UC Irvine

UC Irvine Previously Published Works

Title

Age-related deficits in the mnemonic similarity task for objects and scenes.

Permalink

<https://escholarship.org/uc/item/5qd8w73b>

Authors

Stark, Shauna M
Stark, Craig EL

Publication Date

2017-08-01

DOI

10.1016/j.bbr.2017.06.049

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

Research report

Age-related deficits in the mnemonic similarity task for objects and scenes

Shauna M. Stark^a, Craig E.L. Stark^{a,b,*}^a Department of Neurobiology and Behavior, University of California, Irvine, United States^b Center for the Neurobiology of Learning and Memory, University of California, Irvine, United States

ARTICLE INFO

Keywords:

Pattern separation
Lure discrimination
Aging
Hippocampus
Dentate gyrus

ABSTRACT

Using the Mnemonic Similarity Task (MST), we have demonstrated an age-related impairment in lure discrimination, or the ability to recognize an item as distinct from one that was similar, but not identical to one viewed earlier. A growing body of evidence links these behavioral changes to age-related alterations in the hippocampus. In this study, we sought to evaluate a novel version of this task, utilizing scenes that might emphasize the role of the hippocampus in contextual and spatial processing. In addition, we investigated whether, by utilizing two stimulus classes (scenes and objects), we could also interrogate the roles of the PRC and PHC in aging. Thus, we evaluated differential contributions to these tasks by relating performance on objects versus scenes to volumes of the hippocampus and surrounding medial temporal lobe structures. We found that while there was an age-related impairment on lure discrimination performance for both objects and scenes, relationships to brain volumes and other measure of memory performance were stronger when using objects. In particular, lure discrimination performance for objects showed a positive relationship with the volume of the hippocampus, specifically the combined dentate gyrus (DG) and CA3 subfields, and the subiculum. We conclude that though using scenes was effective in detecting age-related lure discrimination impairments, it does not provide as strong a brain-behavior relationship as using objects.

1. Introduction

Age-related changes in memory have been characterized, in part, by a failure of pattern separation, or the ability to orthogonalize similar inputs into distinct, non-overlapping representations. Pattern separation is critical for the ability to rapidly store (and therefore later successfully retrieve) arbitrary associative information without inducing large amounts of interference across memories [1–4]. Deficits in pattern separation (resulting from alterations of hippocampal circuitry) have been proposed to be a component of the increase in false recognition in older adults [5,6] and the greater reliance on memory for the general features or gist of studied items and the concomitant loss of the specific details of those items in older adults [7,8]. These examples demonstrate the failure of pattern separation processes in providing rich and distinct memory traces as we age.

In 2007, we designed the Mnemonic Similarity Task (MST) as a behavioral measure that could reflect successful or unsuccessful pattern separation [9]. The MST is akin to a traditional recognition memory task that augments the typical repeated items and novel foil items at test with lure items of varying degrees of similarity to previously studied items (aka, related lures). Using the MST, we have reported a linear decline in lure discrimination performance across the lifespan,

identifying similar lure items as “similar” (mnemonic discrimination), with no corresponding decrease in recognition for identifying repeated items as “old” (traditional recognition memory) [10] – a pattern which has also been shown in studies comparing groups of younger and older adults [11–13]. Additionally, performance on these lure trials is substantially impaired in patients with overt hippocampal damage relative to healthy controls [14] and is sensitive to individual differences in memory ability within aging (e.g. healthy older adults categorized as impaired vs. unimpaired relative to young, as “super-agers” vs. typical agers, etc.) [10,15]. In each of these cases, traditional recognition memory measures showed no reliable differences.

A growing number of studies and models propose that the hippocampus uses pattern separation and pattern completion mechanisms to be able to rapidly store and later retrieve arbitrary associative information [3,4,16][3,4,16 for review]. While pattern separation involves the orthogonalization of overlapping representations into distinct memory traces, pattern completion refers to the process by which stored memory representations may be reactivated based on noisy or degraded cues (often thought of as driven by attractor dynamics). Evidence for the role of these hippocampal subfields in pattern separation and completion has been mounting in both animal and human studies. Rodent studies have demonstrated that lesions to the DG result

* Corresponding author at: 320 Qureshey Research Laboratory, University of California, Irvine, CA, 92697-3800, United States.
E-mail address: cestark@uci.edu (C.E.L. Stark).

in failures of pattern separation behavior [17,18] and DG cells have been found to alter their firing in response to small changes in input that are insufficient to alter firing patterns elsewhere in the hippocampus [19,20]. Similarly, in humans, BOLD fMRI activity consistent with pattern separation has been observed in the DG or combined DG/CA3 subfields [21–24].

In animal models of aging, reduced input to the DG is coupled with a decrease in modulation by inhibitory neurons [25] resulting in a dysfunctional DG. The decreased interneuron activity in the DG may result in a failure of the DG to reduce the similarity of input patterns, leading to a decrease in pattern separation performance [26]. In addition, there is a reduction in the inhibition of the recurrent collaterals in CA3 (thought to be a primary mechanism for CA3 pattern completion), thereby strengthening their ability to drive CA3 activity relative to the DG and further reducing pattern separation performance [26]. Consistent with this hypothesis, we have reported a decrease in perforant path (the primary input to the dentate gyrus from entorhinal cortex) integrity in aging in humans [27], which correlates with the age-related decrease in lure discrimination performance on the MST [28,29]. Further, we have reported an increase in DG/CA3 activity during the MST in older adults [12], consistent with the hypothesis that the aged CA3 demonstrates greater representational rigidity, requiring a greater change in the input before stimuli can be orthogonalized. This, in turn, results in decreased lure discrimination performance [28]. In fact, reduction of this hyperactivity in amnesic MCI using a low-dose anti-epileptic has been associated with improved lure discrimination performance on the MST [30,31].

While there are clear alterations of the hippocampal circuit in aging, many other brain regions (including other MTL regions) also experience age-related changes. For example, rodent models of aging [32] have reported age-related deficits in object-recognition, particularly in stimulus sets that include a high level of perceptual similarity, that have been tied to alterations in the perirhinal cortex (PRC) (which may be involved in perception as well as memory). Both rodents and monkeys have demonstrated age-related impairments on object discrimination associated with PRC dysfunction [33]. In contrast, memory for spatial scenes have been associated with the parahippocampal cortex (PHC), which have also been associated with the retrosplenial cortex (RSC) and may operate in conjunction with the PHC for this capacity [34,35]. Activity in the parahippocampal place area has been associated with scene or visual context processing [36], shows age-related volume decline in humans, and may discriminate between healthy aging and early forms of dementia better than hippocampal volume [37].

Thus, while the MST has been used to evaluate age-related alterations hippocampal involvement in pattern separation, here we investigated whether, by utilizing two stimulus classes (scenes and objects), we could also interrogate the roles of the PRC and PHC in aging. The most common version of the MST utilizes simple, everyday objects on a white background and has been a powerful tool for demonstrating decreases in pattern separation behavior in aging and MCI [10,11,13,15,38]. In addition, several variants of the MST or related tasks designed to test pattern separation performance have shown age-related declines manipulating temporal [39], emotional [40,41], verbal [42], and spatial [43–45] dimensions of lure similarity. In this study, we developed a different manipulation: the use of rich, complex scenes in place of simple objects.

Scenes are visually complex and, in addition to the PHC, may heavily rely on the hippocampus, which may support high-resolution binding of different aspects of an event or image [46]. Scenes require the integration of multiple visual features, which is impaired in patients with hippocampal damage [47]. Further, hippocampal activity has been shown for complex discrimination of scenes [48], with evidence for the orthogonalization of scenes in the dentate gyrus [49]. Thus, we investigated whether the MST-Scenes would be more sensitive to age-related decline, with a greater relationship to hippocampal volume than MST-Objects.

We collected behavior from both the MST-Objects and MST-Scenes in both younger and older adults. Participants also completed a neuropsychological battery, evaluating performance on a variety of cognitive domains, as well as high-resolution structural MRI scans to measure volumes of medial temporal lobe (MTL) structures, including hippocampal subfields. We hypothesized that we would observe age-related impairments in lure discrimination performance on both the MST-Objects and MST-Scenes versions, consistent with previous studies and the role of the dentate gyrus as a quasi-universal pattern separator [50]. Next, we predicted that we would find a relationship between lure discrimination performance on both tasks and dentate gyrus volume, consistent with a previous report using MST-Objects [38]. Further, we predicted a relationship between lure discrimination performance on MST-Objects and the volume of the PRC and on MST-Scenes and the volume of the PHC. Ultimately, we sought to determine whether these two versions of the MST capture different aspects of brain aging and reflect processing from distinct brain regions.

