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Anterolateral Entorhinal Cortex Volume is Associated with Memory Retention in Clinically Unimpaired Older Adults

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Abstract

The entorhinal cortex is subdivided into anterolateral (alERC) and posteromedial (pmERC) subregions, which are theorized to support distinct cognitive roles. This distinction is particularly important as the alERC is one of the earliest cortical regions affected by Alzheimer's pathology and related neurodegeneration. The relative associations of alERC/pmERC with neuropsychological test performance have not been examined. We examined how alERC/pmERC

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Ethics Approval: The Institutional Review Board of Columbia University approved all procedures used in this study. All participants gave informed consent before participating in this study.

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volumes differentially relate to performance on 1) the ModRey, a verbal memory test designed to assess memory in normal/pre-clinical populations, 2) the Montreal Cognitive Assessment (MoCA), and 3) the National Alzheimer's Coordinating Center (NACC) neuropsychological battery. We also examined whether alERC/pmERC volumes correlate with Alzheimer's disease cerebrospinal fluid biomarkers. In 65 cognitively healthy (CDR = 0) older adults, alERC, but not pmERC volume was associated with ModRey memory retention. Only alERC volume differentiated between participants who scored above and below the MoCA cutoff score for impairment; evaluating the MoCA subdomains revealed that alERC was particularly associated with verbal recall. On the NACC battery, both alERC and pmERC volumes were associated with Craft story recall and Benson figure copy, but only alERC volume was associated with Craft story retention and semantic fluency. Neither alERC nor pmERC volume correlated with CSF levels of amyloid or tau, and regression analyses showed that alERC volume and CSF amyloid levels were independently associated with ModRey retention performance. Taken together, these results suggest that the alERC is important for memory performance, and that alERC volume differences are related to a pattern of neuropsychological test performance (i.e. impairments in episodic memory and semantic fluency) typically seen in clinical AD.

Keywords

entorhinal cortex; memory; neuropsychology; amyloid; aging

Introduction

The entorhinal cortex (ERC) is a critical brain region that connects the hippocampus to cortex (Duvernoy et al., 2013; Witter et al., 2000) and supports memory processes (Coutureau and Di Scala, 2009). Functional connectivity studies suggest the ERC can be subdivided into two subfields: the anterolateral entorhinal cortex (alERC), and the posteromedial entorhinal cortex (pmERC) (Maass et al., 2015; Navarro Schröder et al., 2015; however, see also Doan et al., 2019). How the ERC subfields differentially support ERC-dependent mnemonic processes has not been clearly addressed. This question is particularly important as Alzheimer's disease (AD)-related tau pathology appears earliest in the alERC (Braak and Braak, 1991; Khan et al., 2014), and PET imaging studies show that tau deposition matches the pattern of neurodegeneration in AD (Ossenkoppele et al., 2016). In healthy older adults, ERC volume differences are associated with the combined presence of abnormal levels of AD cerebrospinal fluid (CSF) amyloid and tau biomarkers (Desikan et al., 2011), which in turn are related to differences in cognition (Desikan et al., 2012). Further, larger alERC, but not pmERC, volumes are related to abnormal CSF tau and amyloid levels in AD patients (Holbrook et al., 2019), as well as to better performance on the MoCA, a short assessment for cognitive decline (Olsen, Yeung et al., 2017).

The "posterior medial, anterior temporal" (PMAT) model suggests that the alERC is involved with learning about/representing concepts/items, whereas the pmERC is involved with constructing/applying contextual models (Ranganath and Ritchey, 2012; Ritchey et al., 2015; however, see also Nilssen et al., 2019 and Wang et al., 2020 for different interpretations of the cognitive functions of the ERC subfields). Experimental studies

suggest that the alERC is involved in remembering and distinguishing similar visual objects (Berron et al., 2018; Reagh and Yassa, 2014; Schultz et al., 2012), processing spatial properties of objects (Tsao et al., 2013; Wilson et al., 2013; Yeung et al., 2019b, 2017), and encoding temporal information in episodic memory (Bellmund et al., 2019; Montchal et al., 2019; Tsao et al., 2018). In contrast, direct recording experiments suggest that the pmERC is important for spatial representation/navigation (Hafting et al., 2005; Jacobs et al., 2013; Killian et al., 2015, 2012; Meister and Buffalo, 2018; Sargolini et al., 2006; Solstad et al., 2008).

ERC volume loss is associated with verbal memory performance decline in both community samples (Gicas et al., 2019; Hays et al., 2019) and AD patients (Di Paola et al., 2007). A retrospective study of temporal lobe resection in epilepsy patients shows that the amount of ERC removed scales with decline in verbal memory (Liu et al., 2017), and smaller ERC volume is associated with worse verbal delayed recall in mild cognitive impairment (Guzman et al., 2013). Longitudinal ERC shrinkage is associated with decline in story and word recall (Stoub et al., 2010). Additionally, experimental work with tau PET tracers show that selective deposition of tau in the ERC/hippocampus and ERC atrophy are related to poorer episodic memory, including delayed verbal memory (Knopman et al., 2019; Maass et al., 2018).

Given the association between ERC volume and verbal memory, are alERC/pmERC volumes differentially related to aspects of verbal recall? The PMAT model would suggest that the alERC's role in item memory underlies verbal memory, and the pmERC's role in context memory also supports verbal recall. The Modified Rey Auditory Learning Test ("ModRey", Hale et al., 2017) is a verbal memory test designed to be more sensitive to individual differences among preclinical/non-clinical populations than standard neuropsychological instruments. We previously showed that ModRey retention is specifically related to ERC cerebral blood volume (Brickman et al., 2014), which is related to subsequent conversion to AD (Khan et al., 2014), and is correlated with cerebrospinal fluid AD biomarkers in older adults without dementia (Yeung et al., 2019a).

This study addressed four questions. First, how do alERC and pmERC volumes in cognitively healthy older adults independently relate to verbal memory? Second, building on our previous work (Olsen, Yeung et al., 2017), how do alERC and pmERC volume relate to performance on the MoCA, a multi-domain screening instrument for cognitive impairment, particularly when accounting for differences in the hippocampal subfield volumes? Third, do the relationships of alERC and pmERC volumes with memory generalize to other cognitive domains, and do they match a prototypical AD cognitive profile? Fourth, how do alERC and pmERC volumes relate to AD biomarkers, and how do ERC subfield volumes and AD biomarkers interact in their effects on cognition? We hypothesized that 1) larger alERC volume is related to better ModRey verbal memory performance, 2) larger alERC volume is related to better MoCA performance, 3) larger alERC volume is related to better performance on standard clinical neuropsychological instruments that track with clinical AD progression, including episodic memory and semantic fluency, and 4) larger ERC subfield volumes are related to lower CSF tau biomarker levels.

Methods

Participants

Sixty-five older adults without cognitive impairment (CDR = 0) who were enrolled in the Columbia University Alzheimer's Disease Research Center (ADRC) were included in the study. Participant demographic data are shown in Table 1. Participants were screened for neurological disease, as well as contraindications for MRI and gadolinium injection. All participants gave informed consent to participate in this study. The Columbia University Institutional Review Board approved all procedures used in this study. We recently reported data on a subset of these participants (Yeung et al., 2019a) with different analyses.

