation videos of London with taxi driver participants highly familiar with the city (Spiers & Maguire, 2007). Recent work has found a relationship between reduced anterolateral entorhinal volume and lower MoCA performance in community-dwelling older adults (Olsen et al., 2017). It is therefore reasonable to interpret these 'at-risk' older adult participants' results in the landmark condition as potential evidence of difficulty deciphering distance to goal or target, which may be linked to possible volume loss in the entorhinal region of the brain as well as possible

hippocampal dysfunction. Further work can test these hypotheses by correlating participants' hippocampal and entorhinal volumes with performance on the most similar landmark judgments. Our patients' results speak to the involvement of the hippocampus in this task, but are not fully consistent with all of our predictions. Further correlational work using volumetric analyses may help with understanding the subtle contributions of the different MTL regions.

No differences were found in performance within the 'at-risk' older adult groups while using the different MoCA cut-off scores on the task. This offers evidence that these task results are not being driven by older adults who scored lower and within MCI range on the MoCA (Carson et al., 2017). However, the sample size of the 'at-risk' group is small with only 15 participants. Further investigation of whether different MoCA cut-off scores can be used to predict task performance with a larger sample size would be helpful.

Patients DA & JD

Amnesic patients DA and JD show preservation on the distance judgment task relative to controls, even in the highest similarity condition. Both patients have MST LDI scores expected for their ages. Both patients were tested with landmark stimuli which were highly familiar and in their home environments unlike the majority of older adult participants who were tested with landmarks, which though highly familiar, were mostly not within their home environments. This is consistent with amnesic patient KC's performance, who had extensive pathology bilaterally in his hippocampus and additional volume loss in the parahippocampal cortex, but still was able to effectively judge distances between landmark pairs, and also decide which of 2 landmarks was closer in distance to a third (Rosenbaum et al., 2000). KC's difficulty was in correctly identifying familiar landmarks and locations of cities in Canada, both of which required more detailed information and speaks to the lack of detail and schematic nature of his representations (Rosenbaum et al., 2000).

Patient DA has a more severe memory impairment than JD and does not often navigate independently. He has, however, been living in his home environment for over 30 years. Prior testing found that DA drew an intact schematic map of his environment that lacked detail, as seen with placement of fewer landmarks and street segments than controls (Herdman et al., 2015). With this depleted knowledge, DA may still be able to determine distances between familiar landmarks, even if the routes themselves may lack detail. Given that the only landmarks

included in the study were those to which DA felt confident navigating, it is likely that DA had intact representations for all the locations and routes tested.

DA's MTL damage is bilateral, with relative preservation in his left hemisphere (Kwan et al., 2013). A past study with younger adults found that participants' left anterior hippocampal activity was related to objective distance between landmarks (Morgan et al., 2011). Given DA's relative preservation in his left hemisphere, this supports his intact task performance which involves determining distances between landmarks. High-resolution MRI scans are not available, so it is not possible to decipher whether DA has CA_3/DG damage, where this ability to discriminate between similar representations would be localized (Yassa & Stark, 2011). DA's intact task performance could be attributed to his high familiarity with his environment, intact schematic knowledge, relative MTL preservation in his left hemisphere and potential CA_3/DG preservation.

Patient JD has been living in the area for approximately 10 years and frequently (almost daily) navigates in the area tested. He navigates independently in the city by relying on intact remote spatial knowledge. JD utilized a more egocentric strategy than most older adult participants who were biased towards allocentric strategies on the task (Table 8). JD described completing the task by imagining himself traveling to the location and thinking of the time needed to get to each location. This strategy and high familiarity may allow JD to compensate for his memory impairments. Unfortunately, due to contraindications we are unable to determine whether he has lesions in the MTL. His neuropsychological test results clearly indicate amnesia, and his anoxia etiology is suggestive of MTL damage.

Patient BL

BL's landmark performance was numerically but not statistically well below chance at the highest similarity judgments of differential distance. He also shows numerically low performance at the lowest similarity conditions. Given BL's bilateral DG lesions, MST task performance and his performance on the highest similarity judgments are consistent with predictions that successful completion of these highly similar judgments necessitates an intact DG/CA_3 and mnemonic discrimination abilities.

However, the stark contrast in performance between the similarity bins is surprising, given the task performance of other participants. The bin division is arbitrary, in that there is no clear theoretical reason to divide bin 1 at 200, 250 or 300 metres. The bin division therefore does not clearly explain why his performance would increase substantially on differential distance judgments greater than 250 metres to then decrease again. It is also important to note that the actual number of trials during the task is quite low, so differences in performance may be amplified by errors. Regardless, in the highest similarity condition BL performed well below chance. BL does not show the same improvement in discriminating between these distances over the bins which decrease in stimulus distance as his control participants or other amnesic patients DA and JD. Given that his amnesia is less severe than patients DA and JD (see Table 5 for neuropsychological test results), his results suggest the importance of his bilateral DG lesions. It is possible that the ability to discriminate between similar representations has generalized to easier similarity trials, which would explain why BL's performance is not intact on lower similarity judgments in addition to being impaired on high similarity judgments.

BL has additional volume loss in his left parietal regions and right precuneus (Stevenson et al., 2016). The precuneus has been shown to be functionally connected to regions important to spatial navigation (Zhang & Chiang-Shan, 2012; Epstein, 2008). BL does not have lesions bilaterally in his precuneus, but his right hemisphere precuneus volume loss indicates that caution should be exercised in interpreting his results.

High Similarity Judgments for Semantic information

Animal knowledge is a well-documented aspect of semantic knowledge (Patterson et al., 2007). The animal size judgments condition provides an important contrast to the landmark condition as it offers a comparison for discriminating between similar representations in memory with stimuli which are not spatial in nature.

Young and Older Adults

Like the landmark condition, there was no significant difference in performance between young and older adult participants. This suggests a preservation of semantic knowledge in the healthy older adults as well as the ability to discriminate between semantic representations when highly similar. Interestingly, healthy older adults actually performed numerically better than

younger adults, which offers credence to the benefit of life experience and also intact cognitive abilities of these healthy older adult participants.

'At-risk' older adult participants show lower accuracy than healthy older adults in the highest similarity bin. This is consistent with our hypotheses that the ability to discriminate between these overlapping representations within prior knowledge would be particularly difficult for older adults who may be at-risk for developing clinically significant cognitive conditions and are demonstrating subtle cognitive changes. The replication of this finding in the animal condition in addition to the landmark condition suggests that this difficulty in discriminating between similar representations is not stimulus specific. Comparing 'at-risk' older adults using the two MoCA cut-off scores (26 and 24) found no difference between participants in 4 of the 5 conditions. In one condition, there was a statistically significant difference. Given the small sample size and the particularly low performance of a single participant, we are reluctant to interpret this result. And regardless of this result, it does not appear that the lowest performing older adult participants (scoring a 23 and below on the MoCA) are driving performance in the highest similarity condition for the at-risk older adult group.

Patients DA & BL

Patients DA and BL showed intact animal performance on the task relative to controls. This is consistent with other accounts of intact semantic knowledge within amnesia (Vargha-Khan et al., 1997). Neither patient has extensive damage to areas outside the MTL region that would suggest issues with semantic knowledge. The semantic system in the human is extensive and encompasses multiple regions outside of the MTL (Binder et al., 2009). DA's animal performance suggests that the hippocampus is not necessary to complete the task and suggests the critical involvement of other brain regions.

BL's intact performance on the animal high similarity trials suggests his difficulties may only exist with stimuli within prior knowledge which are sufficiently complex, taxing, and hippocampally dependent as spatial memory. It is also worth noting BL has intact perirhinal and entorhinal cortices which have been linked to object perception (Baker et al., 2016; Fidalgo et al., 2016) These results also place an importance on acknowledging that there may be other more diffuse damage occurring in the 'at-risk' older adult group while there is no evidence of additional cognitive decline for BL beyond his lesions.

Patient JD

Patient JD did not show task improvement as similarity decreased in the animal condition. Follow-up testing with JD elaborated on his performance by showing his impoverished representations of certain animals, and improper grouping of certain animal sizes. JD immigrated to Canada from Australia, and as such, has personal experience with certain animals that some North Americans may not (for example, certain species of goats, and sheep). His ability to describe these animals in follow-up testing was often linked to semanticized personal memories (Renoult et al., 2012) involving the animal. JD shows impaired semantic fluency and some issues with executive functioning, which suggest damage outside of the medial temporal lobe (Table 3). It is possible that his memory difficulties inhibit his ability to recall sufficient details about animals to make judgments quickly in the experimental task, though this is would not be consistent with BL and DA's intact task performance. Instead, JD's performance on the task and results in follow-up testing offer evidence that the animal condition is relying on semantic memory.

A region of interest given JD's subtle deficits in semantic knowledge would be the anterior ventrolateral temporal lobes, given their involvement in semantic dementia and proximity to the posterior cerebral artery (Binder et al., 2009; Patterson et al., 2007). Testing other patients with anoxia secondary to cardiac arrest and severe memory disturbances on tests of semantic memory may offer some insight into whether this brain area may be related to semantic knowledge impairments with amnesia.

Implications for Mnemonic Discrimination

The performance of the 'at-risk' older adult participants and patient BL offers correlational and causal evidence that the process of discriminating between similar representations within prior knowledge may relate to CA_3/DG integrity. This is supported by the low MST task performance in both groups of participants. The intact performance of healthy older adults and amnesic patients DA and JD is confounded with high experience relative to their control groups (younger adults and other older adults respectively). It also demonstrates that other brain regions are likely being recruited in this process of mnemonic discrimination for prior spatial and semantic knowledge that are critical to task performance.

Theorists posit that pattern separation can occur only at encoding when representations are orthogonalized (Hunsaker & Kesner, 2013). According to this conceptualization, in our task

only retrieval-based representation pattern separation is possible, since all information is based on prior knowledge. If mnemonic discrimination is a retrieval based process, and this task is capturing a hippocampally dependent process through the discrimination of highly similar representations, then task performance should correlate with MST performance, particularly in the landmark condition. This relationship only exists for healthy older adult participants in the landmark condition, and not for 'at-risk' older adults. Regardless, the results suggest a relationship between accuracy in discriminating between two similar representations within well-preserved knowledge and performance on discriminating between similar items on the MST. MST LDI scores for the 'at-risk' group are consistent with impaired pattern separation abilities, as are their animal and landmark results. BL's task performance offers causal evidence for the involvement of the DG in this task.