2. Materials and methods

2.1. Participants

26 younger (mean age = 27.8 years; range = 21–38 years; 12 males) and 28 older (mean age = 70.8 years; range = 59–84; 10 males) healthy, cognitively intact adults participated in the study. Participants were recruited through advertisements and word-of-mouth, and participated for \$15 per hour of testing. Participants were screened for history of psychiatric and neurological disorders. All participants signed consent forms and the study was conducted in compliance with the Institutional Review Board of the University of California at Irvine.

Participants were tested to ensure normal performance on measures of general cognition: Mini Mental State Exam [51]; memory: Rey Auditory Verbal Learning Test [52] and Rey-Osterrieth Complex Figure [53]; executive functioning: Trails A and B [54], Stroop [55], and Letter Number Sequencing [56]; and working memory: Digit Span [56]. The Mini Mental State Exam (MMSE) total score is the sum of all test questions (maximum score of 30). The Rey Auditory Verbal Learning Test has three components: the total score reflects the total number of recalled words for each of the 5 presentations of the same 15-word lists (maximum score of 60), the immediate recall score reflects the total number of words recalled immediately following the presentation of an interference list of novel words (maximum score of 15), and the delayed recall score reflects the total number of words recalled following a 15 min delay after the immediate list recall (maximum score of 15). The Rey-Osterrieth Complex Figure score has two components: Rey-O copy reflects the number of correct components copied from the figure when it is visibly present (maximum score of 38), and the Rey-O delay reflects the number of correct components drawn from memory after a 15-min delay when the figure is no longer present (maximum score of 38). We report that total time in seconds to complete Trails A and B. We utilized three measures from The Stroop Color-Word Test: Stroop Word reflects the total number of words (red, blue, or green) read aloud correctly in one minute; the Stroop Color reflects the number of colored XXXs where the color (red, blue, or green) was named correctly in one minute, and the Stroop Color-Word reflects the number of words read aloud correctly in one minute when the color of ink does not match the word (e.g. the word “red” in green ink). The Letter Number Sequencing score reflects the number of correct sequences of letters and numbers recalled immediately after hearing them (e.g. the correct response to “A-6-H-3” would be “A-H-3-6”) (maximum score of 21). Similarly, the total Digit Span score reflects the number of correct digits recalled, both forward and backward versions (maximum score of 30).

2.2. Task design

All participants completed the MST-Objects and MST-Scenes task

Fig. 1. Participants encoded a series of pictures (A – Objects; B – Scenes), followed by a surprise recognition test, which contained exact repetitions (identical to those in the encoding task; outlined in green), novel foils (completely new items; outlined in red), and similar lures (related, but not identical, to those in the encoding task; outlined in blue). Color outlines are for illustration purposes only and were not presented during the actual task administration. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

separately in their entirety, in that order. We have previously shown that repeated administration of the MST with different stimulus sets does not impact task performance, nor does knowledge of the test structure prior to encoding [13]. Based on the results of pilot testing, we extended the exposure duration to the scenes from the 2 s used for the MST-Objects task to 3 s for the MST-Scenes task for both the encoding and recognition tasks. In pilot testing, we found that the shorter exposure duration significantly impacted recognition for scenes, leading us to conclude that scenes required a longer exposure duration for adequate encoding. In addition, through pilot testing, we carefully culled a set of scene photographs that resulted in recognition rates that were comparable to those observed in the MST-Objects task. For both the objects and scenes, the lure items could vary along a variety of dimensions: size, angle, color, orientation, etc. While many of the scenes contained a central item (e.g. the bear in the river in Fig. 1B), many of them did not (e.g. the plants in Fig. 1B) and the lure items could include changes to a central item, peripheral items, or both. More examples of scene pairs are presented in Supplemental Fig. 1. Therefore, participants were required to encode the entire scene and not simply an object within the scene in order to detect a lure from a target. Additionally, we made every effort to minimize similarity between the items within the objects and scenes sets to reduce interference (i.e. we did not include multiple images of telephones or river scenes, etc.).

For both the Objects and Scenes versions of the MST (Fig. 1), we presented participants with a series of 192 color photographs. Participants were evenly distributed across MST-Objects Sets G and H (publicly available here: <http://faculty.sites.uci.edu/starklab/mnemonic-similarity-task-mst/>). In the first phase, participants engaged in an incidental encoding task consisting of an indoor/outdoor judgment for each object or a natural/man-made judgment for each scene (based on their opinion with no right or wrong answer) via a button press (128 items total, 2 s object presentation and 3 s scene presentation time, 0.5 s ISI). Immediately following the encoding task, participants were shown video instructions describing the test phase to ensure consistent delivery of the instructions. In the test phase, they engaged in a modified recognition memory test in which they identified each item as ‘Old’, ‘Similar’, or ‘New’ via button press (192 items total – 64 repeated items, 64 lure items, and 64 foil items; 2.5s/3 s each, ≥ 0.5 s ISI). The image disappeared from the screen after 2.5 s (or 3 s in the case of scenes), replaced by a white screen until participants responded. One-third of the images in the test phase were exact repetitions of images presented in the encoding phase (targets or repeats); one-third of the images were new images not previously seen (foils); and one-third of the images were similar to the those seen during the encoding phase, but not identical (lures). These trial types were randomly intermixed during the test.

As in our prior work [10,13], the Lure Discrimination Index (LDI) was calculated as the difference between the rate of ‘Similar’ responses given to the lure items minus ‘Similar’ responses given to the foils (to correct for any response biases). Recognition (REC) for repeat items was calculated as the difference between the rate of ‘Old’ responses given

to repeat items minus ‘Old’ responses given to foils (aka ‘corrected recognition memory scores’). These scores correct for any response bias on a per-subject basis. In addition, the LDI and REC scores for MST-Objects were linearly transformed (using a z-score based conversion from independent participants available via a tool posted at: <http://faculty.sites.uci.edu/starklab/mnemonic-similarity-task-mst/>) to match the lure similarity of Sets C and D. In this way, we could view the MST-Objects results on the same scale as those that have been published previously [10,13].

2.3. Brain volumes

25 younger and 26 older adults also participated in structural MRI scans, collected on a 3.0 T Philips scanner. Standard-resolution MRI images were acquired using a T1-weighted magnetization-prepared rapid acquisition with gradient echo (MP-RAGE) sequence with the following parameters: TE = 4.54 ms, flip angle = 18°, slices = 200, voxel size = 0.75 mm isotropic, and a field of view = 240 × 240 × 150 mm. High-resolution structural MRI images of the MTL were acquired using a T2-weighted sequence with the following parameters: TE = 80 ms, flip angle = 90°, slices = 54, slice thickness = 3 mm, matrix size = 384 × 384, voxel size = 0.469 × 0.469 × 2 mm, and an in-plane field of view = 108 × 180 mm. High resolution structural images were aligned as oblique coronals perpendicular to the long axis of the hippocampus and positioned to cover the entire structure.

Anatomical regions of interest (ROIs) for the hippocampus (including the hippocampal subfields), entorhinal cortex (ERC), perirhinal cortex (PRC), and parahippocampal cortex (PHC) were manually segmented on 19 young adult brains (not part of this dataset) to create a multi-atlas model. PRC and ERC were labeled according to landmarks described by Insausti et al. [61], and PHC was defined as the portion of the parahippocampal gyrus caudal to the PRC and rostral to the splenium of the corpus callosum as in our previous research [57,58]. The hippocampal subfields were manually segmented using a slight modification to our prior work [59]. Based on the limitations of 3T structural scans and incomplete protocols for reliable, more specific segmentation, we chose to segment the hippocampus into only three segments: CA1, a combined dentate gyrus and CA3 (DG/CA3), and the subiculum. Initial results from the Hippocampal Subfields Group [60,61] demonstrated clear variance in the CA1/subiculum boundary and we revised our protocol to move this boundary more laterally as a result (sample slices from our segmentation can be found in Supplemental Fig. 2).

To calculate MTL volumes for individuals in the current study, we created a multi-atlas model using ASHS [62] and the aforementioned 19 independent hand-segmented brains (both the MP-RAGE and high-resolution T2 images). Briefly, ASHS performs a non-linear registration between a new participant’s structural scan and each of the scans in the multi-subject atlas using ANTS [63]. A voting procedure is then enacted to determine an initial segmentation based on the degree of

Table 1

Scores on standardized neuropsychological testing: mean score (standard deviation, z-score from standardized mean). Z-scores greater than 1 reflect better performance than standardized norms. Mini Mental State Examination (MMSE), Rey Auditory Verbal Learning Test (RAVLT), Rey-Osterrieth Complex Figure (Rey-O), Letter-Number Sequencing (LN). * denotes a significant difference in test performance between the two groups ($p < 0.05$, correcting for multiple comparisons).

