



forms of context memory may display distinct age-related trajectories, as evidence suggests age may have a greater impact on temporal, compared to spatial context memory performance (Fabiani and Friedman, 1997; Kwon et al., 2016; Parkin et al., 1995; Rajah et al., 2003; Davis et al., 2008; Grady et al., 1999). Importantly, PASA has been observed even after task difficulty was matched between younger and older adults, suggesting that in some instances, compensatory activation may be unrelated to difficulty and instead specific to aging (Festini et al., 2018).

As it is suspected that these patterns of functional overactivation may be compensating for age-related atrophy specific to the MTL (Reuter-Lorenz and Cappell, 2008), it is critical to investigate how age-related differences in the structure of MTL regions relate to these whole-brain patterns of activation consistently observed in healthy aging (Beason-Held et al., 2021; Daseelaar et al., 2015; Nyberg et al., 2010; Salami et al., 2012; Ta et al., 2012; Valenzuela et al., 2015).

Taken together, there are indications to suggest that episodic memory performance and structural atrophy of the MTL may be tightly coupled across the healthy adult lifespan. However, it remains unclear if age-related differences in MTL volumes mediate age-related differences in context memory performance. Furthermore, whereas volumetric trajectories of the aHFC and pHFC, as well as the entorhinal cortex (ERC) have been well described across the lifespan, less is known about the relationship between age and volume of MTL structures such as the perirhinal (PRC), and parahippocampal cortices (PHC) (Gorbach et al., 2017; Langnes et al., 2020; Raz et al., 2004; Veldman et al., 2020; Wisse et al., 2021). Additionally, although influential accounts of neurocognitive aging propose that functional compensation in mid and late life arises due to structural decline in MTL regions, this remains an open question. While previous investigations have taken age-related functional declines as their starting point in addressing this question (Beason-Held et al., 2021; Brastie et al., 2009; Daseelaar et al., 2012; Steffener et al., 2010), in the current study we first employed structural analyses to identify the MTL regions relevant to aging and memory performance, and then explored patterns of functional activation related to the relevant structures (Brassen et al., 2009; Mallett and Rajah, 2011; Valenzuela et al., 2015). Further, whereas previous studies tend to focus on comparisons between younger and older adults, thereby excluding a large portion of the adult lifespan, we here examined a full lifespan (Persson et al., 2010; Rosen et al., 2006; Rosen et al., 2005; Salami et al., 2012; Raz et al., 2004).

Importantly, while the MTL has been found to be central in supporting spatial context memory (Burgess et al., 2001; Ekstrom et al., 2011; Howard et al., 2013; Miller et al., 2013; Nadel et al., 2013; Rajah et al., 2016; Sheldon and Levine, 2015; Shayle et al., 2020; Spiers and Maguire, 2007), its less clear whether similar regions within this system support temporal context memory (Downes, 2002; Duarte et al., 2010; Ekstrom et al., 2011; Howard, 2017; Hsieh et al., 2014; Ranganath, 2010; Rajah et al., 2010). For example, while Ekstrom et al. (2011) observed hippocampal activation during both spatial and temporal context retrieval, activation within the MTL cortex was specific to the spatial task.

Importantly, recent longitudinal studies have revealed that age-related atrophy of the MTL mirrors age-related declines in episodic memory (Gorbach et al., 2017; Langnes et al., 2020; Raz et al., 2004). Of note, Langnes et al. observed distinct age-related quadratic trajectories for each of the hippocampal subregions, such that while volume of the pMTC tended to display age-related atrophy in the fourth decade of life, volume of the aHFC began to decline around the sixth decade of life. Similarly, Gorbach et al. observed linear age-related atrophy of overall hippocampal volume, beginning just after the fifth decade, and found that gray matter decreases in both the hippocampus and parahippocampal gyrus were related to age-related decreases in episodic memory performance, but not declines in processing speed, fluid IQ or word fluency, indicating the specific contribution of these structures to episodic memory. Together, these findings indicate distinct age-related trajectories for MTL regions, following both linear and quadratic trends, which may be linked to age-related deficits in context memory. Importantly, growing evidence suggests that distinct MTL structures not only show distinct age-related trajectories, but are also differentially related to memory for spatial and temporal contextual information (Davachi et al., 2003; Howard et al., 2011; Jenkins and Ranganath, 2010; Ranganath, 2010; Rajah, 2010).

Finally, network models of neurocognitive aging propose that structural declines in the MTL with older age may alter memory-related activation across the cortex (Cabeza, 2002; Cabeza et al., 2018; Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Cappell, 2008; Stern, 2002). In particular, the Seafloor Theory of Aging and Cognition (STAC; Park and Reuter-Lorenz, 2009) and the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH; Reuter-Lorenz and Cappell, 2008; Reuter-Lorenz and Lustig, 2005) propose that older adults rely on greater activation of lateral prefrontal and parietal regions to compensate for structural deterioration during lower task demands, but at higher levels of task demands this functional compensatory response is limited. Similarly, the posterior-to-anterior shift in aging (PASA) model is based on observations that older adults display increased ac-

tivation of lateral prefrontal regions to support performance, and adds that this recruitment of anterior frontal regions is negatively correlated with posterior occipital activation (Daseelaar et al., 2003; Davis et al., 2008; Grady et al., 1999). Importantly, PASA has been observed even after task difficulty was matched between younger and older adults, suggesting that in some instances, compensatory activation may be unrelated to difficulty and instead specific to aging (Festini et al., 2018).

As it is suspected that these patterns of functional overactivation may be compensating for age-related atrophy specific to the MTL (Reuter-Lorenz and Cappell, 2008), it is critical to investigate how age-related differences in the structure of MTL regions relate to these whole-brain patterns of activation consistently observed in healthy aging (Beason-Held et al., 2021; Daseelaar et al., 2015; Nyberg et al., 2010; Salami et al., 2012; Ta et al., 2012; Valenzuela et al., 2015).

Taken together, there are indications to suggest that episodic memory performance and structural atrophy of the MTL may be tightly coupled across the healthy adult lifespan. However, it remains unclear if age-related differences in MTL volumes mediate age-related differences in context memory performance. Furthermore, whereas volumetric trajectories of the aHFC and pHFC, as well as the entorhinal cortex (ERC) have been well described across the lifespan, less is known about the relationship between age and volume of MTL structures such as the perirhinal (PRC), and parahippocampal cortices (PHC) (Gorbach et al., 2017; Langnes et al., 2020; Raz et al., 2004; Veldman et al., 2020; Wisse et al., 2021). Additionally, although influential accounts of neurocognitive aging propose that functional compensation in mid and late life arises due to structural decline in MTL regions, this remains an open question. While previous investigations have taken age-related functional declines as their starting point in addressing this question (Beason-Held et al., 2021; Brastie et al., 2009; Daseelaar et al., 2012; Steffener et al., 2010), in the current study we first employed structural analyses to identify the MTL regions relevant to aging and memory performance, and then explored patterns of functional activation related to the relevant structures (Brassen et al., 2009; Mallett and Rajah, 2011; Valenzuela et al., 2015). Further, whereas previous studies tend to focus on comparisons between younger and older adults, thereby excluding a large portion of the adult lifespan, we here examined a full lifespan (Persson et al., 2010; Rosen et al., 2006; Rosen et al., 2005; Salami et al., 2012; Raz et al., 2004).

In the current study, we first examined the relationship between age and the volume of MTL regions of interest (ROIs). We hypothesized that volume of MTL structures would display age-related differences similar to those observed by Langnes et al. (2020), such that that volume of all ROIs would exhibit negative relationships with age. We then assessed if volume of MTL ROIs mediated the association between age and spatial and temporal context memory performance. We further investigated how whole-brain patterns of functional activity during successful encoding and retrieval were influenced by individual differences in the volume of MTL ROIs. According to the compensation hypotheses of the PASA, STAC, and CRUNCH models, we predicted that older age and smaller MTL volumes would be related to greater activation of lateral prefrontal and parietal, as well as ventral visual regions during correct context memory encoding and retrieval. That is, while older adults with smaller MTL volumes may exhibit worse performance overall, when they correctly encode or retrieve contextual information, we expected to observe greater activation across these cortical regions.