According to theorists on pattern separation and pattern completion, the knowledge-based memory system is where pattern completion processes can occur based on previous event-based memories (Hunsaker & Kesner, 2013). Our hypothesis that the ability to discriminate similar distances and similar sizes in memory is a form of pattern separation is in contradiction to these ideas. The definition of mnemonic discrimination used in this thesis, in which pattern separation occurs at retrieval when participants discriminate between similar representations within prior knowledge, is difficult to conceptualize as a pattern completion process, given that participants must discriminate between two similar options to complete this task. One interpretation consistent with these theories is that participants pattern complete an association between animals or locations to choose the correct response (possibly new or old associations; we did not measure frequency traveling between locations or comparing particular animal sizes). This account offers explanatory value but is not consistent with our findings of lower performance on highly similar trials for our 'at-risk' older adults, the prediction value of the MST LDI score with task performance for healthy older adult participants, or BL's impaired task performance. These results reveal difficulty in discriminating similar representations, consistent with an explanation of pattern separation. A way to disentangle these two processes within remote spatial knowledge would be to have participants state frequently traveled certain routes prior to the experiment, complete distance discrimination for frequently and infrequently traveled routes, and randomly intermix repetition trials to see whether decisions which have been recently activated result in different behaviour.

Our landmark results are explained best by a combination of DG contribution to pattern separation processes and outside brain regions supporting performance. Theorists have proposed the uniqueness of the CA_3 subregion within spatial memory, in which spatial representations may be stored outside the DG (Hunsaker & Kesner, 2013). Given the performance of amnesic patients DA and JD, this account may be the most parsimonious explanation. Patients appear able to recruit other intact brain regions (which the 'at-risk' group and BL appear unable to) to complete these judgments. Supporting this hypothesis, that other major brain regions are involved in mnemonic discrimination for spatial information, is recent work that used scene stimuli in the same manner as objects in a revised MST and found that this did not relate to volumes of the DG/CA3 regions in healthy aging (Stark & Stark, 2017). The task also did not show sensitivity to parahippocampal volume, but only to subiculum volume (Stark & Stark, 2017). Discriminating between visual scenes does appear to invoke other brain regions, the subiculum in particular has been proposed to be involved in remote spatial memory (Zeidman & Maguire, 2016). This work suggests that the landmark condition is likely invoking the DG, but possibly also other brain areas such as the parahippocampus and subiculum. Our results suggest that using spatial and semantic stimuli can provide insight into mnemonic discrimination processes, but the results are complicated by other brain regions which are involved when accessing well-known information.

Contribution to Hippocampal Theory

Despite well-documented hippocampal changes that occur with age, healthy older adults performed as well as (and often numerically better than) younger adults on the landmark condition. Given the relative lack of experience living and navigating in the city, younger adults would be expected to have lower performance than older adults. Given that younger adults have far less experience in the city, yet performed as well as the older adults, suggests a decline or sub-optimal performance for the older adults. With a larger sample size, younger adults with more years living in the city and older adults newer to the city could be compared so that this confound of years of experience could be addressed. Currently, it is difficult to disentangle the explanations of older adults showing preservation on this task or potential loss given their experience.

Contrary to the Cognitive Map Theory (O'Keefe, 1990), and consistent with the Multiple Trace Theory (Moscovitch et al., 2005; Moscovitch et al., 2006), two of our three patients with

amnesia related to hippocampal damage could effectively complete the landmark condition, which is consistent with previous work (Rosenabum et al., 2000, Herdman et al., 2015). As noted above, care was taken to ensure that patients were tested on landmarks which were highly familiar. Given these patients' inability to learn new environments and having lived in the same environments for years if not decades, these landmarks were extremely familiar and frequently visited by all the patients. In contrast, the patients' control participants endorsed familiarity with the locations, and their years of experience and frequency downtown was covaried. As such, the 'at-risk' older adults' low performance is confounded with potential frequency effects that the patients' do not have. Furthermore, older adults almost always used an allocentric strategy to complete the task. Patient JD reported using a purely egocentric strategy to complete the task. Therefore, we can conclude that familiarity and non-hippocampally based strategy can allow for discrimination between highly similar distances even in the face of dense amnesia. Patients appear to be able to rely on schematic, gist-like knowledge to adequately complete this task. However, BL's performance does suggest that when there is high similarity between representations, the DG region of the hippocampus may be needed to make these fine-grained discriminations. This suggests that the CMT may be better revised to consider how making decisions within remote allocentric mental representations may interact with the detail needed within each decision, with decisions between highly similar representations requiring the hippocampus.

Other work has found a shift away from allocentric strategies to egocentric strategies with aging, the latter which are not hippocampally based (Colombo et al., 2017). In our task, our healthy older adult participants reported a higher confidence navigating in new spatial environments than younger adults (Table 1) and a similar strategy to younger adults which was biased allocentric (Table 8). The landmark condition is likely to be done easiest with an allocentric, 'bird's-eye' view strategy, given that route detail is not needed to successfully complete the task, which may explain why older adults used a similar strategy to younger adults. This also may explain why 'at-risk' older adult participants showed impaired performance, if these participants are relying on a hippocampally-based strategy and have more dysfunction, this will be the most difficult for them.

In this paradigm, intracue distance was not systematically varied. Previous work with vector mapping systematically manipulated intracue distance so that landmarks were on opposite

ends of the city, and therefore there were always large intracue distances (Rosenbaum et al., 2012). While intracue distance did not seem to uniformly impact performance in this paradigm, a more systematic investigation of the influence of intracue distance is warranted. It is possible that landmarks in proximity with one another allow a person to utilize their knowledge of the environment and boosts their performance. Alternatively, these landmarks being close to one another may make the task more difficult as the person may need to access fine-grained knowledge of the environment in order to make the distance judgments. It is possible that the lack of effect of intracue distance on the differential distance judgments in this study may be due to these two opposing effects. Further research can systematically varying intracue distance could help elucidate if and how intracue distance influences judgments of distance for highly similar representations.

Future Directions

Given the observed results in the 'at-risk' older adult group, future studies should investigate task performance in populations with well-defined etiology. Recruiting patients with diagnosed MCI and AD and acquiring hippocampal volumes could offer more information as to whether these effects persist with neurodegeneration.

As a consequence of maintaining high ecological validity, many aspects of cognitive maps' complexity was not manipulated. Intracue distance was not systematically varied, landmarks were not controlled for their external appearance, function, or landmark name similarity. The latter points may be particularly influential for older adults, who may struggle more with the interference caused by similar functions or names. For example, two museums in Toronto with different names (Art Gallery of Ontario and the Royal Ontario Museum) have a similar activity association of visiting exhibits and may be more likely to be confused with one another. The kind of landmarks may also be influential. For example, Kensington Market is an area in the city with multiple stores while St. Lawrence market is a single, historic, building with multiple vendors. In this example, area and landmark are confounded as well as function.

Future testing of semantic representations should have all participants describe and categorize animals so that experimenters can evaluate the accuracy of each participants' animal representations. For example, asking all participants to rank animals in order prior to testing would allow for incorrect representations to be excluded from analyses. Currently, animals were

only excluded if subjects reported a lack of familiarity with animals. The animal trials were created in a manner in which similarity was manipulated through intracue distance, and targets were typically smaller in size than cues as well as sometimes being a member of a different animal category (insects, birds, mammals). Future paradigms could systematically vary animal category to investigate whether these effects are generalizable across all animal types.

Conclusion

Our results suggest that there is increased difficulty and differences based in cognitive status within aging when discriminating between similar representations for well-established information. Healthy older adults show preservation on both tasks, supportive of a wealth of previous information showing that remote spatial memory and semantic knowledge are intact in normal aging. However, in a group of community-dwelling participants screened for cognitive impairment and showing MST LDI Scores in line with patients diagnosed with MCI, there is a reduction in performance for highly similar judgments in the landmark and animal conditions – suggestive of hippocampally-dependent declines in judgment. Patient BL shows impaired task performance only in the landmark condition and has numerically lower performance on the highly similar landmark judgments, in accordance with the idea that the dentate gyrus is selectively involved in separating out similar representations in memory. Patient DA, who has well-documented amnesia, shows intact performance on both tasks, which brings to question what other brain regions may be influencing performance for the landmark condition and also the importance of studying multiple amnesic patients with specific lesions. Patient JD, whose lesions are unknown but also has substantial memory impairments is also able to complete the landmark condition comparable to controls. It is possible that high familiarity, strategy differences, and even intracue distance may aid patients to access their cognitive maps in enough detail to perform well on the landmark condition. JD's animal performance is impaired and consistent with difficulties representing animals. His impairment offers additional support for the validity of using the animal condition to assess an aspect of semantic memory. Overall, the results here expand on how and if mnemonic discrimination is involved in prior knowledge across the lifespan, within potential cognitive decline, and how people with memory impairments and hippocampal damage access similar representations within prior-knowledge.

Supplemental Methods

Difference in number of Trials

Of the 19 young adult participants, four young adult participants completed 6 instead of 7 runs. Experimenters found young adults were finishing well before the older adults and did not need additional practice trials, so an extra experimental run was added for the remaining participants.

Participant Exclusion

Despite administering a familiarity survey prior to the experiment, it was not uncommon for participants to report being unfamiliar with landmarks they once reported being familiar with after the experiment. Given the frequency of this occurrence, participants were excluded from analyses if they reported being unfamiliar with at least 3 landmarks in the experiment. If participants reported post-experiment being less unfamiliar with more than 2 landmarks, trials containing these landmarks were removed from analyses. Similarly, Animal trials were removed if participants had knowledge of the animal and told the experimenter at the end of testing. If a person said they were familiar with an animal but it was not highly familiar to them (for example not as familiar with a lynx as they are familiar with a tick) the animal remained in their results.