Structural Image Acquisition

Structural magnetic resonance images were acquired on a 3T GE MR750 scanner using a 32-channel head coil (56 subjects), and a 3T GE Signa Premier scanner using a 48-channel head coil (9 subjects) due to a scanner upgrade. There were no systematic differences in brain volume across the two scanners: total ERC volume (M = 1516.67 mm3, SD = 216.57 mm^3 for the GE MR750, M = 1522.12 mm^3, SD = 126.38 mm^3 on the GE Signa Premier, $t(63) = -0.073$, $p = 0.942$), alERC volume (M = 1169.29 mm^3, SD = 187.89 mm^3 on the GE MR750, M = 1206.89 mm^3, SD = 110.19 mm^3 on the GE Signa Premier, $t(63) = -0.582$, $p = 0.563$), pmERC volume (M = 347.39 mm^3, SD = 66.64 mm^3 on the GE MR750, M = 315.24 mm^3, SD = 57.77 mm^3 on the GE Signa Premier, $t(63) = 1.365$, $p = 0.177$). Participants received a T1-weighted magnetization-prepared, rapid acquisition with gradient echo image (MPRAGE) whole-brain anatomical scan (TE/TR=2.63 ms/2000ms, 176 sagittal slices perpendicular to the AC-PC line, flip angle = 12°, voxel size=1×1×1 mm). The T1-weighted MPRAGE scan was used to obtain measures of brain and head size, and for slice placement during the acquisition of a subsequent high-resolution T2-weighted scan in an oblique-coronal plane, perpendicular to the hippocampal long axis (TE/TR = 68ms/3000ms, 40 slices, flip angle = 125°, voxel size = 0.43×0.43×2 mm). For the high-resolution T2-weighted scan, the first slice was placed anterior to the first appearance of the collateral sulcus, and the last slice placed posterior to the hippocampal tail, to ensure full coverage of the entire hippocampus and MTL cortices.

Manual Entorhinal Cortex Subregion Segmentation

Manual segmentation of the ERC subfields was performed on the T2-weighed images (0.4×0.4mm in plane), in the participants' native space, on the oblique coronal plane, perpendicular to long axis of the hippocampus. A single rater (L.-K.Y.) manually delineated the ERC and subdivided it into alERC and pmERC subregions in FSLView (FMRIB, Oxford, UK). The segmentation protocol used in this study was previously described in Olsen, Yeung et al. (2017).

The ERC was defined following the protocol described by Insausti et al. (1998) based on histological study. The subdivision of the entorhinal cortex into alERC and pmERC was adapted from the protocol of Maass et al. (2015), based on functional connectivity between the entorhinal cortex and the perirhinal and parahippocampal cortices respectively. The two protocols were combined by first defining the entire ERC based on the Insausti protocol, and

subsequently subdividing the ERC into alERC and pmERC subfields using the Maass protocol. Moving anterior to posterior, the ERC appears at the level of the frontal-temporal junction. The pmERC appears at the superior tip of the ERC where the hippocampal head first appears, and increases in size moving posteriorly. The pmERC and alERC are equal in size approximately 2/3rds of the anterior/posterior extent of the hippocampal head, as described by Maass et al. (2015). The last slice of the ERC appears just posterior to the uncal apex. At this level, the pmERC covers the entire ERC.

As in our previous work (Olsen, Yeung et al., 2017), slight alterations were made to the Maass protocol to accommodate the thicker slices used in the current study. Further, as the Insausti protocol defines the lateral edge of the entorhinal cortex based on the depth of the collateral sulcus (as opposed to the Maass protocol, which places the lateral edge of the entorhinal cortex on the medial edge of the collateral sulcus) the entorhinal cortex subfields were extended laterally based on the Insausti protocol's definition (see Figure 1).

All entorhinal cortex volumes were corrected for head size using a regression-based method, to account for differences in brain size between participants. Estimated total intracranial volume was derived from the whole-brain T1-weighted scans using FreeSurfer (v6.0) (Buckner et al., 2004). A regression slope was obtained for each entorhinal cortex subfield in each hemisphere, by regressing the volume of that subfield with the total intracranial volume, and each individual participant's subfield volume was corrected using that regression slope based on the difference between their intracranial volume compared to the mean intracranial volume. Corrected subfield volumes were subsequently summed across the two hemispheres, giving a single total volume for each region for each participant.

Intra-rater reliability was established by comparing the segmentation of ten randomly selected scans, after a delay of several months. Reliability was assessed using the intra-class correlation coefficient (ICC), which evaluates volume reliability (Shrout and Fleiss, 1979) and the Dice metric, which also takes spatial overlap into account (Dice, 1945), computed separately for each region in each hemisphere. Dice was derived using the formula 2*(intersecting region) / (original segmentation + repeat segmentation); a Dice overlap metric of 0 represents no overlap, while a metric of 1 represents perfect overlap. Intra-rater reliability results are shown in Table 2, and are similar to intra-rater reliability for ERC subfields in our previous work (Olsen, Yeung et al., 2017), and for manual segmentation of MTL regions more generally (Wisse et al., 2012; Yushkevich et al., 2015).

Automated Hippocampal Subfield Segmentation

Automated segmentation of the hippocampal subfields (CA1, CA2, CA3, dentate gyrus, subiculum) was performed using the Automatic Segmentation of Hippocampal Subfields (ASHS) package (Yushkevich et al., 2015) on both the T1-weighted MP-RAGE scans and the T2-weighted high resolution scans, using the Magdeburg atlas (Berron et al., 2017, see Figure 1). Note that subfields were partitioned in the hippocampal head and body sections, but not in the tail section, where the stratum radiatum lacunosum moleculare (SLRM), a strip of white matter that separates the subfields, is not visible at the 0.4×0.4mm in-plane resolution. Because it is unclear where the subfield boundaries lie in the hippocampal tail, it

was excluded from the analyses in this study (see also Wisse et al., 2020 addressing concerns about segmenting hippocampal subfields where the SLRM is not visible).

ModRey

Participants were administered the ModRey (Hale et al., 2017), a test of list learning and declarative memory. Fifty-six participants were administered the ModRey on the day of MRI scanning. Of the remaining nine participants, the median delay between scanning and testing was 9 days (average delay = 43.8 days, SD = 48.1 days). Seven of the nine participants were tested within 1.5 months of scanning, and the remaining two were tested within 4 months of scanning. Cognitive performance did not differ on any measure tested in this study between participants who received the ModRey on the same day as scanning versus those who did not. The design of the ModRey is illustrated in Figure 2. In brief, participants first received three learning trials, where they were read 20 unique, semantically and phonetically unrelated words (List A), and were asked to recall these words after each trial. These trials were immediately followed by a 4^{th} learning trial, where participants were read a distractor list of 20 additional semantically and phonetically unrelated words (List B). Subsequently, participants were asked to freely recall as many words as possible from List A (the “short delay free recall”). After an approximately 40-minute delay, during which unrelated cognitive testing occurred, participants were asked to freely recall as many words as possible from both List A and List B separately (“long delay free recall”). These trials were followed by a 66-item forced-choice recognition test where participants were asked to decide if a presented word belongs to List A; distractors came from both List B and a selection of phonetically/semantically related words. Finally, source memory was assessed by asking the participant to match words on a list to either List A or List B.

