Brief Communication

Spatial memory ability during middle age may depend on level of spatial similarity

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Spatial memory impairment is well documented in old age; however, less is known about spatial memory during middle age. We examined the performance of healthy young, middle-aged, and older adults on a spatial memory task with varying levels of spatial similarity (distance). On low similarity trials, young adults significantly outperformed middle-aged adults, who significantly outperformed older adults (*P*s < 0.05). On high similarity trials, young adults significantly outperformed middle-aged and older adults (*P*s < 0.05); however, middle-aged and older adults did not differ. Subtle age-related changes in spatial memory may emerge during middle age, particularly when spatial similarity is high.

Multiple cognitive abilities have been found to decrease in older age; however, one of the most commonly reported deficits associated with aging is memory loss. Some aspects of memory are more adversely affected by aging than others (e.g., source versus item memory), and spatial memory appears to be particularly sensitive to age-related change. Spatial memory decline has been well documented in older adults (for reviews, see Iachini et al. 2009; Holden et al. 2012; Lester et al. 2017). Age-related spatial memory deficits may stem from changes in a variety of brain regions including the hippocampus, temporal lobes, and the frontal-parietal network (Iachini et al. 2009).

While spatial memory impairments have been well documented in older adults, less is known about spatial memory abilities during middle age. A recent study indicated that allocentric spatial processing deficits in middle age are associated with an elevated risk of late-onset Alzheimer's disease (Ritchie et al. 2018); therefore, additional research is needed into spatial memory changes in middle age. Greenwood and colleagues (2005) hypothesize that "cognitive deficits in healthy middle-aged adults are likely to be small and subtle given the early stage of aging being probed." In accordance with this hypothesis, a few recent studies have demonstrated that memory abilities during middle age might depend on the mnemonic similarity or interference among items in memory. Stark and colleagues (2013) found that the ability to discriminate between highly similar visual objects in memory begins to decrease in middle age. Similarly, Rotblatt et al. (2015) found that young adults significantly outperformed middle-aged adults on a temporal order memory test involving items close together in a sequence. However, when items were farther apart in the sequence, no differences were found. Based on these findings, it is possible that middle-aged adults may experience memory difficulties on tests involving stimuli that are highly similar, but may improve when the level of similarity is decreased. Therefore, tests that manipulate stimuli similarity might be useful in detecting subtle memory deficits associated with middle age. The present study aimed to explore the performance of healthy young, middle-aged, and older adults on a spatial recognition memory task in which spatial similarity was systematically manipulated.

Participants included 30 healthy older adults (60 yr of age and older; $M = 71.07$ yr, $SD = 7.53$), 30 healthy middle-aged adults (40–55 yr of age; $M = 50.33$, $SD = 4.25$), and 30 healthy young adults (18–25 yr of age; $M = 19.40$, $SD = 1.57$). Young adults were recruited from a pool of undergraduate students at San Diego State University, whereas middle-aged and older adults were recruited from the San Diego community. Exclusion criteria included a history of traumatic brain injury, history of substance use disorder, and diagnosis of any neurological disorder, major medical condition (e.g., cancer), or psychiatric disorder (with the exception of a mood disorder, for which any current symptoms must be well managed). All participants underwent a near and far visual screening test and all had corrected vision that fell between 20/20 and 20/40. All study procedures were approved by the Institutional Review Board at SDSU and all participants provided informed consent prior to participation in the study.

Older adult participants were administered the Dementia Rating Scale-2 (DRS-2; Jurica et al. 2001) and had scores of 130 or higher ($M = 139.17$, $SD = 3.94$). The Mini-Mental State Examination (Folstein et al. 1975) was administered to young ($M = 28.87$, $SD = 0.86$) and middle-aged ($M = 28.37$, $SD = 1.92$) participants. To screen for depression, older adults were administered the Geriatric Depression Scale (Yesavage et al. 1983) and had a score of 7 or lower ($M = 1.70$, $SD = 1.86$). The Beck Depression Inventory-II (BDI-II; Beck et al. 1996) was given to young ($M = 4.00$, $SD = 3.53$) and middle-aged adults ($M = 6.80$, $SD = 5.90$).