Neuropsychological Test	Young	Aging
MMSE	29.5 (0.6, 0.41)	29.4 (0.7, 1.52)
RAVLT Total	61.8 (6.2, 0.70)	54.4 (8.1, 2.31)*
RAVLT Immediate	13.8 (1.3, 0.94)	12.0 (2.6, 1.3)*
RAVLT Delay	14.0 (1.2, 1.08)	11.9 (2.7, 2.02)*
Rey-O Copy	35.5 (0.9, 1.16)	34.6 (2.6, 1.5)
Rey-O Delay	24.3 (7.1, 0.37)	16.6 (6.5, 0.80)*
Digit Span	20.2 (4.4, 0.73)	18.3 (3.6, 1.08)
LN Sequencing	13.9 (2.5, 0.96)	11.2 (2.9, 1.06)*
Trails Average	32.7 (8.9, -0.51)	46.8 (15.7, -0.87)*
Stroop Word	113 (12.5, 0.32)	98.3 (17.7, -0.38)*
Stroop Color	82.8 (10.7, 0.17)	73.9 (14.3, -0.08)*
Stroop Color-Word	52.3 (7.6, 0.70)	38.4 (8.0, 0.04)*

deformation needed to warp the new participant onto each atlas (less deformation needed implies a higher degree of match and therefore a greater weight of that individual atlas to the segmentation). Finally, an AdaBoost technique is used to detect and remove segmentation biases.

In addition, intracranial and cerebellar volumes were calculated by a Freesurfer [64] segmentation of the MP-RAGE based on a combination of white matter, gray matter, and cerebral spinal fluid. To adjust for head size and age, we calculated an adjusted volume for each structure, such that the adjusted Volume = raw volume - $b \times (ICV - \text{mean ICV})$, where b is the slope of the regression of an ROI volume on ICV [65]. We calculated the slope of the regression for each ROI and the mean ICV based on a larger lifespan dataset ($n = \sim 160$, ages 20–89 years old). The adjusted volumes were calculated for the left and right ROIs separately.

3. Results

3.1. Neuropsychological tests

Mean score, standard deviation, and z-score compared to age-matched norms for each neuropsychological task are presented in Table 1. We evaluated group differences using unpaired t -tests, corrected for multiple comparisons using the Holm-Sidak method with an alpha of $p < 0.05$. As expected, performance on all the neuropsychological measures, with the exceptions of the MMSE, Rey-O Copy, and Digit Span, showed age-related decline. However, all participants scored within 1.5 standard deviations of the mean of their age group.

3.2. Brain volumes

We evaluated group differences in adjusted volumes for the left and the right hemispheres using unpaired t -tests, corrected for multiple comparisons using the Holm-Sidak method with an alpha of $p < 0.05$. As can be seen in Table 2, the adjusted volumes were reduced in the aging group for the right hippocampus, bilateral subiculum, right PRC, bilateral PHC, and bilateral cerebellum. There was a strong trend for reduced volumes in the right DG/CA3 and CA1 (after multiple-comparison corrections, both p 's < 0.10). Thus, consistent with other studies, we find evidence for age-related decline in the volumes of several MTL regions.

3.3. Mnemonic similarity tasks

Response proportions for each stimulus and response type are presented in Table 3 for both MST-Objects and MST-Scenes. In MST-Objects, six young participants were removed from the analysis for using

Table 2

Adjusted volumes in cubic millimeters for each ROI on the left and the right for each group (mean, standard deviation). * denotes a significant difference in volume between the two groups ($p < 0.05$, correcting for multiple comparisons). ^e denotes a marginal difference in volume between the two groups ($p < 0.10$, correcting for multiple comparisons).

Volume	Left		Right	
	Young	Aging	Young	Aging
Hippocampus	3640 (281)	3484 (381)	3870 (286)	3603 (373)*
DG/CA3	860 (86)	860 (133)	828 (40)	765 (152) ^e
CA1	1882 (183)	1795 (218)	2024 (174)	1921 (221) ^e
Subiculum	968 (103)	848 (141)*	875 (82)	770 (102)*
ERC	982 (70)	966 (108)	923 (204)	918 (192)
PRC	3162 (810)	2895 (528)	2686 (420)	2311 (353)*
PHC	3072 (419)	2597 (353)*	3221 (427)	2642 (294)*

Table 3

Percent endorsed for the MST Objects and MST Scenes tasks for the young and older groups for each stimulus and response type, along with standard deviations.

Group	Response	MST Objects			MST Scenes		
		Repeat	Lure	Foil	Repeat	Lure	Foil
Young	Old	0.83 (0.08)	0.32 (0.13)	0.04 (0.05)	0.75 (0.18)	0.33 (0.24)	0.05 (0.16)
	Similar	0.13 (0.07)	0.57 (0.15)	0.15 (0.10)	0.19 (0.17)	0.57 (0.20)	0.19 (0.14)
	New	0.04 (0.03)	0.11 (0.07)	0.81 (0.13)	0.06 (0.05)	0.10 (0.10)	0.76 (0.21)
Older	Old	0.82 (0.12)	0.41 (0.13)	0.04 (0.03)	0.79 (0.13)	0.35 (0.22)	0.05 (0.07)
	Similar	0.12 (0.11)	0.40 (0.15)	0.11 (0.06)	0.14 (0.10)	0.47 (0.19)	0.18 (0.11)
	New	0.06 (0.05)	0.19 (0.10)	0.85 (0.07)	0.07 (0.05)	0.18 (0.11)	0.77 (0.15)

the incorrect response buttons and one was removed for an LDI rate outside two standard deviations from the mean, resulting in a total of 20 young participants. One older participant was removed from the MST-Objects analysis because he never used the similar response, failing to comply with task instructions (consistent with criteria used previously [13]), resulting in 27 older participants. Likewise, three young participants were removed from the MST-Scenes analysis for using the incorrect response buttons, two were removed for having a recognition rates more than two standard deviations outside the mean, and one removed for having an LDI rate more than two standard deviations outside the mean, resulting in 21 young participants in MST-Scenes. Three older participants were removed from MST-Scenes for using the incorrect response buttons and one was removed for having an LDI rate more than two standard deviations outside the mean, resulting in a total of 24 older participants in MST-Scenes.

First, we tested for a replication of our earlier findings in each task independently: namely, matched recognition performance in older and younger adults, with an age-related decrease in LDI performance. Therefore, LDI and REC scores for MST-Objects and MST-Scenes for younger and older adults were entered into two separate 2×2 ANOVAs, with factors of Age and Test Type (Fig. 2). For MST-Objects, there was a main effect of Age ($F(1,44) = 8.8$, $p < 0.01$), a main effect of Test Type ($F(1,44) = 228.2$, $p < 0.001$), and an interaction ($F(1,44) = 6.1$, $p < 0.05$). Bonferroni-corrected multiple comparisons showed no difference in REC (Young: 0.80, Aging: 0.79), but a significant reduction in LDI for older (0.27) compared to younger (0.43) adults ($t(88) = 3.8$, $p < 0.05$). For MST-Scenes, there was no main effect of Age ($F(1,44) = 1.3$, $p = 0.26$), but a main effect of Test Type ($F(1,44) = 163.1$, $p < 0.001$), and an interaction ($F(1,44) = 5.5$, $p < 0.05$). Like the MST-Objects, Bonferroni-corrected multiple comparisons showed no difference in REC (Young: 0.72, Aging: 0.75), but a

Fig. 2. Recognition performance is matched in both the young and aging groups, while lure discrimination (LDI) is impaired in both the objects and scenes versions of the MST.

significant reduction in LDI for older (0.29) compared to younger (0.40) adults ($t(88) = 2.3$, $p < 0.05$). Thus, the age-related decrease in LDI is consistent in both the MST-Objects and MST-Scenes tasks, while recognition performance is unaffected by typical aging. It is worth noting, however, that in regression analyses of each of the MST scores (Scenes LDI and REC, Objects LDI and REC) versus age, the Object LDI ($b = -0.004$, $F(1,44) = 10.00$, $p < 0.01$) accounted for over twice the age-related variance as the Scene LDI ($b = -0.002$, $F(1,44) = 3.66$, $p = 0.06$) (R^2 of 0.2 vs. 0.08).

