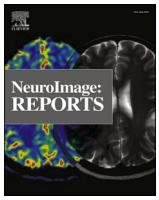
Neuroimage: Reports 3 (2023) 100168

Contents lists available at ScienceDirect

Neuroimage: Reports

journal homepage: www.sciencedirect.com/journal/neuroimage-reports



Associative memory is more strongly predicted by age-related differences in the prefrontal cortex than medial temporal lobes

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ARTICLE INFO

Keywords:
Aging
Grey matter volume
Associative memory

ABSTRACT

It is well established that episodic memory declines with age and one of the primary explanations for this decline is an age-related impairment in the ability to form new associations. At a neural level, both the medial temporal lobe (MTL) and lateral prefrontal cortex (PFC) are thought to be critical for associative memory, and grey matter volume loss in these regions has been associated with age-related declines in episodic memory. While some recent work has compared the relative contributions of grey matter volume in MTL and PFC regions to item and associative memory, studies investigating the unique and shared contributions of age-related differences in the MTL and PFC to memory differences are still rare. In this study, we use a lifespan approach to examine the relationship between grey matter volume within substructures of the MTL and PFC on the one hand and item and associative memory on the other. To this end, we used data from over 300 healthy individuals uniformly spread across the adult lifespan from the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) and tested the multivariate relationship between grey matter volumes and item/associative memory scores using canonical correlation analysis. We show that structures of the PFC alone predict memory performance better than either structures of the MTL alone or PFC and MTL combined. Moreover, our results also indicate that grey matter volume in the inferior frontal gyrus - pars opercularis, superior frontal gyrus, and middle frontal gyrus relates most strongly to memory (particularly associative memory, which loaded higher than item memory) and this effect persists when controlling for age and education. Finally, we also show that the relationship between frontal grey matter volume and memory is not moderated by age or sex. Taken together, these findings emphasize the critical role of the frontal lobes, and the control processes they subserve, in determining the effects of age on associative memory.

1. Introduction

Episodic memory refers to the ability to encode, store and retrieve the details of personal experiences and events within their temporal and spatial contexts (Tulving, 2002). It is well established that aging is associated with episodic memory decline (Dennis and McCormick-Huhn, 2018; Nyberg et al., 2012; Park et al., 2013). This age-related decline in episodic memory has been attributed to a specific deficit in the ability to form new associations (Naveh-Benjamin, 2000), and age differences in item memory tend to be less pronounced than age differences in associative memory (Old and Naveh-Benjamin, 2008). This view places an emphasis on the memory binding process itself (Chalfonte and Johnson, 1996), which associates individual items to each other or their context at encoding and is thought to depend on the medial temporal lobe (particularly, the hippocampus; Ranganath, 2010). However, other accounts of age differences in associative memory attribute a greater role to age-related declines in attention (for a recent review, see Naveh-Benjamin and Mayr, 2018), which may lead

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https://doi.org/10.1016/j.ynirp.2023.100168
Received 30 September 2022; Received in revised form 13 March 2023; Accepted 16 March 2023
Available online 23 March 2023

older adults to form more irrelevant associations at encoding (Campbell et al., 2010; Davis et al., 2021) and/or hinder control processes at retrieval (Castel and Craik, 2003; Cohn et al., 2008; Karl Healey et al., 2013).

Regarding the neural substrates of associative memory, the involvement of the medial temporal lobes (MTL) and the lateral prefrontal cortex (PFC) has been well documented through neuroimaging studies and brain damage case studies (Noulhiane et al., 2007; Simons and Spiers, 2003; Squire, 2009). Overall, there is an established consensus on which functions the MTL and PFC serve: the MTL is critical for the binding process (item-item; item-context) in long-term memory, and the lateral PFC is critical for attentional control functions that support binding through the creation, maintenance, and selection of memory representations (Cabeza, 2006; Simons and Spiers, 2003). Older age leads to a loss of total brain volume, but the degree of change is highly heterogeneous across different structures, with the MTL and PFC demonstrating marked age-related declines in grey matter volume, along with increased inter-individual variability (Raz et al., 2005). Comprehensive reviews suggest that healthy aging has the largest effect on the frontal cortex, followed by more moderate effects in the temporal lobes, posterior association cortex, and occipital regions (Freund & Pettman, 2010; MacDonald and Pike, 2021).