Missing MST Task Data

The MST task crashed and was unavailable for 6 participants (3 older adult participants, 3 younger adult participants). To keep MST as a predictor in models and not lose these participants' data for the task MST LDI Scores were imputed for these participants. Imputed values were generated by using SPSS statistical package. The predictors of MST score, MST LDI Score, MoCA score, age, years of education, gender, and participant group were used in the scholastic regression model. The average of all the imputed values for each participant was calculated to create a single imputed value for each of the 6 participants. While imperfect, this method has been used previously in the literature. All MST graphs do not include any imputed data..

Strategy Usage Scoring

After the experiment, each person was asked how they completed the landmark condition. Their responses were recorded, and they were probed by the experimenter for details (for example if they utilized street names, cardinal directions, subway system). These responses were then coded into five Categories ranging from 1 to 5. A strategy entirely or predominantly allocentric was given a score of 1, a strategy biased allocentrically a score of 2, an equal usage of both strategies given a score of 3, a biased egocentric strategy score given a 4, and an entirely or predominantly egocentric strategy was given a score of 5. These were scored by S.P. and also by a research assistant. Where there were discrepancies in scoring, S.P. evaluated these for consistency with the scoring scheme. Large discrepancies were rare.

References

Bakker, A., Kirwan, C. B., Miller, M., & Stark, C. E. (2008). Pattern separation in the human hippocampal CA3 and dentate gyrus. Science, 319(5870), 1640-1642.

Baker, S., Vieweg, P., Gao, F., Gilboa, A., Wolbers, T., Black, S. E., & Rosenbaum, R. S. (2016). The Human Dentate Gyrus Plays a Necessary Role in Discriminating New Memories. *Current Biology*, *26*(19), 2629-2634.

Binder, J. R., Desai, R. H., Graves, W. W., & Conant, L. L. (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cerebral Cortex*, *19*(12), 2767-2796.

Bonnici HM, Chadwick MJ, Maguire EA. 2013. Representations of recent and remote autobiographical memories in hippocampal subfields. *Hippocampus* 23:849–54

Burgess, N., Maguire, E. A., & O'Keefe, J. (2002). The human hippocampus and spatial and episodic memory. *Neuron*, *35*(4), 625-641.

Carson, N., Leach, L., & Murphy, K. J. (2017). A re-examination of Montreal Cognitive Assessment (MoCA) cutoff scores. *International journal of geriatric psychiatry*.

Chadwick MJ, Bonnici HM, Maguire EA. 2014. CA3 size predicts the precision of memory recall. *PNAS* 111:10720–25

Colombo, D., Serino, S., Tuena, C., Pedroli, E., Dakanalis, A., Cipresso, P., & Riva, G. (2017).

Egocentric and allocentric spatial reference frames in aging: A systematic review. *Neuroscience & Biobehavioral Reviews, 80*, 605-621.

Crawford, J. R. & Garthwaite, P. H. (2002). Investigation of the single case in neuropsychology: Confidence limits on the abnormality of test scores and test score differences. *Neuropsychologia*, 40, 1196-1208.

Ekstrom, A. D., & Ranganath, C. (2017). Space, Time and Episodic Memory: the Hippocampus is all over the Cognitive Map. *Hippocampus*.

Epstein, R. A. (2008). Parahippocampal and retrosplenial contributions to human spatial navigation. *Trends in cognitive sciences*, *12*(10), 388-396.

Fidalgo, C. O., Changoor, A. T., Page-Gould, E., Lee, A. C., & Barense, M. D. (2016). Early cognitive decline in older adults better predicts object than scene recognition performance. *Hippocampus*, *26*(12), 1579-1592.

Herdman, K. A., Calarco, N., Moscovitch, M., Hirshhorn, M., & Rosenbaum, R. S. (2015). Impoverished descriptions of familiar routes in three cases of hippocampal/medial temporal lobe amnesia. *cortex*, *71*, 248-263.

Kivisaari, S. L., Probst, A., & Taylor, K. I. (2013). The perirhinal, entorhinal, and parahippocampal cortices and hippocampus: an overview of functional anatomy and protocol for their segmentation in MR images. In *fMRI* (pp. 239-267). Springer Berlin Heidelberg.

Holden, H. M., Hoebel, C., Loftis, K., & Gilbert, P. E. (2012). Spatial pattern separation in cognitively normal young and older adults. *Hippocampus*, *22*(9), 1826-1832.

Holden, H. M., & Gilbert, P. E. (2012). Less efficient pattern separation may contribute to age-related spatial memory deficits. *Frontiers in aging neuroscience*, *4*, 9.

Kyle, C. T., Stokes, J. D., Lieberman, J. S., Hassan, A. S., & Ekstrom, A. D. (2015). Successful retrieval of competing spatial environments in humans involves hippocampal pattern separation mechanisms. *Elife*, *4*.

Kwan, D., Craver, C. F., Green, L., Myerson, J., & Rosenbaum, R. S. (2013). Dissociations in future thinking following hippocampal damage: evidence from discounting and time perspective in episodic amnesia. *Journal of Experimental Psychology: General*, *142*(4), 1355.

Kwan, D., Craver, C.F., Green, L., Myerson, J., Gao, F., Black, S.E., and Rosenbaum, R.S. (2015). Cueing the personal future to reduce discounting in intertemporal choice: Is episodic prospection necessary? *Hippocampus* 25, 432–443.

Luis, C. A., Keegan, A. P., & Mullan, M. (2009). Cross validation of the montreal cognitive assessment in community dwelling older adults residing in the southeastern US. *International Journal of Geriatric Psychiatry, 24*(2), 197.

Maguire, E. A., Gadian, D. G., Johnsrude, I. S., Good, C. D., Ashburner, J., Frackowiak, R. S., & Frith, C. D. (2000). Navigation-related structural change in the hippocampi of taxi drivers. *Proceedings of the National Academy of Sciences*, *97*(8), 4398-4403.

Manns, J. R., Hopkins, R. O., & Squire, L. R. (2003). Semantic memory and the human

hippocampus. *Neuron*, *38*(1), 127-133.

Morgan, L. K., MacEvoy, S. P., Aguirre, G. K., & Epstein, R. A. (2011). Distances between real-world locations are represented in the human hippocampus. *Journal of Neuroscience*, *31*(4), 1238-1245.

Moscovitch, M., Cabeza, R., Winocur, G., & Nadel, L. (2016). Episodic memory and beyond: the hippocampus and neocortex in transformation. *Annual review of psychology*, *67*, 105-134.

Moscovitch, M., Nadel, L., Winocur, G., Gilboa, A., & Rosenbaum, R. S. (2006). The cognitive neuroscience of remote episodic, semantic and spatial memory. Current opinion in neurobiology, 16(2), 179-190.

Moscovitch, M., Rosenbaum, R. S., Gilboa, A., Addis, D. R., Westmacott, R., Grady, C., … Nadel, L. (2005). Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. *Journal of Anatomy*, *207*(1), 35–66.

Moscovitch, M., Nadel, L., Winocur, G., Gilboa, A., & Rosenbaum, R. S. (2006). The cognitive neuroscience of remote episodic, semantic and spatial memory. *Current opinion in neurobiology*, *16*(2), 179-190.

Moyer, R. S. (1973). Comparing objects in memory: Evidence suggesting an internal psychophysics. *Perception & Psychophysics*, *13*(2), 180–184.

Moyer, R. S., & Landauer, T. K. (1967). Time required for judgements of numerical inequality. *Nature*, *215*(5109), 1519–1520.

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., ... & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695-699.

Newsome, R. N., Duarte, A., Pun, C., Smith, V. M., Ferber, S., & Barense, M. D. (2015). A retroactive spatial cue improved VSTM capacity in mild cognitive impairment and medial temporal lobe amnesia but not in healthy older adults. *Neuropsychologia*, *77*, 148-157.

O'Keefe, J. (1990). A computational theory of the hippocampal cognitive map. *Progress in brain research*, 83, 301-312.

Olsen, R. K., Yeung, L. K., Noly-Gandon, A., D'Angelo, M. C., Kacollja, A., Smith, V. M., ... & Barense, M. D. (2017). Human anterolateral entorhinal cortex volumes are associated with cognitive decline in aging prior to clinical diagnosis. *Neurobiology of aging*, *57*, 195-205.

Palombo, D. J., Bacopulos, A., Amaral, R. S., Olsen, R. K., Todd, R. M., Anderson, A. K., & Levine, B. (2017). Episodic Autobiographical Memory is Associated with Variation in the Size of Hippocampal Subregions. *Hippocampus*.

Patterson, K., Nestor, P. J., & Rogers, T. T. (2007). Where do you know what you know? The

representation of semantic knowledge in the human brain. *Nature Reviews Neuroscience*, *8*(12), 976.

Renoult, L., Davidson, P. S., Palombo, D. J., Moscovitch, M., & Levine, B. (2012). Personal semantics: at the crossroads of semantic and episodic memory. *Trends in cognitive sciences*, *16*(11), 550-558.

Rosenbaum, R. S., Priselac, S., Köhler, S., Black, S. E., Gao, F. Q., Nadel, L., & Moscovitch, M. (2000). Remote spatial memory in an amnesic person with extensive bilateral hippocampal lesions. *Nature Neuroscience, 3,* 1044-1048.

Rosenbaum, R. S., Winocur, G., & Moscovitch, M. (2001). New views on old memories: Re-evaluating the role of the hippocampal complex. *Behavioural Brain Research*, *127*(1-2), 183-197.

Rosenbaum, R. S., Ziegler, M., Winocur, G., Grady, C. L., & Moscovitch, M. (2004). "I have often walked down this street before": fMRI studies on the hippocampus and other structures during mental navigation of an old environment. Hippocampus, 14(7), 826-835.

Rosenbaum, R. S., Moscovitch, M., Foster, J. K., Schnyer, D. M., Gao, F., Kovacevic, N., ... & Levine, B. (2008). Patterns of autobiographical memory loss in medial-temporal lobe amnesic patients. *Journal of Cognitive Neuroscience*, *20*(8), 1490-1506.

Rosenbaum, R. S., Winocur, G., Binns, M. A., & Moscovitch, M. (2012). Remote spatial memory in aging: all is not lost. *Frontiers in Aging Neuroscience*, *4*, 25.

Rolls, E. T. (2016). Pattern separation, completion, and categorisation in the hippocampus and neocortex. *Neurobiology of learning and memory*, *129*, 4-28.

