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Authors

Reagh, Zachariah M
Roberts, Jared M
Ly, Maria
[et al.](#)

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Spatial discrimination deficits as a function of mnemonic interference in aged adults with and without memory impairment

Zachariah M. Reagh, Jared M. Roberts, Maria Ly, Natalie DiProspero, Elizabeth Murray, and Michael A. Yassa*

Department of Psychological and Brain Sciences, Johns Hopkins University, Baltimore, MD 21218

Abstract

It is well established that aging is associated with declines in episodic memory. In recent years, an emphasis has emerged on the development of behavioral tasks and the identification of biomarkers that are predictive of cognitive decline in healthy as well as pathological aging. Here, we describe a memory task designed to assess the accuracy of discrimination ability for the locations of objects. Object locations were initially encoded incidentally, and appeared in a single space against a 5x7 grid. During retrieval, subjects viewed repeated object-location pairings, displacements of 1, 2, 3, or 4 grid spaces, and maximal corner-to-opposite-corner displacements. Subjects were tasked with judging objects in this second viewing as having retained their original location, or having moved. Performance on a task such as this is thought to rely on the capacity of the individual to perform hippocampus-mediated pattern separation. We report a performance deficit associated with a physically healthy aged group compared to young adults specific to trials with low mnemonic interference. Additionally, for aged adults, performance on the task was correlated with performance on the delayed recall portion of the Rey Auditory Verbal Learning Test (RAVLT), a neuropsychological test sensitive to hippocampal dysfunction. In line with prior work, dividing the aged group into unimpaired and impaired subgroups based on RAVLT Delayed Recall scores yielded clearly distinguishable patterns of performance, with the former subgroup performing comparably to young adults, and the latter subgroup showing generally impaired memory performance even with minimal interference. This study builds on existing tasks used in the field, and contributes a novel paradigm for differentiation of healthy from possible pathological aging, and may thus provide an avenue for early detection of age-related cognitive decline.

Keywords

hippocampus; pattern separation; interference; spatial discrimination; neurocognitive aging

1. Introduction

A critical feature of episodic memory is the ability to form conjunctive representations of events. That is, a memory that is episodic is distinguished by its synthesis of information about items, objects, or central features with a spatiotemporal context (Tulving, 2002). Decades of computational models and empirical data have yielded strong evidence for the medial temporal lobe (MTL) cortices and the hippocampus providing a neural substrate for

*Corresponding Author: Michael A. Yassa, Department of Psychological and Brain Sciences, Johns Hopkins University, 3400 N. Charles St, Ames 216A, Baltimore, MD 21218, 410-516-0202 | Fax: 410-516-4478, yassa@jhu.edu.

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such information processing and synthesis to occur (Buckner & Wheeler, 2001; Eichenbaum & Lipton, 2008; Norman, 2010; Norman & O'Reilly, 2003; O'Reilly & Norman, 2002; Staresina & Davachi, 2009; Treves & Rolls, 1994).

The field of learning and memory has had a rich history of studying mnemonic discrimination in the spatial domain (O'Keefe & Nadel, 1978). Recent work in rodents has implicated a computation in the hippocampus referred to as pattern separation as a cornerstone process underlying episodic memory (Gilbert, Kesner, & Lee, 2001; Hunsaker et al., 2008; Leutgeb et al., 2005, 2007; Leutgeb & Leutgeb, 2007; Leutgeb et al., 2004; McTighe et al., 2009). Pattern separation is the process of reducing interference among similar inputs by using non-overlapping representations and is thought to be accomplished in the brain by using distinct neural codes (Marr, 1971; McClelland, McNaughton, & O'Reilly, 1995; Norman, 2010; Norman & O'Reilly, 2003; Shapiro & Olton, 1994; Treves & Rolls, 1994; Yassa & Stark, 2011). Findings in the rodent have been supported in human high-resolution neuroimaging studies using tasks designed to probe pattern separation of object identity rather than of spatial information (Bakker et al., 2008; Lacy et al., 2011). These studies all converge on the hippocampal dentate gyrus (DG) and subregion CA3 as being the primary sites of pattern separation and pattern completion computations (Yassa & Stark, 2011).

These findings have proven to be a fruitful avenue for studying the effects of aging on memory processes in humans. Though the aging brain goes through a number of changes, the process of aging seems to particularly affect the MTL and hippocampus (Driscoll et al., 2005; Good et al., 2001; Raz et al., 2005; Walhovd et al., 2010). Recent human functional neuroimaging studies have reported a specific perturbation in hippocampal activity thought to be reflective of impaired pattern separation in aged adults, which is associated with poor lure discrimination performance and hyperactivity in the hippocampal DG and CA3 (Yassa et al., 2010; Yassa et al., 2011a; Yassa et al., 2011b). Specifically, aged adults, and to a greater extent aged adults with mild cognitive impairment (MCI) and Alzheimer's Disease (AD), appear to shift their bias away from discriminating among similar lures and toward grouping similar items into a common representation. On a computational level, this is hypothesized to result from a bias away from pattern separation in the DG-CA3 network, and a bias toward pattern completion mediated largely by excitatory autoassociation in CA3. In support of this view, a recent study which administered low doses of levetiracetam (an anti-epileptic medication) to patients with MCI reported a reduction in hyperactivity in the DG and CA3, as well as a notable increase in lure discrimination performance (Bakker et al., 2012). Another point of emphasis is that this specific aberration in hippocampal activity and behavior associated with pattern separation may precede anatomical or more general cognitive indices of cognitive decline. As such, tasks designed to tax this computation may have strong potential to detect memory decline at preclinical stages (for a review, see Leal & Yassa, 2013).

Interestingly, despite the dominance of spatial manipulations in rodent models, very few experiments have examined long-term mnemonic discrimination of spatial lures in human subjects. One such study by Stark, Yassa, & Stark (2010) presented subjects with pairs of small images of scenes against a white background, and during test, either kept both locations the same, or moved the location of one of these scenes at a Close (10–20% of screen size), Medium (25–35%), or Far (40–60%) distance from its origin. Subjects were tasked with judging whether the pair was in the same or a different configuration. This study found no overall deficit when comparing older adults to young adults, but observed significant variability within the older adult sample. When older adults were divided into Aged Unimpaired (AU) and Aged Impaired (AI) subgroups (based on performance on the Rey Auditory Verbal Learning Test (RAVLT), a test that is typically sensitive to

hippocampal deficits), a deficit was observed in the AI group relative to both the Young and AU groups, most pronounced at levels of low mnemonic interference (i.e., Medium and Far trials). Though these results are in agreement with findings in the domain of object lures, a limitation of this study is that the use of scenes, as well as the encoding and retrieval of two visual stimuli likely elicited relational encoding and retrieval strategies that may differ markedly from previous studies designed to tax pattern separation in humans.