Grey matter volume loss has been associated with age-related decline and inter-individual differences in episodic memory, however, most structural studies have focused exclusively on the link between hippocampal volume and associative memory functioning in young and older adults, and thus far, results have been mixed (Becker et al., 2015; Carr et al., 2017; DeMaster et al., 2014; Grady and Ryan, 2017; Poppenk and Moscovitch, 2011; Rajah et al., 2010; Schlichting et al., 2017). In young adults, these studies range from finding no relationship between hippocampal volume and associative memory, to a positive, or even a negative association (DeMaster et al., 2014; Poppenk and Moscovitch, 2011; Rajah et al., 2010; Schlichting et al., 2017). In older adults, findings range from no relationship to a positive relationship between hippocampal volume and associative memory (Becker et al., 2015; Carr et al., 2017). Previous studies have tended to look at the hippocampus as a whole (Head et al., 2008; Rodrigue et al., 2013; Ward et al., 2015) or simply divided the hippocampus into anterior vs posterior sections (DeMaster et al., 2014; Driscoll et al., 2003; Langnes et al., 2019; Nordin et al., 2017; Poppenk and Moscovitch, 2011; Rajah et al., 2010; Ta et al., 2012), and this lack of specificity may have contributed to the mixed results of past research. Importantly, recent work suggests that other subregions of the MTL (such as the entorhinal cortex) may also play a critical role in associative binding (Nilssen et al., 2019; Yeung et al., 2019), suggesting that we should also look beyond the hippocampus when examining structural correlates of associative memory in aging. These discrepancies in the literature may also be due to a changing relationship between grey matter volume and associative memory across the lifespan (Langnes et al., 2019; Shing et al., 2010), loss of white matter connections between regions critical for item and associative memory (Henson et al., 2016), and age-related functional reorganization (Bagarinao et al., 2019; Brehmer et al., 2020; Fandakova and Hartley, 2020; Langnes et al., 2019; Shing et al., 2010).

Moreover, previous work on the structural correlates of age differences in associative memory rarely considers the joint contribution of the MTL and PFC. Advancing age has its largest detrimental effects on frontal regions of the brain, and functional brain imaging studies have confirmed the involvement of lateral prefrontal cortex (PFC) regions in episodic memory function (Fandakova et al., 2015; Maillet and Rajah, 2014). Thus, additionally considering age-related differences in prefrontal structures may help further our understating of the underlying causes of age-related differences in episodic memory. To the best of our knowledge, only two studies have directly compared the contributions of regional grey matter volume in the MTL and PFC to item memory and associative memory (Becker et al., 2015; Brehmer et al., 2020). Both of these studies suggested that grey matter volume in the PFC makes a distinct contribution to associative memory functioning in old age. However, these studies only assessed (i) older adults (rather than a lifespan sample) and (ii) one or two regions at a time (either by making pairwise comparisons or through a univariate voxel-based morphometry [VBM] approach). This leaves a gap in our understanding of the relative contribution of MTL and PFC substructures for item and associative memory, which is better assessed using a multivariate approach, and whether this contribution changes across the adult lifespan.

Finally, recent work suggests that biological sex and gender (hereafter we will mainly focus on biological sex) may also play an important role in how memory and the brain change with age. For instance, accelerated brain aging in men compared to women is commonly observed (Cowell et al., 1994; Zheng et al., 2017), and behaviorally, older women generally perform better than older men on associative memory tasks (Herlitz and Rehnman, 2008) though this may depend on the material being tested (Asperholm et al., 2019; Subramaniapillai et al., 2022). Some studies, however, did not find such a sex difference in episodic memory (McDougall et al., 2014). Unfortunately, few studies have looked at sex differences in the relationship between MTL and PFC structures and individual differences in item and associative memory. One study demonstrated that hippocampal volume predicts associative memory in older women, but not in older men (Zheng et al., 2017), but further work is needed on the moderating role of sex in the relationship between grey matter volume and episodic memory performance with age.

