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Original Research Report

Recognition Memory Dysfunction Relates to Hippocampal Subfield Volume: A Study of Cognitively Normal and Mildly Impaired Older Adults

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Abstract

Objectives: The current study examined recognition memory dysfunction and its neuroanatomical substrates in cognitively normal older adults and those diagnosed with mild cognitive impairment (MCI).

Methods: Participants completed the Mnemonic Similarity Task, which provides simultaneous measures of recognition memory and mnemonic discrimination. They also underwent structural neuroimaging to assess volume of medial temporal cortex and hippocampal subfields.

Results: As expected, individuals diagnosed with MCI had significantly worse recognition memory performance and reduced volume across medial temporal cortex and hippocampal subfields relative to cognitively normal older adults. After controlling for diagnostic group differences, however, recognition memory was significantly related to whole hippocampus volume, and to volume of the dentate gyrus/CA3 subfield in particular. Recognition memory was also related to mnemonic discrimination, a fundamental component of episodic memory that has previously been linked to dentate gyrus/CA3 structure and function.

Discussion: Results reveal that hippocampal subfield volume is sensitive to individual differences in recognition memory in older adults independent of clinical diagnosis. This supports the notion that episodic memory declines along a continuum within this age group, not just between diagnostic groups.

Keywords: Medial temporal cortex, Memory, Mild cognitive impairment (MCI), Neuroimaging

Recognition memory describes the ability to identify events that have already been encountered. Whereas it is preserved in cognitively normal adults across the life span, recognition memory declines as a function of cognitive status within aging populations. Relative to cognitively normal older adults, for example, individuals diagnosed with mild cognitive impairment (MCI) are less likely to correctly identify previously encountered events as "old" (hits) and more likely to incorrectly identify novel events as "old" (false alarms; Ally, Gold, & Budson, 2009; Bennett, Golob, Parker, & Starr, 2006). Although this between-group difference in recognition memory suggests a step-wise decline, an alternative view is that memory declines along a continuum across these diagnostic groups.

The diagnostic criteria for amnestic MCI describe individuals whose memory is worse than expected for their age, but not so severe that they meet criteria for dementia (Albert et al., 2011; Petersen, 2011). To date, no single cut point in memory performance is used to distinguish MCI from cognitively normal aging. Thus, consistent with the

notion of a memory continuum, some individuals diagnosed with MCI perform within the range of cognitively normal older adults on some measures of memory and vice versa. This diagnostic threshold issue can reduce sensitivity of analyses that focus on diagnostic group differences, but may benefit correlational approaches that capitalize on individual-level differences across diagnostic groups.

Of particular interest, here is the examination of neuroanatomical (volumetric) substrates of recognition memory dysfunction in cognitively normal and MCI groups. One neuroimaging study reported significant relationships between recognition memory and volume of medial temporal cortical regions (hippocampus, entorhinal cortex, parahippocampal cortex) across cognitively normal, mildly impaired (MCI), and severely impaired (Alzheimer's disease, AD) older adults (Walhovd et al., 2010). However, because diagnostic group was not statistically controlled, these effects may have been driven by group differences in memory performance, regional volume, or both. Other studies in cognitively normal older adults have identified relationships between recognition memory and volume of the DG/CA3/CA4 (dentate gyrus/cornu ammonis 3/cornu ammonis 4) hippocampal subfields, which are too small to distinguish using traditional neuroimaging resolution (Bender, Daugherty, & Raz, 2013; Shing et al., 2011). However, it remains unknown whether volume of these subfields also account for recognition memory dysfunction in mildly impaired older adults, such as those diagnosed with MCI.

Our lab has previously used a modified recognition memory task to assess mnemonic discrimination, which is a component of episodic memory that allows for newly encountered events to be dissociated from highly similar, previously encountered events (Yassa & Stark, 2011). The Mnemonic Similarity Task (MST; Kirwan, Jones, Miller, & Stark, 2007; Stark, Yassa, Lacy, & Stark, 2013) simultaneously measures mnemonic discrimination (identifying lure objects that are similar to memory set objects as "similar") and recognition memory (identifying repeated memory set objects as "old"). In studies of cognitively normal adults, we have demonstrated age-related declines in mnemonic discrimination, but preserved recognition memory, across adults age 20–89 years (Bennett, Huffman, & Stark, 2015; Bennett & Stark, 2016; Stark et al., 2013). In individuals diagnosed with MCI, we have shown additional decreases in both mnemonic discrimination and recognition memory relative to cognitively normal older adults (Stark et al., 2013; Yassa, Stark, Bakker, Albert, Gallagher, & Stark, 2010). Importantly, we predict that mnemonic discrimination is dependent on intact recognition memory. That is, the ability to accurately indicate whether an object is similar to, but not the same as, an object from the memory set (mnemonic discrimination) requires that one remember the memory set objects in the first place (recognition). To date, however, we have not tested for a relationship between recognition memory and mnemonic discrimination.