Participants were administered a new spatial recognition memory task that was based on a test developed to assess the effects of spatial similarity or interference on spatial memory and spatial pattern separation (Holden et al. 2012). During the new task, participants were seated approximately 40 cm in front of a computer screen that was affixed with a 15-cm black border in order to eliminate visual cues for the spatial location of stimuli. Each trial consisted of a sample phase followed by a choice phase. During the sample phase, participants viewed a gray circle measuring 1.7 cm in diameter that appeared on the computer screen for 5 sec (please

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Article is online at http://www.learnmem.org/cgi/doi/10.1101/lm.048280.118.

see Fig. 1). The circle appeared in one of 18 possible locations within a fixed nonvisible horizontal line across the middle of the screen. There was a 10-sec delay between the sample phase and choice phase during which participants were required to look away from the screen and read a designated string of random letters to prevent fixation of the eyes on the location of the sample phase circle. After the 10-sec delay, a tone was sounded to signal the beginning of the choice phase. During the choice phase, a new gray circle appeared, either in the same location ("same" trial) or in a different location ("different" trial) relative to the sample phase. On "different" trials, the choice phase circle was placed in a location that differed from the sample phase location by one of four possible spatial separations (0.5, 1.0, 1.5, or 2.0 cm), to either side of the sample phase circle location. Participants were to choose "same" or "different" to indicate where they thought the choice phase circle was in relation to the sample phase circle location. Participants were allowed 5 sec to make a response. No feedback regarding correct choices was given during the task.

The task consisted of a total of 72 trials, including 24 "same" trials, 24 low similarity "different" trials, and 24 high similarity "different" trials. As a result, there were an equal number of the three trial types. Smaller spatial separations (0.5 and 1.0 cm) on "different" trials were hypothesized to result in greater similarity than larger separations (1.5 and 2.0 cm). Therefore, performance on 0.5 or 1.0 cm separation trials was averaged to form the high similarity condition and performance on 1.5 or 2.0 cm separation trials was averaged to form the low similarity condition. Reducing the number of interference conditions from four to two increased the number of trials per condition, producing a more robust measure of performance. All trials were balanced across the entire width of the screen to ensure that there was not an unintentional bias toward one particular area on the screen. To minimize fatigue effects, the 72 total trials were split into two sets of 36 trials, each identical in design and taking approximately 12–15 min to complete.

Standard signal detection theory procedures were utilized to analyze the recognition memory performance data, whereby the raw number of hits and false positive errors were transformed into conditionalized rates (Macmillan and Creelman 1991). Since measures of performance using signal detection theory are undefined for hit rates equal to 1 or false positive rates equal to zero, a linear transformation was applied to the calculation of hit rates and false positive error rates as suggested by Upton (1978) for log-linear models using the following equations: hit rate (HR) = [(number of hits + 0.05)/(number of targets + 1)] and false positive error rate (FR) = [(number of false positive errors + 0.05)/(number of distractors + 1)]. The *z*-transformation was used to convert the hit rates and false positive error rates into a *z*-score. The sensitivity measure of signal detection theory (d') was then calculated using the formula $d' = [z(\text{HR}) - z(\text{FR})]$.