Rossetti, H. C., Lacritz, L. H., Cullum, C. M., & Weiner, M. F. (2011). Normative data for the Montreal cognitive assessment (MoCA) in a population-based sample. *Neurology*, *77*(13), 1272-1275.

Spiers HJ, Maguire EA. A navigational guidance system in the human brain. *Hippocampus*. 2007; 17:618–626.

Stark, S. M., Stevenson, R., Wu, C., Rutledge, S., & Stark, C. E. L. (2015). Stability of age-related deficits in the mnemonic similarity task across task variations. *Behavioral Neuroscience*, *129*(3), 257–268.

Stark, S. M., Yassa, M. A., Lacy, J. W., & Stark, C. E. L. (2013). A task to assess behavioral pattern separation (BPS) in humans: Data from healthy aging and mild cognitive impairment. *Neuropsychologia*, *51*, 2442–2449.

Tulving, E., Hayman, C. A., & Macdonald, C. A. (1991). Long-lasting perceptual priming and semantic learning in amnesia: A case experiment. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *17*, 595–617.

Vargha-Khadem, F., Gadian, D. G., Watkins, K. E., Connelly, A., Van Paesschen, W., & Mishkin, M. (1997). Differential effects of early hippocampal pathology on episodic and semantic memory. *Science*, *277*(5324), 376-380.

Van Strien, N. M., Cappaert, N. L. M., & Witter, M. P. (2009). The anatomy of memory: an interactive overview of the parahippocampal–hippocampal network. *Nature Reviews Neuroscience*, *10*(4), 272-282.

Westmacott, R., & Moscovitch, M. (2001). Names and words without meaning: incidental postmorbid semantic learning in a person with extensive bilateral medial temporal damage. *Neuropsychology*, *15*(4), 586.

Westmacott, R., Black, S. E., Freedman, M., & Moscovitch, M. (2004). The contribution of autobiographical significance to semantic memory: Evidence from Alzheimer's disease, semantic dementia, and amnesia. *Neuropsychologia*, *42*(1), 25-48.

Yassa, M. A., & Stark, C. E. (2011). Pattern separation in the hippocampus. *Trends in Neurosciences*, *34*(10), 515-525.

Zeidman, P., & Maguire, E. A. (2016). Anterior hippocampus: the anatomy of perception, imagination and episodic memory. *Nature Reviews Neuroscience*, *17*(3), 173-182.

Zhang, S., & Chiang-shan, R. L. (2012). Functional connectivity mapping of the human precuneus by resting state fMRI. *Neuroimage*, *59*(4), 3548-3562.

Tables

Table 1

Young and Older Adult Demographics

	Sample Size	Sex Division	MoCA Score	Age	Years of Education	Years in Toronto	Confidence Navigation New Spatial Locations [1]	Confidence Navigation Old Spatial Locations [1]
Younger adults	N = 19	6M, 13F	NA	25.89 (4.04)	17.42 (2.52)	16.55 (10.39)	7.05 (1.90)	8.90 (0.94)
Healthy Older Adults	N = 18	10M, 8F	27.22 (1.00)	66.89 (4.57)	16.50 (2.01)	54.33 (16.62)	8.22 (1.56)	9.28 (0.83)
At-risk Older Adults	N = 15	10M, 5F	22.93 (2.34)	66.73 (4.70)	16.77 (3.55)	44.67 (13.65)	7.53 (2.00)	9.13 (0.83)

Note: Values in table reflect means and in parentheses are standard deviations

Note: Participants' confidence navigating new and old spatial location was indicated by a 1 to 10 likert scale, 10 being 'Very confident' and 1 being 'Not at all confident'.

Table 2

Patient Demographics and Controls

	DA	**DA Controls**	**JD**	**JD Controls**	**BL**	**BL Controls**
Number of People	1	8	1	7	1	5
Age	66	65.86 (1.35)	65	65.86 (1.35)	57	60.6 (3.65)
Years of Education	17	16.86 (0.90)	19	16.86 (0.90)	13	15.20 (1.64)
Sex	M	5M, 3F	M	5M, 2F	M	4M, 1F

Note: Table values are means and in parentheses are standard deviations. M indicates male sex while F indicates female sex. All control scored 26 or above on the Montreal Cognitive Assessment (MoCA).

Table 3

Demographic and Neuropsychological Data for Patient JD

	J.D	**Description**
Age at injury	60	
Years of Education	19	
WAIS -R[a]		
FSIQ	90th percentile	High average
VIQ	94th percentile	Superior
PIQ	73rd percentile	Average
WMS-IV		
LP-I (percentile)	9	Low average
LP- II (percentile)	1	Impaired
Recognition	10-16%	Low average
CVLT		
Acquisition (*T* score)		
Short delay free (*Z* score)	-2.5	Impaired
Long delay free (*Z* score)	-3.0	Impaired
Recogn. Discrim. (*Z* score)	-3.5	Impaired
Block Design	58	High Average
Judgment of Line (1/2x2)	86+	Superior
Symbol Search	5	Borderline Impaired
Digits	13	High average
Trails A (scaled score)	40	Low average
Trails B (scaled score)	43	Average
Stroop (D-KEFS)		
Color Naming (scaled score)	11	Average
C total errors	0	
Word reading (scaled score)	11	Average
W total errors	0	
Boston Naming Test (/60)	60	Intact
WCST		
Categories (/6)	>16th percentile	Intact
Persev. Response (Z score)	9th percentile	Low average
FAS Fluency[c] (Z score)	-2.98	Impaired
Semantic Fluency (Z score)	-1.95	Borderline Impaired
ROCF		
Copy	16th percentile	Low average
Immediate Recall	4th percentile	Borderline impaired
Delayed Recall	<1 percentile	Impaired
MoCA	21	
Visuospatial/Executive (/5)	4	
Naming (/3)	3	
Attention (/6)	6	
Language (/3)	1	

Abstraction (/2)	2	
Delayed Recall (/5)	0	
Orientation (/6)	5	

Note. WAIS-R _ Wechsler Adult Intelligence Scale–Revised; WMS-R _ Wechsler Memory Scale–Revised; LP _ Logical Passages; CVLT _ California Verbal Learning Test; ROCF _ Rey Osterrieth Complex Figure; WCST _ Wisconsin Card Sorting Test; AI _ Autobiographical Interview; FSIQ _ Full-scale IQ; VIQ _ Verbal IQ; PIQ _ Performance IQ; Recog. Discrim. _ Recognition Discrimination; Persev. Resp. _ Perseverative Responses; MoCA_Montreal Cognitive Assessment

a Scores reflect performance on the Wechsler Abbreviated Scale of Intelligence–II.

b Score is based on the number of animal names produced in 1 min.

c Score is based on the total number of words produced for the letters *F*, *A*, and *S* when given 1 min for each.

Table 4

DA's Demographics neuropsychological testing results, adapted from Kwan et al., 2013

	DA
Age at Injury	47
Years of Education	17
WAIS -R[a]	
FSIQ	117
VIQ	121
PIQ	106
Digits	13
WMS-R	
LP I (percentile)	15th
LP II (percentile)	<1st
Boston Naming/60	56
Semantic Fluency (scaled score)[b]	12
Letter Fluency (scaled score)[c]	8
CVLT	
Acquisition (*T* score)	9
Short delay free (*Z* score)	-4
Long delay free (*Z* score)	-4
Recog. Discrim. (*Z* score)	-4
ROCF (/36)	
Copy	35
Immediate recall	
Delayed recall	0
WCST	
Categories (/6)	6
Persev. Resp. (Z score)	-.5

Note. WAIS-R _ Wechsler Adult Intelligence Scale–Revised; WMS-R _ Wechsler Memory Scale–Revised;LP _ Logical Passages; CVLT _ California Verbal Learning Test; ROCF _ Rey Osterrieth Complex Figure;WCST _ Wisconsin Card Sorting Test; AI _ Autobiographical Interview; FSIQ _ Full-scale IQ; VIQ _ VerbalIQ; PIQ _ Performance IQ; Recog. Discrim. _ Recognition Discrimination; Persev. Resp. _ Perseverative Responses;

[a] Scores reflect performance on the Wechsler Abbreviated Scale of Intelligence–II.

[b] Score is based on the number of animal names produced in 1 min. c Score is based on the total number of words produced for the letters *F*, *A*, and *S* when given 1 min for each.

Table 5

BL Neuropsychological Data, adapted from Baker et al., 2016

			WMS-R/III/IV		Verb Learn.			ROCF	
FSIQ	WCST	LF	LP/M-I	LP/M-II	AQ	LDFC	R	C	DR
92	6	11	8	6	8	7	10	6	5

Note. FSIQ: Wechsler Abbreviated Scale of Intelligence–
IV. WCST: Wisconsin Card Sorting Test, number of completed categories /6. The following measures are reported in scaled scores: LF: letter fluency. Verb Learn: Verbal learning based on California Verbal Learning Test-II; AQ, acquisition; LDFR, long delay free recall; R, recognition. ROCF: Rey-Osterrieth Complex Figure, C, copy, DR, delayed recall.