## 2. Methods

### 2.1. Participants

Participants in this study are part of the Montreal Memory and Aging Lifespan cohort, a cross-sectional adult lifespan sample of 172 individuals tested in Dr. Rajah's laboratory (see Ankudowich et al., 2016 for more details). All participants were right-handed, confirmed using the Edinburgh Inventory for Handedness, and met appropriate inclusion cri-

## Volume of the posterior hippocampus mediates age-related differences in spatial context memory and is correlated with increased activity in lateral frontal, parietal and occipital regions in healthy aging

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### ARTICLE INFO

#### ABSTRACT

Healthy aging is associated with episodic memory decline, particularly in the ability to encode and retrieve object-context associations (context memory). Neuropsychological and neuroimaging studies have highlighted the importance of the medial temporal lobes (MTL) in supporting episodic memory across the lifespan. However, given the functional heterogeneity of the MTL, volumetric declines in distinct regions may impact performance on specific episodic memory tasks, and affect the function of the large-scale neurocomputing networks supporting episodic memory encoding and retrieval. In the current study, we investigated how MTL structure may mediate age-related differences in performance on spatial and temporal context memory tasks. In a sample of 125 healthy adults aged 19–76 years old, Standard T1-weighted MRIs were segmented into the perirhinal, entorhinal and parahippocampal cortices, as well as the anterior and posterior hippocampal subregions. We observed negative linear and quadratic associations between age and volume of the parahippocampal cortex, and anterior and posterior hippocampal subregions. We also found that volume of the posterior hippocampus fully mediated the association between age and spatial, but not temporal context memory performance. Further, we employed a multivariate behavior partial-least-squares analysis to assess how age and regional MTL volumes correlated with brain activity during the encoding and retrieval of spatial context memories. We found that greater activity within lateral prefrontal, parietal, and occipital regions, as well as within the anterior MTL was related to older age and smaller volume of the posterior hippocampus. Our results highlight the heterogeneity of MTL contributions to episodic memory across the lifespan and provide support for the posterior-anterior shift in aging, and scissifolding theory of aging and cognition.

Shohodl and Corwin, 1988; Yonelinas, 1999). However, greater age-related declines in context memory – the ability to encode and retrieve spatial and temporal details about past events – begin to emerge at midlife, and persist into old age (Cabeza et al., 2000; Cansino, 2009).

Across studies, context memory thus broadly refers to the recall of spatial or temporal features associated with studied items. However, these two types of context memory are phenomenologically different, such that spatial context memory refers to the recall of an item's spatial relationship with other items or features of an image, and temporal context memory refers to the recall of information related to the order in which the items appeared (Howard, 2017). Importantly, these two distinct

Healthy aging is associated with episodic memory decline: a reduced ability to encode, store and retrieve information about past experiences in rich contextual detail (Tulving, 1972). This decline is apparent at both the cognitive (Carstlio, 2009; Park and Reuter-Lorenz, 2009; Spencer and Rajah, 1995; Verhaeghen and Salthouse, 1998) and neural levels (Gorbach et al., 2017; Langnes et al., 2020; Malykhin et al., 2008; 2017; Rajah et al., 2010). At the cognitive level, recognition memory – the ability to recognize previously seen stimuli – is relatively preserved in mid and late life (Park and Reuter-Lorenz, 2009;

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**Table 1**  
Demographics, task performance and MTL volumes for the full sample.

	N = 125	Mean ± SD	Intra-rater reliability	Intra-rater reliability
Age	47.90 ± 14.86	-	-	-
Education	15.69 ± 2.12	-	-	-
Spatial easy	0.95 ± 0.10	-	-	-
Spatial hard	0.81 ± 0.12	-	-	-
Temporal easy	0.70 ± 0.13	-	-	-
Temporal hard	0.60 ± 0.11	-	-	-
PRC Volume	4,591.94 ± 1,226.00	0.70	0.69	0.68
ERC Volume	2,120.57 ± 393.89	0.65	0.85	0.82
anHc Volume	3,098.24 ± 490.24	0.79	0.78	0.75
postHc Volume	2,223.12 ± 356.03	0.79	0.78	0.75
PHC Volume	2,782.30 ± 474.15	0.79	0.75	0.75

teria on neuropsychological assessment (Mini-International Neuropsychiatric Interview [MINI], inclusion cut-off = < 2; Mini Mental State Examination [MMSE], exclusion cut-off < 27; the Beck Depression Inventory [BDI], exclusion cut-off < 15). All individuals gave informed consent to participate and were paid, and the ethics board of the Faculty of Medicine at McGill University approved the study protocol. Quality control of structural MRIs, according to the CoBaA laboratory protocol ([https://github.com/CoBaLab/documentation/wiki/Motion-Quality-Control-\(QC\)-Manual](https://github.com/CoBaLab/documentation/wiki/Motion-Quality-Control-(QC)-Manual)) resulted in the exclusion of data from 37 participants (19 young, 4 middle age and 14 older adults; see Bedford, 2017; Bedford et al., 2019; Snytte et al., 2020) for more information). Quality control of fMRI scans resulted in the exclusion of data from 7 participants due to motion and a corrupted data file. Outlier analyses resulted in the exclusion of data from three participants based on Cook's distance and observations of quantile-quantile plots. The final sample included 125 participants, with 31 young adults (range: 19–35 years, mean age 26.19 years, ± 3.54 SD; 19 females, 64 middle age adults (range: 40–58 years mean age 49.86 years, ± 5.30 SD; 50 females), and 30 older adults (range: 61–76 years, mean age 66.13 years, ± 3.73 SD; 21 females). Descriptive data are shown in Table 1.

### 2.3. MRI methods

Structural and functional magnetic resonance images were acquired at the Douglas Brain Imaging Center, using a 3T Siemens Trio scanner. We acquired TI-weighted anatomical images using a 3D gradient echo MPRAGE sequence (TR = 2300 msec, TE = 2.98 msec, flip angle = 9°, 176.1 mm sagittal slices, 1 × 1 × 1 mm voxels, FOV = 256) and these images were used for medial temporal lobe segmentation. During the spatial and context memory tasks, we acquired BOLD images using a single-shot T2\*-weighted gradient echo-planar imaging (EPI) pulse sequence (TR = 2000 msec, TE = 30 msec, FOV = 256, 4 × 4 × 4 mm voxels). Images for the tasks were back-projected onto a screen in the scanner, which participants viewed via a mirror mounted on the head coil. A fibre-optic response box was used to collect behavioral responses.

### 2.3.1. Structural MRI segmentation

We used a modified version of the Olsen-Anatal-Palombo (OAP) protocol to manually segment the PRC, ERC, anHc, postHc and PHC on coronal slices of pre-processed T1 images (Olsen et al., 2013; Fig. 1). While this protocol is typically used to segment hippocampal subfields, we employed several modifications, described below to account for differences in slice thickness of the acquired images (also applied by Snytte et al., 2020). Specifically, we used caudal boundaries of the PRC and ERC defined by Insausti et al. (1998) and Pruessner et al. (2002), where the posterior boundary of ERC occurs prior to the posterior boundary of the PRC. All other boundaries were segmented according to the OAP protocol. Hippocampal subfields were not separately defined, but the anHc and postHc were defined based on the location of the uncus apex (Olsen et al., 2013). Past work has shown that the position of this landmark may fall increasingly anterior with age, which might result in biased estimates of the volume of the anHc and postHc (Poppenk, 2020). To address this potential bias, we first calculated the distances between the disappearance of the uncus apex and both the first slice of the anHc, and the last slice of the postHc. We then calculated the difference between these two distances to obtain a measure of the relative position of the uncus apex within the hippocampus.

Uncal position = (First slice of the anHc – disappearance of uncus apex) / (disappearance of uncus apex – final slice of the postHc).

Thus, a lower difference score would indicate that the position of the uncus was more anterior within the hippocampus, whereas a larger score would indicate a more posterior positioning of the uncus. We then



**Fig. 1.** Medial temporal lobe segmentation shown on sagittal slice of T1 anatomical image. Perirhinal cortex (PRC) shown in pink, entorhinal cortex (ERC) shown in brown, parahippocampal cortex (PHC) shown in yellow, anterior hippocampus (antHc) shown in blue and posterior hippocampus (postHc) shown in brown.