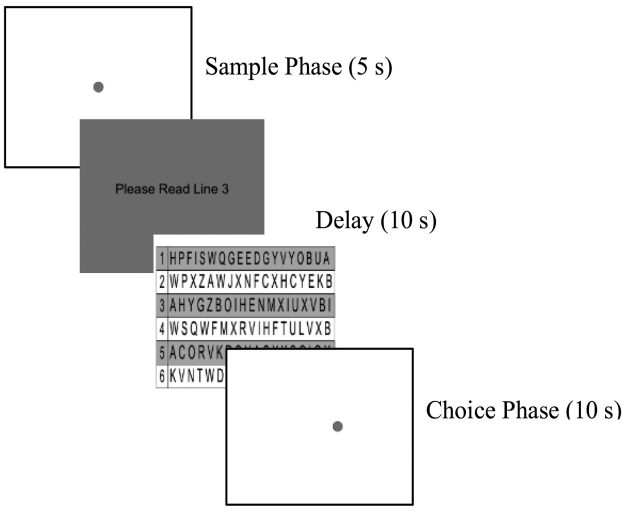

Figure 1. A schematic of the testing procedure showing a sample phase stimulus, the delay instructions, and a choice phase stimulus.

A one-way analysis of variance (ANOVA) test indicated a significant difference in years of education among groups, $F_{(2,87)} = 11.31$, $P < 0.01$. A Tukey post-hoc test revealed that older adults ($M = 15.37$, $SD = 2.06$) completed significantly more years of education than middle-aged ($M = 13.97$, $SD = 1.85$) and young ($M = 13.27$, $SD = 1.20$) adults (Ps < 0.01), whereas there was no significant difference between young and middle-aged adults ($P = 0.27$). A χ^2 analysis revealed a significant difference in proportions of men and women across the young (60% female), middle-aged (80% female), and older adult (46.67% female) groups, χ^2 (2, $N = 90$) = 7.19, $P = 0.03$. Neither years of education nor gender significantly predicted mean d' scores (Ps > 0.10); therefore, these demographic variables were not controlled for in the following analyses.

The mean d' scores for each age group on both spatial similarity conditions are presented in Figure 2. Using d' as the dependent variable, a 3 × 2 repeated measures ANOVA was used to analyze the data with age (older, middle-aged, young) as a between-group factor and similarity (high, low) as a within-group factor. The results revealed a significant main effect of similarity ($F_{(1,87)} = 58.95$, $P < 0.001$, $\eta^2_{\text{partial}} = 0.40$), with individuals performing significantly better on low similarity trials ($M = 2.55$, $SD = 0.96$) than on high similarity trials ($M = 2.02$, $SD = 0.82$). The analysis also revealed a significant main effect of age group ($F_{(2,87)} = 8.78$, $P < 0.001$, $\eta^2_{\text{partial}} = 0.17$) and a significant age group x similarity interaction ($F_{(2,87)} = 3.86$, $P = 0.025$, $\eta^2_{\text{partial}} = 0.08$).

Results of a Newman–Keuls comparison test on the age group x interference interaction indicated that the young adults performed significantly better (Ps < 0.05) than both middle-aged and older adults on the low (MA: $d = 0.59$; OA: $d = 1.11$) and high (MA: $d = 0.74$; OA: $d = 0.76$) similarity trials. Middle-aged adults performed significantly better than older adults on low similarity trials ($P < 0.05$, $d = 0.56$). However, middle-aged adults did not differ significantly from older adults on high similarity trials ($P > 0.05$). ANOVA tests revealed no significant age group differences in c (Ps > 0.10), which is a measure of response bias in signal detection theory.

We also found that young adults performed significantly better ($P < 0.05$, $d = 0.70$) on low similarity trials ($M = 3.06$) compared to high similarity trials ($M = 2.42$). Similarly, middle-aged adults performed significantly better on low similarity trials ($M = 2.53$) than on high similarity trials ($M = 1.85$, $P < 0.05$, $d = 0.87$). In contrast, no significant difference was observed between low ($M = 2.06$) and high ($M = 1.80$) similarity trials in the older adults ($P > 0.05$). Using a Pearson correlation analysis, we found that performance on both the high similarity trials ($r = 0.51$, $P < 0.001$) and low similarity trials ($r = 0.52$, $P < 0.001$) was strongly correlated with performance on a standardized measure of visual spatial memory, the Brief Visuospatial Memory Test-Revised (BVMT-R; Benedict 1997).