Table 6

Mean and standard deviation on task by participant group and MoCA score

Trial Type	Group	Bin Number	MoCA Status	Mean Accuracy	Standard Deviation Accuracy	Number of Participants
Distance	YA	Bin1	*NA*	0.6085	0.16508	19
Distance	YA	Bin2	*NA*	0.64714	0.13578	19
Distance	YA	Bin3	*NA*	0.71922	0.14179	19
Distance	YA	Bin4	*NA*	0.73681	0.12395	19
Distance	YA	Bin5	*NA*	0.84617	0.16221	19
Distance	OA	Bin1	Fail	0.52011	0.13524	15
Distance	OA	Bin1	Pass	0.63595	0.17233	17
Distance	OA	Bin2	Fail	0.64893	0.12879	15
Distance	OA	Bin2	Pass	0.69476	0.15248	18
Distance	OA	Bin3	Fail	0.66955	0.17133	15
Distance	OA	Bin3	Pass	0.74212	0.1901	18
Distance	OA	Bin4	Fail	0.68209	0.16726	15
Distance	OA	Bin4	Pass	0.81655	0.16993	18
Distance	OA	Bin5	Fail	0.81804	0.1001	15
Distance	OA	Bin5	Pass	0.86978	0.16915	18
Animal	YA	Bin1	*NA*	0.8181	0.11007	19
Animal	YA	Bin2	*NA*	0.88426	0.09519	19
Animal	YA	Bin3	*NA*	0.92134	0.09076	19
Animal	YA	Bin4	*NA*	0.97851	0.05467	19
Animal	YA	Bin5	*NA*	0.9726	0.04852	19
Animal	OA	Bin1	Fail	0.81624	0.15418	15
Animal	OA	Bin1	Pass	0.90534	0.06895	18
Animal	OA	Bin2	Fail	0.90838	0.07657	15
Animal	OA	Bin2	Pass	0.94716	0.07198	18
Animal	OA	Bin3	Fail	0.95111	0.08176	15
Animal	OA	Bin3	Pass	0.97474	0.0424	18
Animal	OA	Bin4	Fail	0.95131	0.1037	15
Animal	OA	Bin4	Pass	1	0	18
Animal	OA	Bin5	Fail	0.96732	0.05953	15
Animal	OA	Bin5	Pass	1	0	18

Table 7

Accuracy on task for Patients

Trial Type	Bin Number	Patient	Accuracy
Distance	Bin1	BL	0.25
Distance	Bin2	BL	0.75
Distance	Bin3	BL	0.58
Distance	Bin4	BL	0.64
Distance	Bin5	BL	0.67
Distance	Bin1	DA	0.70
Distance	Bin2	DA	0.75
Distance	Bin3	DA	0.82
Distance	Bin4	DA	0.50
Distance	Bin5	DA	0.92
Distance	Bin1	JD	0.77
Distance	Bin2	JD	0.79
Distance	Bin3	JD	0.71
Distance	Bin4	JD	0.85
Distance	Bin5	JD	1.00
Animal	Bin1	BL	0.92
Animal	Bin2	BL	0.92
Animal	Bin3	BL	1.00
Animal	Bin4	BL	0.92
Animal	Bin5	BL	1.00
Animal	Bin1	DA	0.89
Animal	Bin2	DA	1.00
Animal	Bin3	DA	1.00
Animal	Bin4	DA	1.00
Animal	Bin5	DA	1.00
Animal	Bin1	JD	0.73
Animal	Bin2	JD	0.79
Animal	Bin3	JD	0.75
Animal	Bin4	JD	0.67
Animal	Bin5	JD	0.80

Table 8

Strategy Usage across groups

Group	Mean Strategy Score	Standard Deviation	Number of Participants
Young Adults	2.32	1.25	19
Healthy Older Adults	2.5	1.65	18
'At-risk' Older Adults	2.2	1.26	15

Table 9

Logistic Regression and other model results using accuracy as the criterion for younger adults (Landmark condition)

Predictor	***B (Estimate)***	***Standard error***	***Z- Value***	***Significance***
(Intercept)	0.75	0.57	1.31	0.19
MST LDI Score	0.00	0.00	1.04	0.30
Years Living in Toronto	0.02	0.01	2.76	0.01 **
Years of Education	-0.05	0.03	-1.37	0.17
Intracue Distance	0.00	0.0001	0.96	0.34
Analysis Contrasting Bins			$X^2 = 34.29$	$p < .001$***
Analysis Contrasting Downtown frequency			$X^2 = 9.4566$	0.01**

Note. * indicates p < .05. ** indicates p < .01 *** indicates p <.001

Table 10

Logistic Regression and other model results using accuracy as the criterion for younger adults (Animal condition)

Predictor	***B (Estimate)***	***Standard error***	***Z- Value***	***Significance***
(Intercept)	-2.81	1.03	-2.73	0.01**
MST LDI Score	0.01	0.01	1.16	0.25
Age	0.11	0.04	2.57	0.01*
Years of Education	0.07	0.07	1.06	0.29
Analysis Contrasting Bins			X^2 = 52.82	p <.001***

Note. * indicates p < .05. ** indicates p < .01 *** indicates p <.001

Table 11

Logistic Regression and other model results using accuracy as the criterion for healthy older Adults (Landmark condition)

Predictor	***B* *(Estimate)***	***Standard error***	***Z- Value***	***Significance***
(Intercept)	1.29	2.29	0.56	0.57
MST LDI Score	-0.01	0.01	-2.14	0.03 *
MoCA Executive Function Subscale score	0.18	0.17	1.10	0.27
MoCA Memory Subscale score	-0.16	0.13	-1.27	0.20
Years Living in Toronto	-0.01	0.01	-1.23	0.22
age	-0.02	0.03	-0.71	0.48
Years of Education	0.10	0.07	1.50	0.13
Intracue Distance	-0.0001	0.0001	-1.51	0.13
Analysis Contrasting Bins			$X^2 = 35.629$	p <.001
Analysis Contrasting Downtown frequency			$X^2 = 1.9354$	0.58

Note. * indicates p < .05. ** indicates p < .01 *** indicates p <.001

Table 12

Logistic Regression and other model results using accuracy as the criterion for healthy older adults (Animal condition)

Predictor	***B (Estimate)***	***Standard error***	***Z- Value***	***Significance***
(Intercept)	10.80	3.97	2.72	0.01 **
MST LDI Score	-0.01	0.01	-0.59	0.55
MoCA Executive Function Subscale score	-0.29	0.25	-1.14	0.25
MoCA Memory Subscale score	-0.26	0.20	-1.29	0.20
Age	-0.09	0.04	-2.25	0.02*
Years of Education	-0.02	0.11	-0.20	0.84
Analysis Contrasting Bins			$X^2 = 43.959$	$p < .001$

Note. * indicates p < .05. ** indicates p < .01 *** indicates p <.001

Table 13

Logistic Regression and other model results using accuracy as the criterion for 'at-risk' older adults (Landmark condition)

Predictor	***B (Estimate)***	***Standard error***	***Z- Value***	***Significance***
(Intercept)	-2.21	2.25	-0.98	0.33
MST Lure Score	0.01	0.01	0.56	0.58
MoCA Executive Function Subscale score	-0.02	0.11	-0.17	0.87
MoCA Memory Subscale score	-0.08	0.07	-1.07	0.28
Years Living in Toronto	0.01	0.01	0.50	0.61
Age	0.03	0.03	0.92	0.36
Years of Education	0.02	0.04	0.39	0.70
Intracue Distance	-0.0001	0.0001	-1.19	0.24
Analysis Contrasting Bins			X^2 = 37.73	p < .001***
Analysis Contrasting Downtown frequency			X^2 = 1.21	0.55

Note. * indicates p < .05. ** indicates p < .01 *** indicates p <.001

Table 14

Logistic Regression and other model results using accuracy as the criterion for ‘at-risk’ older adults (Animal condition)

Predictor	*B (Estimate)*	*Standard error*	*Z- Value*	*Significance*
(Intercept)	-0.70	3.83	-0.18	0.85
MST Lure Score	0.04	0.02	2.21	0.03*
MoCA Executive Function Subscale score	0.29	0.23	1.29	0.20
MoCA Memory Subscale score	-0.39	0.16	-2.40	0.02*
Age	0.03	0.06	0.53	0.60
Years of Education	0.02	0.08	0.23	0.82
Analysis Contrasting Bins			X^2 = 22.7 97	p <.001

Note. * indicates p < .05. ** indicates p < .01 *** indicates p <.001

Table 15

Logistic Regression and other model results using accuracy as the criterion for young adults and healthy older adults (Landmark condition)

Predictor	***B (Estimate)***	***Standard error***	***Z- Value***	***Significance***
(Intercept)	0.80	0.67	1.18	0.24
MST LDI Score	-0.01	0.004	-1.9	0.06
Group	-0.29	0.20	-1.46	0.14
Years of Education	0.017	0.04	0.48	0.63
Intracue Distance	-0.00001	0.00005	-0.23	0.82
Analysis Contrasting Bins			X^2 = 68.08	p < .001 ***
Analysis Contrasting Group			X^2 = 6.55	0.09

Note. * indicates p < .05. ** indicates p < .01 *** indicates p <.001

Table 16

Logistic Regression and other model results using accuracy as the criterion for young adults and healthy older adults (Animal condition)

Predictor	***B (Estimate)***	***Standard error***	***Z- Value***	***Significance***
(Intercept)	2.40	0.25	9.61	$p < .001$***
MST LDI Score	0.003	0.01	0.53	0.60
Analysis Contrasting Bins			$X^2 = 90.73$	$p < .001$***
Analysis Contrasting Group			$X^2 = 11.70$	$p <.001$***

Note. * indicates p < .05. ** indicates p < .01 *** indicates p <.001

Table 17

Logistic Regression and other model results using accuracy as the criterion for healthy older adults and 'at-risk' older adults (Landmark condition)

Predictor	***B (Estimate)***	***Standard error***	***Z- Value***	***Significance***
(Intercept)	0.04	1.37	0.03	$p < .001$***
MST LDI Score	-0.01	0.004	-2.34	0.02*
MoCA Status<26 cut-off	0.44	0.19	2.35	0.02*
Years of Education	-0.003	0.03	-0.10	0.92
Age	0.006	0.02	0.30	0.76
Intracue Distance	-0.0001	0.00006	-1.93	0.05*
Analysis Contrasting Bins			$X^2 = 70.681$	p < .001***
Analysis Contrasting Downtown Frequency			$X^2 = 1.9555$	0.58
Analysis Contrasting MoCA Group			$X^2 = 5.36$	0.02*

Note. * indicates p < .05. ** indicates p < .01 *** indicates p <.001

Table 18

Logistic Regression and other model results using accuracy as the criterion for healthy older adults and 'at-risk' older adults (Animal condition)

Predictor	***B (Estimate)***	***Standard error***	***Z- Value***	***Significance***
(Intercept)	5.60	2.48	2.26	0.02*
MST LDI Score	0.004	0.01	0.47	0.64
MoCA Status < 26 cut-off	0.80	0.34	2.38	0.02*
Years of Education	0.003	0.06	0.06	0.95
Age	-0.06	0.04	-1.62	0.10
Analysis Contrasting Bins			X^2 = 55.18 2	p <.001***
Analysis Contrasting MoCA Group			X^2 = 5. 29	.02*

Note. * indicates p < .05. ** indicates p < .01 *** indicates p <.001

Figure Captions

Figure 1: Schematic of Task for both landmark and animal conditions

Figure 2: BL Hippocampal Segmentation of patent BL (in A) and a control participant (B) adapted from Baker et al., 2016. Borders in red outline the CA3&DG subregions, in Green the CA1-2 transition, in yellow the CA1 region, and in blue the subiculum.