Another recent study by Holden and colleagues (2012) presented young and older adult subjects with delayed match-to-sample task in which subjects first viewed a gray dot against a computer screen, and after a 10 second delay, were presented with a red and blue dot, one of which represented the position of the original grey dot. The distance between test dots (corresponding to degree of interference) was varied between 0, 0.5, 1.0, and 1.5cm. Subjects were tasked with choosing the dot in the original location. Holden and colleagues reported a general deficit in discrimination in older adults compared to young, which became more pronounced as the distance between dots increased. The authors additionally divided the older adult group into older unimpaired and older impaired subgroups. They reported that while the unimpaired group did not differ in performance from young adults, the impaired group showed global deficits in spatial pattern separation. While somewhat consistent with Stark and colleagues' (2010) results, this study has several differences in experimental design. First, the 10 second delay between encoding and retrieval in a delayed match-to-sample task may have preferentially taxed working memory rather than long term memory in its human subjects. Second, the authors examined the main effect of group, but did not investigate interactions with the level of mnemonic interference, possibly overlooking important nuances in performance (for example, at the 1.0cm distance, the older unimpaired and impaired groups do not appear to differ significantly despite the overall main effect).

We designed a task to tax mnemonic discrimination of spatial information. This task was designed to correspond to prior studies in humans performing mnemonic object lure discrimination as well as to animal work in relying on shared hippocampal computations (i.e. pattern separation). It is important to note that while this task as designed very likely taxes hippocampal pattern separation, we collected only behavioral indices, and thus cannot draw strong direct conclusions about underlying neural computations. As such, we have chosen to refer to this as a Mnemonic Discrimination task in the Spatial domain (MD-S), and further discussion of pattern separation will refer to the neural computation occurring in the hippocampus. We compared performance across young and aged adults, and in line with several prior studies, we additionally operationally divided the aged adult group into unimpaired and impaired subgroups. We found that young adults outperformed aged adults in general when mnemonic interference was low (i.e., moderate spatial displacements), but that this relative deficit was eliminated by completely minimizing mnemonic interference (i.e., maximal spatial displacements). Dividing the aged group according to their performance on RAVLT delayed recall resulted in two distinct patterns of performance, with AU adults clearly outperforming AI adults. However, unlike prior studies, we closely compared performance across all 3 groups, and found that AU adults were nonetheless outperformed by young adults at several degrees of interference. Furthermore, the AI group remains impaired even when interference is minimized, unlike the AU group. As such, this task may offer a novel and highly sensitive index of mnemonic ability in aged adults, and with additional testing may serve to differentiate healthy from possibly pathological aging.

2. Materials and Methods

2a. Spatial Mnemonic Discrimination Task

One hundred forty images of common objects were selected from an existing set previously used by Brady and colleagues (2008). Images were presented on a computer monitor with the total screen area divided into discrete spaces comprising a 5x7 grid (not visible to subjects). This layout was chosen to accommodate the dimensions of common widescreen displays, and allowed for 35 possible grid spaces in which an object could be presented.

The MD-S task consisted of two phases. In the first phase, subjects viewed a sequence of 140 objects appearing at pseudorandomly assigned grid locations, and were tasked with judging whether each object would be more likely found indoors or outdoors. As such, encoding of these objects in their respective locations was incidental. Following a 5-minute delay, subjects completed the second phase in which subjects viewed a second sequence of the same objects viewed during incidental encoding. However, in this phase some objects were presented in the same location as before, and some were presented in a different location. Subjects were tasked with judging whether each object was in the same location as before, or whether it had moved (Figure 1A). Of the 140 originally viewed objects, 40 Targets were presented in a repeated grid space. The remaining 100 images were divided evenly among 5 types of Lures (20 per type) designed to elicit parametrically varying degrees of mnemonic interference. Importantly, unlike much prior work employing similar Lure items, Lures in this task were identical objects to those seen in the first phase of the task, but differed only in spatial location with respect to their original positions.

Lure types consisted of objects that were displaced by one, two, three, or four grid spaces (1-Move, 2-Move, 3-Move, and 4-Move Lures, respectively), as well as objects that were first observed in a corner of the screen and were displaced into the opposite corner (Corner Lure). Given that 1-Move through 4-Move Lures varied displacement across objective metric distances, these were designed to allow us to make parametric comparisons across levels of mnemonic interference. Corner Lures were designed to provide subjects with trials in which mnemonic interference was minimal within the constraints of the task (i.e., this was the farthest amount of spatial displacement possible, and should be the easiest possible Lure trial in the task). Given the relative ease of recognizing displacement from a corner, only Corner Lures could appear in these spaces (i.e., Targets and other displacement types were precluded from occupying a corner). Direction of displacement of lures was pseudorandomly assigned for each participant, and was balanced across trials such that all grid spaces during the first and second phase were used equally as much as was possible given the number of images used. Specifically, each space of the grid (excluding corners) was equally likely to contain an object, and vertical and lateral displacement was equally likely in either phase of the task. Diagonal displacements were not used. A schematic of screen segmentation and lure displacement is displayed in Figure 1B&C. The task was programmed using PsychoPy presentation software (Peirce, 2007, 2008).

2b. Participant Selection

Twenty-seven young adult participants (19 female, 8 male, mean age 21.7 SD 4.2 years) were healthy volunteers recruited from the Johns Hopkins University community by institutional email advertising, as well as flyer advertising. A second group of twenty-six aged adult participants (18 female, 8 male, mean age 69.7 SD 7.4 years) were healthy volunteers recruited from newspaper advertisements, as well as direct contact with individuals who had previously participated in our lab's studies, and who consented to future recruitment. Exclusion criteria included any major medical conditions (e.g., diabetes, heart disease), neurologically-active medications, current diagnosis of mental or psychiatric

disorder (e.g., depression, dementia). Informed consent was obtained from all participants in accordance with the Johns Hopkins University Institutional Review Board.

All subjects received a battery of neuropsychological tests, and of particular interest was the Rey Auditory Verbal Learning Test (RAVLT). We divided the Aged group into Aged Unimpaired (AU) and Aged Impaired (AI) subgroups akin to what has been done in rodent work (Gallagher et al., 2006; Gallagher et al., 2003; Gallagher, Burwell, & Burchinal, 1993), as well as in human studies (Stark, Yassa, & Stark, 2010; Stark et al., 2013) of impairment with aging. Within our Aged group, we observed a mean RAVLT Delay score of 8.7 (out of 15). We thus bisected the group into an AU subgroup (RAVLT Delay \geq 9, 10 female, 4 male, mean age 71.2 SD 7.2 years) and an AI subgroup (RAVLT Delay $<$ 9, 7 female, 5 male, mean age 67.8 SD 7.7 years). We note that this distinction is not reflective of a clinical diagnosis (though RAVLT scores are often used in combination with other measures diagnostically), and only serves to operationally divide participants for the purposes of the current study. Dividing the Aged group into the AU and AI subgroups yielded highly comparable samples, which differed significantly only on RAVLT performance and not on other measures such as age, education, and performance on working memory manipulations such as digit span (Table 1). In addition, using the RAVLT Delay score of 9 as a criterion, 2 young adult participants were excluded from analyses as a result of RAVLT Delay scores $<$ 9 (final sample for Young group: 17 female, 8 male, mean age 21.8 SD 4.2 years).