Taken together, the current study aims to capitalize on individual-level differences across cognitively normal and mildly impaired (MCI) older adults to assess the neuroanatomical substrates of recognition memory dysfunction and the contribution of recognition memory dysfunction to mnemonic discrimination. After assessing and controlling for diagnostic group differences, analyses of primary interest will examine relationships between recognition memory and (a) volume of medial temporal cortical regions (hippocampus, entorhinal, perirhinal, parahippocampal, temporal pole) and hippocampal subfields (DG/CA3, CA1, subiculum) and (b) mnemonic discrimination performance. Consistent with previous reports, we predict that individuals diagnosed with MCI will exhibit impaired recognition memory and mnemonic discrimination, and reduced medial temporal and hippocampal subfield volume, relative to cognitively normal older adults. More importantly, after controlling for these diagnostic group differences, we further predict that recognition memory will be significantly related to medial temporal (hippocampus, entorhinal, and parahippocampal, but not temporal pole) and hippocampal subfield (DG/CA3) volumes, and to mnemonic discrimination performance.

Methods

Participants

Twenty-seven individuals diagnosed with MCI (77.7 ± 5.3 years, 10 female) and 27 cognitively normal older adults (79.1 ± 5.8 years, 15 female) were initially recruited from the University of California, Irvine (UCI) Alzheimer's Disease Research Center (ADRC) and nearby Orange County communities. Four individuals diagnosed with MCI (82.3 ± 1.9 years, 1 female) were subsequently excluded for below chance performance on the MST (probability of correctly responding "old" to repeated target objects or "new" to novel foil objects <0.33; see task details below). Thus, the final sample included 23 individuals diagnosed with MCI (78.5 ± 6.1 years, 66–89 years; 9 female; 15.3 ± 2.7 years of education) and 23 age- and education-matched, cognitively normal older adults (78.3 ± 5.6 years, 66–87 years; 11 female; 16.6 ± 2.4 years of education).

Individuals with amnestic MCI were diagnosed through consensus procedures at the UCI ADRC, which are consistent with the revised clinical criteria for MCI (Albert et al., 2011): presence of cognitive complaint, absence of dementia; impaired functioning in memory and possibly other cognitive domains (1.5 *SD*s below age and education standard norms); normal global functioning; and intact activities of daily living. Accordingly, all individuals diagnosed with MCI had Clinical Dementia Rating (CDR) scores of 0.5 (Hughes, Berg, Danziger, Coben, & Martin, 1982), indicating mild decline in overall functional capacity.

All participants completed a comprehensive neuropsychological test battery that assessed general cognition using the Mini-Mental State Exam (Folstein, Folstein, &

McHugh, 1975); memory using the Ray Auditory Verbal Learning Task (Rey, 1941), and Wechsler Memory Scale Logical Memory (Wechsler, 1997b); executive functioning using Trails A and B (Reitan & Wolfson, 1985), Verbal Fluency (Spreen & Benton, 1977), and Letter Number Sequencing (Wechsler, 1997a); working memory using Digit Span (Wechsler, 1997a); and general intelligence using Wechsler Adult Intelligence Score III (WAIS IQ; Wechsler, 1997a). Some tests had missing scores from one (Logical Memory, WAIS IQ) or two (Letter Number Sequencing) individuals with MCI. Neuropsychological test data are presented in Table 1.

Participants provided informed consent, and the UCI Institutional Review Board approved the experimental procedures. All participants were compensated for their time.

Mnemonic Similarity Task

Participants completed the MST (Kirwan et al., 2007; Stark et al., 2013) outside of the scanner. It consists of an incidental encoding phase immediately followed by a test phase, with no training prior to the memory test. During the encoding phase, they viewed 128 common objects (the memory set) and indicated whether they were "indoor" or "outdoor" objects using a keyboard press. During the test phase, they viewed repetitions of memory set objects (64 targets), objects similar to those in the memory set (64 lures), and novel objects (64 foils) and indicated whether each object was "old", "similar", or "new" using a keyboard press. For both task phases, objects were presented as a color photograph on a white background for 2 s with a 0.5 s interstimulus interval, allowing 2.5 s for participant responses to be recorded. For additional information about the MST or to download the task, visit http://faculty.sites.uci.edu/starklab/mnemonic-similarity-task-mst/.

Recognition memory was calculated as the probability of correctly responding "old" to repeated target objects (hits) minus the probability of incorrectly responding "old" to novel foil objects (false alarms). Mnemonic discrimination was assessed using a lure discrimination index (LDI), calculated as the probability of correctly responding "similar" to similar lure objects minus the probability of incorrectly responding "similar" to novel foil objects to correct for any bias in responding "similar" overall.