Figure 3: Patient DA's MRI. Adapted from Kwan et al., 2013. Coronal T1 MRI. Image is presented according to radiological convention (right hemisphere is on the left side of the image).

Figure 4: MST Accuracy across younger adults and older adult participant groups. Error bars represent standard error.

Figure 5: MST LDI scores across younger adults and older adult participant groups. Error bars represent standard error.

Figure 6. Bar graph depicting accuracy for the landmark condition for healthy young and older adult participants. Error bars show standard error.

Figure 7. Bar graph depicting accuracy for the landmark condition for healthy and at-risk older adult participants. Error bars show standard error.

Figure 8. Bar graph depicting accuracy for the animal condition for healthy young and older adult participants. Error bars show standard error.

Figure 9. Bar graph depicting accuracy for the animal condition for healthy and at-risk older adult participants. Error bars show standard error.

Figure 10. Line graph depicting animal and landmark condition accuracy for patient JD compared to 7 control participants, including his wife.

Figure 11. Patient JD Follow-Testing Documents. This image is a copy of JD's ranking of animals used in the experiment in size

Figure 12. Line graph depicting animal and landmark condition accuracy for patient DA compared to 8 control participants, including his wife.

Figure 13. Line graph depicting animal and landmark condition accuracy for patient BL compared to 5 control participants.