In accordance with prior studies (Stark et al. 2010; Holden et al. 2012; Reagh et al. 2014), we found that spatial memory is impaired in older adults relative to young adults on tests that manipulate spatial similarity or interference. These age-related differences were associated with large effect sizes. The more novel finding in our study is that middle-aged adults also were impaired relative to young adults on trials involving low and high spatial similarity. The difference between young and middle-aged adults was associated with a moderate effect size on low similarity trials. However, the effect size for the difference between young and

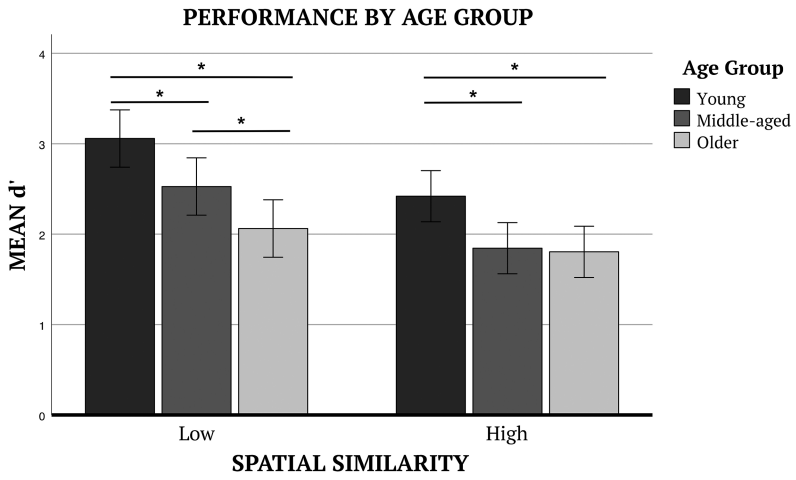

Figure 2. Spatial recognition memory task performance (as measured using *d'*) across age groups (young, middle-aged, and older adults) and interference conditions (low or high). Error bars represent 95% confidence interval estimates. Asterisks (*) indicate significant pairwise comparisons across age groups ($P < 0.05$).

middle-aged adults increased by 25% on high similarity trials. Moreover, middle-aged adults outperformed older adults on trials when spatial similarity was low but decreased to the level of older adults on trials with high spatial similarity. The strong correlation found between performance on our task and performance on the BVMT-R offers evidence that our test may rely on visuospatial memory. However, visual memory also may play a role in performance on our test. Taken together, these data provide significant evidence that spatial memory may decrease during middle age; furthermore, spatial memory in middle-aged adults may worsen under conditions involving increased spatial similarity to resemble the performance of older adults.

One possible mechanism that may play a significant role in reducing mnemonic similarity or interference is referred to as pattern separation. Pattern separation is a mechanism for separating partially overlapping patterns of activation so that one pattern may be retrieved as separate from other patterns. The dentate gyrus (DG) and CA3 hippocampal subregions have been reported to support pattern separation (Kesner 2007; Gilbert and Brushfield 2009; Rolls 2010; Yassa and Stark 2011; Schmidt et al. 2012). Age-related changes in these subregions have been hypothesized to result in less efficient pattern separation due to strengthened processing of stored information at the expense of processing new information (Wilson et al. 2006; Yassa and Stark 2011). Therefore, one possible interpretation of the present findings is that pattern separation for spatial information is less efficient in both middle-aged and older adults. As we discussed previously, prior studies also have found that middle-aged adults demonstrated significant deficits compared to young adults on tasks that manipulate the similarity among visual objects (Stark et al. 2013) and temporal order information (Rotblatt et al. 2015). These tasks have also been hypothesized to increase demand for pattern separation. A recent study reported that mnemonic discrimination in older adults may be more impaired for visual object information than for spatial information (Reagh et al. 2016). Furthermore, studies have indicated that there may be domain-specific medial temporal lobe pathways supporting spatial and nonspatial discrimination (Schultz et al. 2012; Reagh and Yassa 2014; Berron et al. 2018; Reagh et al. 2018), which may have important implications for the differential effects of aging on these pathways. A recent study from our group, using the present task, found that performance on the high similarity trials was significantly associated with hippocampal atrophy in a sample of individuals with temporal lobe epilepsy (Reyes et al. 2018). These findings offer preliminary evidence that performance on our test may relate to the hippocampus; however, future studies are clearly needed to investigate the neural substrate(s) that underlie test performance.