Table 1. Neuropsychological Test Data

	Cognitively normal	MCI	Group comparison
MMSE	28.3 ± 1.3	26.2 ± 3.0	***p* < .003**
RAVLT Immed	10.0 ± 3.0	3.6 ± 2.8	***p* < .001**
RAVLT Delay	9.7 ± 3.1	2.9 ± 2.7	***p* < .001**
WMS Immed	45.0 ± 8.4	31.5 ± 12.7	***p* < .001**
WMS Delay	27.6 ± 6.2	16.0 ± 11.8	***p* < .001**
Trails A	32.7 ± 10.4	38.8 ± 19.0	*p* < .18
Trails B	82.3 ± 29.9	134.3 ± 69.1	***p* < .002**
Letter Fluency	45.1 ± 10.4	37.9 ± 10.2	*p* < .03
Digit Span	17.3 ± 4.6	15.6 ± 4.2	*p* < .21
LN Seq	9.3 ± 2.2	6.7 ± 1.9	***p* < .001**
WAIS IQ	114.2 ± 10.5	106.9 ± 8.9	*p* < .02

Note. Neuropsychological test scores (mean ± standard deviation) are presented separately for cognitively normal older adults and individuals diagnosed with MCI. Significant between-group differences (Bonferroni corrected at $p < .004$) are indicated in bolded text. MMSE = Mini-Mental State Examination, RAVLT = Ray Auditory Verbal Learning Task, WMS = Wechsler Memory Scale, LN Seq = Letter Number Sequencing, WAIS IQ = Wechsler Adult Intelligence Score III.

Imaging Data Acquisition

Participants were scanned using a Philips Achieva 3-Tesla MRI system fitted with an 8-channel SENSE receiver head coil. Fitted padding was used to minimize head movements.

One whole-brain, T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) was acquired: repetition time (TR)/echo time (TE) = 11/4.6 ms, field of view (FOV) = 240 × 231 mm, flip = 18°, 200 sagittal slices, and 0.75 mm^3 spatial resolution.

A high-resolution, T2-weighted Fast Spin Echo image was also acquired with oblique coronal oriented slices aligned with the main axis of bilateral hippocampi: TR/TE = 3,000/80 ms, FOV = 180 × 180 × 108 mm, flip = 90°, 54 coronal slices, and 0.469 × 0.469 × 2 mm spatial resolution.

Imaging Data Analysis

Medial temporal cortex (hippocampus, HIPP; entorhinal cortex, EC; perirhinal cortex, PERI; parahippocampal cortex, PARA; temporal pole, POLE) and hippocampal subfields (dentate gyrus and cornu ammonis 2, 3, and 4, DG/CA3; cornu ammonis 1, CA1; subiculum, SUB) were automatically segmented for each participant using Automatic Segmentation of Hippocampal Subfields (ASHS; Yushkevich et al., 2010; Yushkevich et al., 2015b), which has yielded reliability comparable to manual segmentations and other automatic segmentation approaches (Wisse et al., 2017a; Yushkevich et al., 2015b).

A multisubject atlas model was created using manually segmented brains (both T1-weighted and T2-weighted images) from an independent sample of 19 younger adults (not part of this data set). Separate templates were used to define medial temporal and hippocampal subfield regions. For the medial temporal cortex template, HIPP, EC, PERI, and POLE were labeled according to landmarks described by Insausti et al. (1998), with the transentorhinal region being included in both the EC and PERI labels. PARA was defined as the portion of the parahippocampal gyrus caudal to PERI and rostral to the splenium of the corpus callosum as in our previous research (Huffman & Stark, 2014; Kirwan & Stark, 2004). For the hippocampal subfield

template, only three regions were segmented owing to the limitations of 3T structural scans and incomplete protocols for reliable, more specific segmentation. These subfields were defined along the full anterior-posterior extent of the hippocampus using protocols described in our prior work (Kirwan et al., 2007), except that the CA1/SUB boundary was moved more laterally (see Stark & Stark, 2017) based on discussion by the Hippocampal Subfields Group (Yushkevich et al., 2015a; Wisse et al., 2017b).

For each participant, ASHS performed a nonlinear registration between their structural data and each of the images in the multisubject atlas using ANTS (Avants, Tustison, & Song, 2009). A voting procedure determined an initial segmentation based on the degree of deformation needed to warp the participant's scan onto each atlas and an AdaBoost technique detected and removed segmentation biases. Segmentation accuracy was confirmed by visual inspection and manually edited when necessary. To reduce the number of comparisons, volumes in the left and right hemisphere were averaged to create a single measure for each region of interest.

Individual differences in brain size were corrected using the residual, or covariance, normalization method (Jack et al., 1989). For each participant, intracranial volume was measured using estimated total intracranial volume ($eTIV_{indiv}$) generated by Freesurfer (Buckner, Head, Parker, Fotenos, & Marcus, 2004). Premorbid relationships between $eTIV_{indiv}$ and region of interest volume were estimated by calculating the slope of regression lines between $eTIV_{indiv}$ and volumes from each medial temporal and hippocampal subfield region within the cognitively normal older group (β). Mean eTIV was also calculated by averaging $eTIV_{indiv}$ values within the cognitively normal older group ($eTIV_{mean}$). Normalized volumes ($Volume_{norm}$) were then calculated separately from the raw volumes of each medial temporal and hippocampal subfield region ($Volume_{raw}$) in each participant using the following equation: $Volume_{norm} = Volume_{raw} - \beta\ (eTIV_{indiv} - eTIV_{mean})$. Normalized volumes were used for all analyses.