The primary ModRey outcome variable was the “short-delay retention” score: the ratio of the number of items from List A correctly recalled freely at the short delay, to the number of items correctly recalled freely during the last List A learning trial. This variable was chosen because it is tightly linked to function of the entorhinal cortex (Brickman et al., 2014, 2011; Fernández et al., 1999; Schon et al., 2004). Additional ModRey outcome variables analyzed in this study included total learning, short-delay free recall, long-delay free recall, recognition discrimination and source memory.

Two psychometrically similar (Hale et al., 2017) versions of the ModRey were used, each with its own unique Lists A and B. Half of the participants received one version of the ModRey, and the other half received the other. There were no differences in short-delay retention, or any of the other outcome variables between the two versions. Accordingly, all analyses collapsed across the two versions.

NACC-UDS3 Neuropsychological Battery

All of the participants received the National Alzheimer’s Coordinating Center (NACC) Uniform Data Set (UDS) neuropsychological battery, version 3 (NACC-UDS3, Weintraub et al., 2018). This is a standardized set of neuropsychological tests used by Alzheimer’s Disease Centers across the United States. The battery includes the MoCA (Nasreddine et al., 2005), Craft Story (Craft et al., 1996), Digit Span (Weschler, 1987), Semantic and Verbal

Fluency (Morris et al., 1989), Trail Making Test Parts A and B (Reitan and Wolfson, 1985), Benson Complex Figure Test (Possin et al., 2011), and the Multilingual Naming Task (MINT, Gollan et al., 2012). The NACC-UDS3 is administered to all participants in the Columbia ADRC cohort annually.

Because of concerns about practice effects, the baseline performance on the entire NACC-UDS3 battery was used for each participant. Forty-two out of the 65 participants (64.6%) received the NACC-UDS3 battery for the first time within 1 year prior to scanning, and an additional 13 participants (20%) received the battery for the first time within 2 years prior scanning. No participant received the battery for the first time more than 3.5 years before the scan. There were no significant differences in performance between participants who were scanned within one year of taking the battery versus participants who were scanned before. The median delay between NACC-UDS3 testing and the scan was 103 days.

CSF Biomarkers

Cerebrospinal fluid (CSF) was obtained via lumbar puncture, performed with standard clinical research methods in aseptic fashion by a board-certified neurologist. CSF was obtained for 59 of the 65 participants in this study. CSF was always collected during a separate session from testing to avoid influencing performance on cognitive testing. Up to 15 cc of CSF was removed using a Sprotte 24G spinal needle and placed in two 12 cc polypropylene tubes. All samples were centrifuged briefly, aliquoted using polypropylene pipettes within 30 minutes, and stored for both biomarker analysis and CSF-banking at −80°C. Levels of three CSF biomarkers (Aβ42, phosphorylated tau, total tau) were analyzed in duplicate by a bead-based multiplex method using the Innogenetics Alz-Bio3 kits on a Luminex (LS-100) platform with 96-well plates. Coefficient of variation (CV) was generally less than 10% (samples with higher CV were repeat analyzed).

Statistical Analysis

ModRey performance & alERC/pmERC volumetric analyses—A multiple regression model was run to evaluate the relationship between alERC/pmERC volumes and ModRey performance. In this model, ModRey short-delay retention was the dependent variable, with alERC volume and pmERC volume as predictors, and age, years of education, gender and race/ethnicity as covariates.

These analyses were followed by additional exploratory multiple regression models that examined each of the other ModRey outcome measures (total learning, short-delay free recall, long-delay free recall, recognition discrimination and source memory) as the dependent variable, again with alERC and pmERC volume as predictors, and age, years of education, gender and race/ethnicity as covariates.

MoCA performance and alERC/pmERC volumetric analyses—To replicate analyses performed in our previous work in a separate sample (Olsen, Yeung et al., 2017), participants were divided into two groups based on their MoCA score (<26, ≥26; with 26 being the MoCA threshold score). The volumes of the alERC, pmERC, as well as the other segmented hippocampal subfields and MTL cortices were compared across these two groups

using t-tests. Note that since these two groups did not differ in age, t(63) = 0.397, p = 0.693, 95% CI [−3.000, 4.488], years of education, t(63) = 1.169, p = 0.247, 95% CI [−0.433, 1.653], or gender, $\chi^2(1, N=65) = 0.190$, p = 0.663, structural volumes for these t-tests were not adjusted for age, gender or years of education.

Given that Olsen, Yeung et al. (2017) found that only alERC volume differed between the MoCA groups after correction for multiple comparisons, a multiple regression model was run with all the regional volumes as predictors, age, years of education, gender and race/ethnicity as covariates, and MoCA score as the dependent variable, with the goal of testing if alERC volume, or any other MTL/hippocampal subfield volume, was related to MoCA score after accounting for other subfield volume differences.

As a post-hoc analysis, performance on the MoCA was divided into subdomains (visuospatial/executive, naming, attention, language/abstraction, memory, and orientation). Pearson's correlations were used to evaluate the association of each MoCA subdomain score with alERC/pmERC volumes, and age, years of education, gender and race/ethnicity as covariates.

NACC UDS-ERC subfield analyses—Exploratory multiple regression models were also used to evaluate the relationship of the alERC and pmERC (as regressors), with each of the NACC-UDS3 measures (as the dependent variable): Craft immediate recall, Craft delayed recall, Craft retention, digit span, semantic fluency, Trails A & B (and the ratio of Trails B to Trails A), Benson figure copy, Benson figure delayed recall, MINT, and verbal fluency. These multiple regression models included age, years of education, gender and race/ethnicity as covariates.

Pearson's correlations were used to test if ERC subfield volumes correlated with three cerebrospinal fluid (CSF) AD biomarkers (Aβ−42, phospho-tau and total tau levels), or with ratios of the CSF tau biomarkers to the Aβ−42 biomarker, with age, years of education, gender and race/ethnicity as covariates. Post hoc analyses examined the correlations between hippocampal subfield volumes and CSF AD biomarker levels. Because our previous results in this sample showed that CSF amyloid was related to ModRey short-delay retention in cognitively healthy older adults (Yeung et al., 2019a), multiple regression analysis was also used to determine if CSF amyloid and alERC volume were independent predictors of ModRey performance, with age, years of education, gender and race/ethnicity as covariates.

Results

ModRey performance and alERC/pmERC volumetric analyses

The multiple regression model examining how ModRey short-delay retention performance was related to alERC and pmERC volumes showed that larger alERC volume was associated with better performance on the primary ModRey outcome measure, short-delay retention, t(58) = 2.009, p = 0.049, β = 0.258, 95% CI [0.001, 0.514], sr = 0.255 (Figure 3a). However pmERC volume was not significantly associated with ModRey performance, t(58) = 0.301, p = 0.764, β = 0.043, 95% CI [−0.243, 0.330], sr = 0.040.