The aim of this study was to investigate the contribution of grey matter volume within substructures of the MTL and PFC to age-related differences in item and associative memory across the adult lifespan. We were also interested in the effects of sex on the relationship between grey matter volume and episodic memory performance to determine if sex affects neurocognitive aging. To this end, we used data from over 300 individuals uniformly spread across the adult lifespan (18–87 years) from the Cambridge Centre for Ageing and Neuroscience (Cam-CAN; www.cam-can.org) project (Shafto et al., 2014). Measures of item and associative memory were obtained from the emotional memory task previously reported by Henson et al. (2016). Structural images were submitted to the Automatic Segmentation of Hippocampal Subfields (ASHS; Yushkevich et al., 2015) software package to obtain volume estimates for several MTL regions (including the anterior and posterior hippocampi, entorhinal cortex, perirhinal cortex – Brodmann areas 35 and 36, parahippocampal cortex, and an estimate of intracranial volume). Using FreeSurfer, we also extracted grey matter volume estimates from the superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus - pars orbitalis, inferior frontal gyrus - pars triangularis, inferior frontal gyrus - pars opercularis, and orbital sulci. These are the same PFC regions used by Brehmer et al. (2020), and activity in these brain regions has also been positively linked to associative memory performance in older adults (Duarte et al., 2010; Fandakova et al., 2015; Maillet and Rajah, 2014). We tested the multivariate relationship between grey matter volumes and item/associative memory scores using a series of canonical correlation analyses, comparing MTL-only and PFC-only models to one that combined both MTL and PFC regions together. We hypothesized that grey matter volume of structures in the PFC would be more strongly related to associative memory performance than structures in the MTL (Becker et al., 2015; Brehmer et al., 2020), which would suggest a critical role for attention and executive functions in age-related differences in associative memory. Moreover, we expected sex to moderate the effect of age on both grey matter volume and memory scores, and possibly the relationship between them.

2. Methods

Participants. An initial sample of 312 participants (18–87 years old; mean 54.24; SD 18.22; 158 men and 154 women; approximately equally distributed across the lifespan) was taken from the population-derived Stage 2 sample of the Cambridge Centre for Aging and Neuroscience

(Cam-CAN) project (Shafto et al., 2014). Participants reported their sex during the home interview phase (Stage 1) but were not asked about their gender identity. After image processing and outlier removal (described below), our final sample included 307 participants (18–87 years old; mean 54.43; SD 18.26; 155 men and 152 women). Demographic information of the final sample is provided in Table 1 (divided into age groups for illustrative purposes, but note that all analyses used age as a continuous variable). Participants were included if they had no contraindications to MRI, no self-reported history of drug or alcohol abuse, no neurological disorders, and no brain abnormalities detected. Participants were native English speakers, had normal or corrected-to-normal vision and hearing, and scored 25 or higher on the Mini Mental State Exam (MMSE; Folstein et al., 1975). Informed consent was obtained from all participants and the study was approved by the Cambridgeshire 2 Research Ethics Committee, United Kingdom (Shafto et al., 2014).

Memory Assessment. Item and associative memory performance were assessed by a behavioral task given outside the scanner (Henson et al., 2016). The study phase was comprised of 120 trials, split into two blocks, with a short break between blocks. Each trial began with a background scene that could have positive, negative, or neutral valence (40 trials per valence; scenes taken from the International Affective Pictures System (Lang et al., 1997). After 2s, a neutral object was superimposed on the scene for 7.5s. Participants were instructed to press a key when they had mentally formed a story that linked the object to the scene and continue to elaborate the story until the images disappeared. A 0.5s blank screen was shown between trials. Participants were not informed that their memory would be tested later. The test phase was given after a 10-min break and was comprised of 160 trials (using 120 objects from the Study phase and 40 new objects), split into 4 blocks. On each trial, measures of object priming, item recognition, and associative memory were obtained. First, a pixilated version of the object appeared, and participants had to respond as quickly as they could to identify the object (this measure of object priming is not used in the current analyses). Next, the pixilation was removed, and a clear version of the object was shown to test item memory. Participants indicated whether the object had been shown in the Study phase and their level of confidence in their response ("sure new", "think new", "think studied", "sure studied"). If participants selected "think studied" or "sure studied", then associative memory was tested by asking participants to first report the valence of the background scene that the object had been paired with (positive, neutral, negative, don't know) and then describe the scene.

Memory Accuracy. For Item memory, we used d' as a measure of discriminability (Green et al., 1966), calculated as the difference in inverse normal transformed probabilities of Hits and False Alarms. Hits and False Alarms were collapsed across "sure" and "think" confidence levels (the number of low confidence answers was too small to perform separate analyses). For associative memory, the number of correctly described background scenes was used as our measure of interest.[1] Participants needed to describe the background scene in enough detail to distinguish it from other background images.

Table 1
Participant demographics and cognitive scores.

Age group	Young	Middle	Older	Total
n	37	140	130	307
Age range (years)	18–30	31–59	60–87	18–87
Sex (men/women)	16/21	71/69	68/62	155/152
Highest education				
University	27 (73%)	100 (71.4%)	62 (47.7%)	189 (61.6%)
A' levels	6 (16.2%)	22 (15.7%)	30 (23.1%)	58 (18.9%)
GCSE grade	4 (10.8%)	16 (11.4%)	19 (14.6%)	39 (12.7%)
None over 16	0 (0.0%)	2 (1.4%)	18 (13.8%)	20 (6.5%)
Cognitive Scores				
MMSE	29.46 (0.90)	29.17 (1.11)	28.43 (1.47)	28.89 (1.32)
ACE-R	96.70 (3.79)	96.43 (3.40)	93.49 (5.08)	95.22 (4.47)

*Note. Participants are divided into age groups for descriptive purposes, but all analyses used age as a continuous variable. *tEducation, MMSE, and ACE-R data missing for one participant. GCSE = general certificate of secondary education. MMSE* = Mini-Mental State Exam. *ACE-R = Addenbrooke's Cognitive Examination-Revised* (Mioshi et al., 2006).