### 2.4. Statistical analyses

#### 2.4.1. Behavioral analyses – associations between age and memory Performance

We computed generalized additive models (GAMs) to assess associations between age and memory performance, across the easy and hard spatial and temporal context memory tasks. We computed four models, with accuracy as the dependent variable, and age as the independent variable. We made the selection to use GAMs to assess these relationships, as simple linear regressions may not be ideally suited to map the potential non-linear trends we might expect. The "gam" function from the "mgcv" library (version 1.80) in R (version 4.0.2) was used to fit each model (Wood, 2017). GAMs utilize a smoothing term on the independent variable, which attempts to minimize the residual sums of squares while also penalizing more "wiggly" fits, to prevent overfitting. We report the variance explained by each model as  $R^2$  as well as the effective degrees of freedom (EDF), which represents the degree of non-linearity of the curve (Wood, 2006).

#### 2.4.2. Associations between volume and age

To assess the relationship between age and volume of MTL ROIs, we computed GAMs for each ROI; using volume as the dependent variable and age as the independent variable. This type of analysis is recommended for assessing associations between brain structure and age, as it is robust to factors such as the age-range of the sample, which can cause problems when utilizing polynomial regressions (Fiebelkorn et al., 2010). As ICV, biological sex and years of education may be potentially confounding variables, we residualized the volume variables by these terms.

#### 2.4.3. Mediation analysis

To investigate if age-related differences in the volumes of MTL ROIs mediated age-related differences in context memory performance we computed four parallel mediation models. We conducted these mediation analyses within a structural equation modelling framework to test for direct and indirect effects within a single model. While we employed generalized additive models to assess the relationships between age and memory performance, and age and volume due to issues that polynomial regressions present for assessing these types of relationships, typical mediation analyses do assume linear relationships across each path. To account for the fact that associations between age and volume, and age and performance may be best described as quadratic (Langnes et al., 2020; Raz et al., 2004), we also computed the mediation analyses with the quadratic age term included (Supplementary Fig. 1A, B). Biological sex and years of education were regressed out from all variables included in the model, and ICV was regressed out of each ROI. Our mediation models were specified as follows: age was set as the independent variable, the MTL ROIs were included as parallel mediators and memory performance from either the spatial easy, spatial hard, tempo-

### 2.3.2. Functional MRI processing

Preprocessing for functional imaging data is described in detail by Ankudowich et al. (2017). Briefly, the first 10 s of scanning prior to task onset were discarded to ensure all tissue had reached steady state magnetization. The origin of each image was re-oriented to the anterior commissure of the T1 anatomical image, for each participant. All functional images were realigned to the first acquired image and corrected for motion artifacts with a six-parameter spatial transformation. Finally, images were spatially normalized to the MNI EPI template in FSPM ( $4 \times 4 \times 4$  mm voxel resolution) and spatially smoothed (8 mm FWHM isotropic Gaussian kernel).

ral easy, or temporal hard tasks, was set as the outcome variable. Mediation models were computed using the *lavaan* package in R, using the "twls" likelihood estimation to produce coefficients matching those typically produced by ordinary least squares regression (Version 0.6; Rossouw, 2012). Due to differences in range and units, all variables were standardised before being entered into the mediation model, and covariates between all mediators were included in each model. To correct for multiple comparisons, given that we computed four mediation models, we applied a Bonferroni correction to our confidence intervals, and thus report the beta estimates for each path and their percentile bootstrapped 99% confidence intervals (1000 bootstraps).

#### 3.4.4. Structure/function interactions

To investigate the association between MTL structure and task-related functional activity during correct encoding and retrieval we employed a multivariate behavior partial least squares analysis (B-PLS). This type of analysis was selected to investigate the hypothesis that greater lateral frontal and parietal activations would be related to both greater age, and reduced MTL volumes, as it provides the ability to observe spatially and temporally distributed patterns of activation that are related to our measures of interest. Computing this analysis by including both age and the ROIs which emerged as significant predictors from our previous analyses (residualized for LCV, gender and education), allowed us to examine this region-specific hypothesis, as well as explore how activation across the entire brain was related to these two vectors. fMRI data from correct trials were collected into a matrix and coded for phase (encoding and retrieval) and difficulty (easy and hard). For each correct event, activity across 7 TRs was included following the event onset (2 s TR \* 7 TRs = 14 s of activity per event). Each column in the data matrix represents the averaged IFR for each voxel concatenated column-wise. We computed the B-PLS analysis to examine activity during conditions where we observed significant mediating effects of MTL volumes on age. Specifically, the fMRI data matrix for the PLIS consisted of 4 conditions: encoding Spatial Easy (eSE), encoding Spatial Hard (eSH), retrieval Spatial Easy (rSE), retrieval Spatial Hard (rSH). Each condition included fMRI data for correctly encoded (based on subsequent memory) and retrieved events. Event-related activity was baseline corrected to the event onset to control for low frequency signal drifts due to potential environmental or physiological noise. To create the brain-behavior correlation matrix, the coded fMRI data was then cross-correlated with our behavioral vectors of interest. Finally, to extract latent variables which maximized the covariance between our behavioral vectors of interest, and functional activation during correct encoding and retrieval trials, singular vector decomposition (SVD) was applied (Mentosh and Lobough, 2004). Each LV produced by the PLIS analysis includes a singular value reflecting the amount of cross-block covariance explained by the LV, as well as a correlation profile indicating how the behavioral vectors correlate with the identified patterns of brain activity, and finally a singular image containing a pattern of brain activity that is symmetrically related to the correlation profile. Whereas typical GLM analyses associate levels of activation uniquely with each predictor in the model, LVs extracted by the PLIS analysis include a singular image that maximally covaries with all behavioral vectors. Permutation tests were used to test the significance of each LV ( $p < 0.05$ , 1000 permutations), and the stability of each voxel's contribution to an LV was assessed using bootstrapping bootstrap ratio (BSR) =  $\pm 3.28$ ,  $p < 0.001$ , 500 iterations, minimum cluster size = 10 voxels). While all lags are included in the analysis, our results section focuses on peak time lags 2–5 (4–10 s post event onset), as in previous work these lags demonstrated the maximal task differences (Anikudowich et al., 2016; Subramanianpillai et al., 2013).

Peak voxel coordinates were converted from MNI space to Talairach space using the icbm2tal function (Lancaster et al., 2007) in GingerALE 2.3. (Eichhoff et al., 2009). Cluster reports were generated using Talairach Client 2.4.3 to determine additional attributes of the ROIs, such as their spatial extent and nearest Brodmann's area, and de-

pict the specific lags in which activation significantly mapped onto the correlation profiles (Lancaster et al., 1997, 2009).

### 3. Results

#### 3.1. Behavioral results – associations between age and memory performance

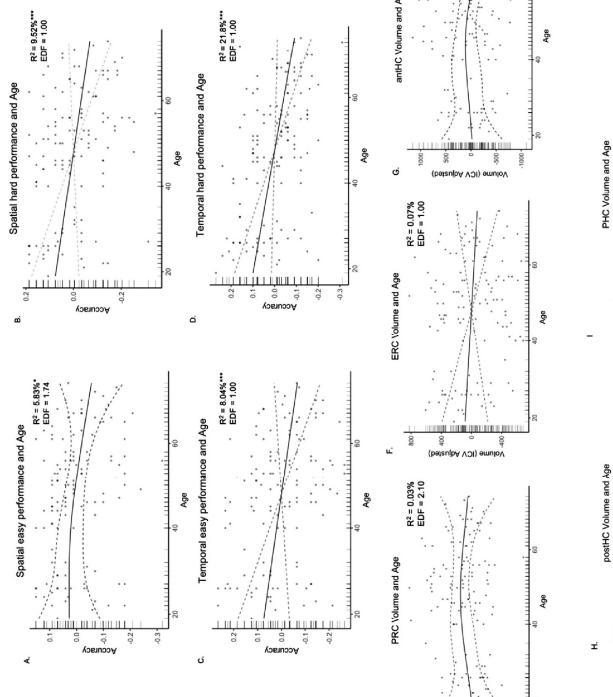
We computed four generalized additive models to assess the associations between age and memory performance on the easy and hard components of the spatial and temporal context memory tasks. We observed significant negative associations between age and performance on the spatial easy task ( $F = 3.85$ , EDF = 1.00,  $R^2 = 5.83\%$ ,  $p < 0.05$ ), spatial hard ( $F = 1.41$ , EDF = 1.00,  $R^2 = 8.04\%$ ,  $p < 0.001$ ), temporal easy ( $F = 11.84$ , EDF = 1.00,  $R^2 = 9.52\%$ ,  $p < 0.001$ ), temporal hard tasks ( $F = 35.49$ , EDF = 1.00,  $R^2 = 21.80\%$ ,  $p < 0.001$ ). While the association between age and performance on the spatial easy task was curvilinear (Fig. 2 A), the associations between age and performance on the other tasks were all best described as linear (Fig. 2, B–D).