2c. Analysis of Behavioral Data

Given the binary “No Move” or “Move” judgments in the task, the measure of interest was simple proportion of correct responses (i.e., percent correct). For repeated locations, the proportion of correct judgments (Target Recognition) was derived as $p(\text{“No Move”}|\text{Target})$. For Lures, the proportion of correct judgments (Lure Discrimination) was derived as $p(\text{“Move”}|\text{Lure})$. When making comparisons at particular levels of interference, we simply used Lure Discrimination at that level (e.g., accuracy for 1-Move Lures). Comparisons over general Lure Discrimination performance across all lure types were done over an area-under-the-curve (AUC) measure for each group, which quantified accuracy across levels of interference into a single cumulative value. Also as a result of only two possible responses, no corrections for response bias or data transformations were necessary prior to statistical analyses.

For our first set of analyses, the Young group was compared with the Aged group in the absence of any subgroup divisions. We first compared Target Recognition using an independent samples *t*-test. We then compared the two groups on Lure Discrimination using a 2x5 mixed analysis of variance (ANOVA) with group as the between-subjects variable and lure displacement as the within-subjects variable. Specific comparisons were then carried out to parse the effects and interaction using an independent-samples *t*-test (main effect of Group, carried out using AUC) and *post-hoc* contrasts (main effect of Displacement and interaction).

We next calculated correlations between performance on the RAVLT battery (RAVLT total, RAVLT immediate, and RAVLT Delay) with Lure Discrimination for the Young and Aged adults. These analyses were carried out to provide validation for using RAVLT Delay scores as a relevant neuropsychological index, as well as a tool for subdividing the Aged group into Unimpaired and Impaired subgroups based on prior studies. We adjusted our familywise error rate in evaluating the significance of correlations using the Holm sequentially-rejective Bonferroni correction (Holland & Copenhaver, 1987; Holm, 1979). As RAVLT Delay was our primary neuropsychological test of interest, we limit our depictions of the correlations to this particular test. However, any significant correlations are reported in our results below.

For our second analyses, we divided the Aged group into Unimpaired and Impaired subgroups as described above. Target Recognition was compared across Young, AU, and AI participants using a one-way ANOVA, and *post-hoc* comparisons were carried out using Tukey's HSD. To compare Lure Discrimination, we used a 3x5 mixed ANOVA with group as the between-subjects variable and lure displacement as the within-subjects variable. We further analyzed the effects and interaction by conducting *post-hoc* pairwise comparisons via Tukey's HSD (main effect of Group, carried out using AUC) and contrasts (main effect of Displacement and interaction).

We finally calculated another set of correlations between RAVLT scores and Lure Discrimination (AUC) for AU and AI subgroups. Significance of this set of correlations was again evaluated according to a Holm sequentially-rejective Bonferroni corrected threshold (Holm, 1979). Similar to our approach above, our depictions in figures are limited to RAVLT delay, though any significant correlations are reported below. Statistical analyses were conducted using SPSS v. 20.0 (IBM Corp., released 2011, Armonk, NY). All analyses over within-subjects data were corrected for error non-sphericity, and all multiple *post-hoc* comparisons over a family of data were adjusted to a corrected alpha of 0.05. *Post-hoc* contrasts additionally accounted for unequal sample sizes in the error terms from which respective F-values were derived.

3. Results

3a. Aged adults exhibit a general spatial discrimination deficit

An independent samples t-test revealed that the Young group did not differ significantly from the Aged group in Target Recognition ($t(24) = 1.708, p = 0.1$) (Figure 2A). Nonetheless, it warrants noting that this comparison does approach significance. We next tested for group differences on Lure Discrimination performance. A 2x5 mixed ANOVA revealed a significant effect of Lure displacement ($F(4,196) = 142.282, p < 0.001$ corrected), a significant effect of Group ($F(1,49) = 8.748, p = 0.005$), and a significant interaction ($F(4,196) = 6.374, p < 0.001$ corrected). Prior to between-group comparisons, we ensured that age was not significantly correlated with averaged Lure Discrimination ($R^2 = 0.005$, n.s.), as might be expected if age alone was responsible for observed deficits.

Examining the main effect of Group, AUC comparisons revealed that the Aged group was generally outperformed by the Young group ($t(24) = 3.292, p < 0.05$) (Figure 2B). In order to more closely interpret the main effect of Lure displacement, we performed trend analysis on accuracy as a function of displacement. We observed a significant linear trend in overall performance ($F(1,49) = 485.847, p < 0.001$ corrected), indicating that, as expected, accuracy increases as interference decreases. A cubic trend was marginal, but not significant ($F(1,49) = 1.850, p = 0.068$ corrected).

We next examined group differences at different interference levels using simple effect contrasts. These data are displayed in Figure 2C. Contrasts were corrected for multiple comparisons using Scheffé's method (adjusted critical $F_s = 9.64$). These comparisons revealed that the Young group did not differ from the Aged group on 1-Move ($F(1,196) = 0.559$, n.s.) or 2-Move trials ($F(1,196) = 1.914$, n.s.). Conversely, the Young group significantly outperformed the Aged group on 3-Move ($F(1,196) = 12.335, p < 0.05$ corrected) and 4-Move trials ($F(1,196) = 11.803, p < 0.05$ corrected). Finally, the groups did not differ in performance on the Corner trials ($F(1,196) = 2.04$, n.s.). Together, these results suggest that the deficits present in the Aged group relative to the Young group are specific to trials with moderate to low mnemonic interference, but that deficits are overcome at the lowest levels of interference (i.e., Corner Lures).

Given the parametric nature of our manipulation, we chose to parse the interaction by contrasting performance of Young vs. Aged groups with increasing steps in object displacement. Contrasts over the interaction were corrected using Scheffé's method (adjusted critical $F_s = 9.64$). These comparisons revealed that the Young group had a significantly steeper performance curve than the Aged group from 1-Move to 2-Moves ($F(1,196) = 55.454, p < 0.05$ corrected) and from 2-Moves to 3-Moves ($F(1,196) = 103.517, p < 0.05$ corrected), indicating that the former group is more readily able than the latter to capitalize on small to moderate decreases in mnemonic interference. Conversely, the groups did not differ in slope from 3-Moves to 4-Moves ($F(1,196) = 1.038, n.s.$), suggesting similar gains in low-interference trials. That is, although it is this part of the curves in which the Young and Aged groups differ significantly on individual 3-Move and 4-Move trial types, gains in performance across groups most resemble one another as interference decreases go from moderate to large. Finally, we observed that the groups again differ significantly from the 4-Move to Corners trials ($F(1,196) = 47.799, p < 0.05$ corrected). In this case, the Aged group demonstrates a steeper slope than the Young group. In concert with the fact that the two groups do not significantly differ in performance on Corner trials, this suggests that Aged adults are capable of 'catching up' to the performance of the Young group, but that minimal mnemonic interference is required for such performance gains to occur.