MRI Data. Grey matter volume (GMV) was estimated from the T1-weighted MR images (1 mm^3). Scanning took place at the Medical Research Council Cognition and Brain Sciences Unit (MRC-CBSU) in a 3T Siemens TIM Trio, with a 32-channel head-coil. The 3D T1-weighted structural image (field of view - FOV = 256 mm × 240 mm x 192 mm; voxel size = 1 mm^3) was acquired using a Magnetization Prepared RApid Gradient Echo (MPRAGE) sequence (Shafto et al., 2014; Taylor et al., 2017). The Automatic Segmentation of Hippocampal Subfields (ASHS) software (Yushkevich et al., 2015) (https://sites.google.com/view/ashs-dox/home) and the ASHS-PMC-T1 atlas (Xie et al., 2016) (https://sites.google.com/view/ashs-dox/mri-data/ashs-pmc-t1-atlas-requirements) were used to estimate volumes of the following MTL structures (left and right separately): anterior and posterior hippocampi, entorhinal cortex, Brodmann areas 35 and 36 (both subregions of the Perirhinal cortex), parahippocampal cortex, and an estimate of intracranial volume (eICV). For the purpose of quality control (QC), all segmentations obtained from ASHS were visually inspected and scored by two raters who were blind to participant age and sex. A five-point rating scale was used based on the number of voxels that were over/-undersegmented for a given structure (1 - Perfect, or near-perfect outputs; 0.75 - Small, contained errors; 0.5 - Moderate errors; 0.25 - Large and expansive errors; 0 - Totally misses the mark). Only participants with segmentation scores of 0.5 and above were kept for volume assessment and statistical analysis (no participants needed to be excluded). The rating reliability between raters was assessed through Intraclass Correlation Coefficient (ICC) (Koo and Li, 2016; Liljequist et al., 2019), and the average ICC across ratings for the assessed brain regions was 0.783, indicating moderate to good reliability (Koo and Li, 2016). FreeSurfer v7 (Fischl et al., 2004) (https://surfer.nmr.mgh.harvard.edu/) and the 'Segmentation of hippocampal subfields and nuclei of the amygdala tool' (Saygin et al., 2017) were used to estimate volumes of the amygdala. Free-Surfer was also used for the following frontal lobe structures superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus - pars orbitalis, inferior frontal gyrus - pars triangularis, inferior frontal gyrus - pars opercularis, and orbital sulci (H-shaped sulci). Five participants were excluded from the original sample due to extreme MTL structure volume values (values that were more than 3.0 times the interquartile range below the first quartile or above the third quartile). All volumes were corrected for head size using the linear regression method, in which each volume of interest and eICV are used to predict ICV-adjusted volumes as follows: $[Volume\_adjusted(i) = Volume\_raw(i) - \beta(ICV\_raw(i) - ICV\_mean)]$, where β is the slope of the regression line between ICV and the volume of interest (Voevodskaya, 2014).

Statistics. We first used a series of linear regression analyses to predict item memory, associative memory, and grey matter volumes from age, sex, and the age × sex interaction (controlling for education). The multivariate association between brain volumes and memory performance was tested using a multivariate approach. We adopted a two-level procedure (Passamonti et al., 2019; Tsvetanov et al., 2016, 2021, 2022). In the first-level analysis, the relationship between brain volumes and memory performance was identified using canonical correlation

[1] Note. The same pattern of results is found if we use a proportional score for associative memory instead (i.e., the number of backgrounds correctly described out of the total number of possible trials, which was dependent on correctly identifying the cued object as "old"). Further, similar results are also obtained when Associative memory scores are calculated as % Hits - % False Alarms (using participants' recall of the background scene valence, rather than their descriptions of the background scenes, as used in Henson et al., 2016). This analysis is shown in the Supplementary Materials (Figure S9 and Table S1).

analysis (CCA) (Hotelling, 1936; Zhuang et al., 2020). The goal of CCA is to compute the linear combination of variables that maximizes the correlation between two multivariate data sets (X and Y) without assuming any form of directionality. In our study, the relationship between GMV in multiple brain regions of interest (X) and six memory scores (Y) was evaluated in three distinct models (see Table 2). To determine the best set of regions that predicts memory performance (MTL-only regions or PFC-only or MTL and PFC regions together), we compared model fits between the three models with a bootstrapping approach (5000 iterations) and determined the significance of the loadings of the best fit model with a permutation-based cross-validation approach (Efron and Tibshirani, 1986; Tsvetanov et al., 2018). We were primarily interested in determining which model offers the best fit to the data and focused our subsequent analyses on the winning model. Loadings were compared by examining the 95% confidence intervals around each mean (derived from the bootstrapping).