#### 3.2. Associations between age and MTL structure

We computed five separate generalized additive models to assess the associations between age and MTL volumes. In investigating these relationships, we failed to observe significant associations between volume of the PRC and age ( $F = 1.95$ , EDF = 1.00,  $R^2 = 0.08\%$ ,  $p = 0.16$ ), and volume of the ERC and age ( $F = 1.95$ , EDF = 1.00,  $R^2 = 0.08\%$ ,  $p = 0.16$ ) (Fig. 2 E, F). However, we did observe negative associations between age and volume of the antHC ( $F = 3.94$ , EDF = 2.42,  $R^2 = 7.92\%$ ,  $p = 0.05$ ), postHC ( $F = 17.93$ , EDF = 1.89,  $R^2 = 24.80\%$ ,  $p < 0.001$ ), and PHC ( $F = 19.20$ , EDF = 1.00,  $R^2 = 12.8\%$ ,  $p < 0.001$ ) (Fig. 2 G–I). Specifically, while the associations between postHC and antHC volumes and age can be best described as approximating quadratic curves,

#### 3.3. Age-related deficits in spatial context memory are mediated by volume of the postHC

To test if age-related declines in the volume of MTL ROIs mediated age-related declines in context memory performance, we computed four parallel mediation models, with age as the independent variable, volume of MTL ROIs which displayed age-related differences as parallel mediators (antHC, postHC and PHC), and accuracy on either easy or hard trials (antHC, postHC and PHC), and accuracy on either easy or hard trials (antHC, postHC and PHC). As the dependent variable, we again observed a significant full mediation via the postHC. After controlling for the mediating effect of the MTL ROIs, we did not observe a significant unique association between age and memory performance ( $\beta_{age} = -0.23$ , 99% CI [-0.45, -0.03]). For the mediation model with memory performance on the spatial hard task as the dependent variable, we again observed a significant full mediation via the postHC. After controlling for the mediating effect of the MTL ROIs, we did not observe a significant unique association between age and memory performance ( $\beta_{age} = -0.16$ , 99% CI [-0.39, 0.13]). Examining the effect of age on the mediators, we observed significant negative associations between age and postHC ( $\beta_{age} = -0.48$ , 99% CI [-0.66, -0.31]) and PHC volumes ( $\beta_{age} = -0.38$ , 99% CI [-0.58, -0.17]). However, we did not observe significant associations between age and antHC volume ( $\beta_{age} = 0.16$ , 99% CI [-0.36, 0.07]). Examining the effect of mediators on memory performance we observed a significant unique association between postHC volumes and performance on the easy spatial memory task ( $\beta_{postHC} = 0.28$ , 99% CI [0.02, 0.57]). However, we did not observe significant associations between easy spatial memory task and antHC ( $\beta_{antHC} = 0.01$ , 99% CI [-0.25, 0.25]), or PHC volumes ( $\beta_{PHC} = 0.08$ , 99% CI [-0.24, 0.34]) volumes. Taking together the indirect effects, we found that volume of the postHC significantly mediated the association between age and memory performance



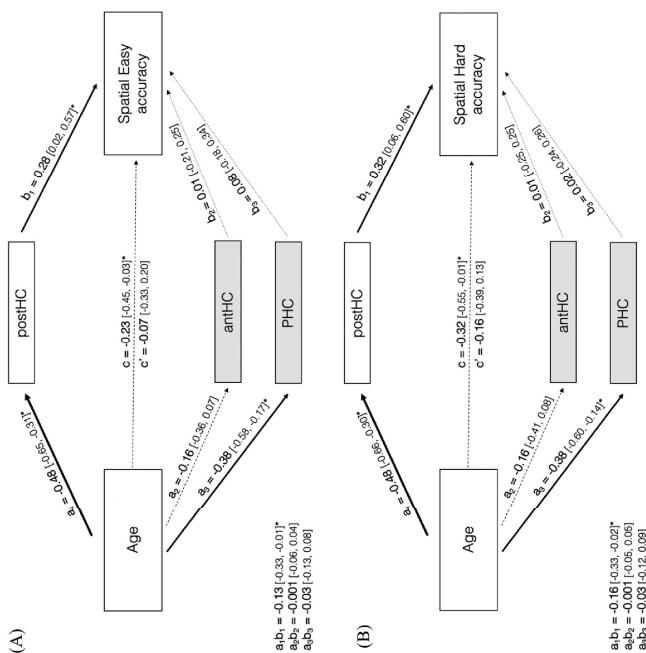
**Fig. 2.** Associations between age and context memory performance (A–D), and MTL volumes (E–I) across the adult lifespan. All relationships are examined with generalized additive models (GAMs). EDF= Effective degrees of freedom, \*\*\*=  $p < 0.001$ , \* =  $p < 0.05$

between age and memory performance ( $\beta_{age} = -0.16$ , 99% CI [-0.33, -0.02]). No other indirect effects played a significant mediating role. Additionally, the total effect of both age and the mediators on memory performance was also positive and significant ( $\beta_{total} = 0.32$ , 99% CI [0.55, -0.01]). These two mediation models are displayed in Fig. 3A and 3B, where all significant paths are indicated with solid lines where confidence intervals did not include zero.

For the mediation models with easy and hard temporal context memory performance as the dependent variable, we did not observe any significant indirect effects between MTL volumes and memory performance. However, we did observe a significant negative direct effect between age and easy temporal memory accuracy ( $\beta_{age} = -0.25$ , 99% CI [-0.45, -0.03]). These models are not discussed further, but are presented in Supplementary Fig. 1C, D.

#### 3.4. The effect of the position of the uncus apex on age, MTL volumes and memory performance

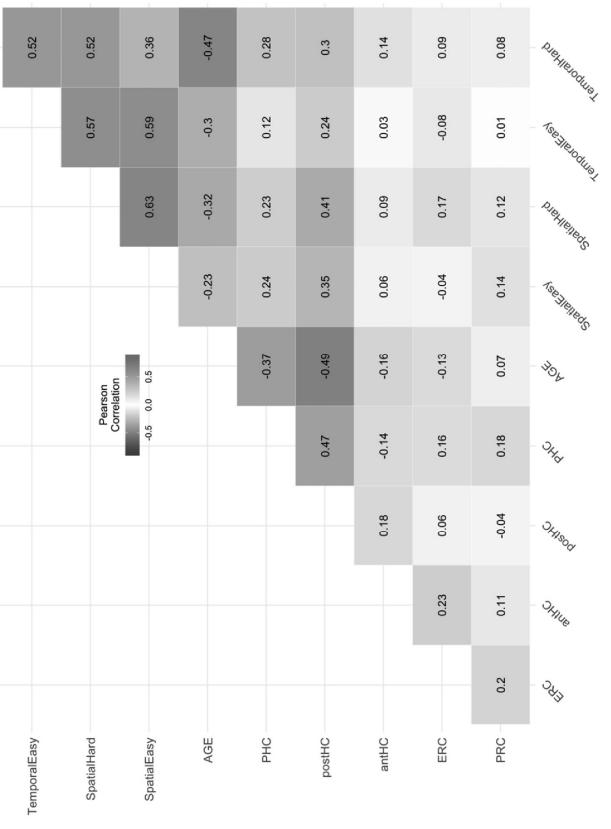
Given previous work suggesting that the uncus apex retracts with age, we computed a measure of the relative position of this structure (Poppenk, 2020). In the current sample we did not find a significant



**Fig. 3.** Parallel mediation model for (A) easy and (B) hard spatial context memory performance. This figure depicts full mediation of the age effect on spatial memory accuracy via the indirect  $ab_1$  path through the postHC. Dotted lines indicate non-significant effects and solid lines indicate significant effects (95% CI). Thickness of lines correspond to value of coefficients. PFC: Perirhinal cortex; ERC: Entorhinal cortex; antHC: anterior hippocampus; postHC: posterior hippocampus; PHC: Parahippocampal cortex.