Results

Diagnostic Group Differences in Memory Performance

Separate unpaired *t* tests compared cognitively normal older adults and individuals diagnosed with MCI on measures of recognition memory (recognition, hits, false alarms) from the MST (Figure 1). Significant effects survived Bonferroni correction for three comparisons, $p < .017$. Results revealed significantly worse recognition in the MCI (0.57 ± 0.22) versus cognitively normal (0.77 ± 0.11) group, $t(44) = 3.8$, $p < .001$, 95% confidence interval [CI] [0.09, 0.30]. This effect can be attributed to a significant MCI-related increase in false alarms (0.19 ± 0.16 versus 0.08 ± 0.09), $t(44) = 3.0$, $p < .01$, 95% CI [–0.19, –0.04], and a trend for an MCI-related decrease in hits (0.76 ± 0.15 versus 0.84 ± 0.08), $t(44) = 2.2$, $p < .04$, 95% CI [0.01, 0.15].

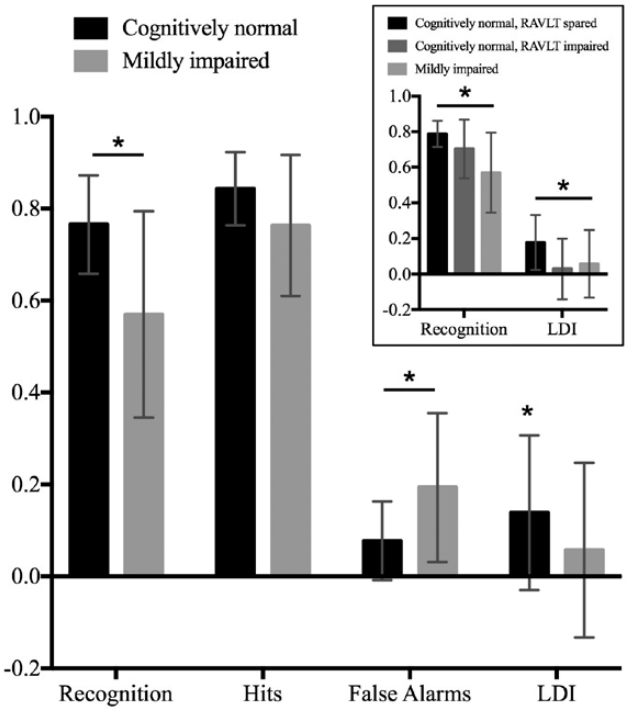

Figure 1. Recognition (recognition, hits, false alarms) and mnemonic discrimination (LDI) performance on the MST task is plotted separately for cognitively normal older adults (black) and individuals diagnosed with MCI (gray). Cognitively normal older adults demonstrated significantly better recognition memory than the MCI group (bar with asterisk, $p < .01$), with mnemonic discrimination performance that significantly differed from zero (asterisk, $p < .001$). These effects were largely driven by an "aged-unimpaired" subset of cognitively normal older adults with spared RAVLT performance (RAVLT delay ≥ 8) that demonstrated significantly better recognition (bar with asterisk, $p < .001$) and mnemonic discrimination (bar with asterisk, $p < .04$) performance than the MCI group.

Unpaired *t* tests also compared cognitively normal older adults and individuals diagnosed with MCI on mnemonic discrimination from the MST (Figure 1). Results revealed no significant diagnostic group difference for LDI performance, $p > .13$. However, one-sample *t* tests indicated that LDI was significantly different than zero for the cognitively normal (0.14 ± 0.17), $t(22) = 4.0$, $p < .001$, 95% CI [0.07, 0.21], but not the MCI (0.06 ± 0.19), group, $p > .16$.

For comparison to our previous work on mnemonic discrimination (for additional details see Stark, Yassa, & Stark, 2010; Stark et al., 2013), cognitively normal older adults were further separated into "aged-unimpaired" ($n = 17$) and "aged-impaired" ($n = 6$) groups depending on whether their Ray Auditory Verbal Learning Task (RAVLT) Delay performance was above or below (inclusive) seven. In this way, the "aged-impaired" group captures individuals who perform at or below the age-expected metanorm (Schmidt, 1996) and at least 1 *SD* below the mean of cognitively normal older adults in the current sample on an independent memory measure that has hallmarks of tasks that tap mnemonic discrimination. Unplanned *t* tests revealed that

LDI performance was significantly worse in the MCI group (0.06 ± 0.19) relative to the "aged-unimpaired" subset of cognitively normal older adults (0.18 ± 0.15), $t(38) = 2.1$, $p < .04$, 95% CI [0.12, 0.06] (Figure 1 insert). There was also a trend for better LDI performance in the "aged-unimpaired" versus "aged-impaired" group, $t(38) = 2.0$, $p < .07$, 95% CI [−0.30, 0.01].