Figure 1

Task Schematic

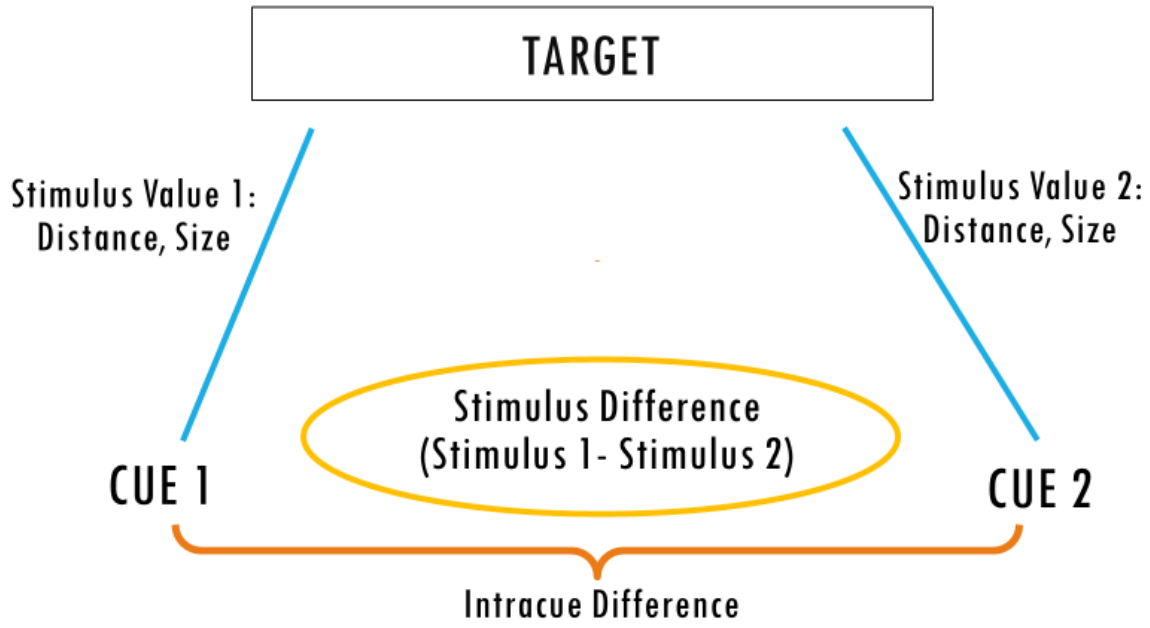


Figure 2

Hippocampal Segmentation for Patient BL

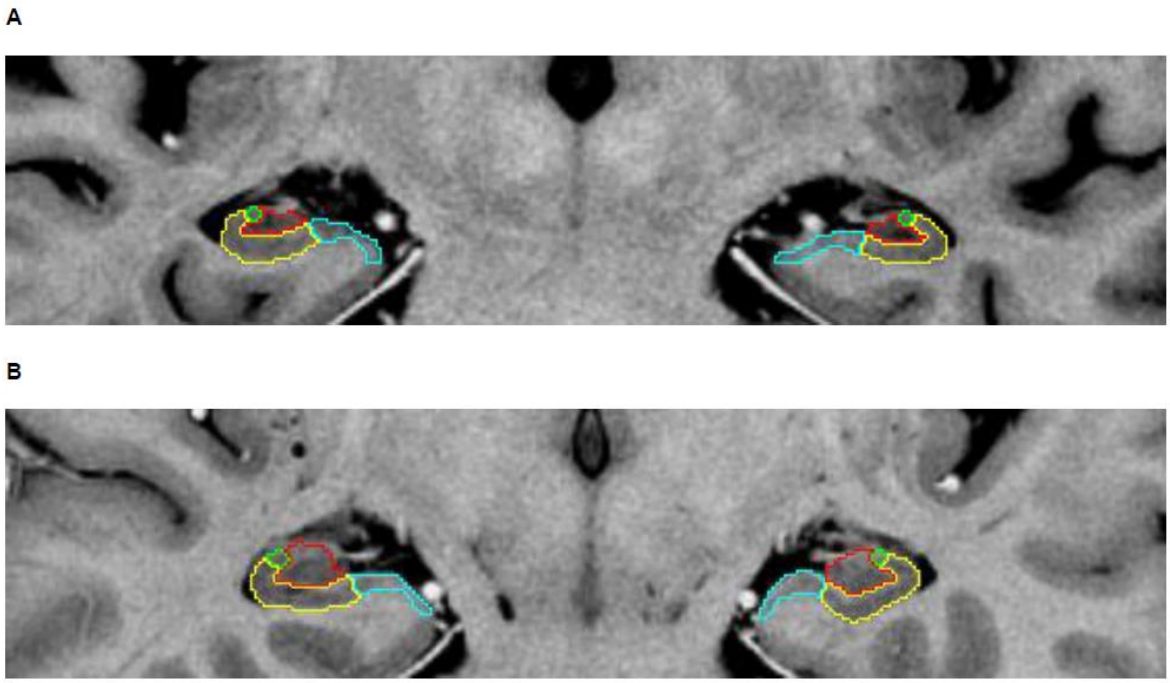


Figure 3

MRI for Patient DA

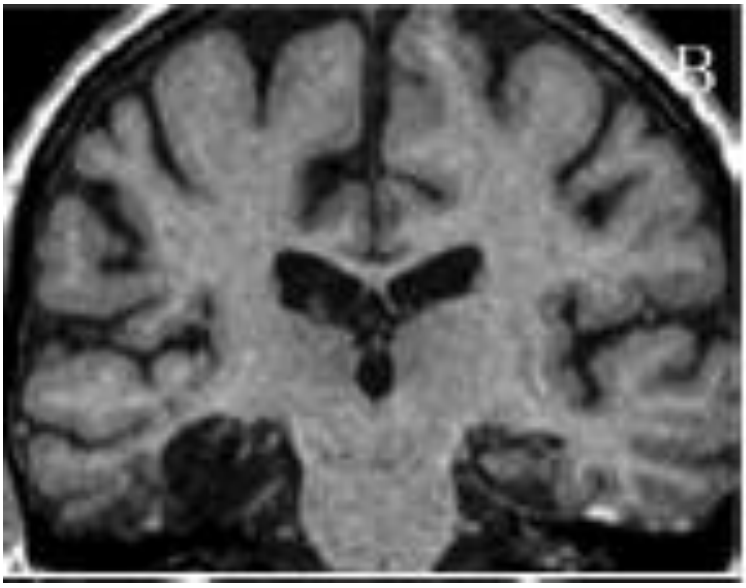


Figure 4

Young and Older Adult MST Recognition Accuracy Performance

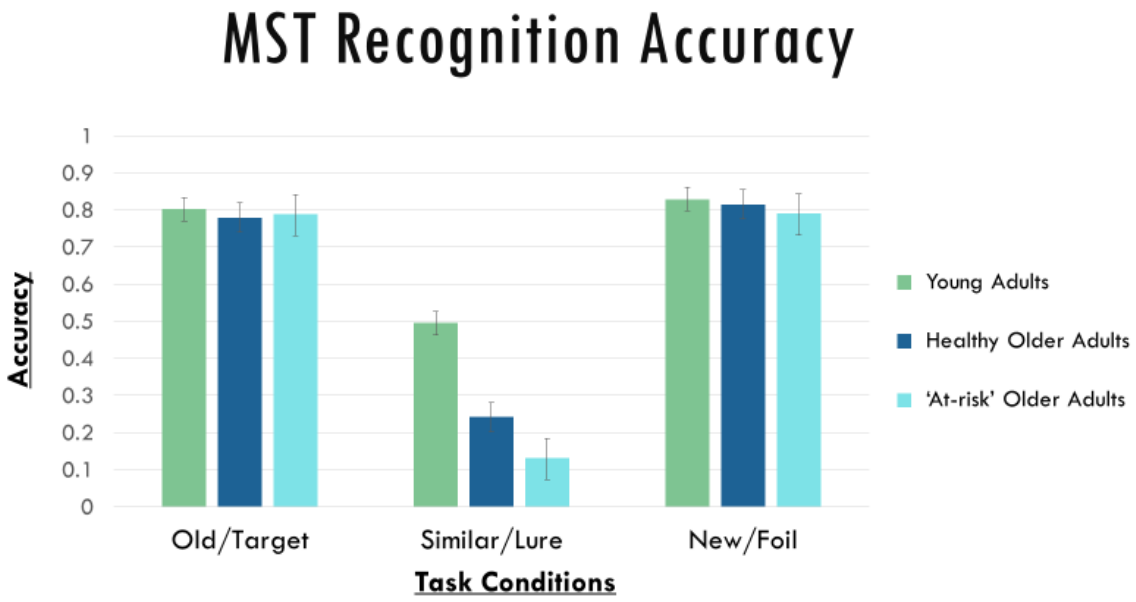


Figure 5

Young and Older Adult MST LDI Score performance

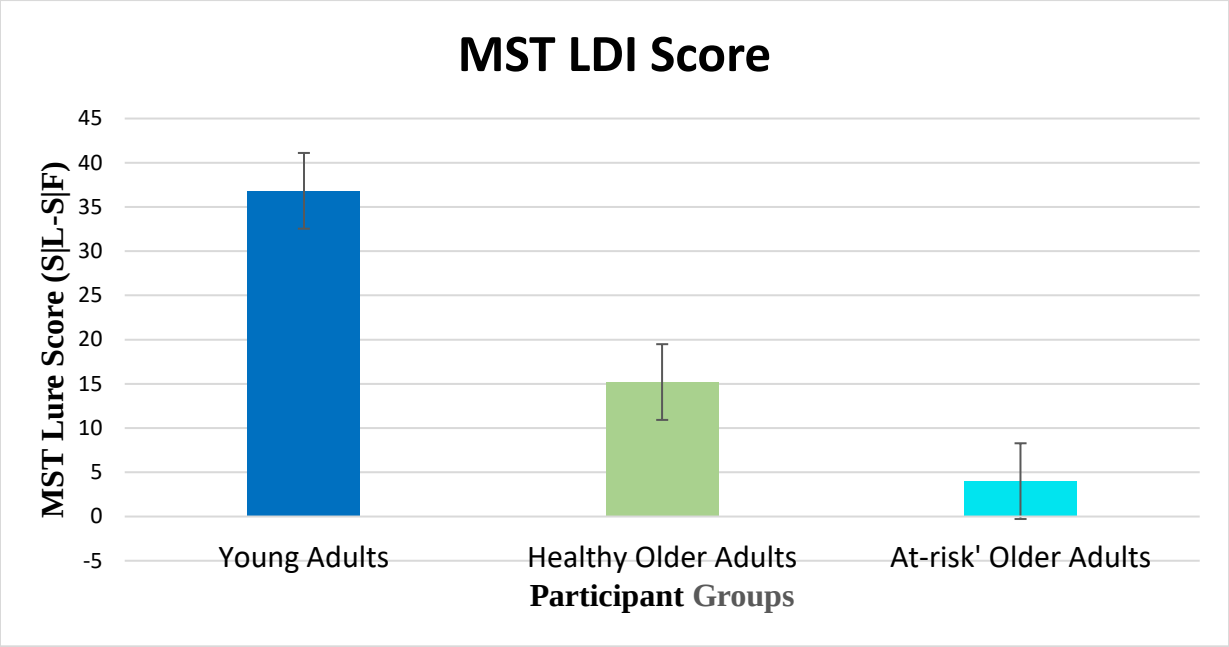


Figure 6

Young and Healthy Older Adult Landmark Accuracy

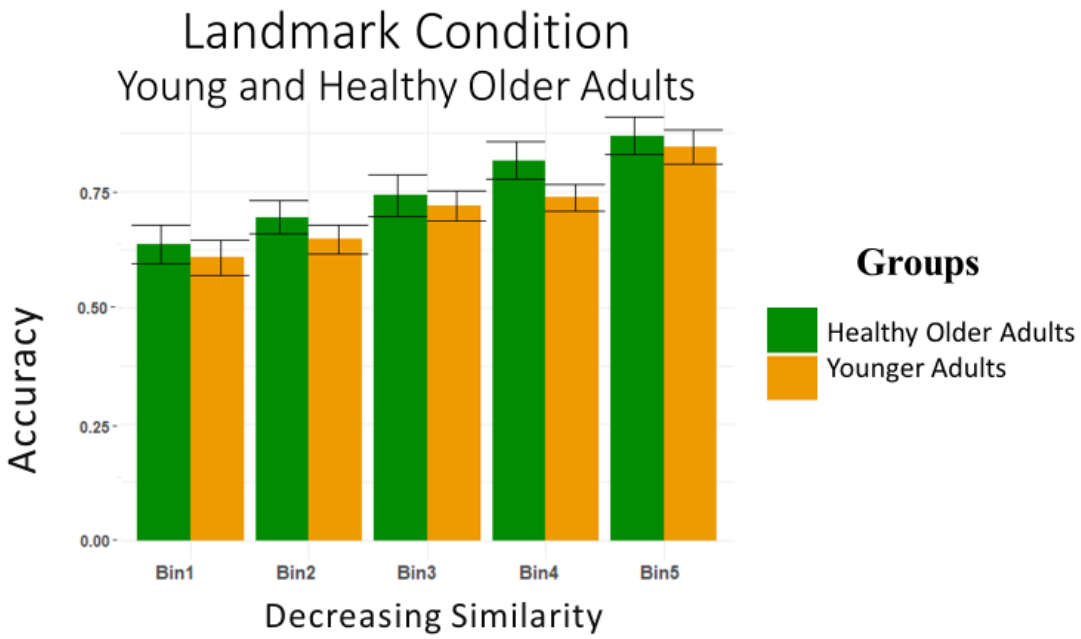


Figure 7

Healthy and At-risk Older Adult Landmark Accuracy

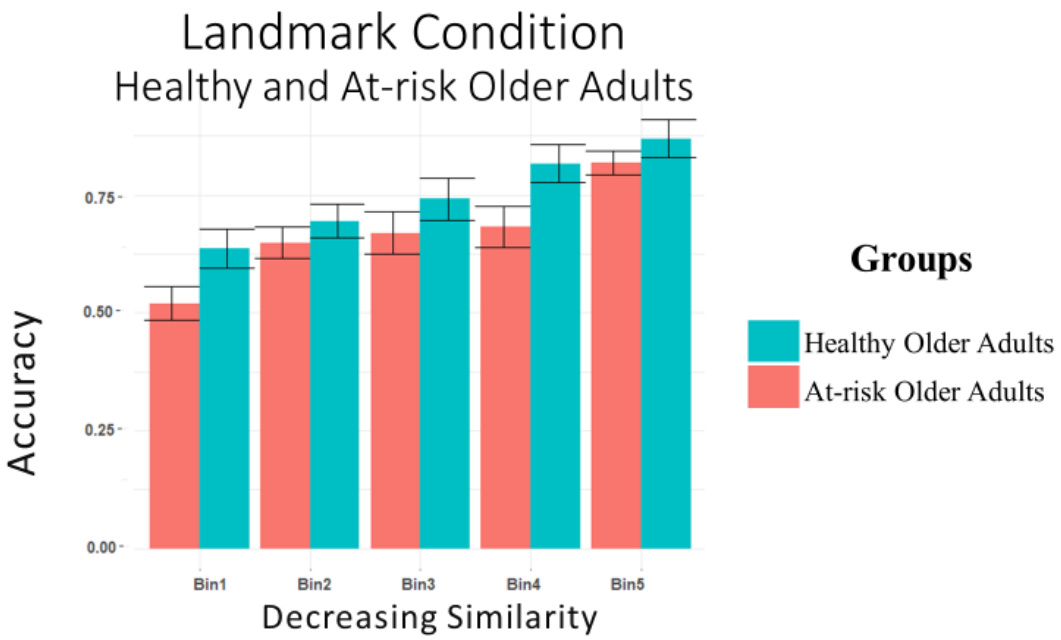


Figure 8

Young and Healthy Older Adult Animal Accuracy

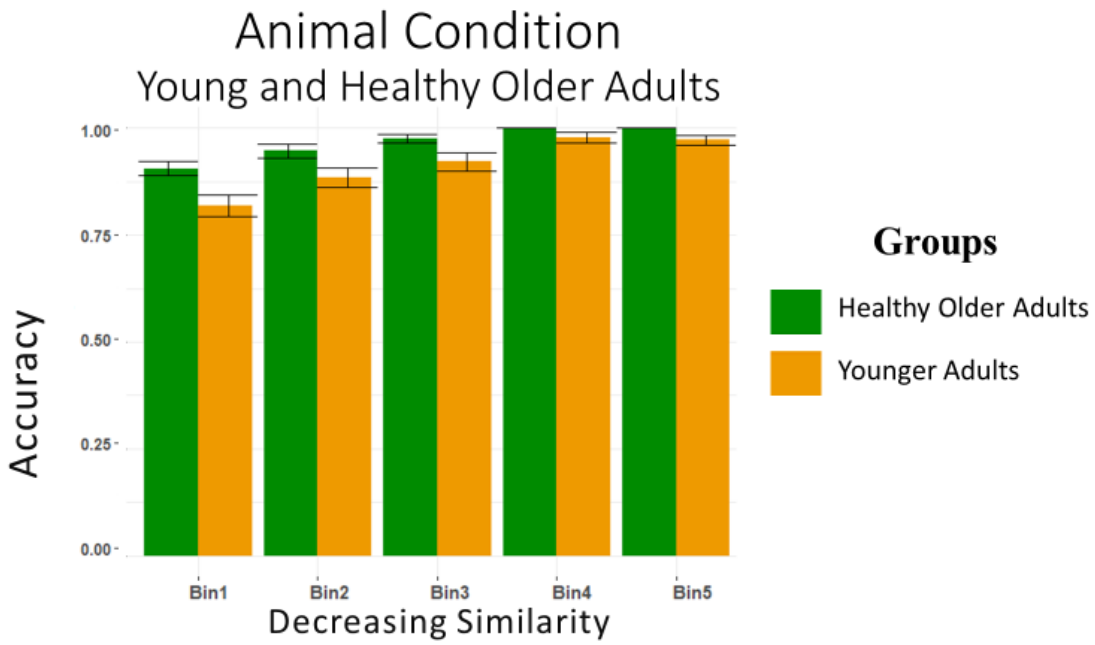