Next, we tested whether the relationship between GMV and memory performance identified by the winning model 1) remains after controlling for age and education, and 2) is moderated by age and sex. To this end, we performed a second-level analysis using multiple linear regression. Predictor variables included subject GMV scores (from the winning CCA model), age, sex, their interaction terms (GMV x age, GMV x sex). The dependent variable was subject memory scores (from the winning CCA model). Education was entered as a covariate of no interest. The model therefore can identify the unique variance explained by each of the predictors, i.e., whether GMV scores predicted memory scores over and above age, or evidence for moderation by age and/or sex.

Table 2
CCA models.

Models	X (Brain Regions)	Y (Memory Scores)
Model 1	MTL only model • Anterior hippocampus • Posterior hippocampus • Entorhinal cortex • Perirhinal cortex - Br35 • Perirhinal cortex - Br36 • Parahippocampal cortex • Amygdala	• Item Memory - Positive Background • Item Memory - Neutral Background • Item Memory - Negative Background • Associative Memory - Positive Background • Associative Memory - Neutral Background • Associative Memory - Negative Background
Model 2	PFC only model • Superior frontal gyrus • Middle frontal gyrus • Inferior frontal gyrus - Pars orbitalis • Inferior frontal gyrus - Pars triangularis • Inferior frontal gyrus - Pars opercularis • Orbital sulci (H-shaped sulci)	• Item Memory - Positive Background • Item Memory - Neutral Background • Item Memory - Negative Background • Associative Memory - Positive Background • Associative Memory - Neutral Background • Associative Memory - Negative Background
Model 3	MTL and PFC model • Anterior hippocampus • Posterior hippocampus • Entorhinal cortex • Perirhinal cortex - Br35 • Perirhinal cortex - Br36 • Parahippocampal cortex • Amygdala • Superior frontal gyrus • Middle frontal gyrus • Inferior frontal gyrus - Pars orbitalis • Inferior frontal gyrus - Pars triangularis • Inferior frontal gyrus - Pars opercularis • Orbital sulci (H-shaped sulci)	• Item Memory - Positive Background • Item Memory - Neutral Background • Item Memory - Negative Background • Associative Memory - Positive Background • Associative Memory - Neutral Background • Associative Memory - Negative Background

3. Results

Age and sex effects on memory. Figure S1 shows mean item and associative memory (averaged across valence) plotted against age. Figure S2 shows each valence separately.[2] For item memory, a regression predicting item memory from age, sex, and the age × sex interaction (controlling for education) was significant ($R^2 = 0.23$, $F = 30.2$, $p < 0.001$). Age was the only significant predictor ($\beta = 0.007$, $p < 0.001$). For associative memory, a regression predicting associative memory from age, sex, and the age × sex interaction (controlling for education) was significant ($R^2 = 0.358$, $F = 56.4$, $p < 0.001$). This model showed a significant effect of age ($\beta = -0.584$, $p < 0.001$) and an age × sex interaction ($\beta = 0.12$, $p = 0.01$), indicating that the age-related differences in associative memory was slightly steeper in men (see Figure S1B). In line with previous findings, age was associated with a decrease in memory performance; however, in contrast to previous work showing a disproportionate age effect on associative relative to item memory, there was no difference in the effect of age on item and associative memory in this case (tested by comparing the correlations between age and item memory, and age and associative memory; $z = 1.44$; $p = 0.15$).

Age and sex effects on grey matter volume. Figures S3 and S4 show mean grey matter volume (sum of both hemispheres) plotted against age for the MTL and frontal lobe structures, respectively (see Figures S5-S8 for the left and right hemispheres separately). We performed a series of linear regressions predicting the volume in each structure (averaged across hemispheres) from age, sex, and the age × sex interaction, while controlling for False Discovery Rate (FDR) using the Benjamini–Hochberg method (Benjamini and Hochberg, 1995). As shown in Table 3, increasing age was negatively associated with grey matter volume volume in all structures (except for the posterior hippocampus), and this effect was most pronounced in the perirhinal cortex – Br36, parahippocampal cortex, and amygdala. In the frontal lobes, age-related differences were most pronounced in the middle frontal gyrus, superior frontal gyrus, and inferior frontal gyrus - Pars opercularis. Turning to the effects of sex, none of the main effects of sex nor the interactions between sex and age survived FDR correction. Thus, in the current sample, grey matter volume was negatively associated with age in all structures except the posterior hippocampus and similar effects of age were observed for both men and women.