3.4. Correlation matrix

We were specifically interested in how the memory measures that showed age-related change interacted with each other and with the MTL volumes. Therefore, we entered the following variables of interest into a correlation matrix: RAVLT Delayed Recall, Rey-O Delayed Recall, Scenes LDI, Objects LDI, and adjusted-volumes for the average of the left and right hippocampus, ERC, PRC, PHC, and CA, DG/CA3, and subiculum. Given the goal of linking brain findings to behavior and to contain the number of comparisons, the matrix only included the four behavioral measures along one dimension (i.e., it does not correlate brain volumes in one region with another). Correlation coefficients and associated p-values are presented in Table 4 (with scatterplots presented in Supplemental Fig. 3A & B).

Consistent with our earlier work that showed a relationship between LDI and RAVLT Delay performance [10], we found a positive relationship between Objects LDI and RAVLT Delay, as well as with Rey-O Delay. In contrast, the relationship with RAVLT Delay was notably absent with Scenes LDI, but there was a positive relationship with Rey-O Delay. While the RAVLT taps verbal memory, performance on the Rey-O relies visual memory and spatial relationships, similar to the visual memory demands of both MST tasks.

Next, we were interested in the relationships between MTL volumes and memory performance. We found that hippocampal volume was

positively correlated with performance on Objects LDI, RAVLT Delay, and Rey-O delay, but not Scenes LDI. Breaking the hippocampus into its subfields, we found that the DG/CA3 and subiculum volumes were both positively related to Objects LDI, RAVLT Delay, and Rey-O delay performance (although the DG/CA3 and Objects LDI relationship was less reliable). We also found that the CA1 volume correlated with Rey-O Delay recall. Finally, like hippocampal volume, PHC volume correlated with better performance on Objects LDI, RAVLT Delay, and Rey-O delay, but not Scenes LDI.

We were specifically interested in relating these behavioral and brain measures in an effort to understand their relationship. However, our broad age range, coupled with the fact that both many of the behavioral measures and many of the regional volume measures show age-related decline leads to a clear potential for age being a confounding variable. Our brain-behavior relationships might be induced entirely by shared age-related variance. To address this issue, we performed a linear regression on this dataset, regressing the effect of age out of both the memory and the brain measures. We then calculated the same correlation matrix on the residuals and found highly similar results, maintaining the vast majority of the relationships between brain and behavior (Table 5), particularly for the Objects LDI and Rey-O. In contrast, the previously observed relationship between Scenes LDI and the volume of the subiculum was greatly reduced. These data emphasize the strength of the relationship between Objects LDI performance and Rey-O Delayed recall and the volumes of the hippocampus and PHC and are suggestive of these relationships being driven by individual differences in neuroanatomy as well as age-related decline.

4. Discussion

The first goal of this study was confirmed by an age-related decline in both MST-Objects and MST-Scenes lure discrimination performance, consistent with previous studies using object [10,11,13,15,38], temporal [45], emotional [40,41], verbal [42], and spatial [43–45]

Table 4

Pearson R correlation coefficients and corresponding p-values for our variables of interest. Shaded cells highlight those relationships that pass (or approach) a statistical alpha threshold of 0.05.

	Objects LDI	Scenes LDI	RAVLT Delay	Rey-O Delay
Objects LDI	---	$r=.67$ ($p<.01$)	$r=.33$ ($p<.05$)	$r=.52$ ($p<.01$)
Scenes LDI		---	$r=.25$ ($p=.10$)	$r=.35$ ($p<.05$)
RAVLT Delay			---	$r=.19$ ($p=.17$)
Hippocampus Avg	$r=.34$ ($p<.05$)	$r=.17$ ($p=.29$)	$r=.28$ ($p<.05$)	$r=.41$ ($p<.01$)
DG/CA3 Avg	$r=.27$ ($p=.08$)	$r=.20$ ($p=.21$)	$r=.29$ ($p<.05$)	$r=.34$ ($p<.05$)
CA1 Avg	$r=.22$ ($p=.15$)	$r=.03$ ($p=.84$)	$r=.24$ ($p=.10$)	$r=.35$ ($p<.05$)
Subiculum Avg	$r=.52$ ($p<.01$)	$r=.32$ ($p<.05$)	$r=.40$ ($p<.01$)	$r=.45$ ($p<.01$)
ERC Avg	$r=.01$ ($p=.95$)	$r=.11$ ($p=.50$)	$r=.17$ ($p=.23$)	$r=.14$ ($p=.33$)
PRC Avg	$r=.21$ ($p=.18$)	$r=-.02$ ($p=.88$)	$r=.21$ ($p=.14$)	$r=.25$ ($p=.08$)
PHC Avg	$r=.48$ ($p<.01$)	$r=.21$ ($p=.18$)	$r=.37$ ($p<.05$)	$r=.52$ ($p<.01$)

Table 5

Pearson R correlation coefficients and corresponding p-values for our variables of interest on the residuals after age was regressed out. Shaded cells highlight those relationships that pass (or approach) a statistical alpha threshold of 0.05.

	Objects LDI	Scenes LDI	RAVLT Delay	Rey-O Delay
Objects LDI	---	$r=.61$ ($p<.01$)	$r=.16$ ($p=.29$)	$r=.38$ ($p<.01$)
Scenes LDI		---	$r=.13$ ($p=.40$)	$r=.26$ ($p=.09$)
RAVLT Delay			---	$r= -.05$ ($p=.73$)
Hippocampus Avg	$r=.27$ ($p=.08$)	$r=.13$ ($p=.41$)	$r=.14$ ($p=.38$)	$r=.27$ ($p=.05$)
DG/CA3 Avg	$r=.27$ ($p=.08$)	$r=.19$ ($p=.22$)	$r=.24$ ($p=.09$)	$r=.29$ ($p<.05$)
CA1 Avg	$r=.18$ ($p=.24$)	$r=.01$ ($p=.99$)	$r=.13$ ($p=.38$)	$r=.25$ ($p=.08$)
Subiculum Avg	$r=.41$ ($p<.05$)	$r=.26$ ($p=.11$)	$r=.23$ ($p=.11$)	$r=.26$ ($p=.07$)
ERC Avg	$r= -.01$ ($p=.96$)	$r=.13$ ($p=.42$)	$r=.13$ ($p=.35$)	$r=.09$ ($p=.51$)
PRC Avg	$r=.04$ ($p=.81$)	$r= -.10$ ($p=.54$)	$r=.04$ ($p=.77$)	$r=.06$ ($p=.67$)
PHC Avg	$r=.34$ ($p<.05$)	$r=.12$ ($p=.47$)	$r=.08$ ($p=.57$)	$r=.27$ ($p=.06$)

dimensions of lure similarity. Thus, age-related decline in the “detailed”, “high-fidelity”, or “high-resolution” memory believed to be supported by pattern separation in the hippocampus appears quite domain-general and not specific to any particular feature or domain. Further, lure discrimination performance on both versions were highly correlated with each other. In contrast with lure discrimination, recognition memory performance was remarkably similar across age groups and stimulus types. These findings reflect age-related changes in the hippocampal circuit that shifts the balance of processing away from pattern separation to a greater reliance on gist rather than specific details [34]. The MST, in its variety of incarnations, has proven to be a robust measure of age-related memory decline, as well as sensitive to memory decline associated with mild cognitive impairment [10,66,67], depression [40,41,68–70], schizophrenia [71,72], and sleep deprivation [76].

Next, we evaluated the relationship between hippocampal volume and performance on the MST. We found a decrease in hippocampal volume in the aging group, with evidence for reduced volumes in each of the subfields: CA1, DG/CA3, and subiculum. We had hypothesized that in its role as a universal or “domain agnostic” pattern separator, we should find a relationship between the hippocampus (and the DG/CA3 specifically) in lure discrimination performance. Computational models propose that, by virtue of its unique anatomical properties and functional organization, the dentate gyrus (DG) subfield of the hippocampus is responsible for reducing the similarity of inputs associated via pattern separation [3,16,73–75]. In contrast, the CA3 subfield of the hippocampus receives strong projections from the DG, in addition to housing a strong recurrent collaterals, which may function as an auto-associative pattern completion network [16–19]. The CA1 subfield of the hippocampus, in contrast, is often thought to compute a graded match/mismatch between an experience and an expectation (roughly akin to a “degree of novelty”) [76–78]. Here, we found some evidence for a positive relationship with the DG/CA3 for MST-Objects, but not for MST-Scenes, though both tasks were correlated with the volume of the subiculum. These data serve, in part, as a replication of Doxey & Kirwan [44], who also found an age-related correlation between DG/CA3 volume and lure discrimination on MST-Objects.