Figure 9

Healthy and At-risk Older Adult Animal Accuracy

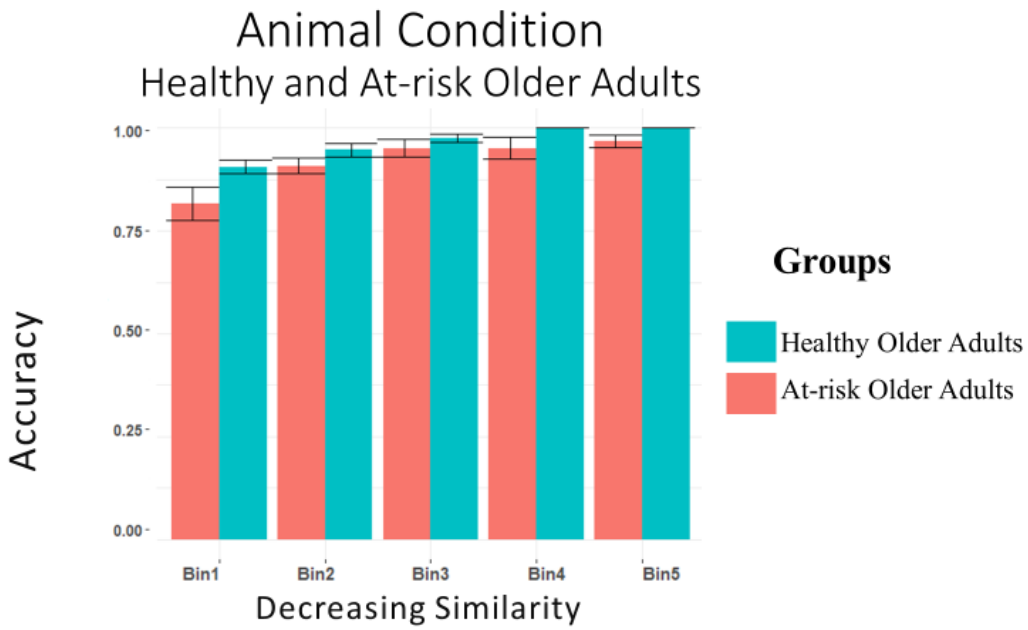


Figure 10

Patient JD Task Performance

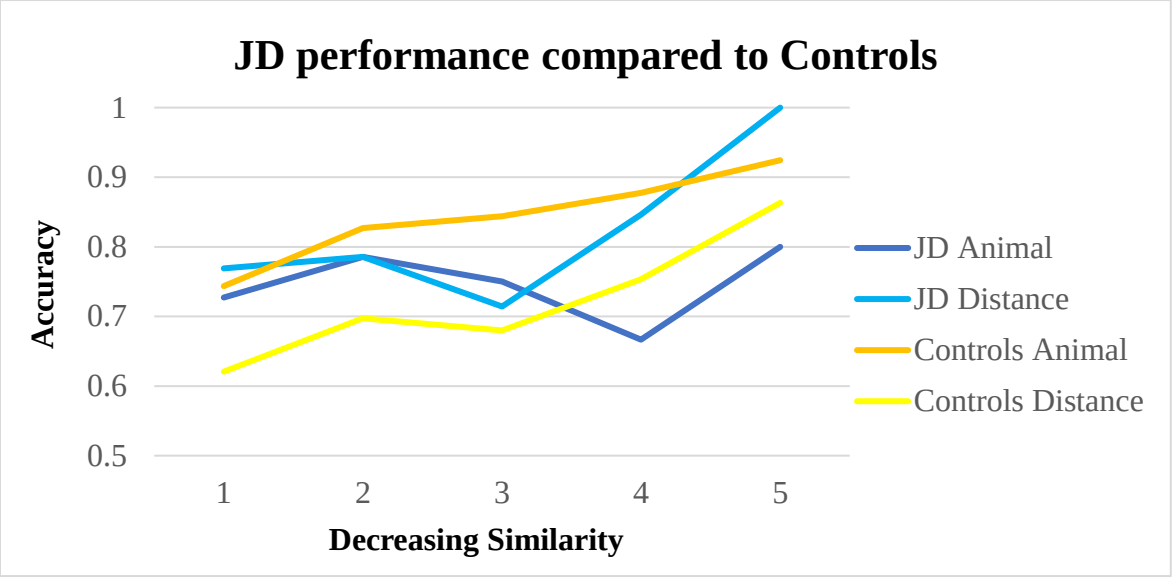
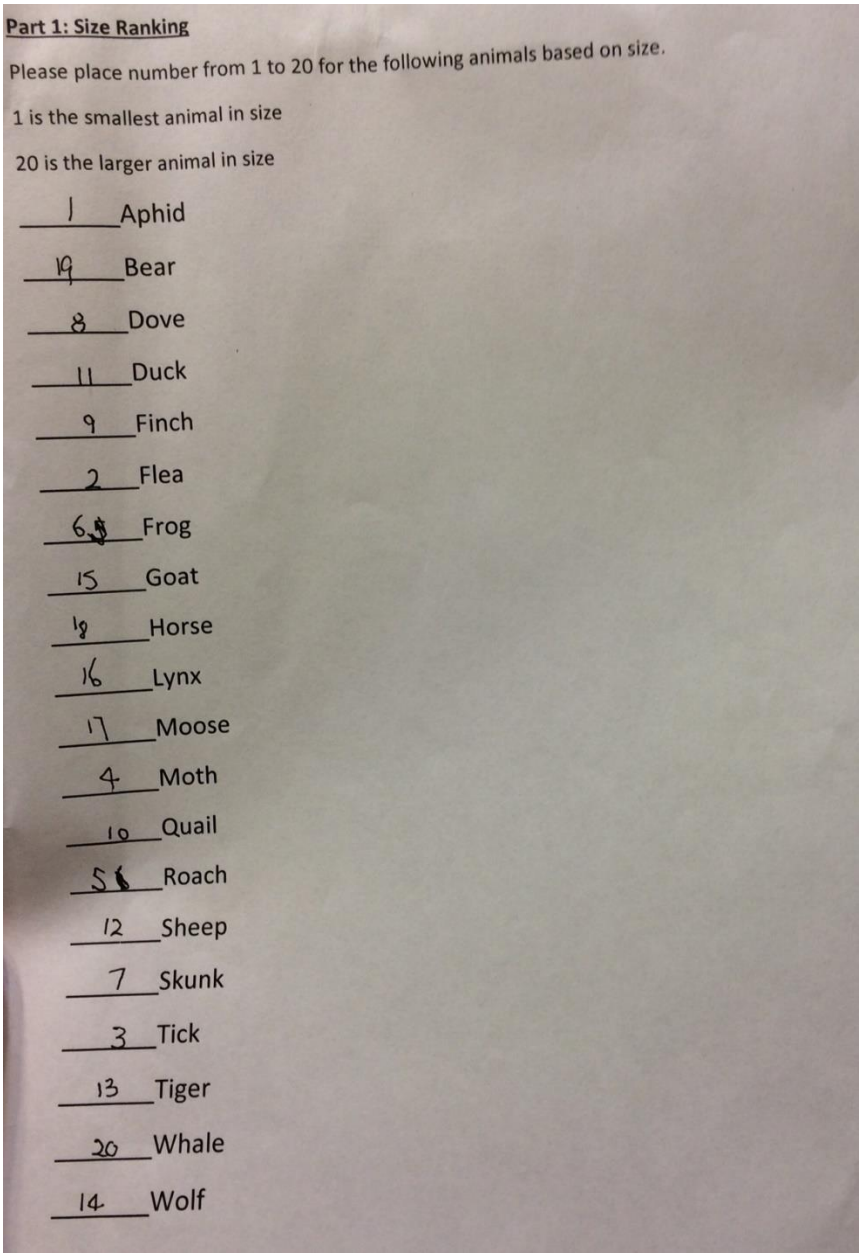


Figure 11

Patient JD's animal rankings



Part 1: Size Ranking

Please place number from 1 to 20 for the following animals based on size.

1 is the smallest animal in size

20 is the larger animal in size

1 Aphid

19 Bear

8 Dove

11 Duck

9 Finch

2 Flea

6 Frog

15 Goat

18 Horse

16 Lynx

17 Moose

4 Moth

10 Quail

5 Roach

12 Sheep

7 Skunk

3 Tick

13 Tiger

20 Whale

14 Wolf

Figure 12

Patient DA Task Performance

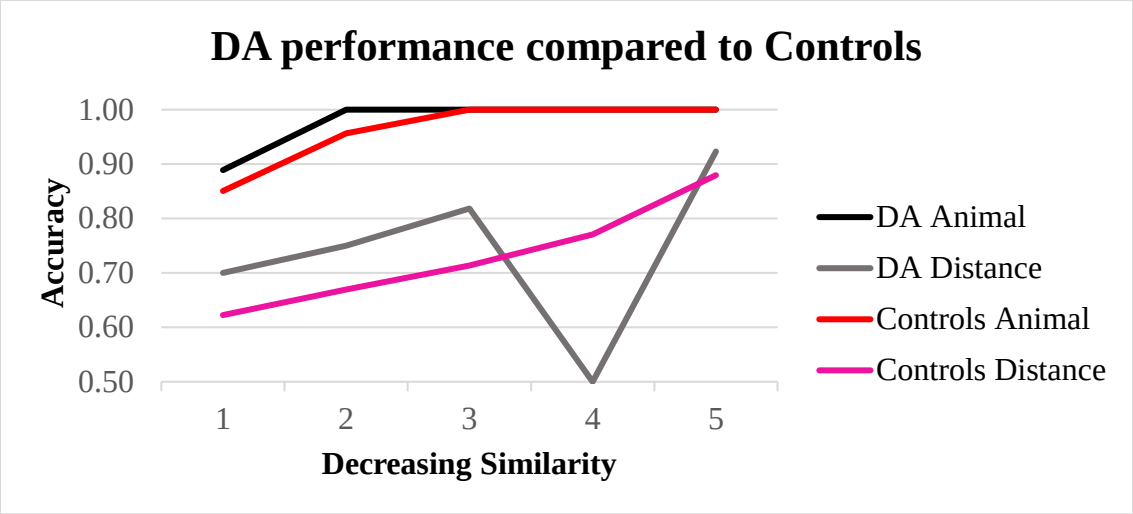


Figure 13

Patient BL Task Performance