Exploratory multiple regression analyses examining the effects of alERC and pmERC volume on other ModRey measures showed that larger alERC volume was also significantly associated with better performance on total learning, short-delay accuracy, and number of false positive errors (Table 3), while pmERC volume was only significantly associated with the number of intrusions.

MoCA performance and alERC/pmERC volumetric analyses

The mean MoCA score across all participants was 26.5 (SD = 2.3, range = 20–30). Independent samples t-tests showed that participants with MoCA scores of 26 or above (i.e. above the MoCA threshold score) had larger alERC volumes compared to those with MoCA scores below 26 (see Table 4). In contrast, the volumes of pmERC and the other measured hippocampal subfields or MTL cortical areas did not differ between the two groups.

Because the volume of MTL regions and hippocampal subfields are necessarily highly correlated (see Table 5), multiple regression analysis was performed to evaluate the specific associations of each regional volume (alERC, pmERC, BA35, BA36, CA1, CA2, CA3, dentate gyrus, subiculum) with MoCA score. Among all the regions evaluated, only alERC volume uniquely related to MoCA score positively, $t(50) = 3.532$, $p = 0.001$, $\beta = 0.518$, 95% CI [0.224, 0.813], $sr = 0.417$ (Figure 3b).

As a post-hoc analysis, the association between MoCA subdomain scores (visuospatial/executive, naming, attention, language, abstraction, memory, orientation) and alERC volumes was tested using Pearson's correlations. These analyses showed that only the memory subdomain score, which is a measure of delayed recall, was significantly positively associated with alERC volume, $r(59) = 0.367$, 95% CI [0.123, 0.569], $p = 0.004$.We note that alERC volume was also marginally correlated with the visuospatial/executive subdomain, $r(59) = 0.248$, 95% CI [−0.008, 0.473], $p = 0.054$, and the orientation subdomain, $r(59) = 0.241$, 95% CI [−0.016, 0.468], $p = 0.061$.

NACC UDS-ERC subfield analyses

Multiple regression analyses were run to examine the associations of alERC and pmERC volume with performance on each measure from the NACC-UDS3 battery. Table 6 lists the association of the ERC subfield predictors in these models. Notably, pmERC volume was significantly associated with performance on Craft story immediate recall and delayed recall. alERC volume was significantly associated with both Craft story delayed recall and retention (Figure 3c). Both subfield volumes were associated with Benson figure copy performance, while alERC volume, but not pmERC volume was significantly related to performance on a test of semantic fluency (Figure 3d).

CSF biomarker analyses

Pearson's correlations were run to explore the associations between CSF biomarkers in this participant cohort. Aβ42 levels were not correlated with phosphorylated tau levels, $r(59) = 0.159$, 95% CI [−0.101, 0.398], $p = 0.228$, but Aβ42 levels were inversely correlated with total tau, $r(59) = 0.307$, 95% CI [0.056, 0.522], $p = 0.018$. Phosphorylated tau and total tau levels were strongly correlated, $r(59) = 0.656$, 95% CI [0.481, 0.780], $p < 0.001$.

Pearson's correlations were run to examine the relationship between ERC subfield volume and CSF biomarkers of AD. Neither alERC volume, nor pmERC volume correlated with CSF levels of Aβ−42, phospho-tau or total tau, or the ratios of the tau measures with Aβ−42 (see Table 7). Exploratory post hoc analyses using Pearson's correlations to examine the relationship between MTL region/hippocampal subfield volumes and CSF biomarkers showed that among all the segmented regions, only the dentate gyrus volume was significantly correlated with CSF Aβ−42.

As both alERC volume and CSF Aβ−42 (Yeung et al., 2019a) have been shown to relate to ModRey short-delay retention in this cohort, multiple regression analysis was performed to examine the independence of their contributions to ModRey short-delay retention. alERC volume and CSF Aβ−42 levels were entered as predictors for ModRey short-delay retention performance. This model showed that alERC volume, $t(52) = 2.043$, $p = 0.046$, $\beta = 0.257$, 95% CI [0.004, 0.510], sr = 0.254, and CSF Aβ−42 levels, $t(52) = 2.186$, $p = 0.033$, $\beta = 0.345$, 95% CI [0.029, 0.662], sr = 0.271 were independently associated with ModRey short delay retention, accounting for age, education, gender and race/ethnicity as covariates. Post-hoc analyses revealed no significant interaction between alERC volume and CSF Aβ−42 (i.e. no moderation), and neither variable mediated the relationship between the other and ModRey short-delay retention.

To address concerns that the presence of biomarker-positive participants might drive the observed structure-cognition associations, the multiple regression models predicting ModRey retention were repeated, excluding participants who were biomarker positive, based on previously-established CSF thresholds (Aβ−42 < 325 pg/mL, t-tau > 72 pg/mL, p-tau > 31 pg/mL, p-tau/Aβ−42 ratio < 0.1, see Yeung et al., 2019a). As shown in Table 8, excluding participants who were biomarker positive did not greatly affect the observed effect of the alERC predictor on ModRey retention.

Discussion

In a group of cognitively-unimpaired older adults, we demonstrated that larger alERC volume is related to better performance short-delay retention on the ModRey (Hale et al., 2017), a memory test designed for preclinical and cognitively-healthy older adults. Among hippocampal and ERC subfields, alERC volume is also selectively positively associated with performance on the MoCA, a short assessment that tracks cognitive decline, and differs between participants who score above/below the MoCA threshold score; this observation replicates the findings of Olsen, Yeung et al. (2017) in a separate participant sample. Extending this finding, we showed that the positive relationship between alERC and MoCA is largely based on the delayed recall component of the MoCA. Further, we demonstrated that on the NACC-UDS3 neuropsychological battery, the volume of both alERC and pmERC is positively related to clinical measures of memory and visuospatial processing, while alERC volume, but not pmERC volume, is also positively related to memory retention and semantic fluency. Finally, we showed that higher alERC volume and CSF amyloid levels (i.e. healthier levels of CSF amyloid) have independent positive associations with ModRey retention.