Recognition Memory Relates to Mnemonic Discrimination

Separate partial correlation analyses assessed relationships between mnemonic discrimination and measures of recognition memory (recognition, hits, false alarms), controlling for diagnostic group (Figure 2). Significant effects survived Bonferroni correction for three comparisons, $p < .017$. Results revealed that worse mnemonic discrimination was significantly associated with worse recognition memory as measured by an increase in false alarms, $r = -.38$, $p < .012$, 95% CI [−0.91, −0.13]. The relationship for the recognition measure did not remain significant after controlling for diagnostic group, $p > .07$, whereas the effect for hits did not approach significance, $p > .91$. A similar pattern of results was observed when also controlling for chronological age.

Diagnostic Group Differences in Regional Volume

Diagnostic group differences in volume of medial temporal cortex were assessed with a group (cognitively normal, MCI) × region (HIPP, EC, PERI, PARA, POLE) repeated-measure analysis of variance (ANOVA) (Figure 3). Results revealed a significant main effect of group, with significantly smaller overall medial temporal cortex volume in the MCI (2274.4 ± 896.1) versus cognitively normal (2502.0 ± 967.5) group, $F(1, 44) = 5.2$, $p < .03$. As expected, a significant main effect of region revealed greater volume in HIPP (3177.3 ± 444.1) and PERI (2984.9 ± 800.0) relative to POLE (2462.8 ± 440.7) and PARA (2406.1 ± 425.9), all of which were significantly greater than EC volume (910.0 ± 137.2), $F(4, 176) = 245.1$, $p < .001$. However, the group × region interaction did not approach significance, $p > .22$.

Diagnostic group differences in volume of hippocampal subfields were assessed with a group (cognitively normal, MCI) × region (DG/CA3, CA1, SUB) repeated-measure ANOVA (Figure 3). Results revealed a significant main effect of group, with smaller hippocampal subfield volume in the MCI (960.6 ± 459.9) versus cognitively normal (1057.5 ± 452.1) group, $F(1, 44) = 5.7$, $p < .03$. As expected, a significant main effect of region revealed significantly smaller volume in DG/CA3 (700.8 ± 138.2) and SUB (717.1 ± 140.2) relative to CA1 (1609.1 ± 211.0), $F(2, 88) = 1226.4$, $p < .001$. However, the group × region interaction did not approach significance, $p > .47$.

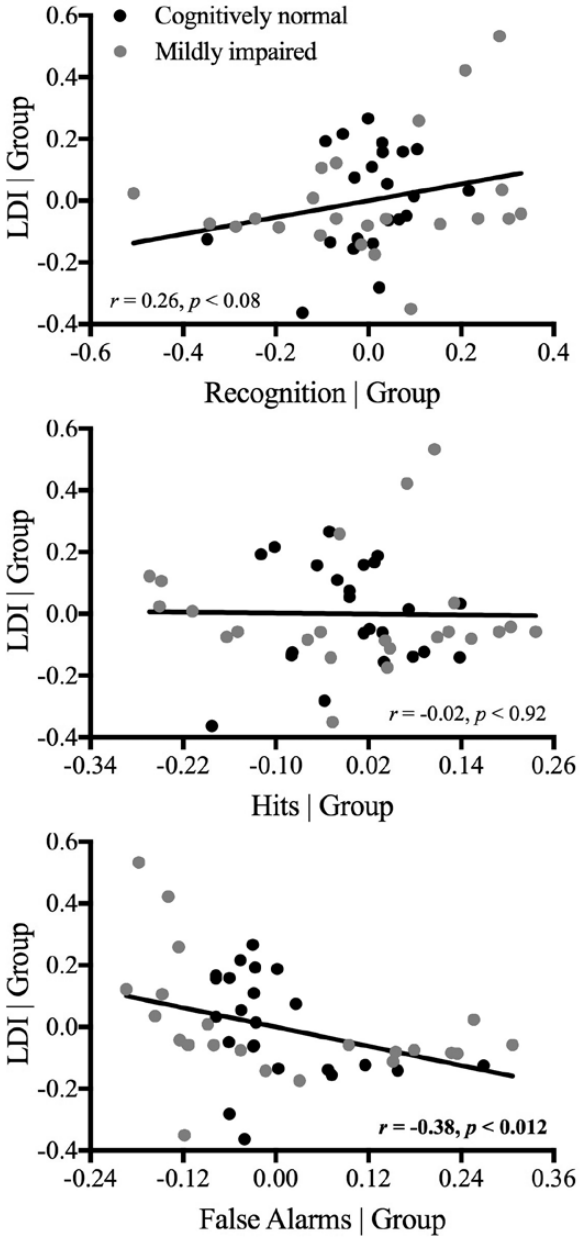

Figure 2. Relationships between each recognition measure (recognition, hits, false alarms) and mnemonic discrimination (LDI) performance are presented, controlling for diagnostic group. Cognitively normal older adults (black) and individuals diagnosed with MCI (gray) are plotted separately. Worse mnemonic discrimination was significantly associated with worse recognition memory as measures by an increase in false alarm rates (bolded).

Recognition Memory Relates to Hippocampal Volume

Separate partial correlations assessed positive relationships between each measure of recognition memory (recognition, hits, false alarms) and volume of each medial temporal region (HIPP, EC, PERI, PARA, POLE), controlling for diagnostic group. Significant one-tailed effects survived Bonferroni correction for five comparisons per recognition

measure, p <.01. A similar pattern of results was observed when also controlling for chronological age.