The current study offers unique insight into the effects of similarity or interference on spatial memory during middle and old age. The findings show that age-related spatial memory deficits may be detectable as early as middle age on a test that involves elevated levels of spatial similarity or interference. Given the importance of identifying cognitive tests that are sensitive to early cognitive changes in the adult lifespan, the current results demonstrate that these spatial memory tests may have significant value. The current findings also are significant in light of a recent study reporting that allocentric spatial processing deficits in middle age are associated with an elevated risk of late-onset Alzheimer's disease (Ritchie et al. 2018). Finally, the current study provides theoretical insight into a potential mechanism that might undergo changes during middle age that contribute to the deficits observed in the present study.

Acknowledgments

This research was supported by a National Institutes of Health Grants awarded to P.E.G. (R01 AG034202).

References

Beck AT, Steer RA, Ball R, Ranieri W. 1996. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. *J Pers Assess* **67:** 588–597. doi:10.1207/s15327752jpa6703_13

Benedict RHB. 1997. *Brief visuospatial memory test-revised: professional manual*. Psychological Assessment Resources, Inc., Lutz, FL.

Berron D, Neumann K, Maass A, Schütze H, Fliessbach K, Kiven V, Jessen F, Sauvage M, Kumaran D, Düzel E. 2018. Age-related functional changes in domain-specific medial temporal lobe pathways. *Neurobiol Aging* **65:** 86–97. doi:10.1016/j.neurobiolaging.2017.12.030

Folstein MF, Folstein SE, McHugh PR. 1975. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12:** 189–198. doi:10.1016/0022-3956(75)90026-6

Gilbert PE, Brushfield AM. 2009. The role of the CA3 hippocampal subregion in spatial memory: a process oriented behavioral assessment. *Prog Neuropsychopharmacol Biol Psychiatry* **33:** 774–781. doi:10.1016/j.pnpbp.2009.03.037

Greenwood PM, Lambert C, Sunderland T, Parasuraman R. 2005. Effects of apolipoprotein E genotype on spatial attention, working memory, and their interaction in healthy, middle-aged adults: results from the National Institute of Mental Health's BIOCARD study. *Neuropsychology* **19:** 199–211. doi:10.1037/0894-4105.19.2.199

Holden HM, Hoebel C, Loftis K, Gilbert PE. 2012. Spatial pattern separation in cognitively normal young and older adults. *Hippocampus* **22:** 1826–1832. doi:10.1002/hipo.22017

Iachini I, Iavarone A, Senese VP, Ruotolo F, Ruggiero G. 2009. Visuospatial memory in healthy elderly, AD and MCI: a review. *Curr Aging Sci* **2:** 43–59. doi:10.2174/1874609810902010043

Jurica PJ, Leitten CL, Mattis S. 2001. *Dementia Rating Scale-2: professional manual*. Psychological Assessment Resources, Odessa, FL.

Kesner RP. 2007. A behavioral analysis of dentate gyrus function. *Prog Brain Res* **163:** 567–576. doi:10.1016/S0079-6123(07)63030-1

Lester AW, Moffat SD, Wiener JM, Barnes CA, Wolbers T. 2017. The aging navigational system. *Neuron* **95:** 1019–1035. doi:10.1016/j.neuron.2017.06.037

Macmillan NA, Creelman CD. 1991. *Detection theory: a user's guide*. Cambridge University Press, New York.