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**Fig. 4.** Heatmap displaying Pearson correlations between our variables of interest.

correlation between the relative position of the uncus and age ( $r = -0.12$ ,  $p = 0.18$ ). Additionally, we found that the associations between spatial easy ( $r = -0.38$ ,  $p < 0.001$ ), and spatial hard accuracy ( $r = -0.46$ ,  $p < 0.001$ ) and postHC volume, respectively, were still significant after controlling for the position of the uncus apex. Finally, we found that age was significantly negatively correlated with postHC (linear:  $r = -0.53$ ,  $p < 0.001$ ; quadratic:  $r = 0.55$ ,  $p < 0.001$ ), but not antHC (linear:  $r = -0.13$ ,  $p = 0.17$ ; quadratic:  $r = -0.16$ ,  $p = 0.07$ ), when controlling for uncus position. To summarize the relationships between our variables of interest, we present a correlation heatmap in Fig. 4.

### 3.5. fMRI results – relationship between postHC volume, age, and functional activity

To assess how functional activity during correct encoding and retrieval trials of the spatial context memory task were associated with age and postHC volume, we used a B-PLS fMRI analysis. We included postHC volume, because of its observed mediating effect between age and memory performance on both the easy and hard trials of the spatial context memory task. We examined activity during correct trials in the following four conditions where we observed the significant moderating effect: spatial easy encoding, spatial hard encoding, spatial easy retrieval and spatial hard retrieval. On average participants completed 29.32 (SD = 4.43) trials during both the spatial easy encoding and retrieval conditions and 28.12 (SD = 5.12) trials during both the spatial hard encoding and retrieval conditions.

The B-PLS analysis identified two significant LVs. The first LV (LV1)

identified a set of positive salience regions, whose activity was positively related to postHC volume and negatively related to age, as well as a set of negative salience regions, whose activity was negatively related to postHC volume and positively related to age. These effects were significant for both vectors of age and postHC volume during correct easy and hard encoding and correct easy retrieval trials, and for only the age vector in hard retrieval (Fig. 5A). Negative salience regions (cool colors in Fig. 5A) consisted mostly of lateral prefrontal and parietal regions such as the left middle frontal gyrus (BA 6), left inferior frontal gyrus (BA 46), BA 47, right inferior parietal lobe (BA 40), and other regions including the left precentral gyrus (BA 6), right postcentral gyrus (BA 1), the left middle and inferior occipital gyrus (BA 19 and BA 18, respectively), and the right entorhinal/parahippocampal area, within the parahippocampal gyrus (BA 35), with this cluster extending into the anterior hippocampus. Positive salience regions (warm colors in Fig. 5A) consisted mostly of subcortical regions such as the right claustrum, left insula (BA 13), left thalamus, and bilateral head of the caudate, right body of the caudate, and right posterior lobe of the cerebellum, as well as midline cortical regions such as the left posterior cingulate cortex (BA 23), bilateral dorsomedial PFC (BA 6, BA 9), and also included the right superior temporal gyrus (BA 21), the right precentral gyrus (BA 6) and right anterior cingulate cortex (BA 24). Thus, according to this LV, older age and smaller postHC volumes were related to greater activation of lateral prefrontal and parietal regions, anterior MTL and visual regions, and less activation of subcortical and midline cortical regions, during correct encoding and retrieval. Thus, LV1 depicts a relationship between age, postHC volume and functional activity that is consistent across encoding and retrieval. The cluster report for this LV is displayed in Table 2.

**Table 2** Cluster report for latent variable 1. 10 mm cluster size, with a bootstrap ratio set at  $\pm 3.28$ . Coordinates are in Talairach space.

Lag	X	Y	Z	Hemisphere	Lobe	Gyral location	Brodman area	BSR	P-value	Cluster size (voxels)	
2	24.86	-67.93	-12.55	Right	Cerebellum	Posterior Lobe	Declive	*	5.2717	0	
2	28.31	-22.29	20.66	Right	Cerebellum	Sub-lobular	Claustrum	*	4.8882	0	
2	-19.4	28.49	3.04	No Gray Matter				4.7722	0	130	
2	-32.56	-17.89	3.04	Left	Cerebellum	Sub-lobular	Insula	13	4.6052	0	
2	32.16	19.03	21.04	No Gray Matter				4.0352	0.0001	18	
2	58.27	-12.56	-3.13	No Gray Matter				3.9094	0.0001	36	
2	-56.66	-44.48	-6.39	Right	Cerebellum	Posterior Lobe	Temporal Lobe	3.6869	0.0002	11	
2	57.78	-23.49	31.86	Right	Cerebellum	Left Cerebellum	Occipital Lobe	4.7553	0	36	
3	-3.37	29.94	22.04	Left	Cerebellum	Limbic Lobe	Posterior Cingulate	40	-3.8717	0.0001	18
3	32.02	-0.3	26.41	Right	Cerebellum	Frontal Lobe	Precentral Gyrus	6	4.9265	0	36
3	23.26	42.02	18.67	Left	Cerebellum	Frontal Lobe	Medial Frontal Gyrus	9	4.3866	0	22
3	21.21	23.85	10.07	Right	Cerebellum	Limbic Lobe	Anterior Cingulate	24	4.0298	0.0001	17
3	-26.89	31.56	-10.5	Right	Cerebellum	Sub-lobular	Caudate Body	3.9344	0.0001	11	
3	-56.71	-64.83	-10.42	No Gray Matter				3.8433	0.0001	22	
3	57.78	-23.49	31.86	Left	Cerebellum	Parietal Lobe	Inferior Parietal Lobule	3.6069	0.0003	10	
4	-1.34	-18.76	24.1	Right	Cerebellum	Posterior Lobe	Middle Occipital Gyrus	19	-4.1032	0	11
4	49.64	20.06	13.29	Left	Cerebellum	Posterior Lobe	Inferior Cerebellum	5.1723	0	15	
4	-60.56	3.55	28.81	Left	Cerebellum	Posterior Lobe	Cingulate Gyrus	3.8135	0.0001	12	
4	57.78	-23.49	31.86	Right	Cerebellum	Posterior Lobe	Superior Frontal Gyrus	5.1723	0	15	
4	-38.21	-46.93	8.21	Left	Cerebellum	Posterior Lobe	Prescentral Gyrus	5.5931	0	13	
4	21.33	-14	56.41	Left	Cerebellum	Posterior Lobe	Occipital Lobe	5.5148	0	105	
4	-31.22	23.82	57.74	Right	Cerebellum	Posterior Lobe	Parahippocampal Gyrus	5.6424	0	49	
5	13.54	-7.31	21.83	Right	Cerebellum	Posterior Lobe	Middle Frontal Gyrus	4.7225	0	21	
5	24.07	9.83	-1.18	Left	Cerebellum	Posterior Lobe	Postcentral Gyrus	4.0668	0	11	
5	-10.26	14.1	16.78	Left	Cerebellum	Posterior Lobe	Caudate	4.8765	0	86	
5	-8.21	42.57	5.57	Right	Cerebellum	Posterior Lobe	Thalamus	4.6754	0	53	
5	-38.03	42.57	16.78	Left	Cerebellum	Posterior Lobe	Anterior Cerebellum	3.7318	0.0002	10	
5	-4.38	42.57	16.78	Left	Cerebellum	Posterior Lobe	Posterior Cerebellum	-5.6294	0	56	
5	-4.38	42.57	16.78	Left	Cerebellum	Posterior Lobe	Posterior Cerebellum	-4.3023	0	30	
5	-3.8063	42.57	16.78	Left	Cerebellum	Posterior Lobe	Posterior Cerebellum	-3.8063	0.0001	10	
5	-3.6866	42.57	16.78	Left	Cerebellum	Posterior Lobe	Posterior Cerebellum	-3.6866	0.0002	10	