Taken together, our results suggest that the alERC broadly supports memory processing, including recall, retention, and rejecting false positives, across multiple neuropsychological instruments, while the pmERC may be necessary only when contextual information is needed for memory. Interpreting our results within the "posterior medial, anterior temporal" (PMAT) framework (Ritchey et al., 2015), alERC volume is positively related to memory measures across numerous different neuropsychological instruments, and to semantic fluency scores, because these require memory for single items and their associations, without necessarily requiring additional contextual information. In turn, pmERC volumes are positively related to memory only on the Craft story task because the narrative structure of the stimuli makes contextual information more useful for recall. Likewise, the positive relationship of both alERC and pmERC volume to better Benson copy performance might be explained by the importance of spatial relations between the different line segments in that task. Interestingly, alERC volume was positively associated with immediate recall on both the Benson complex figure task and the ModRey, but not with delayed recall. However, on the Craft story, alERC volume was positively associated with performance on both immediate and delayed recall trials. This pattern of alERC-memory relationships does not seem to be related to the length of the delay, as the delay for the ModRey (40min) was greater than the Benson complex figure task (15 min) or the Craft story (20 min). Rather, our results might reflect the importance of the alERC (as the main hippocampal input) for narrative events (Rosenbaum et al., 2008) versus single items, or the greater impact of alERC dysfunction on more interconnected stimuli. The lack of association between alERC volumes and ModRey long-delay recall in our study is not necessarily discrepant with previously-reported association between delayed recall and functional activity in the ERC (Brickman et al., 2011). A recent study highlighted how performance on spatial navigation tasks within a reasonable range of normal performance - which have previously been shown to elicit functional activity in the hippocampus - do not relate to hippocampal volume in healthy participants (Clark et al., 2020). This model suggests that within a certain range, functional activation and cognitive performance might be linked independent of brain structure volume. Relationships between brain volume and cognitive function may emerge only brain volume limits the amount of functional activation possible, e.g. when task performance is sufficiently taxing, or when participants are undergoing volumetric decline. In the context of aging, this model would predict that it is plausible that structure-cognition relationships become more significant as atrophy progresses. This idea aligns with the prediction that arises from the PMAT model that we should expect to see pmERC volume differences have a larger effect on memory performance in more cognitively impaired populations, because contextual information would become more helpful for recall as memory for individual items weakens. Additionally, the alERC results are broadly in line with the revised models (Doan et al., 2019; Nilssen et al., 2019), which argue that the alERC is a critical convergence zone for sensory information representing the content of episodic memory. We note however, that the associations between pmERC volume and cognition we report do not necessarily align with the allocentric spatial coding proposed by this model. This discrepancy may arise through our functional connectivity-based definition of the ERC subfields, which could attribute some portion of the alERC as being pmERC instead, in contrast to the histological definition used in the revised model.

It is well established that ERC atrophy is commonly observed in AD patients (Bobinski et al., 1999; Du et al., 2001; Herukka et al., 2008; Juottonen et al., 1998; Killiany et al., 2000; Pennanen et al., 2004) and correlates with clinical severity (Du et al., 2003; Fennema-Notestine et al., 2009; McDonald et al., 2009). Based on the lack of associations between alERC volume and CSF biomarkers in our sample (in contrast to the findings of Holbrook et al., 2019 in AD patients), and the independent effects of CSF amyloid and alERC volume on ModRey retention, one interpretation is that our results represent either a range of normal variation in alERC volume relating to cognitive performance in healthy older adults, or a non-AD related neurodegeneration effect. On the other hand, alERC volume in our data is related specifically to a canonically AD-like pattern of cognitive test performance on the NACC-UDS3 neuropsychological battery (i.e. specific deficits in episodic memory and semantic fluency), with relatively spared performance in other cognitive domains (Salmon et al., 2002, 1999). Speculatively, when our findings are viewed in context with those of Holbrook et al (2019), it is possible that our results reflect some antecedent cause of alERC neurodegeneration, that combined with the presence of amyloid/tau biomarkers, may subsequently be related to development of AD. Longitudinal follow-up testing on these participants will help untangle which of these two interpretations is more accurate.

There are important limitations that need to be considered in interpreting these findings. It is important to note that our participant group are all cognitively unimpaired (CDR = 0), and it is unknown whether they will go on to develop AD. Thus, any interpretation of our data in the context of AD is necessarily speculative. Because our sample is drawn from an ongoing study involving both lumbar punctures to collect cerebrospinal fluid and gadolinium-contrast MRI, the sample size is not particularly large. The sample was mostly white and highly educated, and the findings may not generalize to a more diverse or less educated population. Further, there is an underlying assumption that entorhinal cortex volume loss and synaptic/neuronal loss are linearly related, which may not actually be the case. It is possible that neuronal loss might not initially cause detectable volume loss using MRI, which would suggest our data are understating the strength of the alERC-cognition association. As we examined grey matter volumes, our method does not account for changes in white matter structure (e.g. the integrity of the perforant pathway from the ERC into the hippocampus). Our study has a cross-sectional design, and we can only speak to the association of ERC subfield volume differences to cognition. While it is possible to extrapolate that our results reflect individuals at different points along a trajectory of neurodegeneration, longitudinal data are necessary to confirm this hypothesis.

An interesting implication of the results is that the ModRey might be a particularly sensitive instrument for detecting cognitive changes in otherwise asymptomatic older adults, which may be related to AD. We previously showed in the same group of participants that ModRey short-delay retention is related to CSF levels of amyloid and tau (Yeung et al., 2019a), which are biomarkers for AD. This study shows ModRey performance in cognitively healthy older adults is related to alERC volume differences, a neurodegenerative biomarker for AD. Strikingly, we find that alERC volumes are related to a classical neuropsychological presentation of AD: relative deficits in delayed recall and semantic fluency. Combining these two results suggests that ModRey performance might reflect subtle preclinical cognitive changes that are not currently regarded as pathological, but may predict subsequent decline.

If that is true, then the ModRey may be a useful instrument for the early detection of AD, and for tracking progression in very early clinical phases.

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- The anterolateral entorhinal cortex (alERC) is affected by AD pathology early
- In unimpaired older adults, alERC volume correlates with ModRey, corrected for age
- alERC volume also correlates with other neuropsych tasks impaired early in AD
- alERC volume and CSF amyloid independently related to ModRey memory retention
- alERC volume differences might underlie preclinical AD-related cognitive changes