Association between brain volumes and memory performance. The multivariate association between brain volumes of interest and memory scores was evaluated in three distinct CCA models (Fig. 1). Model 1 assessed the relationship between structures of the medial temporal lobe and memory performance (Fig. 1A-Left). Model 2 assessed the relationship between structures of the frontal lobes and memory performance (Fig. 1A-Center). Model 3 assessed the relationship between structures of both the medial temporal and frontal lobes and memory (Fig. 1A-Right). When comparing model fit (Fig. 1B), we found that Model 2 (which included the frontal regions alone) predicted memory performance better than Model 1 (which included the medial temporal lobe regions alone), $t = 161.77$, $p < 0.001$, and better than Model 3 (which included both medial temporal and frontal regions), $t = 261.67$, $p < 0.001$. Further, Model 3, predicted memory performance better than Model 1, $t = 11.06$, $p < 0.001$ (see Fig. 1B). Similar results are obtained when using % Hits - % False Alarms as a measure of associative memory instead (see Figure S9).

[2] Note: We do not focus on valence effects here as 1) this was not our primary question of interest and 2) this was covered extensively in Henson et al. (2016) using the same data. Nevertheless, each valence was entered into the CCA analyses separately as this method lends itself well to the inclusion of multiple outcome measures.

Table 3
List of regression models and significant effects.

Region of Interest	Model Fit			Predictor variable p-values			
	R^2	F	p	age		sex	age*sex
Anterior hippocampus	0.036	3.82	0.01	0.003	*	0.138	0.453
Posterior hippocampus	0.015	1.51	0.212	0.562		0.040	0.941
Entorhinal cortex	0.033	3.49	0.02	<0.001	*	0.669	0.795
Perirhinal cortex - Br35	0.051	5.38	0.001	<0.001	*	0.257	0.906
Perirhinal cortex - Br36	0.127	14.6	<0.001	<0.001	*	0.459	0.920
Parahippocampal cortex	0.04	4.16	0.007	0.003	*	0.055	0.925
Amygdala	0.114	12.9	<0.001	<0.001	*	0.632	0.957
Inferior frontal gyrus - Pars opercularis	0.061	6.58	<0.001	<0.001	*	0.344	0.234
Inferior frontal gyrus - Pars orbitalis	0.076	8.33	<0.001	<0.001	*	0.401	0.933
Inferior frontal gyrus - Pars triangularis	0.067	7.33	<0.001	<0.001	*	0.265	0.138
Middle frontal gyrus	0.059	6.33	<0.001	<0.001	*	0.404	0.233
Superior frontal gyrus	0.101	11.45	<0.001	<0.001	*	0.032	0.505
Orbital sulci (H-shaped sulci)	0.056	5.98	<0.001	<0.001	*	0.741	0.402

Note. p-values reported for each predictor in the model. * = significant after FDR correction. The same pattern of results is found if we include total grey matter volume as a covariate in the models.

After assessing model fit, we evaluated the significance of the loadings of the best model (Model 2). Only the first canonical variate was significant ($p < 0.001$), and it explained 33.18% of the covariance between X and Y. As show in Table 4, all memory scores (except item memory for objects that were superimposed on a positive background) loaded significantly on this component. We also found that loadings for the associative memory scores were higher than loadings for the item memory scores across all background valences (as indexed by the non-overlapping 95% CIs), suggesting a stronger relationship between grey matter volume and associative memory than item memory (Table 4). In terms of brain regions, the inferior frontal gyrus - pars opercularis loaded the highest, followed by the superior frontal gyrus, and finally the middle frontal gyrus, with no other regions loading significantly, suggesting that age-related variability in these regions contributes to age-related differences in memory. See Table S1 for results obtained while calculating associative memory as % Hits - % False Alarms.