The second LV identified by this B-PLS accounted for 22.56% of the cross-block covariance, ( $p < 0.05$ ), and identified a set of positive salience regions, positively correlated with postHFC volume during correct easy encoding, and age at easy and hard retrieval, and negatively correlated with postHFC volume during correct easy and hard retrieval, and age at easy encoding. Negative salience regions (cool colors in Fig. 5B) included the right dorsal anterior cingulate cortex (BA 32), left anterior frontal gyrus (BA 9 dlPFC, and BA 45 gyrus triangulans), left fusiform gyrus (BA 19) and right midoccipital gyrus (BA 19). Positive salience regions (warm colors in Fig. 5B) included the right putamen, the right IPL (BA 40), left parahippocampal gyrus (BA 34, EBC), right STG (BA 38), left dmPFC (BA 6), and right precentral gyrus (BA 4). According to this LV, greater age and less postHFC volume were related to greater activation of lateral frontal, ventral visual, and limbic regions, and less activation of lateral parietal and temporal, and medial temporal and frontal regions during correct easy encoding. In contrast, greater age and less postHFC volume were related to greater activation of lateral parietal and temporal, and medial temporal and frontal regions, and less activation of lateral frontal, ventral visual and limbic regions during correct easy and hard retrieval on the spatial context memory task. Thus, LV2 reflects an interaction between age and postHFC volume, and task-phase (i.e. encoding vs. retrieval). The cluster report for this LV is displayed in Table 3. Visualization of PLS results for Fig. 5A and

B were created with Mango version 4.10 (surface projections; Research Imaging Institute, UTHealthCA) and FSLeyes version 0.33.0 (tightbox transverse slices; Jenkinson et al., 2012).

#### 4. Discussion

In the current study we aimed to investigate the structural and functional correlates of age-related differences in context memory performance, with a special focus on the medial temporal lobes. Given converging findings of episodic memory deficits in middle age and older adults (Ankudowich et al., 2016; Cabeza et al., 2000; Canisino, 2009; Kwon et al., 2016), along with large scale longitudinal studies of hippocampal and MTL structure in aging (Görbisch et al., 2017; Langner et al., 2020; Raz et al., 2009), we sought to examine if volume of MTL structures mediated the association between context memory ability and age. First, by segmenting the perirhinal, entorhinal and parahippocampal cortices, as well as the anterior and posterior hippocampal subregions, we assessed the nature of the associations between volume of our five MTL ROIs and age and observed negative associations between age and postHFC, amnestic and PHC volumes. Next, we examined how volume of these MTL structures mediated the association between context memory ability and age. We found that only the volume of the postHFC fully mediated the relationship between age and spatial, but

not temporal context memory performance. Finally, to address the hypothesis that lateral frontal and parietal overactivations commonly observed in older age are related to MTL atrophy (Reuter-Lorenz and Cappell, 2008), we examined how patterns of whole-brain activation during correct encoding and retrieval trials from the spatial context memory task were related to age and postHFC volume. Employing a B-PLS analysis to investigate this question revealed patterns of increased activation across lateral frontal, parietal and occipital regions correlated with greater age and smaller postHFC volumes. In the following sections we discuss these findings in the context of anterior-posterior (i.e. long-

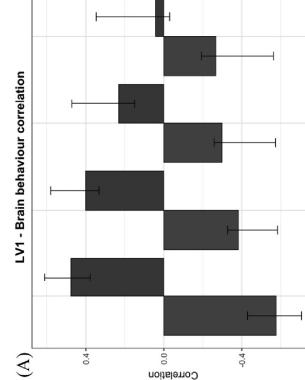
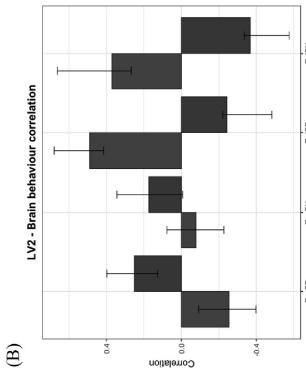
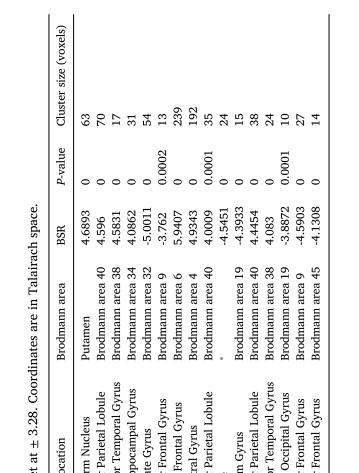


Fig. 5. Continued

Table 3

Cluster report for latent variable 2, 10 mm cluster size, with a bootstrap ratio set at $\pm 3.28$ . Coordinates are in Talairach space.						
Lag	X	Y	Z	Hemisphere	Lobe	Gyrus location
2	25.03	-0.86	-6.19	Right	Cerebrum	Sub-labial
2	61.36	-35.39	38	Right	Cerebrum	Temporal lobe
2	43.82	19.42	-21.97	Right	Cerebrum	Limbic lobe
2	-23.04	-0.26	-10.57	Left	Cerebrum	Parahippocampal gyrus
2	2.43	25.59	31.97	Right	Cerebrum	Cingulate gyrus
2	-42.03	10.91	29.82	Left	Cerebrum	Frontal lobe
3	-13.73	49.73	53.62	Left	Cerebrum	Frontal lobe
3	35.31	-18.02	58.62	Right	Cerebrum	Precentral gyrus
3	54.05	-34.65	30.74	Right	Cerebrum	Inferior Parietal lobe
3	28.55	-71.08	12.84	Right	Cerebrum	Posterior lobe
3	-26.98	-75.12	-14.11	Left	Cerebrum	Posterior lobe
4	53.91	-35.7	41.44	Right	Cerebrum	Frontal lobe
4	51.2	8.2	-22.91	Right	Cerebrum	Temporal lobe
4	28.23	-38.67	7.16	Right	Cerebrum	Occipital lobe
5	-56.81	3.88	25.3	Left	Cerebrum	Frontal lobe
5	-45.27	28.97	-0.95	Left	Cerebrum	Frontal lobe
						Brodmann area 32
						Brodmann area 40
						Brodmann area 34
						Brodmann area 9
						Brodmann area 6
						Brodmann area 40
						Brodmann area 19
						Brodmann area 38
						Brodmann area 9
						Brodmann area 45



not temporal context memory performance. Finally, to address the hypothesis that lateral frontal and parietal overactivations commonly observed in older age are related to MTL atrophy (Reuter-Lorenz and Cappell, 2008), we examined how patterns of whole-brain activation during correct encoding and retrieval trials from the spatial context memory task were related to age and postHFC volume. Employing a B-PLS analysis to investigate this question revealed patterns of increased activation across lateral frontal, parietal and occipital regions correlated with greater age and smaller postHFC volumes. In the following sections we discuss these findings in the context of anterior-posterior (i.e. long-

axis) functional models of the MTL, as well as theories of neurocognitive aging.

**4.1. Context memory performance and MTL volumes decline with age**  
In observing age-related declines in both spatial and temporal context memory performance, our results generally complement previous work displaying similar findings from both cross-sectional and longitudinal samples (Cassino, 2009; Chalfonte and Johnson, 1996; Kessels et al., 2007; Park et al., 2002; Verhaeghen and Salthouse, 1998). In the

correlations in the bar plot, Lags 2–5 are displayed.

**(A)**

**(B)**

**(C)**

current study we observed mostly linear associations between spatial and temporal context memory performance and age, where the steepest decline was present on the hard version of the temporal context memory task. This finding resonates with previous work observing greater age-related deficits in temporal, compared to spatial context memory (Fabiani and Friedman, 1997; Parkin et al., 1995). For further discussion on age-related differences in spatial and temporal context memory performance for this cohort please see Anikudowich et al. (2016) and Subramaniampillai et al. (2019).