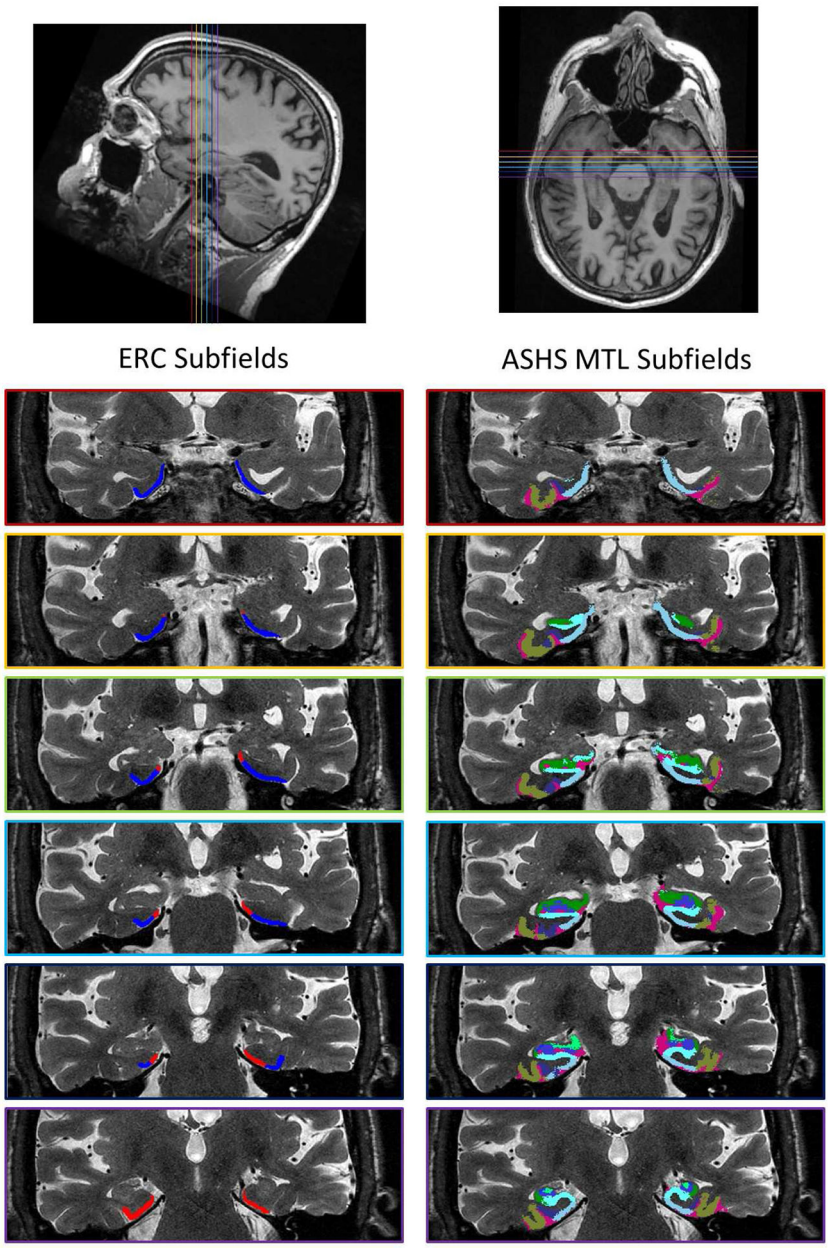

Figure 1:
Example of manual segmentation of ERC subfields (left) and ASHS automated segmentation of hippocampal subfields/MTL regions (right), shown on coronal plane. Position of color-coded coronal slices on axial and sagittal views shown at top. In the ERC subfield segmentation, alERC indicated in blue, and pmERC indicated in red. In the ASHS hippocampal/MTL segmentation, CA1 indicated in green, dentate gyrus in blue, CA3 in light green, subiculum in light blue, BA35 indicated in violet, BA36 indicated in tan. CA2 and PHC were also measured, but are not visible on these slices. ERC (navy) and empty spaces (magenta) also shown in figure, but not used for analyses.

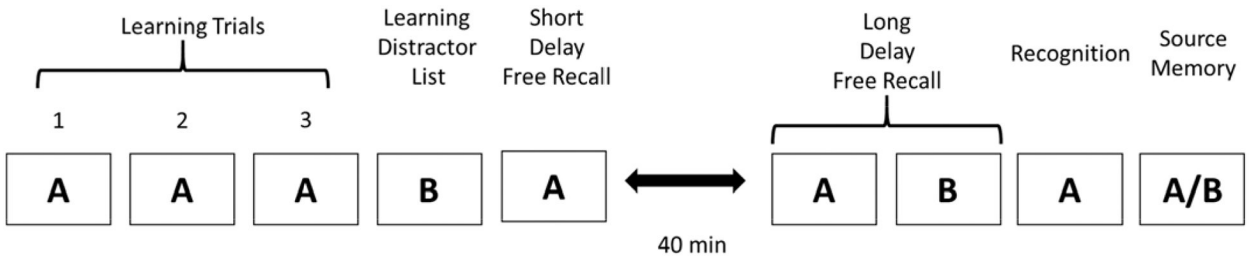

Figure 2:
Experimental design of the ModRey verbal memory task

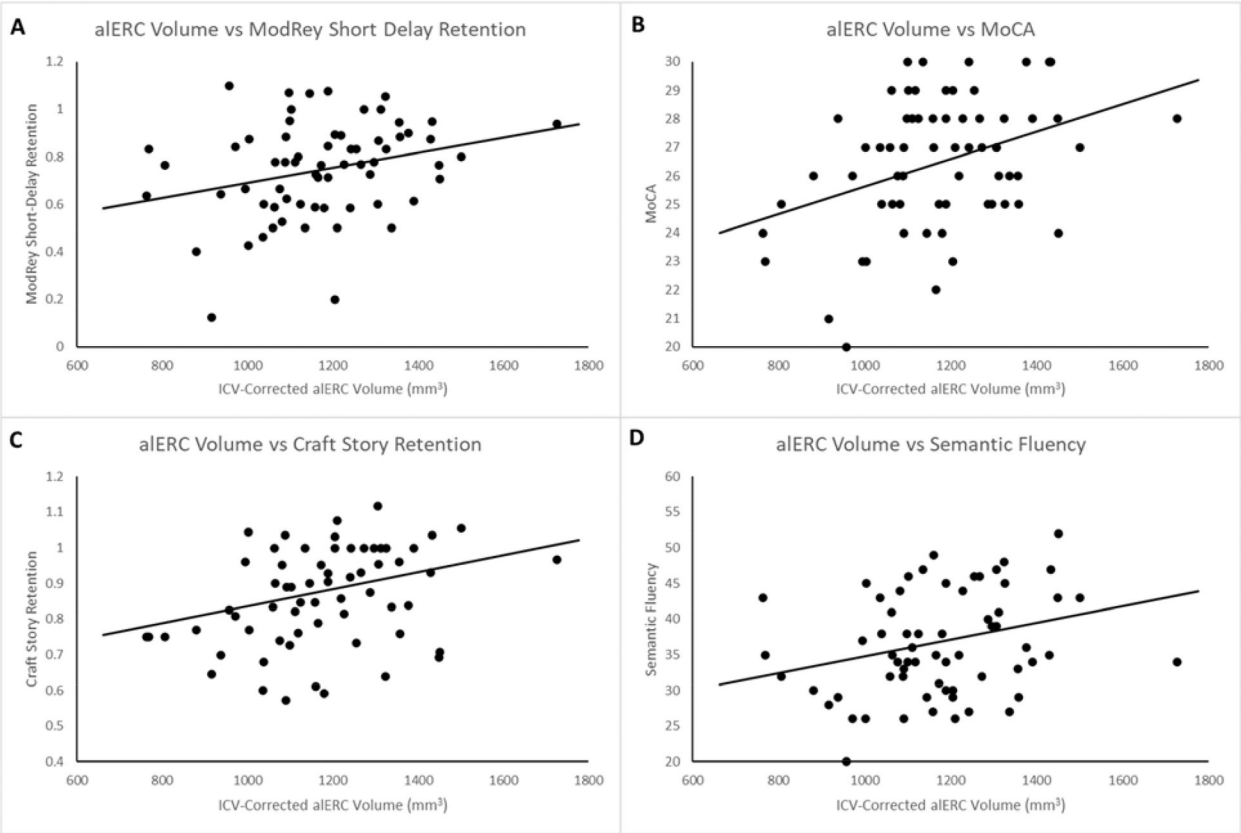

Figure 3:
Correlation of alERC volume with a) ModRey short-delay retention, b) MoCA, c) Craft story retention, and d) semantic fluency