3b. Lure Discrimination correlates with word list recall only in aged adults

We did not observe any significant correlations in Young adults between Lure Discrimination (AUC) and scores on the RAVLT Total ($R^2 = 0.009, n.s.$), the RAVLT Immediate ($R^2 = 0.032, n.s.$), or the RAVLT Delay ($R^2 = 0.062, n.s.$) (Figure 3A). Conversely, Lure Discrimination was significantly correlated with scores on the RAVLT Total ($R^2 = 0.282, p = 0.005$), the RAVLT Immediate ($R^2 = 0.251, p = 0.009$), and the RAVLT Delay ($R^2 = 0.556, p < 0.001$) in Aged adults (Figure 3B). Together, these findings indicate that variability in performance on the MD-S task was predictive of neuropsychological measures of memory deficits in Aged adults, but not Young adults. RAVLT Delay scores seemed to be particularly predictive in this regard.

3c. Individual differences in lure discrimination performance exist in aged adults

A one-way ANOVA comparing Target Recognition across the Young, AU, and AI groups was significant ($F(2,48) = 5.859, p = 0.005$). To assess specific differences among groups, corrected pairwise comparisons were carried out using Tukey's HSD ($HSD = 0.1$). We observed that the AI group had significantly lower Target Recognition scores compared to both the Young group (difference = 0.130, $p < 0.05$) and the AU group (difference = 0.121, $p < 0.05$). On the other hand, the Young and AU groups did not differ (difference = 0.009, $n.s.$) (Figure 4A).

Assessing Lure Discrimination, a 3x5 mixed ANOVA revealed a significant effect of Lure displacement ($F(4,196) = 128.895, p < 0.001$ corrected), a significant effect of Group ($F(1,49) = 6.514, p = 0.003$), and a significant interaction ($F(8,196) = 5.181, p < 0.001$ corrected). We first examined the main effect of Group, in this case using Tukey's HSD to address pairwise comparisons ($HSD = 0.38$). Pairwise comparisons over AUC revealed that the AI group had significantly lower Lure Discrimination accuracy than the Young group (difference = 0.58, $p < 0.05$) and the AU group (difference = 0.39, $p < 0.05$). Similar to our Target Recognition results, we found that the Young and AU groups did not differ (difference = 0.21, $n.s.$) (Figure 4B). However, unlike in Target Recognition, we here observed that the Young group did outperform the AU group to a noticeable (albeit not statistically significant) extent. Indeed, a linear contrast on these data was significant ($F(1,48) = 212.861, p < 0.001$). While we recognize the interpretational limitations inherent to analyzing polynomial trends over categorical independent variables, we nonetheless take

this to suggest that general Lure Discrimination performance features a slight decrease with age, which is considerably more severe in the AI group. We again examined the main effect of Lure displacement via trend analysis, and again observed a significant linear trend ($F(1,48) = 462.995, p < 0.001$ corrected), and in this case, a cubic trend (indicative of reversals of direction) reached significance ($F(1,48) = 5.194, p = 0.027$ corrected). Specifically, we again observed that performance increased with decreasing interference, but splitting the Aged group into AU and AI subgroups revealed significant deviations from a linear increase in discrimination ability.

We used simple effect contrasts to compare Lure Discrimination across groups at different levels of interference. These data are displayed in Figure 4C. Scheffé's method was used to correct for multiple comparisons (adjusted critical $F_s = 9.68$). Performance did not differ for 1-Move trials. For 2-Move trials, we observed that the AI group was outperformed by both the Young ($F(1,192) = 17.8, p < 0.05$ corrected) and the AU ($F(1,192) = 11.608, p < 0.05$ corrected) groups. The Young and AU groups did not differ for 2-Move lures ($F(1,192) = 0.179, n.s.$). This indicates that performance of the AI group diverges from Young adults sooner than the AU group along this continuum of mnemonic interference. For 3-Move lures, Young adults outperformed both AI ($F(1,192) = 41.9, p < 0.05$ corrected) and AU ($F(1,192) = 15.059, p < 0.05$ corrected) subjects. AU adults did not significantly outperform AI adults at the level of 3-Move lures ($F(1,192) = 8.179, n.s.$), though we note that this comparison approaches significance even at our corrected threshold. This suggests that performance of the 3 groups begins to diverge at this moderate-to-low level of mnemonic interference, though given that the AU group narrowly missed significantly higher performance than the AI group, this level of interference is perhaps difficult for aged adults irrespective of any additional cognitive deficits. Performance fully diverges at the level of 4-Move lures, where Young adults outperform both the AI ($F(1,192) = 46.684, p < 0.05$ corrected) and AU ($F(1,192) = 13.487, p < 0.05$ corrected) groups, and the AI group is outperformed by the AU group ($F(1,192) = 10.899, p < 0.05$ corrected). Finally, in the Corners condition, the AI group is outperformed by both the Young ($F(1,192) = 15.596, p < 0.05$ corrected) and AU ($F(1,192) = 11.111, p < 0.05$ corrected) groups, and the Young and AU groups do not differ significantly from one another ($F(1,192) = 0.041, n.s.$). That is, at the lowest level of mnemonic interference, performance of the AU group seems to be able to 'catch up to' performance of the Young group, similar to our prior analysis above with an undivided Aged group. However, the present analysis suggests that a subset of older adults represented by the AI group may have a more global deficit in spatial memory that continues to manifest even at the lowest levels of mnemonic interference. .

We parsed the interaction similarly to what was reported above, this time comparing across 3 groups. Contrasts over the interaction were corrected using Scheffé's method (adjusted critical $F_s = 19.36$). We found that from 1-Move to 2-Moves, the AI group shows a flatter slope of gains in performance than both the Young ($F(1,192) = 214.514, p < 0.05$ corrected) and AU ($F(1,192) = 91.94, p < 0.05$ corrected) groups. The latter groups' slopes did not differ ($F(1,192) = 3.392, n.s.$), suggesting that the AU, but not the AI group, made similar gains in performance from even small decreases in mnemonic interference. From 2-Moves to 3-Moves, the Young group showed a steeper slope than both the AI ($F(1,192) = 148.903, p < 0.05$ corrected) and AU groups ($F(1,192) = 242.096, p < 0.05$ corrected), and the slopes of the two Aged groups did not differ ($F(1,192) = 5.333, n.s.$). That is, while Young adults continue to improve, Aged adults, whether Impaired or Unimpaired, show diminishing increases in performance. From 3-Moves to 4-Moves, Young adults again show a steeper slope in gains than the AI group ($F(1,192) = 26.643, p < 0.05$ corrected). However, at this segment of their curves, the slopes of the Young and AU groups do not differ ($F(1,192) = 0.409, n.s.$), and the AU group has a significantly steeper increase in gains than the AI group ($F(1,192) = 19.527, p < 0.05$ corrected). This suggests that although AU subjects are

generally outperformed by Young subjects at these levels of mnemonic interference (as shown by our simple effect contrasts), their gains in performance due to reductions in interference are similar. Finally, from 4-Move to Corners, Young adults show a flattening of their slope relative to both AI ($F(1,192) = 102.191, p < 0.05$ corrected) and AU ($F(1,192) = 232.505, p < 0.05$ corrected) subjects. Additionally, the AU group has a steeper slope of performance gains than the AI group ($F(1,192) = 20.191, p < 0.05$ corrected). This indicates that Aged adults generally benefit more from larger decreases in mnemonic interference than do young adults, though it warrants noting that the Young group is approaching near-ceiling performance. These results further suggest that although the AI adults show this performance increase, it is attenuated relative to the increase shown by the AU group (which, as shown by our simple effect contrasts reported previously, ultimately comes to match performance of the Young adult group).