While our results depicting age-related differences in MTL volumes align well with previous work (Gorbach et al., 2017; Langseth et al., 2020; Li et al., 2018; Nordin et al., 2017; Pruessner et al., 2001; Rajah, Kromas, et al., 2010; Yedidia et al., 2020; Wisse et al., 2021), some research suggests that the hippocampus may not be as affected by healthy aging such that both activation and structural integrity within this region are preserved into older age (Hedden and Gabrieli, 2004; Persson et al., 2011; West, 1993). However, given recent longitudinal studies in large datasets, it is clear that this structure does display both hippocampal (a portion of the postHIC) with temporal context accuracy in healthy young adults. However, no association between MTL structure and memory performance was observed in older adults. The different relationships observed in the current study may partially be due to the fact that we are focusing on a full lifespan sample, including middle age adults, whereas previous work has found associations between antHIC volume and performance in younger adults only (Becker et al., 2019; Rajah, Kromas, et al., 2010). Still, recent work examining the link between episodic memory, aging and MTL integrity revealed that older adults displayed smaller antHIC volumes compared to middle age adults; and that antHIC volume was positively related to memory performance in both middle age and older adults (Nordin et al., 2017). Specifically, Nordin et al. (2017) employed an episodic memory task that required participants to encode pairs of unrelated words for later retrieval. Due to the nature of the stimuli, this type of task may tap into the semantic and linguistic systems, which are proposed to be more strongly connected to the antHIC, via connections within the anterior temporal lobe and medial PFC (Gilboa and Moscovitch, 2021; Ranganath and Ritchey, 2012; Sheldon et al., 2019). In contrast, regions within the posterior MTL, such as the postHIC, are proposed to be preferentially connected with perceptual processing regions, critical to encoding the faces used as stimuli in the current paradigm (Cooper et al., 2021; Cooper and Ritchey, 2019; Gururyan and Sheldon, 2019; Ritchey and Cooper, 2020). Thus, while our finding of the mediating effect of the postHIC into these subregions may lead to a better understanding of how the structure of this region differs with age (Braak and Braak, 1995; Khan et al., 2014; Olsen et al., 2017; Taylor and Probst, 2008; Young et al., 2019).

**4.2. Volume of the postHIC mediates age-related decline in spatial context memory performance**

Our finding that individual differences in gray matter volume of the postHIC mediated the relationship between age and spatial context memory performance is consistent with functional-anatomical models of the MTL which have proposed that anterior MTL structures play a role in recognizing single items and conceptual information, whereas posterior structures are involved in encoding and retrieving relational information, such as item-context associations (Eichenbaum et al., 2007; Poppoek et al., 2013; Ritchey et al., 2019; Sheldon et al., 2019).

While much evidence supporting these models comes from fMRI studies (Oavach et al., 2003; Evanson et al., 2013; Gururyan and Sheldon, 2019; Lacet et al., 2017; Muglia et al., 2016; Nadel et al., 2013; Spars and Maguire, 2007; Ranganath et al., 2019; Rosenbaum et al., 2004; Sheldon and Levine, 2019), this may be particularly specialized for spatial learning (Brodbeck et al., 2004; Birnec et al., 2019; Burgess et al., 2001; Eichenbaum et al., 1999; Ekstrom et al., 2011; Moser and Moser, 1998; Sherry et al., 1992; Shrager et al., 2007; Spars and Maguire, 2007).

#### 4.3. Age and MTL volume effects on brain activity in lateral frontal, parietal, occipital and anterior MTL regions during correct encoding and retrieval – L1V

On the spatial context memory task while greater age was related to worse memory performance, middle age and older adults still completed many correct encoding and retrieval trials. Thus, to investigate how individuals may have functionally compensated for age-related differences in postHIC volume at the trial-level, we examined whether functional activity during correct encoding and retrieval trials was related to age and postHIC volume. According to the first L1V identified by the B-PLS analysis, smaller postHIC volumes and greater age were related to greater activation in lateral prefrontal, parietal and occipital regions, as well as in the anterior MTL, and less activation of midline cortical, limbic and striatal regions during correct easy and hard encoding, as well as correct easy retrieval trials. Thus, L1V reflects commonalities in activation during encoding and retrieval, associated with both age and postHIC volume. The lateral frontal overactivations we observed with greater age are in line with the basic postulates of the PASA and STAC models, which propose that compared to younger adults, older adults display increased frontal recruitment to correctly encode and recall episodic information (Davis et al., 2008; Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Cappell, 2008). Specifically, we observed greater activation within prefrontal areas BA 46 and BA 46, which have previously been associated with executive functions such as shifting and updating (Hanakawa et al., 2002; Tanaka et al., 2005), as well as recognition related cognitive control processes (Dobkins et al., 2003; Rajah, Langseth, et al., 2010; Rajah and McIntosh, 2008). Furthermore, a great deal of evidence has pinpointed these regions, particularly the left BA 46, as displaying age-related differences in activation during memory encoding and retrieval (Cappell et al., 2010; Rajah and McIntosh, 2008; Ryipa and D'Esposito, 2000, 2001; Yae and Hsieh, 2021).

This result, along with the similar pattern of activity we observed across the task difficulty levels, are further in line with observations of the PASA model, as greater age and smaller postHIC volume were related to both increased lateral frontal activation and decreased posterior medial deactivation with age. However, this is not perfectly consistent with the PASA model as we observed increased activation in lateral frontal regions with age and decreased activation in the medial PFC (Daselaar et al., 2003; Davis et al., 2008; Festini et al., 2018; Grady et al., 1999). Still, this finding supports the proposition that functional compensation in prefrontal regions in aging may occur due to atrophy within the MTL. The functional compensation we observed may reflect a dedifferentiation of function with age and may not result in task-level compensation, as these anterior regions may not support the same operations (Poppenk et al., 2013; Ranganath and Ritchey, 2012).

Examining the positive salience regions within this L1V, greater age and smaller postHIC volumes were related to less activation of cortical regions which are part of the recollection network (Anikudowich et al., 2017; Cooper and Ritchey, 2012; Svoboda et al., 2006). It is possible that younger adults, with intact posterior hippocampus, activate these regions due to their greater ability to vividly remember details of the faces and their locations, as activation within these midline cortical regions has been related to perceptual vividness of remembered stimuli (Ford and Kensinger, 2016; Ritchier et al., 2016; Mitchell and Johnson, 2009; Ranganath and Ritchey, 2012; Sheldon and Levine, 2013). Thus, older adults may be relying less on episodic and perceptual strategies, and instead on higher-order executive functions supported by the PFC.

Alternatively, there is strong evidence for the role of these regions in task-unrelated thinking which has been associated with worse task performance (Christoff et al., 2016; Mallet et al., 2017; Mason et al., 2007; Raichle et al., 2001). Thus, it is possible that not only do older adults with smaller postHIC volumes display greater activation in lateral frontal and parietal regions when correctly encoding and retrieving contextual

we only observed a relationship between antHIC volume and patterns of correct activity during hard retrieval trials, and these behavioral-functional associations were clearly driven by age (see Supplementary Fig. 2 for a more in-depth interpretation). In other related work, Valenzuela et al. (2015) observed that older adults with hippocampal atrophy displayed greater recruitment of a posterior compensatory network including occipital and posterior parietal cortical regions, at low levels of demand on a spatial working memory task. This increased compensatory activation in posterior visual regions goes against the PASA model, but overlaps with our observations (Davis et al., 2008; Grady et al., 1999). This may indicate that while greater age is generally accompanied by decreases in functional activity in occipital regions as observed in the PASA, this relationship may be modulated by hippocampal volumes.

Finally, recent studies have revealed that task-related activity within the hippocampus is significantly reduced in aging, even after controlling for age-related differences in hippocampal volume (Beason-Held et al., 2021; Salami et al., 2012). In the current study, rather than identifying activation maps unique to age, specifically isolated from effects of hippocampal structure, we attempted to detect patterns of activity related to both age and volumes of structures relevant to our task (here the posterior hippocampus). While previous work suggests that task-related functional activity within the hippocampus may be related to the posterior hippocampus, such as the posterior hippocampus, we did not observe local structure-function interactions (Salami et al., 2012; Ta et al., 2012). Specifically, neither L1V produced by the PLS analysis depicted a positive relationship between postHIC volume and its task-related activation. However, we did observe a negative relationship between postHIC volume and activation of the right anterior MTL. Specifically, a cluster within the anterior MTL, including portions of the PRC, ERC and antHIC, displayed greater activation with greater age and less postHIC volume. This may suggest that when a structure that is critical for a specific memory task contains less gray matter, and thus likely less synapses, proximal regions within the same system may help compensate by activating during the task. This result is indirectly supported by previous work that suggests an posterior-to-anterior shift in aging within the hippocampus, such that aging impacts the posterior prior to the antHIC (Daninoiseau et al., 2016; Driscoll, 2003; Langseth et al., 2020; Maylahn et al., 2008). Examining functional connectivity across the adult lifespan, Daninoiseau et al. observed that whereas greater age was related to reduced functional connectivity between the left and right postHIC and related default network regions, greater age was not related to reductions in aRHC connectivity. Given the anterior-posterior functional gradient that has been proposed within the MTL, the functional compensation we observed may reflect a dedifferentiation of function with age and may not result in task-level compensation, as these anterior regions may not support the same operations (Poppenk et al., 2013; Ranganath and Ritchey, 2012).