For the recognition measure, results revealed that worse performance was significantly related to smaller HIPP volume, r = .34, p = .01, 95% CI [0.05, 0.57]. Effects for EC, PERI, PARA, and POLE volume did not attain significance, ps > .09. Follow-up analyses compared regression coefficients in these regions using Steiger's Z-tests for correlated correlations, where one variable (i.e., the recognition measure) is common to both relationships being compared (Meng, Rosenthal, & Rubin, 1992). Results revealed that the relationship between recognition and HIPP volume was significantly larger than the relationship for EC volume, p <.05, but not relationships for PERI, PARA, or POLE volume, ps >.12. These data are presented in Figure 4.

For hits, there was a trend for worse performance being related to smaller HIPP volume, r = .31, p <.04, 95% CI [0.02, 0.55]. Effects for EC, PERI, PARA, and POLE volume did not attain significance, ps >.07. For false alarms, no effects approached significance, ps >.27.

Given the significant effect for hippocampus volume, separate partial correlations also tested for positive relationships between each measure of recognition memory (recognition, hits, false alarms) and volume of each hippocampal subfield (DG/CA3, CA1, SUB), controlling for diagnostic group. Significant one-tailed effects survived Bonferroni correction for three comparisons per recognition measure, p <.017.

For the recognition measure, results revealed that worse performance was significantly related to smaller DG/CA3 volume, r = .32, p <.017, 95% CI [0.03, 0.56]. There was also a trend for worse recognition being related to smaller CA1 volume, r = .25, p <.06, 95% CI [−0.05, 0.50], but not SUB volume, p >.18. Follow-up analyses comparing regression coefficients in these regions using Steiger's Z-tests for correlated correlations (Meng et al., 1992) revealed that the relationship between recognition and DG/CA3 volume was not significantly larger than relationships for CA1 or SUB volume, ps >.19. These data are presented in Figure 4.

For hits, there was a trend for worse performance being related to smaller DG/CA3 volume, r = .28, p <.04, 95% CI [−0.01, 0.53]. Effects for CA1 and SUB volume did not attain significance, ps >.07. For false alarms, no effects approached significance, ps >.13.

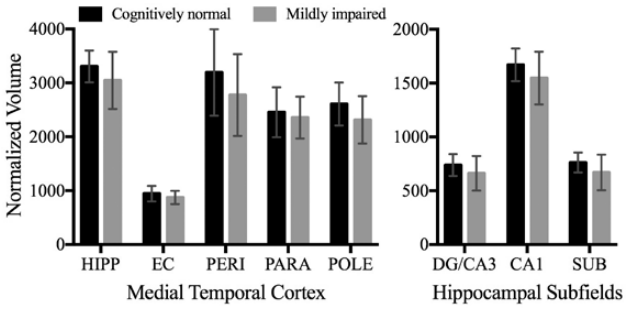

Figure 3. Volumes are plotted separately for each medial temporal cortex (hippocampus, HIPP; entorhinal cortex, EC; perirhinal cortex, PERI; parahippocampal cortex, PARA; temporal pole, POLE) and hippocampal subfield (dentate gyrus/cornu ammonis 3, DG/CA3; cornu ammonis 1, CA1; subiculum, SUB) region in cognitively normal older adults (black) and individuals diagnosed with MCI (gray). Results revealed significantly smaller volumes in the MCI group that did not vary across regions.