3d. Lure Discrimination correlates with word list recall in AI and AU subgroups

Lure Discrimination (AUC) scores were significantly correlated with RAVLT Immediate ($R^2 = 0.444, p = 0.009$) and RAVLT Delay ($R^2 = 0.687, p < 0.001$) in the AU group (Figure 5A). A correlation between Lure Discrimination and RAVLT Total trended toward significance in this group, but did not surpass our corrected threshold ($R^2 = 0.296, p = 0.044$). In the AI group, only RAVLT Delay scores correlated significantly with Lure Discrimination ($R^2 = 0.492, p = 0.011$) (Figure 5B). Consistent with correlational analyses prior to splitting the Aged group, this further indicates a strong relationship between Lure Discrimination in this task and RAVLT Delay performance and further suggests that the correlations previously reported were not simply driven by the presence of two distinct subpopulations. Within-group correlations strongly suggest that these deficits are likely on a continuum of impairment from healthy to pathological.

All subject groups performed well within their age-matched norms (van der Elst et al., 2005) on the RAVLT delayed recall component. The range for normal performance for subjects aged 25 years old is 8.2 – 15 across males and females. Mean performance in our young adult sample was 13.2, which is within the normative range. Although the mean age of our young sample was 21.8 years, we used the 25-year old normative data as an approximation as robust normative data are not available for younger subjects. The range for normal performance for subjects aged 70 years old is 5.1 – 12.7 across males and females. Mean performance in our AU sample was 11 and for our AI sample was 6.1, both of which are within the normal range for this age group.

4. Discussion

This study sought to examine memory for spatial locations in young and aged adult humans. Subjects first viewed a stream of objects in various locations on the screen, and during retrieval, objects retained their original location, or were parametrically displaced 1, 2, 3, or 4 spaces from their original location, or moved maximally from corner to opposite corner. The results indicated a general deficit in spatial Lure Discrimination in Aged adults compared to Young adults. More specific analyses revealed that Aged adults were only relatively impaired at moderate to low levels of mnemonic interference (i.e., 3-Move and 4-Move Lures), and that this impairment was largely overcome with minimal interference (i.e., Corner Lures). Interestingly, Aged adults and Young adults did not differ significantly at Target Recognition, though a marginal difference was apparent.

In line with prior studies (Holden et al., 2012; Stark, Yassa, & Stark, 2010), we divided the Aged group into impaired and unimpaired subgroups based on neuropsychological testing. We repeated our analyses across the 3 group dataset. Results indicated a general deficit in Lure Discrimination in AI adults compared to Young and Aged Unimpaired, and a possible

slight deficit in the AU group compared to Young (as evinced by a downward linear trend). Consistent with this main effect, AI adults were outperformed by both Young and AU adults at nearly all levels of mnemonic interference. AU adults demonstrated deficits relative to Young adults only at the 3-Move and 4-Move levels (a pattern retained from our analysis prior to splitting the Aged adults), and were virtually identical in performance to Young adults otherwise. With the Aged group split, we observed a clear deficit in Target Recognition in AI adults compared to both Young and AU.

Correlational analyses revealed that scores on the Rey Auditory Verbal Learning Test were strongly predictive of performance of Aged adults in the MD-S task. This was especially the case for the RAVLT Delay, which was robustly correlated with Lure Discrimination in Aged adults, as well as the Unimpaired and Impaired subgroups. Together, these data suggest that this task is sensitive to age-related variability in mnemonic performance, and furthermore may be sensitive to the detection of more pathological age-related memory deficits. It is worth noting the fact that performance on the MD-S task, designed to specifically tax mnemonic discrimination of spatial information, was strongly correlated with word list recall assessed via the RAVLT. While these comprise distinct information domains, it has been hypothesized that the hippocampus performs pattern separation in a domain-agnostic fashion (Reagh & Yassa, submitted). That is, the hippocampal dentate gyrus is thought to orthogonalize inputs irrespective of information type, and may do so equally for spatial information and verbal information. Consistent with this notion, we have previously observed similar deficits in aged adults on a verbal mnemonic discrimination task (Ly, Murray, & Yassa, 2013).

Our findings are largely in agreement with those of Stark and colleagues (2010), and extend the investigation of spatial mnemonic discrimination to using a fuller spectrum of 5 levels of mnemonic interference. A major difference between studies, however, is that we observed a general aging effect in addition to a differentiation in the aged group based on individual differences. We additionally observed that the AI group showed impaired Target Recognition compared to the AU group, whereas the aforementioned study found no such effect. This may simply reflect a difference in the level of processing involved in judging a single object having retained its location as compared to judging whether a spatial configuration has remained the same. However, considered alongside additional differences observed along the interference continuum, this raises the possibility that this particular task is more sensitive to age-related effects on mnemonic ability in general. This aspect of our results is consistent with Holden and colleagues (2012). However, as previously mentioned, our approach differs markedly in several ways. In particular, the present task was designed to more directly tax long-term memory mechanisms, and we furthermore compared performance across groups at specific levels of mnemonic interference. An additional important distinction of our data is that we observed the “closure” of performance curves in aged adults (and particularly the AU group) relative to young adults (i.e., at minimal levels of interference in the Corners condition). This critically demonstrates that the task is not simply measuring a global deficit in processing, but is rather sensitive to differences in discrimination ability at particular levels of mnemonic interference. Along these lines, the fact that the AI group’s curve did not “close” with minimal interference may be suggestive of a global memory deficit. This interpretation is compatible with the observed impairment of the AI group at Target Recognition. Thus, in addition to sensitivity to typical or “healthy” aging, this task may be particularly sensitive to differentiating healthy from possible pathological aging (Figure 6).

Overall, these results are highly consistent with prior findings in the domain of object similarity discrimination, which have demonstrated effects of healthy aging, as well as more severe deficits related to impaired RAVLT performance (Yassa et al. 2010a; Stark et al.,

2013). The consistency of behavior on the MD-S task with this model is suggestive of a related and similarly sensitive assessment of cognitive decline in the spatial domain. Furthermore, as discussed above, additional differences in performance revealed by the MD-S task may be indicative of a greater sensitivity to memory deficits.

This task, in conjunction with Unimpaired or Impaired status via RAVLT Delay scores, may be predictive of one's transition from healthy aging to MCI or Alzheimer's Disease. However, we propose that this task may in fact be a more powerful index of mnemonic ability than the RAVLT alone. In terms of task content, the requirement of integrating an object and its relative location likely taps into episodic memory processes (binding "what" and "where") and is more independent from possible semantic influences than memory for a list of words. There are several distinct advantages of the MD-S task. First, based on much available data, the episodic (and spatial) nature of the task would be expected to be sensitive to hippocampal integrity. Second, the parametric nature of mnemonic discriminations within this task allows for a much more nuanced assessment of memory ability. With further testing for reliability and consistency of performance, the MD-S task can potentially serve as a powerful diagnostic tool. We hope that combining this task with high-resolution functional MRI in the future can also aid in developing novel biomarkers for cognitive decline.