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information, they may also inhibit these cortical midline regions to stay on task and complete these trials correctly.

#### 4.4. Modulation of the effects age and volume on activity in lateral frontal, temporal and parietal, and subcortical regions during correct encoding vs. retrieval – Lv1

Our B-PLS analysis also produced a second latent variable that indicated effects that were somewhat similar to Lv1 during easy encoding. However, this was inverted at retrieval, such that this Lv reflects an interaction between age and postHC volume, and task-phase (i.e. encoding vs. retrieval). That is, within Lv2, greater age and smaller postHC volumes were related to greater activation of anterior frontal, ventral visual and limbic regions, and less activation of lateral parietal and temporal, and medial temporal and frontal regions during correct encoding trials. Yet, at both easy and hard retrieval, greater age and smaller postHC volumes were related to greater activation of these lateral parietal and temporal, and medial temporal and frontal regions, and less activation of anterior frontal, ventral visual and limbic regions. Our results are consistent with previous work indicating that ventrolateral prefrontal (VLPFC) and lateral parietal regions typically display greater activation at encoding, compared to retrieval, and that older adults are more well-aligned with this pattern (Anikudowich et al., 2017; Maillot and Rajah, 2014; Spaniol et al., 2009). For example, Anikudowich et al. (2017) observed that age was positively associated with activation in VLPFC and lateral parietal regions at encoding, and negatively associated with activation within these regions at retrieval. Furthermore, we found that volume of the postHC also mapped onto this interaction between age and task-phase, such that less volume of this region was associated with greater VLPFC and lateral parietal activation at encoding, and less activation within these regions at retrieval. Previous studies suggest that greater activation of VLPFC at encoding may be related to an up-regulation of control processes in order to selectively attend to item-specific features Badre and Wagner, 2004, 2007; Blumenfeld et al., 2011; Chiou and Lambon Ralph, 2018; Romanski and Chafee, 2021). In observing that activation within ventral visual regions (BA 19) also display this age-by-phase interaction, we speculate that this LV may indicate the collaboration of prefrontal, control and occipito-temporal visual systems, previously identified as supporting focus for task-related processing information (Blumenfeld et al., 2011; Blumenfeld and Ranganath, 2007). The association we observed between hippocampal volume and activity within the inferior PFC is also consistent with previous structure-function analyses in young adults from experiments employing similar tasks (Becker et al., 2019; Maillot and Rajah, 2011). For example, Becker et al. observed that less gray matter within the inferior frontal gyrus (BA 47, 44, 46) during successful encoding in an associative memory paradigm. Additionally, consistent with our findings, this study observed that greater activity in other JEG regions (BA 45, 46, 48), and in the ERG was related to less postHC volume (BA 45–48). This highlights the importance of distal PFC–hippocampal structure-function relationships in episodic memory, particularly at encoding. As we have previously observed and discussed the opposing phase effects observed across regions in Lv2 in relation to age, (Anikudowich et al., 2016, 2017; Elshiekh et al., 2020; Subramaniampillai et al., 2019), and for the sake of brevity, we move on to discussing the limitations and implications of this study.

In the present study we applied a mediation analysis to investigate associations between MTL structure, age, and context memory performance. While mediation analyses may imply causality due to their directionality, we cannot speculate that any association we observed

are causal or related to changes in any of these measures due to the cross-sectional nature of our data. In fact, mediation results from cross-sectional studies do not always align with results from studies including longitudinal mediators, and this is thus an important caveat of this analysis (this limitation and more are discussed further by Lindenberger et al., 2011). A second important limitation of our structural analyses is the fact that we examined volumetric data, rather than morphometric or surface-based data. Volumetric analyses do not take into account individual differences in folding patterns, and are primarily based on the location of specific anatomical landmarks. For example, the location of the uncus apex along the long-axis of the hippocampus is an important landmark in our segmentation protocol (Olson et al., 2013). However, there lies great anatomical variation between individuals in the folding patterns and location of this landmark within the hippocampus, and its location plays a large role in determining volumes for our ROIs (Chang et al., 2018; de Flores et al., 2019). While automated surface parcelation methods exist to assess these individual differences in hippocampal morphology and should be used in the future to assess the relationship between hippocampal structure, aging and memory performance, these types of analyses were outside the scope of the hypotheses tested in the current manuscript (Cabeza et al., 2021). Furthermore, while the semi-automated segmentation protocols, with the rationale provided by anatomical work from Borcardi et al. (2015) and Duvernoy (2005), it is important to consider the biases that appear when assessing developmental samples. Specifically, Popken (2020) observed repositioning of the uncus apex across the healthy adult lifespan, and concluded that this retrospective biased estimates of antHC and postHC volumes. While we did measure the position of this landmark, and assess its contribution to our findings statistically, it is still noteworthy to consider how this anatomical change that occurs with age may have had an effect on our volumetric measurements. These structural limitations should also be kept in mind when interpreting results from the structure-function analyses we conducted.

From a behavioral perspective, we must also refrain from interpreting the results from our tasks as differentiating between context and item memory. Specifically, in this task, participants are not shown any new items at retrieval, and thus we are providing them with the item, and solely asking them to recall the contextual information the location (or the order). Still, participants may have not encoded certain stimuli, or access to those items may have been interrupted, such that at retrieval they could not provide the contextual information because they had forgotten the item. Further, participants may have employed different strategies, such as a recall-to-reject strategy which may have differed with age, and thus this may lead to some noise in our behavioral data (Healy et al., 2005; James et al., 2016).

An important caveat is that we cannot assert that our functional results indicate the presence of compensation in relation to age and individual differences in postHC volume, as strict criteria must be met in order to claim that this overactivation plays a compensatory role (Cabeza et al., 2016). First, increased activation with greater age must be related to a gap between neural resources and task-demands. In the present study we were able to meet this criterion as middle-age and older adults displayed deficits on this task, and displayed less neural resources relevant to the task (as identified in the mediation analysis). Second, the overactivation must be identified in the mediation analysis, this study observed that greater activity in other JEG regions (BA 45–48), and in the ERG was related to less postHC volume (BA 45–48). This highlights the importance of distal PFC–hippocampal structure-function relationships in episodic memory, particularly at encoding. As we have previously observed and discussed the opposing phase effects observed across regions in Lv2 in relation to age, (Anikudowich et al., 2016, 2017; Elshiekh et al., 2020; Subramaniampillai et al., 2019), and for the sake of brevity, we move on to discussing the limitations and implications of this study.

#### 4.5. Caveats

In the present study we applied a mediation analysis to investigate associations between MTL structure, age, and context memory performance. While mediation analyses may imply causality due to their directionality, we cannot speculate that any association we observed

#### Data and code availability statement

The data collected in the current study are available upon request from the corresponding author. The data are not currently publicly available as the authors are currently working with the institution to make the dataset open-access.

Third party code is referenced in the article, and manuscript-specific scripts for parallel mediation, quadratic regression and B-PLS analysis will be made available on OSF.

#### Credit authorship contribution statement

Jamie Snytje: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Visualization, Funding acquisition. Can Fenerci: Formal analysis, Methodology, Writing – review & editing, Strichardana Rajagopal: Methodology, Validation, Camille Beaudoin: Methodology, Writing – review & editing, Kiera Hooper: Methodology, Writing – review & editing, Signy Sheldon: Conceptualization, Writing – review & editing, Rosanna K. Olsen: Methodology, Writing – review & editing, M. Natasha Rajah: Conceptualization, Methodology, Writing – review & editing, Supervision, Data curation, Methodology, Writing – review & editing, Supervision, Funding acquisition.

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#### Supplementary materials

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