For completeness, we also report the results from the other two models. For Model 1 (the MTL model), only the first canonical variate was significant ($p < 0.001$), and it explained 21.44% of the covariance between X and Y. Interestingly, the only region of the MTL with significant loadings in Model 1 was the parahippocampal cortex ($p = 0.008$). All of the memory score loadings (except item memory for objects that were superimposed on a positive background) were significant (p's < 0.05) and the difference between item and associative memory loadings was generally less pronounced than it was for Model 2 (see Fig. 1A). For Model3 (the joint MTL and PFC model), only the first canonical variate was significant ($p < 0.001$), and this model explained 36% of the covariance between X and Y. The brain regions with significant loadings in Model 3 were the parahippocampal cortex ($p = 0.028$), inferior frontal gyrus - pars opercularis ($p < 0.001$), middle frontal gyrus ($p = 0.01$), superior frontal gyrus ($p = 0.004$), and orbital sulci (H-shaped sulci) ($p = 0.034$). All of the memory score loadings (except item memory for objects that were superimposed on a positive background) were significant (p's < 0.05) and the difference between item and associative memory loadings was similar to the difference observed in Model 2.

Moderation Effects. For the best fitting model (Model 2), we also evaluated whether the relationship between PFC volume scores and memory scores remains after controlling for age and education, and whether the volume-performance relationship is moderated by the effects of either age or sex. For this purpose, we ran a moderation analysis testing the moderating effects of age and sex in the same model. Our results show that the model was significant ($R^2 = 0.542$, $F = 58.9$, $p < 0.001$; Table 5), with memory subject scores significantly predicted by PFC subject scores, age, sex, and education. However, the relationship between memory and PFC subject scores was not moderated by either age or sex (see Fig. 2). Importantly, PFC volume scores remained a significant predictor of memory scores ($B = 0.118$, $p = 0.046$), confirming that the relationship between frontal lobe volumes and memory is not simply driven by age.

4. Discussion

In this study, we evaluated the relationship between grey matter volume within substructures of the medial temporal and frontal lobes and individual differences in item and associative memory across the adult lifespan. As expected, age was negatively associated with both memory performance and grey matter volume. Nevertheless, in contrast to previous studies showing a disproportionate age effect on associative relative to item memory, we observed similar effects of age for both item and associative memory. We also observed an interaction between the effects of age and sex for associative memory, indicating that age-related differences in associative memory were more pronounced in men. Regarding age-related differences in grey matter volume, grey matter volume was negatively associated with age in all structures of the medial temporal (except the posterior hippocampus) and frontal lobes, and similar age-related differences were observed for both men and women. After testing the multivariate relationship between grey matter volumes and memory performance, our results showed that the structures of the PFC alone predicted memory performance better than either the structures of the MTL alone or the structures of the PFC and MTL combined. Our results also indicated that grey matter volume in the inferior frontal gyrus - pars opercularis, superior frontal gyrus, and middle frontal gyrus related most strongly to memory (particularly associative memory, which loaded more strongly than item memory) and this effect persisted when controlling for age. Finally, this relationship between frontal grey matter volume and memory was not moderated by age or sex.

In our study, associative memory performance was found to relate more strongly to grey matter volume in the PFC than structures in the MTL. This is in line with previous studies showing that grey matter volume in dorso- and ventrolateral prefrontal regions is a better predictor of associative memory performance in older adults than grey matter volume in MTL regions (Becker et al., 2015; Brehmer et al., 2020). The associative deficit hypothesis (ADH) suggests that age-related differences in episodic memory are largely due to impaired associative binding at encoding in older adults (Naveh-Benjamin, 2000). Although the MTL, especially the hippocampus, is critical for the binding process itself, the lateral PFC also supports binding through control functions at encoding and retrieval (Cabeza, 2006; Ranganath, 2010). The PFC undergoes several structural and functional changes during healthy aging that result in impaired aspects of cognitive control, including selective attention and inhibitory control (Zanto and Gazzaley, 2019; Hasher, 2016), which may lead older adults to form more irrelevant associations than younger adults (Campbell et al., 2010; Davis