In addition to the DG/CA3 volume, we found a relationship between subiculum volume and lure discrimination performance on MST-Objects and MST-Scenes, as well as RAVLT and Rey-O delayed recall. The subiculum receives projections from entorhinal and perirhinal cortex directly and sits at the end of the classic trisynaptic loop of ERC-DG-CA3-CA1-subiculum (as well as sending projections back to the DG). Thus, this region is involved in both the input and output from the hippocampus, possibly amplifying the output from the hippocampus proper [79]. We observed an age-related decline in subiculum volume, consistent with some findings in the literature [38,80–82], but no age-related decline reported in others [83]. Much of this inconsistency may stem from differential segmentation methods (manual vs automatic),

definitions of subfield boundaries, and longitudinal vs. cross-sample comparisons. In young adults, activity in the subiculum has been associated with encoding and retrieval of face-name associations [84], is modulated by memory performance and confidence for both faces and scenes [85], and in response to the incidental version of the MST-Objects task [21,22]. In aging, subiculum volume has not previously been associated with various neuropsychological tasks [86] or with performance on a variation of MST-Objects in an independent sample [38]. However, we would like to note again that the same factors that influence the variation in age-related volumetric change apply here as well, namely different segmentation protocols and procedures, and behavioral tasks. Based on the computational models of pattern separation, we would not conclude from these data that the subiculum plays a strong role in this process. Yet, mounting evidence suggests that subiculum volume declines with age (as do the other hippocampal subfields). We suggest that its relationship to performance in this task may reflect an impairment in output of pattern separation processing occurring in the hippocampus. However, functional MRI reflecting local processing would be necessary to further evaluate a more direct contribution from this region.

We had predicted a positive relationship between lure discrimination performance on MST-Objects and the volume of the PRC and on MST-Scenes and the volume of the PHC. Both regions showed an age-related decline in volume, consistent with other reports in the literature [37,38], but MST-Scenes did not have a relationship with any of the cortical MTL volumes. While we had expected to see a relationship with PRC due to documented age-related alterations in this region [33,87], none was observed. However, it is quite possible that these alterations of the PRC may not induce volumetric changes. Thus, we caution against any strong interpretation of this null result. Instead, we found a relationship with the volume of the PHC and MST-Objects, but no relationship with PRC. Activity in the PHC has been associated with scene or visual context processing [36] and navigation performance on a virtual water maze task [88]. Therefore, we were surprised at the lack of relationship between MST-Scenes and the volume of the PHC. However, as discussed below, discrimination performance on MST-Scenes may have been susceptible to other strategies or cognitive processes that have mitigated its relationship with the PHC. Functional MRI reflecting local processing would be necessary to further evaluate the age-related role of PHC in discrimination performance for objects in this task.

Several studies have demonstrated that memory performance on the RAVLT is correlated with lure discrimination performance [10,44,45]. Here, we added the Rey-O as an independent memory measure as successful performance on the task requires the sort of high-fidelity or nearly veridical memory of the complex drawing that is the hallmark of the computational models of pattern separation in the hippocampus. Recall on both the RAVLT and the Rey-O was correlated with MST-Objects lure discrimination, though only the Rey-O recall was

correlated with MST-Scenes lure discrimination. Given that the Rey-O emphasizes visual memory, the strength of this relationship is not surprising. In addition, we found that both RAVLT and Rey-O delayed recall was correlated with hippocampal volume (and its subfields) and PHC volume. These four measures of memory performance (MST-Objects LDI, MST-Scenes LDI, RAVLT delay, and Rey-O delay) appear strongly related and dependent on the hippocampus and surrounding MTL cortices, relationships that are largely maintained even when age is regressed out of the relationships (with the notable exception of MST-Scenes LDI).

Despite the clear effect of age and correlations with other tasks, our results do not promote the utility of the MST-Scenes. This version of the task was not differentially sensitive to PHC volume and showed the weakest relationships to other brain and behavior measures. MST-Scenes also faces challenges for participants not found in MST-Objects. The criteria for a “similar” response can be more challenging for participants to understand and matching performance required extending the encoding period for each image (therefore lengthening the task). Even so, scenes are much more complex than the objects, leading to many more possibilities for details that might change, and therefore many more bits of information that must be attended to even before one asks the question whether they are successfully encoded. If a clear function of the hippocampus is the “automatic encoding and initial storage of attended experience” [89], increasing the number of features that must be attended to without any control over the amount of attention directed to the critical features can only lead to more variance in performance. Simply adding even more additional time for encoding might lead to attention being spread across the image more, but it might also allow for the development of cognitive strategies that may be counterproductive for attempts to measure hippocampal function. The possible shift in strategy may account for the difference in new responses to lures between MST-Objects and MST-Scenes. While older adults show reduced similar responses in both tasks, they show an increase in new responses in MST-Scenes (see Table 3). This pattern of responses does not follow from the simple prediction one would make if older adults’ performance was driven by a shift towards gist processing. Whether such a shift exists for scenes or not, the observed difference does indicate some combination of a shift in their decision criteria for identifying a scene as new vs. similar and an effect of the complexity and sheer amount of information to encode in a limited time. Both of these raise potential concerns when using complex scenes as stimuli in the task.

The notion of negating cognitive strategies is an important one. When we developed the stimulus sets for MST-Objects, we deliberately allowed the lure items to vary across many different dimensions (e.g. color, orientation, size, added or missing parts, etc.). By allowing the lures to vary in different ways (yet keeping the same verbal label), we hoped to minimize strategies that might be brought to bear in remembering them that would simplify the task and remove much of the memory load. The only way to detect the lure is to have a relatively veridical memory of the original item as virtually any aspect of the item could have changed. By varying the ways that the object lures could vary, we tried to reduce the likelihood that strategies could alter performance on the task (e.g. if we only varied by color, participants could explicitly encode the color of each object, but ignore other details, such as orientation). Perhaps this is why the MST-Objects shows little if any effect of repeated testing [13]. In contrast, tasks like random word recall on the RAVLT can be solved using different strategies that are non-memory related, but will boost memory performance (e.g. creating a story or mental image out of 3 or 4 items from the list).

There are several limitations to this study, such as small sample sizes. While we tested approximately 24 individuals in each group, typical for much of the literature on age-related changes in memory, data from studies of this size must be replicated to validate these findings. To ultimately address issues regarding the contributions of the PRC and PHC to age-related changes in aging, we need studies that

measure activity in these regions more directly than correlations with volumes. Nevertheless, the data presented here indicates that the PHC is likely involved in the age-related decrease in lure discrimination here, which warrants further investigation.

5. Conclusions

We had set out to develop a new version of the MST that might tap into hippocampal function better than the standard objects version that has been utilized so productively in the field. Instead, we found little evidence to support a benefit to using scenes over objects in the MST. While both tasks resulted in an age-related decline in lure discrimination performance, relationships with hippocampal and MTL volumes were much stronger for MST-Objects. Likewise, Objects LDI showed a stronger relationship with standardized measures of memory (RAVLT and Rey-O delayed recall). Our data also suggests that the Rey-O may be a stronger measure of memory and possibly less prone to non-memory strategy that would alter performance, though that is partly speculation on our part. In conclusion, these findings emphasize the utility of MST-Object lure discrimination in revealing age-related memory changes and the relationship to hippocampal circuit alterations.

Acknowledgements

This research was supported in part by a grant from the National Institutes on Aging R01 AG034613 and P50 AG016573 (subaward). We thank Samantha Rutledge and Patricia Place for assistance in data collection.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.bbr.2017.06.049>.