Table 1:

Participant Demographics

	Mean	Standard Deviation	Range
Age	70.5	7.1	56–93
Education (Years)	16.6	2.0	12–20
Gender	32 Women / 33 Men		
Race/Ethnicity	50 Non-Hispanic White (76.9%) 11 African American (16.9%) 2 Asians/Pacific Islander (3.1%) 2 Hispanic White (3.1%)		
MoCA	26.5	2.3	20–30
Craft Story Immediate	22.6	6.1	7–33
Craft Story Delayed	19.8	6.0	4–33
Craft Story Retention	0.878	0.164	0.571–1.500
Digit Span Forwards	7.0	1.3	4–9
Digit Span Backwards	5.3	1.5	2–8
Trails A	35.0s	19.1s	15s-148s
Trails B	89.1s	51.7s	33s-300s
MINT	30.1	1.9	22–32
Semantic Fluency	36.8	8.1	20–66
Verbal Fluency	30.7	7.4	17–46
Benson Figure Copy	16.1	1.0	14–17
Benson Figure Delayed	11.9	2.8	4–17

Table 2:

Intra-rater reliability for ERC subfield segmentations

Subregion	Intra-rater:Dice		Intra-rater ICC	
	Left	Right	Left	Right
alERC	0.82	0.81	0.86	0.93
pmERC	0.75	0.77	0.84	0.93

Table 3 –

alERC/pmERC volumes as predictors in multiple regression models for additional ModRey outcome variables. Each row represents an individual multiple regression model, with the specified ModRey outcome measure as the dependent variable, and alERC volume, pmERC volume, age, years of education, gender, and race/ethnicity as predictors. $p < 0.05$ indicated in bold

	alERC				pmERC			
	β	**95% CI**	**t**	**p**	**β**	**95% CI**	**t**	**p**
Total Learning	0.276	[0.032, 0.520]	2.268	**0.027**	0.144	[−0.129, 0.416]	1.055	0.296
Total Perseverations	0.086	[−0.157, 0.330]	0.708	0.482	−0.045	[−0.317, 0.227]	−0.329	0.743
Total Intrusions	0.020	[−0.237, 0.278]	0.159	0.874	−0.288	[−0.576, −0.001]	−2.006	**0.049**
Short-Delay Accuracy	0.341	[0.099, 0.583]	2.818	**0.007**	0.092	[−0.179, 0.363]	0.680	0.499
Long-Delay Accuracy	0.195	[−0.054, 0.444]	1.567	0.123	0.119	[−0.159, 0.397]	0.856	0.396
Long-Delay Retention	0.046	[−0.211, 0.304]	0.360	0.720	0.085	[−0.203, 0.373]	0.590	0.557
Recognition (Hits)	0.006	−0.257, 0.269]	0.045	0.964	0.122	[−0.172, 0.416]	0.828	0.411
Recognition (False Positives)	−0.259	[−0.510, −0.008]	−2.064	**0.044**	−0.071	[−0.352, 0.209]	−0.510	0.612
Source Memory	0.159	[−0.103, 0.421]	1.215	0.229	0.122	[−0.171, 0.415]	0.835	0.407

Table 4 –

Average volumes of entorhinal cortex subfields, hippocampal subfields, and MTL cortices in participant groups divided by MoCA threshold score, and t-tests comparing volume differences between those groups, df = 63, $p < 0.05$ indicated in bold

Region	MoCA ≥ 26 (N=43, M M±SD mm^3)	MoCA < 26 (N=22, M±SD mm^3)	95% CI of difference	t	p
pmERC	345.66 ± 65.34	337.61 ± 68.56	[−26.75, 42.85]	0.454	0.651
alERC	1211.14 ± 164.56	1102.86 ± 187.94	[17.82, 198.75]	2.254	**0.028**
CA1	1310.35 ± 189.26	1271.32 ± 220.41	[−65.83, 143.88]	0.705	0.484
CA2	60.90 ± 23.37	59.94 ± 21.83	[−11.03, 12.93]	0.162	0.872
DG	693.38 ± 158.88	694.39 ± 148.21	[−82.41, 80.40]	0.025	0.980
CA3	244.76 ± 84.30	230.41 ± 60.70	[−26.11, 54.81]	0.786	0.435
Subiculum	2156.78 ± 276.51	2148.36 ± 240.61	[−130.43, 147.27]	0.127	0.900
BA 35	1065.91 ± 194.73	1071.42 ± 253.12	[−118.62, 107.62]	0.089	0.929
BA 36	4410.12 ± 742.56	4349.05 ± 831.62	[−344.05, 466.18]	0.289	0.773
PHC	735.20 ± 161.92	760.07 ± 173.78	[−111.81, 62.07]	0.556	0.580

Table 5 –

Pearson's correlations between the volumes of all segmented regions. df = 65 for all comparisons. $p < 0.05$ indicated in bold, $p < 0.10$ indicated in italics

		alERC	pmERC	CA1	CA2	DG	CA3	Sub.	BA35	BA36	PHC
alERC	r	1	0.251	0.093	0.361	0.312	0.235	0.044	.331	0.061	0.216
	p		**0.044**	0.463	**0.003**	**0.011**	*0.059*	0.730	**0.007**	0.627	*0.084*
pmERC	r	0.251	1	0.376	0.054	0.106	0.369	0.445	0.299	0.042	0.276
	p	**0.044**		**0.002**	0.669	0.399	**0.002**	**0.000**	**0.016**	0.741	**0.026**
CA1	r	0.093	0.376	1	0.409	0.646	0.391	0.516	0.348	0.230	0.351
	p	0.463	**0.002**		**0.001**	**0.000**	**0.001**	**0.000**	**0.004**	*0.066*	**0.004**
CA2	r	.0361	0.054	0.409	1	0.736	0.203	0.122	0.388	0.443	0.402
	p	**0.003**	0.669	**0.001**		**0.000**	0.104	0.331	**0.001**	**0.000**	**0.001**
DG	r	0.312	0.106	0.646	0.736	1	0.173	0.215	0.368	0.321	0.401
	p	**0.011**	0.399	**0.000**	**0.000**		0.167	*0.085*	**0.003**	**0.009**	**0.001**
CA3	r	0.235	0.369	0.391	0.203	0.173	1	0.328	0.530	0.194	0.344
	p	*0.059*	**0.002**	**0.001**	0.104	0.167		**0.008**	**0.000**	0.121	**0.005**
Sub.	r	0.044	0.445	0.516	0.122	0.215	.328	1	0.487	0.323	0.185
	p	0.730	**0.000**	**0.000**	0.331	*0.085*	**0.008**		**0.000**	**0.009**	0.140
BA35	r	0.331	0.299	0.348	0.388	0.368	0.530	.487	1	0.591	0.411
	p	**0.007**	**0.016**	**0.004**	**0.001**	**0.003**	**0.000**	**0.000**		**0.000**	**0.001**
BA36	r	0.061	0.042	0.230	0.443	0.321	0.194	0.323	0.591	1	0.156
	p	0.627	0.741	*0.066*	**0.000**	**0.009**	0.121	**0.009**	**0.000**		0.216
PHC	r	0.216	0.276	0.351	0.402	0.401	0.344	0.185	0.411	0.156	1
	p	*0.084*	**0.026**	**0.004**	**0.001**	**0.001**	**0.005**	0.140	**0.001**	0.216	