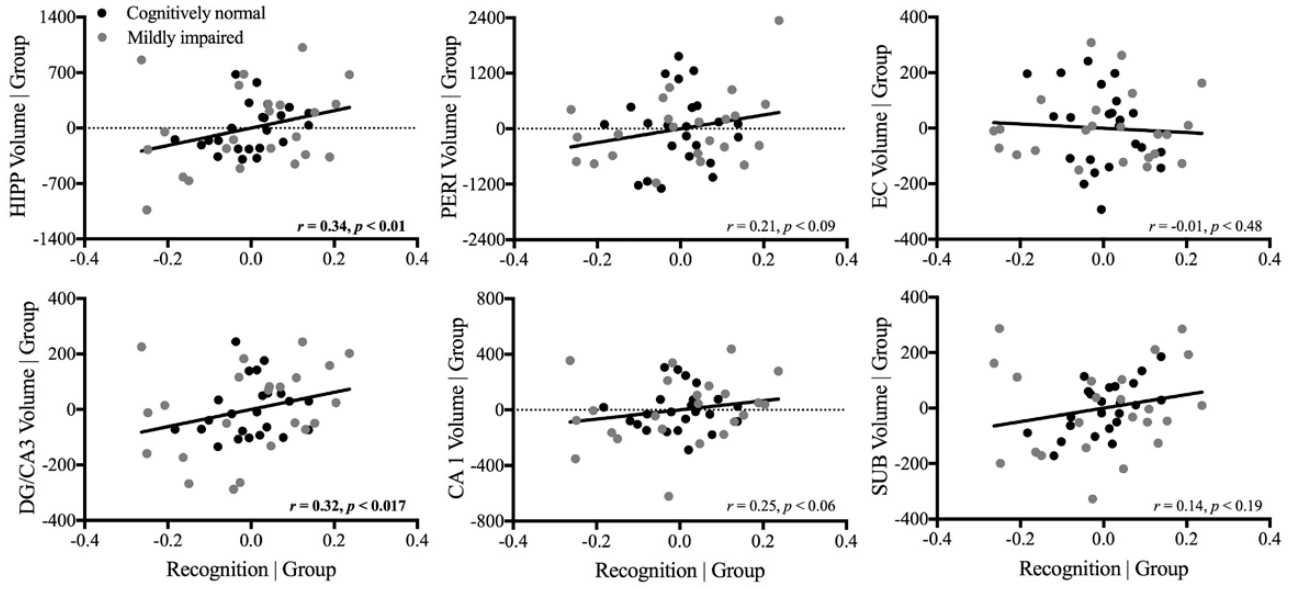

Figure 4. Scatterplots show relationships between recognition memory on the MST and volume of medial temporal cortex (top: hippocampus, HIPP; perirhinal cortex, PERI; entorhinal cortex, EC) and hippocampal subfields (bottom: dentate gyrus/cornu ammonis 3, DG/CA3; cornu ammonis 1, CA1; subiculum, SUB), controlling for diagnostic group. Cognitively normal older adults (black) and individuals diagnosed with MCI (gray) are plotted separately. Worse recognition performance was significantly related to smaller whole hippocampus and DG/CA3 subfield volumes (bolded).

Discussion

The current study examined the neuroanatomical substrates of recognition memory dysfunction and the contribution of recognition memory to mnemonic discrimination in cognitively normal and mildly impaired (MCI) older adults. As expected, individuals diagnosed with MCI exhibited significant decrements in recognition memory (recognition, hits, false alarms) and reduced volume across all medial temporal cortex (hippocampus, entorhinal, perirhinal, parahippocampal, temporal pole) and hippocampal subfield (DG/CA3, CA1, subiculum) regions relative to cognitively normal older adults. After controlling for these diagnostic group differences, worse recognition memory was significantly related to smaller hippocampal volume (recognition), especially for the DG/CA3 subfield. Recognition memory decrements were also significantly related to impaired mnemonic discrimination (false alarms). By focusing on individual differences in memory performance, rather than clinical diagnoses, the current study revealed that the dentate gyrus of the hippocampus is particularly sensitive to recognition memory dysfunction in older adults independent of diagnostic group.

Diagnostic group differences were observed for recognition memory performance and volume of medial temporal cortex and hippocampal subfield regions. Consistent with previous reports (Ally et al., 2009; Bennett et al., 2006), individuals diagnosed with MCI had a significantly lower hit rate and higher false alarm rate, resulting in worse performance on the recognition measure, relative to cognitively normal older adults. Individuals diagnosed with MCI also exhibited significantly smaller volumes across all regions examined relative to cognitively normal older adults. Some studies suggest that entorhinal cortex and the CA1 subfield of the hippocampus are more sensitive to atrophy in individuals diagnosed with MCI (Gertje et al., 2016; Pluta, Yushkevich, Das, & Wolk, 2012), owing to their vulnerability to pathology associated with AD. However, this type of interaction was not observed here, possibly due to limited power to detect such effects. Instead, the current finding of comparable MCI-related decrements across all regions was consistent with previous studies that used the same segmentation protocol in similar diagnostic groups with a larger sample size (Wolk et al., 2017). Rather than focus on these diagnostic group differences, however, the analyses of primary interest here assessed effects that were independent of clinical diagnosis.

After controlling for the previously described diagnostic group differences, results revealed a significant relationship between recognition memory and hippocampal volume. Specifically, worse performance on the recognition measure was associated with smaller whole hippocampus volume and smaller DG/CA3 subfield volume (note that effects were seen for volume in both left and right hemispheres; data not shown). These findings are consistent with at least one study that reported a relationship between recognition memory and volume of hippocampus, as well as other medial temporal regions (entorhinal cortex, parahippocampal cortex), across cognitively normal, mildly impaired (MCI), and severely impaired (AD) older adults (Walhovd et al., 2010). Because diagnostic group was statistically controlled in the current study, our data further suggest that the relationship between recognition memory and hippocampus volume is not solely driven by group differences in memory performance or regional volume. Our findings also extend the work of another group that found similar relationships between recognition memory and DG/CA3/CA4 subfield volume in cognitively normal older adults (Bender et al., 2013; Shing et al., 2011). By examining cognitively normal and mildly impaired older adults, the current data suggest that individual differences in volume of the DG/CA3 subfield, and the hippocampus more generally, rather than MCI-related degradation of these regions, may contribute to recognition memory dysfunction in older adults independent of diagnostic group.