References

- [1] J.L. McClelland, B.L. McNaughton, R.C. O'Reilly, Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory, *Psychol. Rev.* 102 (1995) 419–457.
- [2] J.J. Knierim, J.P. Neunuebel, Tracking the flow of hippocampal computation: pattern separation, pattern completion, and attractor dynamics, *Neurobiol. Learn. Mem.* 129 (2016) 38–49, <http://dx.doi.org/10.1016/j.nlm.2015.10.008>.
- [3] K.A. Norman, R.C. O'Reilly, Modeling hippocampal and neocortical contributions to recognition memory: a complementary-learning-systems approach, *Psychol. Rev.* 110 (2003) 611–646.
- [4] M.A. Yassa, C.E. Stark, Pattern separation in the hippocampus, *Trends Neurosci.* 34 (2011) 515–525, <http://dx.doi.org/10.1016/j.tins.2011.06.006>.
- [5] M.K. Johnson, S. Hashtroudi, D.S. Lindsay, Source monitoring, *Psychol. Bull.* 114 (1993) 3–28.
- [6] D.L. Schacter, W. Koutstaal, M.K. Johnson, M.S. Gross, K.E. Angell, False recollection induced by photographs: comparison of older and younger adults, *Psychol. Aging* 12 (1997) 203–215.
- [7] E.A. Kensinger, D.L. Schacter, When true memories suppress false memories: effects of ageing, *Cogn. Neuropsychol.* 16 (1999) 399–415.
- [8] V.A. Carr, A.D. Castel, B.J. Knowlton, Age-related differences in memory after attending to distinctiveness or similarity during learning, *Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn.* 22 (2015) 155–169, <http://dx.doi.org/10.1080/13825585.2014.898735>.
- [9] C.B. Kirwan, C.E.L. Stark, Overcoming interference: an fMRI investigation of pattern separation in the medial temporal lobe, *Learn. Mem.* 14 (2007) 625–633.
- [10] S.M. Stark, M.A. Yassa, J.W. Lacy, C.E. Stark, A task to assess behavioral pattern separation (BPS) in humans: data from healthy aging and mild cognitive impairment, *Neuropsychologia* 51 (2013) 2442–2449, <http://dx.doi.org/10.1016/j.neuropsychologia.2012.12.014>.
- [11] C.K. Toner, E. Pirogovsky, C.B. Kirwan, P.E. Gilbert, Visual object pattern separation deficits in nondemented older adults, *Learn. Mem. Cold Spring Harb. N. Y.* 16 (2009) 338–342.
- [12] M.A. Yassa, J.W. Lacy, S.M. Stark, M.S. Albert, M. Gallagher, C.E.L. Stark, Pattern separation deficits associated with increased hippocampal CA3 and dentate gyrus activity in nondemented older adults, *Hippocampus* 21 (2011) 968–979.
- [13] S.M. Stark, R. Stevenson, C. Wu, S. Rutledge, C.E. Stark, Stability of age-related deficits in the mnemonic similarity task across variations, *Behav. Neurosci.* 129