Reagh ZM, Yassa MA. 2014. Object and spatial mnemonic interference differentially engage lateral and medial entorhinal cortex in humans. *Proc Natl Acad Sci* **111:** E4264–E4273. doi:10.1073/pnas.1411250111
Reagh ZM, Roberts JM, Ly M, DiProspero N, Murray E, Yassa MA. 2014. Spatial discrimination deficits as a function of mnemonic interference in aged adults with and without memory impairment. *Hippocampus* **24:** 303–314. doi:10.1002/hipo.22224
Reagh ZM, Ho HD, Leal SL, Noche JA, Chun A, Murray EA, Yassa MA. 2016. Greater loss of object than spatial mnemonic discrimination in aged adults. *Hippocampus* **26:** 417–422. doi:10.1002/hipo.22562
Reagh ZM, Noche JA, Tustison NJ, Delisle D, Murray EA, Yassa MA. 2018. Functional imbalance of anterolateral entorhinal cortex and hippocampal dentate/CA3 underlies age-related object pattern separation deficits. *Neuron* **97:** 1187–1198. doi:10.1016/j.neuron.2018.01.039
Reyes A, Holden HM, Chang YA, Uttarwar VS, Sheppard DP, DeFord NE, DeJesus SY, Kansal L, Gilbert PE, McDonald CR. 2018. Impaired spatial pattern separation performance in temporal lobe epilepsy is associated with visuospatial memory deficits and hippocampal volume loss. *Neuropsychologia* **111:** 209–215. doi:10.1016/j.neuropsychologia.2018.02.009
Ritchie K, Carrière I, Howett D, Su L, Hornberger M, O'Brien JT, Ritchie CW, Chan D. 2018. Allocentric and egocentric spatial processing in middle-aged adults at high risk of late-onset Alzheimer's disease: the PREVENT dementia study. *J Alzheimers Dis* **65:** 885–896. doi:10.3233/JAD-180432
Rolls ET. 2010. A computational theory of episodic memory formation in the hippocampus. *Behav Brain Res* **215:** 180–196. doi:10.1016/j.bbr.2010.03.027
Rotblatt LJ, Sumida CA, Van Etten EJ, Turk EP, Tolentino JC, Gilbert PE. 2015. Differences in temporal order memory among young, middle-aged, and older adults may depend on the level of interference. *Front Aging Neurosci* **7:** 28. doi:10.3389/fnagi.2015.00028
Schmidt B, Marrone DF, Markus EJ. 2012. Disambiguating the similar: the dentate gyrus and pattern separation. *Behav Brain Res* **226:** 56–65. doi:10.1016/j.bbr.2011.08.039
Schultz H, Sommer T, Peters J. 2012. Direct evidence for domain-sensitive functional subregions in human entorhinal cortex. *J Neurosci* **32:** 4716–4723. doi:10.1523/JNEUROSCI.5126-11.2012
Stark SM, Yassa MA, Stark CE. 2010. Individual differences in spatial pattern separation performance associated with healthy aging in humans. *Learn Mem* **17:** 284–288. doi:10.1101/lm.1768110
Stark SM, Yassa MA, Lacy JW, Stark CEL. 2013. A task to assess behavioral pattern separation (BPS) in humans: data from healthy aging and mild cognitive impairment. *Neuropsychologia* **51:** 2442–2449. doi:10.1016/j.neuropsychologia.2012.12.014
Upton GJ. 1978. *The analysis of cross-tabulated data*. Wiley, New York, NY.
Wilson IA, Gallagher M, Eichenbaum H, Tanila H. 2006. Neurocognitive aging: prior memories hinder new hippocampal encoding. *Trends Neurosci* **29:** 662–670. doi:10.1016/j.tins.2006.10.002
Yassa MA, Stark CE. 2011. Pattern separation in the hippocampus. *Trends Neurosci* **34:** 515–525. doi:10.1016/j.tins.2011.06.006
Yesavage JA, Brind TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO. 1983. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* **17:** 37–49. doi:10.1016/0022-3956(82)90033-4

Received August 27, 2018; accepted in revised form October 29, 2018.