Prior work in rodents has established the utility of splitting aged groups based on individual differences (Gallagher et al., 2006; Gallagher et al., 2003; Gallagher et al., 1993; Stranahan et al., 2011). Recent work by Stranahan and colleagues (2011) demonstrated an association between age-related cognitive deficits and reduced reelin expression in the lateral entorhinal cortex, which was associated with increased levels of phospho-tau and behavioral deficits in spatial memory (Stranahan, Haberman, & Gallagher, 2011). A growing body of research has demonstrated that the entorhinal cortex is the first brain region affected by Alzheimer's related pathology (Braak & Braak, 1995, 1996; Braak, Braak, & Bohl, 1993; Stranahan & Mattson, 2010; Yang, Ang, & Strong, 2005). Given the above points, though this task almost certainly engages the hippocampus, it is possible that this task is tapping into mechanistic disruptions in mnemonic processing that occur at the very earliest stages of cognitive decline along the way to MCI and Alzheimer's Disease. Importantly, entorhinal cortex is the source of primary input to the dentate gyrus via the perforant path, which shows signs of degradation in aged adults (Yassa et al., 2010). Furthermore, this degradation is correlated with performance indices on tasks designed to tax pattern separation (Yassa et al., 2011). An open question is the extent to which computations in the entorhinal cortex upstream of the dentate gyrus contribute to pattern separation. Much available data ascribes mnemonic discrimination to activity in hippocampal subfields, though other recent studies have suggested that the entorhinal cortex and its subdivisions may at least facilitate this process.

Recent work has demonstrated that some degree of spatial/contextual signaling may occur in lateral entorhinal cortex (Deshmukh & Knierim, 2012; Hunsaker & Kesner, 2013), though spatial processing is known to more robustly engage medial entorhinal cortex (Deshmukh et al., 2010; Hargreaves et al., 2005). That is, while this task likely engages lateral entorhinal cortex to some extent, it is reasonable to propose that it would more robustly engage medial entorhinal cortex. This task may contribute a novel and highly sensitive behavioral index to a growing literature on domain-specific processing in the medial temporal lobe, and may be useful in exploring age-related memory deficits that are asymmetric with respect to information domain (e.g., object vs. spatial). Future fMRI studies using this and similar paradigms may elucidate early functional abnormalities that may be predictive of cognitive decline in aged adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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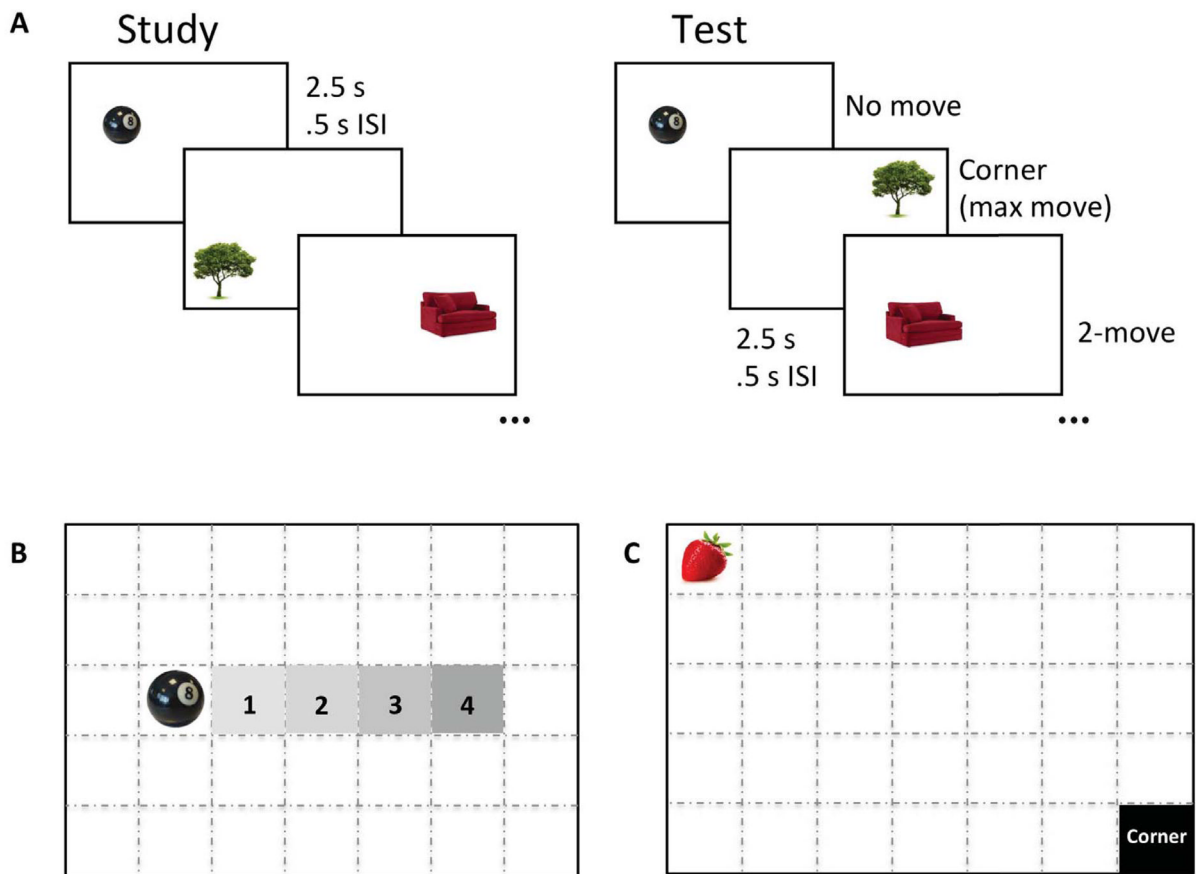


Figure 1.

Example of the 5x7 grid (not visible to subjects) dividing the total screen space. (A) Example images during Study (incidental encoding with “Indoor” or “Outdoor” judgments) and Test (second phase with “Move” or “No Move” mnemonic judgments). (B) Diagram of a 1-Move, 2-Move, 3-Move, or 4-Move displacement relative to an object’s original location during encoding (respective decreasing of mnemonic interference). These displacements occurred vertically or horizontally. (C) Diagram of a corner displacement, the minimal amount of mnemonic interference in the MD-S task.