- (2015) 257–268.
- [14] C.B. Kirwan, A. Hartshorn, S.M. Stark, N.J. Goodrich-Hunsaker, R.O. Hopkins, C.E. Stark, Pattern separation deficits following damage to the hippocampus, *Neuropsychologia* 50 (2012) 2408–2414, <http://dx.doi.org/10.1016/j.neuropsychologia.2012.06.011>.
 - [15] H.M. Holden, C.K. Toner, E. Pirogovsky, C.B. Kirwan, P. Gilbert, Visual object pattern separation varies in nondemented older adults, *Learn. Mem.* 20 (2013) 358–362.
 - [16] E.T. Rolls, Pattern separation, completion, and categorisation in the hippocampus and neocortex, *Neurobiol. Learn. Mem.* 129 (2016) 4–28, <http://dx.doi.org/10.1016/j.nlm.2015.07.008>.
 - [17] P.E. Gilbert, R.P. Kesner, I. Lee, Dissociating hippocampal subregions: double dissociation between dentate gyrus and CA1, *Hippocampus* 11 (2001) 626–636, <http://dx.doi.org/10.1002/hipo.1077>.
 - [18] N.J. Goodrich-Hunsaker, M.R. Hunsaker, R.P. Kesner, The interactions and dissociations of the dorsal hippocampus subregions: how the dentate gyrus, CA3, and CA1 process spatial information, *Behav. Neurosci.* 122 (2008) 16–26, <http://dx.doi.org/10.1037/0735-7044.122.1.16>.
 - [19] S. Leutgeb, J.K. Leutgeb, Pattern separation pattern completion, and new neuronal codes within a continuous CA3 map, *Learn. Mem. Cold Spring Harb. N. Y.* 14 (2007) 745–757.
 - [20] J.P. Neunuebel, J.J. Knierim, CA3 retrieves coherent representations from degraded input: direct evidence for CA3 pattern completion and dentate gyrus pattern separation, *Neuron* 81 (2014) 416–427.
 - [21] A. Bakker, C.B. Kirwan, N.I. Miller, C.E.L. Stark, Pattern separation in the human hippocampal CA3 and dentate gyrus, *Science* 319 (2008) 1640–1642.
 - [22] J.W. Lacy, M.A. Yassa, S.M. Stark, L.T. Muftuler, C.E. Stark, Distinct pattern separation related transfer functions in human CA3/dentate and CA1 revealed using high-resolution fMRI and variable mnemonic similarity, *Learn. Mem.* 18 (2011) 15–18, <http://dx.doi.org/10.1101/lm.197111>.
 - [23] D. Berron, H. Schütze, A. Maass, A. Cardenas-Blanco, H.J. Kuijff, D. Kumaran, E. Düzel, Strong evidence for pattern separation in human dentate gyrus, *J. Neurosci.* 36 (2016) 7569–7579, <http://dx.doi.org/10.1523/JNEUROSCI.0518-16.2016>.
 - [24] N.G. De Shetler, J. Rissman, Dissociable profiles of generalization/discrimination in the human hippocampus during associative retrieval, *Hippocampus* 27 (2017) 115–121, <http://dx.doi.org/10.1002/hipo.22684>.
 - [25] J. Vela, A. Gutierrez, J. Vitorica, D. Ruano, Rat hippocampal GABAergic molecular markers are differentially affected by ageing, *J. Neurochem.* 85 (2003) 368–377.
 - [26] I.A. Wilson, M. Gallagher, H. Eichenbaum, H. Tanila, Neurocognitive aging: prior memories hinder new hippocampal encoding, *Trends Neurosci.* 29 (2006) 662–670.
 - [27] M.A. Yassa, L.T. Muftuler, C.E.L. Stark, Ultra-high-resolution microstructural diffusion tensor imaging reveals perforant path degradation in aged humans in vivo, *Proc. Natl. Acad. Sci. U. S. A.* 107 (2010) 12687–12691.
 - [28] M.A. Yassa, A.T. Mattfeld, S.M. Stark, C.E.L. Stark, Age-related memory deficits linked to circuit-specific disruptions in the hippocampus, *Proc. Natl. Acad. Sci.* 108 (2011) 8873–8878.
 - [29] I.J. Bennett, C.E.L. Stark, Mnemonic discrimination relates to perforant path integrity: an ultra-high resolution diffusion tensor imaging study, *Neurobiol. Learn. Mem.* (2015), <http://dx.doi.org/10.1016/j.nlm.2015.06.014>.
 - [30] A. Bakker, G.L. Krauss, M.S. Albert, C.L. Speck, L.R. Jones, C.E. Stark, M.A. Yassa, S.S. Bassett, A.L. Shelton, M. Gallagher, Reduction of hippocampal hyperactivity improves cognition in amnesic mild cognitive impairment, *Neuron* 74 (2012) 467–474, <http://dx.doi.org/10.1016/j.neuron.2012.03.023>.
 - [31] A. Bakker, M.S. Albert, G. Krauss, C.L. Speck, M. Gallagher, Response of the medial temporal lobe network in amnesic mild cognitive impairment to therapeutic intervention assessed by fMRI and memory task performance, *Neuroimage Clin.* 7 (2015) 688–698, <http://dx.doi.org/10.1016/j.nicl.2015.02.009>.
 - [32] S.N. Burke, L. Ryan, C.A. Barnes, Characterizing cognitive aging of recognition memory and related processes in animal models and in humans, *Front. Aging Neurosci.* 4 (2012) 15, <http://dx.doi.org/10.3389/fnagi.2012.00015>.
 - [33] S.N. Burke, J.L. Wallace, A.L. Hartzell, S. Nematollahi, K. Plange, C.A. Barnes, Age-associated deficits in pattern separation functions of the perirhinal cortex: a cross-species consensus, *Behav. Neurosci.* 125 (2011) 836–847, <http://dx.doi.org/10.1037/a0026238>.
 - [34] S.D. Vann, J.P. Aggleton, E.A. Maguir, What does the retrosplenial cortex do? *Nat. Rev. Neurosci.* 10 (2009) 792–802, <http://dx.doi.org/10.1038/nrn2733>.
 - [35] C. Ranganath, M. Ritchey, Two cortical systems for memory-guided behaviour, *Nat. Rev. Neurosci.* 13 (2012) 713–726, <http://dx.doi.org/10.1038/nrn3338>.
 - [36] R. Epstein, M. Smith, E. Ward, What is the function of the parahippocampal place area? Testing the context hypothesis, *J. Vis.* 9 (2009) 963, <http://dx.doi.org/10.1167/9.8.963>.
 - [37] C. Echavarrri, P. Aalten, H.B.M. Uylings, H.I.L. Jacobs, P.J. Visser, E.H.B.M. Gronenschild, F.R.J. Verhey, S. Burgmans, Atrophy in the parahippocampal gyrus as an early biomarker of Alzheimer's disease, *Brain Struct. Funct.* 215 (2011) 265–271, <http://dx.doi.org/10.1007/s00429-010-0283-8>.
 - [38] C.R. Doxey, C.B. Kirwan, Structural and functional correlates of behavioral pattern separation in the hippocampus and medial temporal lobe, *Hippocampus* 25 (2015) 524–533, <http://dx.doi.org/10.1002/hipo.22389>.
 - [39] J.M. Roberts, M. Ly, E. Murray, M.A. Yassa, Temporal discrimination deficits as a function of lag interference in older adults, *Hippocampus* 24 (2014) 1189–1196, <http://dx.doi.org/10.1002/hipo.22303>.
 - [40] S.L. Leal, M.A. Yassa, Effects of aging on mnemonic discrimination of emotional information, *Behav. Neurosci.* 128 (2014) 539–547, <http://dx.doi.org/10.1037/bne0000011>.
 - [41] S.L. Leal, J.A. Noche, E.A. Murray, M.A. Yassa, Age-related individual variability in memory performance is associated with amygdala-hippocampal circuit function and emotional pattern separation, *Neurobiol. Aging* 49 (2017) 9–19, <http://dx.doi.org/10.1016/j.neurobiolaging.2016.08.018>.
 - [42] M. Ly, E. Murray, M.A. Yassa, Perceptual versus conceptual interference and pattern separation of verbal stimuli in young and older adults, *Hippocampus* 23 (2013) 425–430, <http://dx.doi.org/10.1002/hipo.22110>.
 - [43] Z.M. Reagh, M.A. Yassa, Object and spatial mnemonic interference differentially engage lateral and medial entorhinal cortex in humans, *Proc. Natl. Acad. Sci. U. S. A.* 111 (2014) E4264–E4273, <http://dx.doi.org/10.1073/pnas.1411250111>.
 - [44] Z.M. Reagh, H.D. Ho, S.L. Leal, J.A. Noche, A. Chun, E.A. Murray, M.A. Yassa, Greater loss of object than spatial mnemonic discrimination in aged adults, *Hippocampus* 26 (2016) 417–422, <http://dx.doi.org/10.1002/hipo.22562>.
 - [45] S.M. Stark, M.A. Yassa, C.E.L. Stark, Individual differences in spatial pattern separation performance associated with healthy aging in humans, *Learn. Mem.* 17 (2010) 284–288.
 - [46] A.P. Yonelinas, The hippocampus supports high-resolution binding in the service of perception, working memory and long-term memory, *Behav. Brain Res.* 254 (2013) 34–44, <http://dx.doi.org/10.1016/j.bbr.2013.05.030>.
 - [47] A.C.H. Lee, M.J. Buckley, S.J. Pegman, H. Spiers, V.L. Scahill, D. Gaffan, T.J. Bussey, R.R. Davies, N. Kapur, J.R. Hodges, K.S. Graham, Specialization in the medial temporal lobe for processing of objects and scenes, *Hippocampus* 15 (2005) 782–797, <http://dx.doi.org/10.1002/hipo.20101>.
 - [48] M.D. Barense, R.N.A. Henson, A.C.H. Lee, K.S. Graham, Medial temporal lobe activity during complex discrimination of faces, objects, and scenes: effects of viewpoint, *Hippocampus* 20 (2010) 389–401, <http://dx.doi.org/10.1002/hipo.20641>.
 - [49] D. Berron, H. Schütze, A. Maass, A. Cardenas-Blanco, H.J. Kuijff, D. Kumaran, E. Düzel, Strong evidence for pattern separation in human dentate gyrus, *J. Neurosci.* 36 (2016) 7569–7579, <http://dx.doi.org/10.1523/jneurosci.0518-16.2016>.
 - [50] M. Azab, S.M. Stark, C.E.L. Stark, Contributions of human hippocampal subfields to spatial and temporal pattern separation, *Hippocampus* 24 (2014) 293–302, <http://dx.doi.org/10.1002/hipo.22223>.
 - [51] M.F. Folstein, S.E. Folstein, P.R. McHugh, Mini-mental state. A practical method for grading the cognitive state of patients for the clinician, *J. Psychiatr. Res.* 12 (1975) 189–198.
 - [52] A. Rey, L'examen psychologique dans les cas d'encephalopathie traumatique, *Arch. Psychol.* 28 (1941) 286–340.
 - [53] J.E. Meyers, K.R. Meyers, Rey Complex Figure Test and Recognition Trial (RCFT), Professional Manual, Psychological Assessment Resources (PAR), Inc., Odessa, TX, 1995.
 - [54] T.N. Tombaugh, Trail making Test A and B: normative data stratified by age and education, *Arch. Clin. Neuropsychol.* 19 (2004) 203–214, [http://dx.doi.org/10.1016/S0887-6177\(03\)00039-8](http://dx.doi.org/10.1016/S0887-6177(03)00039-8).
 - [55] C. Golden, Stroop Color and Word Test: A Manual for Clinical and Experimental Uses, Psychological Assessment Resources (PAR), Inc., Chicago, Illinois, 1978.
 - [56] D. Wechsler, Wechsler Adult Intelligence Scale (WAIS-III): Administration and Scoring Manual, The Psychological Corporation, San Antonio, TX, 1997.
 - [57] C.B. Kirwan, C.E.L. Stark, Medial temporal lobe activation during encoding and retrieval of novel face-name pairs, *Hippocampus* 14 (2004) 910–930.
 - [58] D.J. Huffman, C.E.L. Stark, Multivariate pattern analysis of the human medial temporal lobe revealed representationally categorical cortex and representationally agnostic hippocampus, *Hippocampus* 24 (2014) 1394–1403, <http://dx.doi.org/10.1002/hipo.22321>.
 - [59] C.B. Kirwan, C. Jones, M.I. Miller, C.E.L. Stark, High-resolution fMRI investigation of the medial temporal lobe, *Hum. Brain Mapp.* 28 (2007) 959–966.
 - [60] P.A. Yushkevich, R.S. Amaral, J.C. Augustinack, A.R. Bender, J.D. Bernstein, M. Boccardi, M. Bocchetta, A.C. Burggren, V.A. Carr, M.M. Chakravarty, G. Chetelat, A.M. Daugherty, L. Davachi, S.L. Ding, A. Ekstrom, M.I. Geerlings, A. Hassan, Y. Huang, J.E. Iglesias, R. La Joie, G.A. Kerchner, K.F. LaRocque, L.A. Libby, N. Malykhin, S.G. Mueller, R.K. Olsen, D.J. Palombo, M.B. Parekh, J.B. Pluta, A.R. Preston, J.C. Pruessner, C. Ranganath, N. Raz, M.L. Schlichting, D. Schoemaker, S. Singh, C.E. Stark, N. Suthana, A. Tompar, M.M. Turowski, K. Van Leemput, A.D. Wagner, L. Wang, J.L. Winterburn, L.E. Wisse, M.A. Yassa, M.M. Zeineh, Quantitative comparison of 21 protocols for labeling hippocampal subfields and parahippocampal subregions in in vivo MRI: Towards a harmonized segmentation protocol, *Neuroimage* (2015), <http://dx.doi.org/10.1016/j.neuroimage.2015.01.004>.
 - [61] L.E.M. Wisse, A.M. Daugherty, R.K. Olsen, D. Berron, V.A. Carr, C.E.L. Stark, R.S.C. Amaral, K. Amunts, J.C. Augustinack, A.R. Bender, J.D. Bernstein, M. Boccardi, M. Bocchetta, A. Burggren, M.M. Chakravarty, M. Chupin, A. Ekstrom, R. de Flores, R. Insausti, P. Kanel, O. Kedo, K.M. Kennedy, G.A. Kerchner, K.F. LaRocque, X. Liu, A. Maass, N. Malykhin, S.G. Mueller, N. Ofen, D.J. Palombo, M.B. Parekh, J.B. Pluta, J.C. Pruessner, N. Raz, K.M. Rodrigue, D. Schoemaker, A.T. Shafer, T.A. Steve, N. Suthana, L. Wang, J.L. Winterburn, M.A. Yassa, P.A. Yushkevich, R. la Joie, Hippocampal Subfields Group, A harmonized segmentation protocol for hippocampal and parahippocampal subregions: why do we need one and what are the key goals? *Hippocampus* 27 (2017) 3–11, <http://dx.doi.org/10.1002/hipo.22671>.
 - [62] P.A. Yushkevich, H. Wang, J. Pluta, S.R. Das, C. Craige, B.B. Avants, M.W. Weiner, S. Mueller, Nearly automatic segmentation of hippocampal subfields in in vivo focal T2-weighted MRI, *Neuroimage* 53 (2010) 1208–1224, <http://dx.doi.org/10.1016/j.neuroimage.2010.06.040>.
 - [63] B.B. Avants, C.L. Epstein, M. Grossman, J.C. Gee, Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain, *Med. Image Anal.* 12 (2008) 26–41, <http://dx.doi.org/10.1016/j.media.2007.06.004>.