An existing literature has debated the role of the hippocampus in various forms of recognition memory (e.g., Barker & Warburton, 2011; Brown & Aggleton, 2001; Manns, Hopkins, Reed, Kitchener, & Squire, 2003). It has been proposed that the hippocampus is engaged during recollection of specific details about a previously encountered event, whereas other medial temporal regions (perirhinal cortex) are engaged when a previously encountered event feels familiar but is not recalled. The current finding of a relationship between recognition memory and whole hippocampus volume fits with this view because accurate recognition memory in the MST task likely requires recollection of specific details about the memory set objects in order for them to be correctly identified as "old" and not "similar". This contrasts with traditional recognition memory tasks (i.e., those not containing similar lure objects) in which participants can simply identify repeated memory set objects as "old" when either low-fidelity familiarity or high-fidelity recollection occur naturally at retrieval. Because the MST task requires participants to use high-fidelity signals to distinguish between repeated targets and similar lures, even for accurate recognition performance, the current results suggest a specific role for the DG/CA3 subfield of the hippocampus in this type of recollection-based recognition memory.

Results also revealed that worse recognition memory, measured as increased false alarms rates, was significantly related to impaired mnemonic discrimination, after controlling for diagnostic group. Given this relationship, it is not surprising that the neuroanatomical substrates of recognition memory observed here overlap with previous research demonstrating relationships between mnemonic discrimination and DG/CA3 volume in cognitively normal adults (Doxey & Kirwan, 2015) and decreased DG/CA3 (and CA1) subfield volume in individuals diagnosed MCI who also had decreased mnemonic discrimination relative to cognitively normal older adults (Yassa et al., 2010). Importantly, this finding supports the notion that

mnemonic discrimination is dependent on recollection-based recognition memory and suggests that both processes may be mediated by the dentate gyrus of the hippocampus. That is, an intact dentate gyrus may be required to remember specific details about objects from the memory set (recollection-based recognition), which in turn allows for accurate identification of an object that is similar to, but not the same as, an object from the memory set (mnemonic discrimination).

Of note, interpretations of the mnemonic discrimination effects reported here need to consider that conservative exclusion criteria were used in this study relative to other studies using the MST that focus on mnemonic discrimination. Four individuals diagnosed with MCI were excluded from the initial sample for demonstrating below chance performance on the MST (i.e., probability of correctly saying "old" to a repeated target or "new" to a novel foil was less than 0.33—more than 2 *SD*s below performance in the cognitively normal group). However, we elected to retain participants who made few "similar" responses as this response does not affect recognition performance, which was the focus of the current study. In contrast, making few "similar" responses does affect measures of mnemonic discrimination, with the LDI measure being significantly related to the number of "similar" responses (r = .44, p < .01, after controlling for diagnostic group). For this reason, participants who make few "similar" responses are often excluded from studies that focus on mnemonic discrimination using the MST. Such strict criteria would exclude an additional 12 individuals diagnosed with MCI and 5 cognitively normal older adults, significantly under powering the recognition memory effects of interest. Importantly, in spite of these liberal inclusion criteria, there was a significant diagnostic group difference in mnemonic discrimination when comparing individuals diagnosed with MCI to cognitively normal older adults with spared RAVLT performance, as in our earlier work (Stark et al., 2013). The observed relationship between recognition memory and mnemonic discrimination was also in line with our expectations. And although there were no significant relationships between mnemonic discrimination and volume of medial temporal cortex or hippocampal subfield regions after controlling for diagnostic group (data not shown), performance–volume relationships were seen for the recognition measures of interest. Thus, it is unlikely that using conservative exclusion criteria to enrich the sample with a greater range of recognition memory performance affected our aim to assess the neuroanatomical substrates of recognition memory.

Additional research will be necessary to rule out potential confounds. For example, memory performance may be affected by perceptual deficits in these aging populations. Our group has previously demonstrated that cognitively normal older adults did not show perceptual deficits relative to younger adults on a working memory version of the MST in which repeated targets, similar lures, and novel foil objects were presented sequentially (Yassa et al., 2011). Although we have not conducted this perceptual control in individuals diagnosed with MCI, there is some evidence that they have difficulty perceiving objects (e.g., Alegret et al., 2009). Thus, we cannot rule out the possibility that perceptual deficits are contributing to the MCI-related decrements observed in both recognition memory and mnemonic discrimination. In addition, accuracy of the volumetric measures may be affected by limitations of our ASHS segmentation protocol (e.g., lower spatial resolution of 3T scans, untested reliability of our multisubject atlas, deriving the subfield atlas from younger adults, and inclusion of the hippocampal head and tail in our subfield template).

In closing, this study revealed that recognition memory dysfunction is significantly related to reduced hippocampal and DG/CA3 subfield volume and to mnemonic discrimination deficits across cognitively normal older adults and individuals diagnosed with MCI. These volumetric data extend our previous diffusion imaging work that identified age- and MCI-related degradation of a white matter tract that provides direct input to the dentate gyrus of the hippocampus from entorhinal cortex, the perforant path (Bennett et al., 2015; Bennett & Stark, 2016; Yassa et al., 2010). By focusing on individual differences in memory performance, rather than clinical diagnoses, they also support the notion that recognition memory declines along a continuum within older adults, not just across diagnostic groups.

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Conflict of Interest

None reported.

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