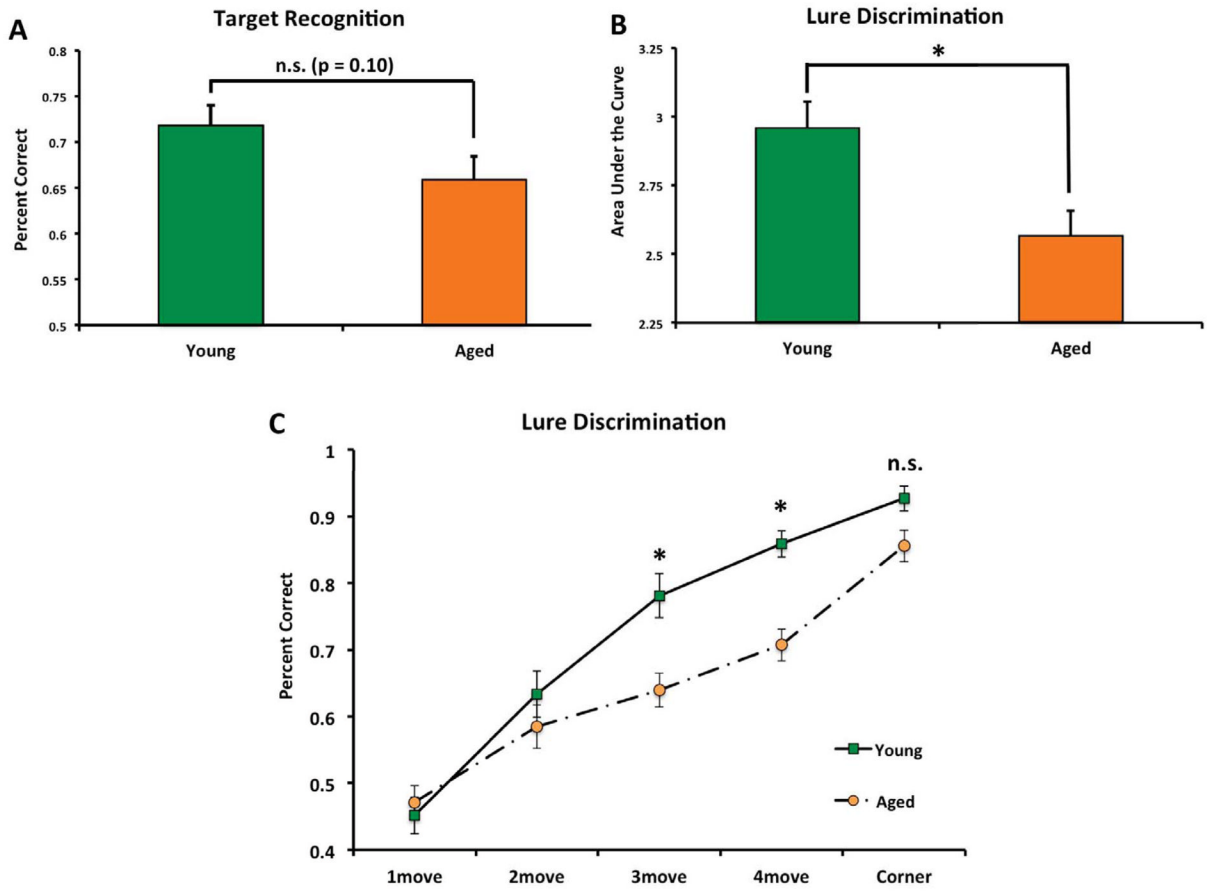


Figure 2. Performance on the MD-S task comparing the Young group to the Aged group. (A) Target Recognition scores. Young and Aged groups did not differ significantly, though a trend may have been present. (B) Total Lure Discrimination scores, assessed via area under the curve (AUC). (C) Lure Discrimination scores at each level of mnemonic interference. Young>Aged (*); not significant (n.s.).

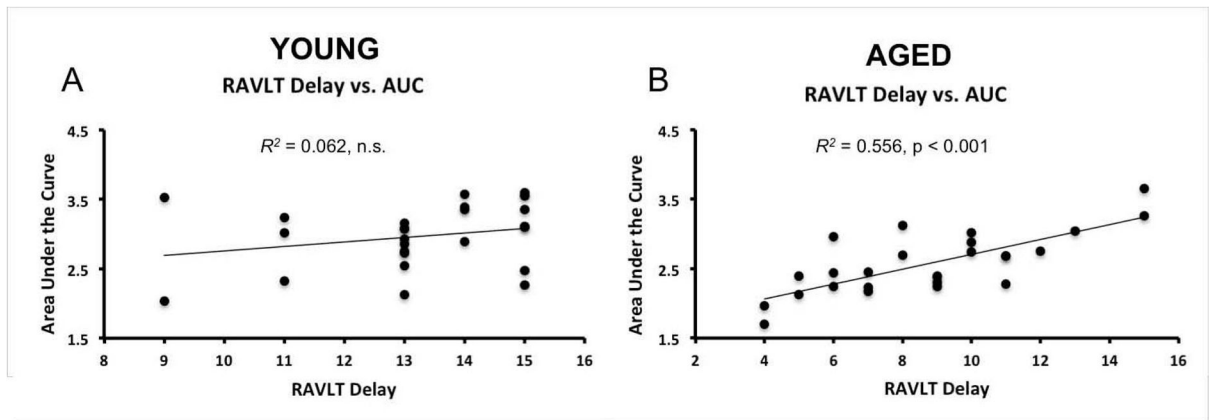


Figure 3. Correlations between Lure Discrimination (AUC) and RAVLT Delayed Recall scores for Young and Aged groups. (A) RAVLT Delay was not significantly correlated with Lure Discrimination in the Young group. (B) RAVLT Delay was significantly correlated with Lure Discrimination in the Aged group. Correlations were Holm-Bonferroni corrected for multiple comparisons.