- [64] B. Fischl, D.H. Salat, E. Busa, M. Albert, M. Dieterich, C. Haselgrove, A. van der Kouwe, R. Killiany, D. Kennedy, S. Klaveness, A. Montillo, N. Makris, B. Rosen, A.M. Dale, Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain, *Neuron* 33 (2002) 341–355.
- [65] C.R. Jack, C.K. Twomey, A.R. Zinsmeister, F.W. Sharbrough, R.C. Petersen, G.D. Cascino, Anterior temporal lobes and hippocampal formations: normative volumetric measurements from MR images in young adults, *Radiology* 172 (1989) 549–554, <http://dx.doi.org/10.1148/radiology.172.2.2748838>.
- [66] B.A. Ally, E.P. Hussey, P.C. Ko, R.J. Molitor, Pattern separation and pattern completion in Alzheimer's disease: evidence of rapid forgetting in amnesic mild cognitive impairment, *Hippocampus* 23 (2013) 1246–1258, <http://dx.doi.org/10.1002/hipo.22162>.
- [67] M.A. Yassa, S.M. Stark, A. Bakker, M.S. Albert, M. Gallagher, C.E. Stark, High-resolution structural and functional MRI of hippocampal CA3 and dentate gyrus in patients with amnesic Mild Cognitive Impairment, *Neuroimage* 51 (2010) 1242–1252, <http://dx.doi.org/10.1016/j.neuroimage.2010.03.040>.
- [68] S.L. Leal, S.K. Tighe, C.K. Jones, M.A. Yassa, Pattern separation of emotional information in hippocampal dentate and CA3, *Hippocampus* 24 (2014) 1146–1155, <http://dx.doi.org/10.1002/hipo.22298>.
- [69] D.J. Shelton, C.B. Kirwan, A possible negative influence of depression on the ability to overcome memory interference, *Behav. Brain Res.* 256 (2013) 20–26, <http://dx.doi.org/10.1016/j.bbr.2013.08.016>.
- [70] N. Déry, A. Goldstein, S. Becker, A role for adult hippocampal neurogenesis at multiple time scales: a study of recent and remote memory in humans, *Behav. Neurosci.* 129 (2015) 435–449, <http://dx.doi.org/10.1037/bne0000073>.
- [71] T. Das, E.I. Ivleva, A.D. Wagner, C.E.L. Stark, C.A. Tamminga, Loss of pattern separation performance in schizophrenia suggests dentate gyrus dysfunction, *Schizophr. Res.* 159 (2014) 193–197, <http://dx.doi.org/10.1016/j.schres.2014.05.006>.
- [72] C. Martinelli, S.S. Shergill, Clarifying the role of pattern separation in schizophrenia: the role of recognition and visual discrimination deficits, *Schizophr. Res.* 166 (2015) 328–333, <http://dx.doi.org/10.1016/j.schres.2015.06.004>.
- [73] A. Treves, E.T. Rolls, Computational analysis of the role of the hippocampus in memory, *Hippocampus* 4 (1994) 374–391.
- [74] H.E. Scharfman, C.E. Myers, Corruption of the dentate gyrus by dominant granule cells: implications for dentate gyrus function in health and disease, *Neurobiol. Learn. Mem.* 129 (2016) 69–82, <http://dx.doi.org/10.1016/j.nlm.2015.09.005>.
- [75] E.T. Rolls, A theory of hippocampal function in memory, *Hippocampus* 6 (1996) 601–620.
- [76] M.E. Hasselmo, The role of hippocampal regions CA3 and CA1 in matching entorhinal input with retrieval of associations between objects and context: theoretical comment on Lee et al. (2005), *Behav. Neurosci.* 119 (2005) 342–345.
- [77] D. Kumaran, E.A. Maguire, Novelty signals: a window into hippocampal information processing, *Trends Cogn. Sci.* 13 (2009) 47–54.
- [78] K. Duncan, C. Curtis, L. Davachi, Distinct memory signatures in the hippocampus: intentional States distinguish match and mismatch enhancement signals, *J. Neurosci.* 29 (2009) 131–139, <http://dx.doi.org/10.1523/JNEUROSCI.2998-08.2009>.
- [79] S.M. O'Mara, S. Commings, M. Anderson, J. Gigg, The subiculum: a review of form, physiology and function, *Prog. Neurobiol.* 64 (2001) 129–155, [http://dx.doi.org/10.1016/S0304-0082\(00\)00054-X](http://dx.doi.org/10.1016/S0304-0082(00)00054-X).
- [80] G. Chetelat, M. Fouquet, G. Kalpouzos, I. Denghien, V. De la Sayette, F. Viader, F. Mezenge, B. Landeau, J.C. Baron, F. Eustache, B. Desgranges, Three-dimensional surface mapping of hippocampal atrophy progression from MCI to AD and over normal aging as assessed using voxel-based morphometry, *Neuropsychologia* 46 (2008) 1721–1731.
- [81] R. La Joie, M. Fouquet, F. Mézenge, B. Landeau, N. Villain, K. Mevel, A. Pélerin, F. Eustache, B. Desgranges, G. Chetelat, Differential effect of age on hippocampal subfields assessed using a new high-resolution 3T MR sequence, *Neuroimage* 53 (2010) 506–514, <http://dx.doi.org/10.1016/j.neuroimage.2010.06.024>.
- [82] R. de Flores, R. La Joie, B. Landeau, A. Perrotin, F. Mézenge, V. de La Sayette, F. Eustache, B. Desgranges, G. Chetelat, Effects of age and Alzheimer's disease on hippocampal subfields, *Hum. Brain Mapp.* 36 (2015) 463–474, <http://dx.doi.org/10.1002/hbm.22640>.
- [83] A.M. Daugherty, A.R. Bender, N. Raz, N. Ofen, Age differences in hippocampal subfield volumes from childhood to late adulthood, *Hippocampus* 26 (2016) 220–228, <http://dx.doi.org/10.1002/hipo.22517>.
- [84] M.M. Zeineh, S.A. Engel, P.M. Thompson, S.Y. Bookheimer, Dynamics of the hippocampus during encoding and retrieval of face-name pairs, *Science* 299 (2003) 577–580.
- [85] A.R. Preston, A.M. Bornstein, J.B. Hutchinson, M.E. Gaare, G.H. Glover, A.D. Wagner, High-resolution fMRI of content-sensitive subsequent memory responses in human medial temporal lobe, *J. Cogn. Neurosci.* 22 (2010) 156–173, <http://dx.doi.org/10.1162/jocn.2009.21195>.
- [86] A.N. Voineskos, J.L. Winterburn, D. Felsky, J. Pipitone, T.K. Rajji, B.H. Mulsant, M.M. Chakravarty, Hippocampal (subfield) volume and shape in relation to cognitive performance across the adult lifespan, *Hum. Brain Mapp.* 36 (2015) 3020–3037, <http://dx.doi.org/10.1002/hbm.22825>.
- [87] M.G. Baxter, I've seen it all before: explaining age-related impairments in object recognition. Theoretical comment on Burke et al. (2010), *Behav. Neurosci.* 124 (2010) 706–709, <http://dx.doi.org/10.1037/a0021029>.
- [88] A.M. Daugherty, P. Yuan, C.L. Dahle, A.R. Bender, Y. Yang, N. Raz, Path complexity in virtual water maze navigation: differential associations with age, sex, and regional brain volume, *Cereb. Cortex.* 25 (2015) 3122–3131, <http://dx.doi.org/10.1093/cercor/bhu107>.
- [89] R.G.M. Morris, Elements of a neurobiological theory of hippocampal function: the role of synaptic plasticity, synaptic tagging and schemas, *Eur. J. Neurosci.* 23 (2006) 2829–2846, <http://dx.doi.org/10.1111/j.1460-9568.2006.04888.x>.