Table 6 –

alERC & pmERC volumes as predictors in multiple regression models for performance on NACC battery tasks (with age, gender, race/ethnicity and years of education as covariates). Each row represents an individual multiple regression model, with the specified NACC-UDS3 outcome measure as the dependent variable, and alERC volume, pmERC volume, age, years of education, gender, and race/ethnicity as predictors. $p < 0.05$ indicated in bold, $p < 0.10$ indicated in italics

	alERC				pmERC			
	β	**95% CI**	**t**	**p**	**β**	**95% CI**	**t**	**p**
Craft Story Immediate	0.148	[−0.100. 0.396]	1.194	0.237	0.369	[0.091, 0.646]	2.662	**0.010**
Craft Story Delayed	0.274	[0.028, 0.519]	2.230	**0.030**	0.296	[0.021, 0.571]	2.161	**0.035**
Craft Story Retention	0.246	[−0.013, 0.504]	1.899	*0.062*	−0.009	[−0.292, 0.274]	−0.063	0.950
Digit Span Forwards	−0.009	[−0.259, 0.241]	−0.071	0.943	−0.111	[−0.389, 0.166]	−0.802	0.426
Digit Span Backwards	−0.058	[−0.303, 0.187]	−0.477	0.635	0.116	[−0.157, 0.390]	0.852	0.398
Trails A	−0.178	[−0.428, 0.073]	−1.421	0.161	0.225	[−0.055, 0.504]	1.608	0.113
Trails B	−0.065	[−0.311, 0.182]	−0.525	0.601	−0.066	[−0.342, 0.209]	−0.481	0.632
Trails B / Trails A	0.041	[−0.211, 0.292]	0.324	0.747	−0.246	[−0.527, 0.035]	−1.756	*0.084*
MINT	0.123	[−0.128, 0.374]	0.980	0.331	0.007	[−0.274, 0.289]	0.051	0.959
Semantic Fluency	0.277	[0.023, 0.530]	2.187	**0.033**	−0.062	[−0.346, 0.221]	−0.441	0.661
Verbal Fluency	0.084	[−0.173, 0.342]	0.657	0.514	0.144	[−0.143, 0.431]	1.003	0.320
Benson Figure Copy	0.323	[0.086, 0.561]	2.721	**0.009**	0.257	[−0.009, 0.523]	1.935	*0.058*
Benson Figure Delayed	0.152	[−0.109, 0.413]	1.167	0.248	−0.028	[−0.320, 0.264]	−0.193	0.847

Table 7 –

Pearson's correlations of CSF biomarker levels with alERC/pmERC volumes, controlling for age, years of education, gender, and race/ethnicity, df = 53. $p < 0.05$ indicated in bold, $p < 0.10$ indicated in italics

		Aβ42	Phospho-Tau	Total Tau	Phospho-Tau / Aβ42	Total Tau / Aβ42
alERC	r	0.055	−0.082	−0.145	−0.119	−0.171
	p	0.688	0.553	0.292	0.387	0.213
	95% CI	[−0.218, 0.320]	[−0.344, 0.192]	[−0.399, 0.130]	[−0.377, 0.156]	[−0.421, 0.104]
pmERC	r	0.001	−0.105	−0.099	−0.003	−0.039
	P	0.996	0.447	0.473	0.984	0.777
	95% CI	[−0.269, 0.271]	[−0.364, 0.170]	[−0.359, 0.176]	[−0.273, 0.267]	[−0.306, 0.233]
CA1	r	0.201	0.120	0.162	−0.056	−0.039
	p	0.141	0.385	0.237	0.686	0.778
	95% CI	[−0.073, 0.447]	[−0.155, 0.378]	[−0.113, 0.414]	[−0.321, 0.217]	[−0.306, 0.233]
CA2	r	0.186	0.216	0.107	−0.026	−0.098
	p	0.174	0.114	0.435	0.853	0.479
	95% CI	[−0.088, 0.434]	[−0.057, 0.459]	[−0.168, 0.366]	[−0.294, 0.246]	[−0.358, 0.176]
DG	r	0.268	0.181	0.226	−0.202	−0.167
	p	**0.048**	0.185	*0.097*	0.140	0.224
	95% CI	[0.000, 0.502]	[−0.093, 0.430]	[−0.047, 0.467]	[−0.447, 0.072]	[−0.418, 0.108]
CA3	r	0.055	0.128	0.167	0.211	0.185
	p	0.688	0.351	0.223	0.122	0.177
	95% CI	[−0.218, 0.320]	[−0.147, 0.384]	[−0.108, 0.418]	[−0.062, 0.455]	[−0.089, 0.433]
Sub.	r	−0.144	0.076	−0.125	0.229	0.064
	p	0.295	0.582	0.362	*0.092*	0.641
	95% CI	[−0.398, 0.131]	[−0.198, 0.339]	[−0.382, 0.150]	[−0.044, 0.470]	[−0.209, 0.328]
BA35	r	0.186	0.128	0.132	0.009	−0.053
	p	0.174	0.351	0.336	0.945	0.699
	95% CI	[−0.088, 0.434]	[−0.147, 0.384]	[−0.143, 0.388]	[−0.261, 0.278]	[−0.318, 0.220]
BA36	r	0.175	0.191	0.028	−0.060	−0.178
	p	0.201	0.163	0.840	0.666	0.192
	95% CI	[−0.100, 0.425]	[−0.083, 0.438]	[−0.244, 0.296]	[−0.325, 0.213]	[−0.427, 0.096]
PHC	r	−0.068	−0.005	−0.066	−0.054	−0.085
	p	0.622	0.970	0.632	0.696	0.537
	95% CI	[−0.332, 0.206]	[−0.274, 0.265]	[−0.330, 0.208]	[−0.319, 0.219]	[−0.347, 0.189]

Table 8 –

The effect of the alERC predictor in multiple regression models predicting ModRey short-delay retention in biomarker-negative only subgroups, with pmERC, age, education, gender and race/ethnicity as additional predictors. $p < 0.05$ indicated in bold, $p < 0.10$ indicated in italics

Group	N	β	sr	t	P
All participants	65	0.258	0.249	2.009	**0.049**
Aβ-42 negative	51	0.313	0.303	2.178	**0.035**
P-tau negative	52	0.244	0.235	1.685	*0.099*
T-tau negative	52	0.290	0.276	2.040	**0.047**
P-Tau/Amyloid < 0.1	54	0.304	0.293	2.194	**0.033**
Negative for all 3 biomarkers	41	0.354	0.350	2.177	**0.037**