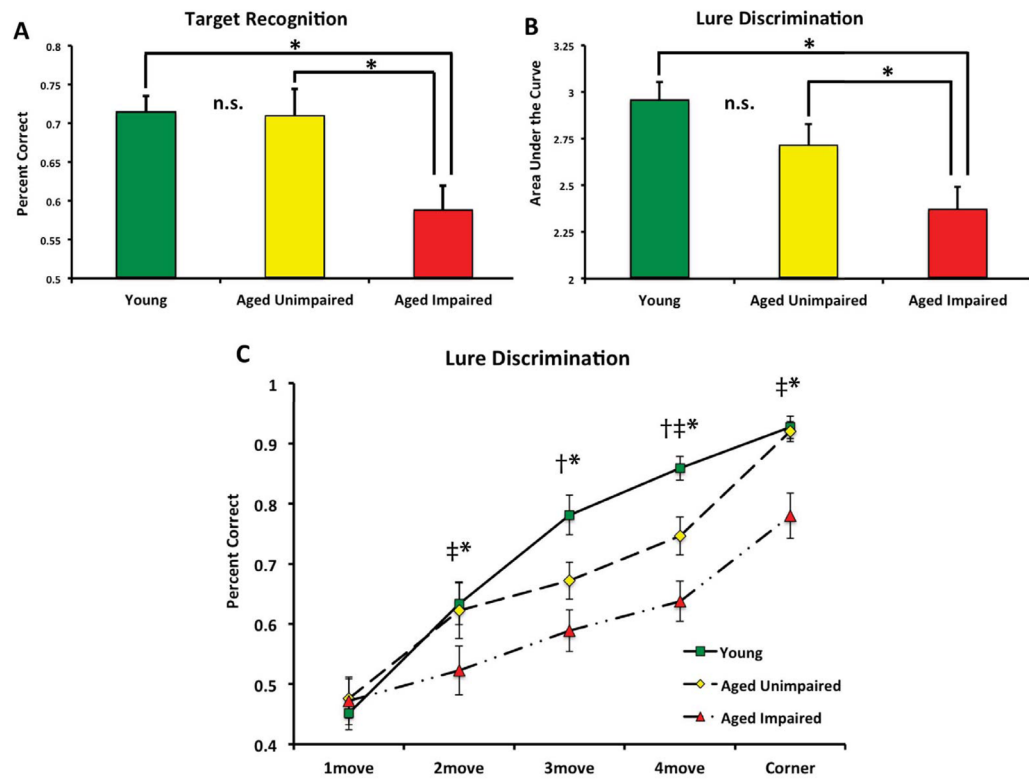


Figure 4. Performance on the MD-S task compared across the Young, Aged Unimpaired, and AI groups. (A) Target Recognition scores. (B) Total Lure Discrimination scores, assessed via area under the curve (AUC). (C) Lure Discrimination scores at each level of mnemonic interference. Statistically significant comparisons: Young>AU (†); AU>AI (‡); Young>AI (*).

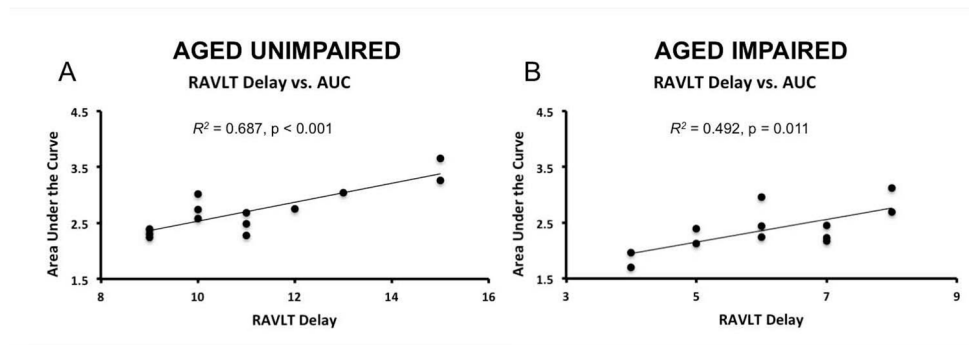


Figure 5. Correlations between Lure Discrimination (AUC) and RAVLT Delayed Recall scores for Aged Unimpaired and Aged Impaired groups. (A) RAVLT Delay was significantly correlated with Lure Discrimination in the Aged Unimpaired group, (B) as well as the Aged Impaired group. Correlations were Holm-Bonferroni corrected for multiple comparisons.

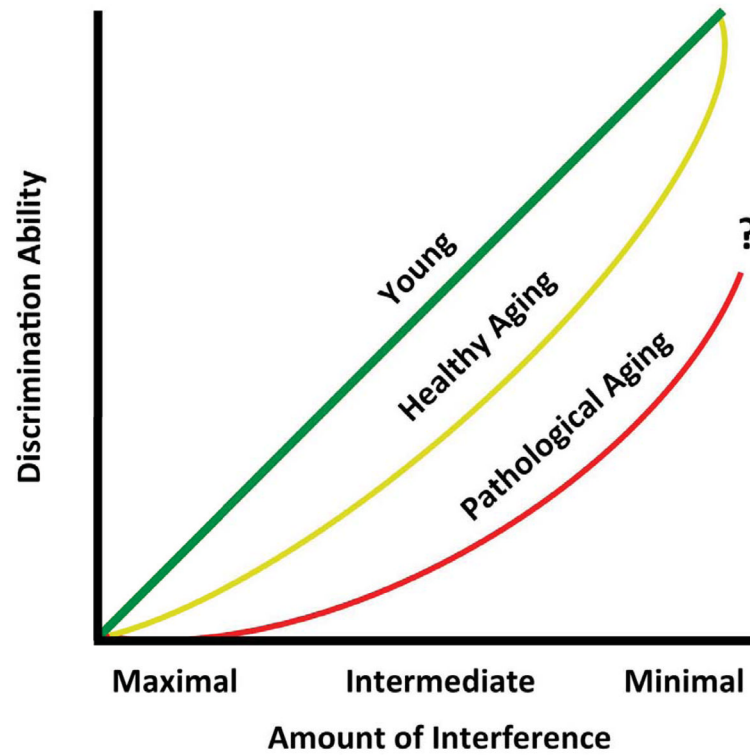


Figure 6.

Model of spatial discrimination ability as a function of mnemonic interference at different points along the aging continuum, based on the present data. Young adults demonstrate a linear gain in performance as interference is reduced. This gain is slowed in healthy aging (proposed to be represented by the AU subgroup), but such individuals are able to capitalize on minimal interference in a way that is comparable to young adults. Pathological aging (proposed to be represented by the AI subgroup) features a dramatic shift from performance of young adults as well as healthy aged adults, and it is unclear from the present data and that from other similar tasks whether performance never matches that of other groups, even under conditions of minimal mnemonic interference. We propose that healthy aging shows a characteristic deficit in the intermediate interference range, whereas pathological aging differs throughout the spectrum and most markedly so at minimal levels of interference.

Table 1

Demographics and neuropsychological performance

	Young N = 25	AU N = 14	AI N = 12	Sig.
Age	21.85 (4.25)	71.71 (1.35)	68.75 (1.54)	† *
Gender	17F, 8M	10F, 4M	7F, 5M	n.s.
Education	13.08 (2.13)	15.86 (2.66)	14.67 (2.99)	n.s.
MMSE	29.54 (1.37)	28.29 (1.90)	27.97 (2.35)	n.s.
BDI-II	5.31 (3.52)	3.79 (4.23)	5.0 (2.66)	n.s.
RAVLT Total	61.12 (6.24)	53.5 (10.26)	40.58 (4.76)	‡ *
RAVLT Immediate	13.08 (1.83)	11.21 (2.15)	6.91 (1.62)	‡ *
RAVLT Delay	13.19 (1.74)	11.0 (2.08)	6.08 (1.37)	‡ *
Digit Span	20.0 (2.87)	16.64 (3.52)	17.0 (4.16)	† *
Trails A	17.48 (5.61)	36.39 (15.63)	33.26 (16.30)	† *
Trails B	45.40 (19.89)	93.22 (48.48)	88.11 (39.80)	† *

Data are presented as mean(*SD*). Significant group differences are denoted in the rightmost column (t-tests corrected using Holm's sequentially rejective Bonferroni correction). Statistically significant comparisons: Young>AU (†); AU>AI (‡); Young>AI (*). MMSE: Mini-Mental State Exam; BDI-II: Beck Depression Inventory-II; RAVLT: Rey Auditory Verbal Learning Test.