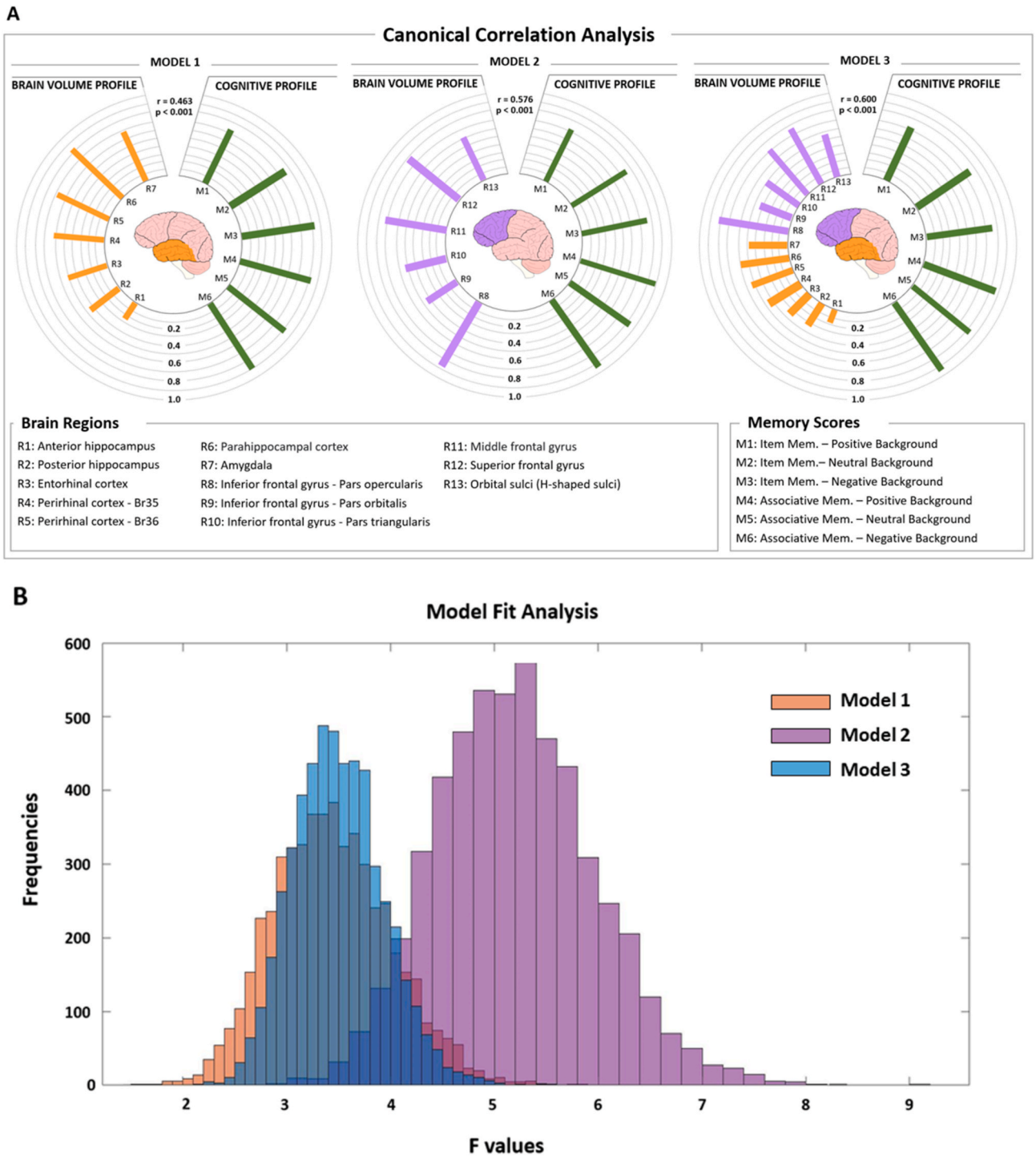

Fig. 1. Canonical Correlation Analysis (CCA) - The relationship brain volumes and memory performance. A) Heliograph of variate loadings (correlations) for the first canonical variate, where the size of the correlations is indicated by the length of the bars. Item Memory scores (% Hits – % False Alarms). Associative Memory scores (number of correctly recalled background scenes). The statistical relationships between brain structures (brain volume profile) and memory performance (cognitive profile) are for Model 1 ($r = 0.463$, $p < 0.001$), for Model 2 ($r = 0.576$, $p < 0.001$), and for Model 3 ($r = 0.600$, $p < 0.001$). B) Model Fit Analysis (Bootstrapping approach). Histogram showing the frequencies of F values (5000 occurrences per model), representing the distribution of the ratio of explained variance to unexplained variance for each model.

et al., 2021). In addition to guiding attention at encoding, control processes also play a critical role at retrieval, by guiding the memory search, rejecting familiar but incorrect responses, and overcoming interference (Castel and Craik, 2003; Cohn et al., 2008; Karl Healey et al., 2013). Our findings and those of previous studies which emphasize the role of the lateral PFC in associative memory in older adults (Becker et al., 2015; Brehmer et al., 2020) lend support to the idea that age differences in cognitive control are a primary contributor to impairments in episodic memory (Campbell et al., 2010; Hasher, 2016). These findings are also in line with the long-standing 'frontal lobe hypothesis' of aging (West, 2000), which points to the fact that structural declines are most pronounced in the PFC and age differences tend to be most pronounced for tasks that rely on frontal control mechanisms (Raz et al., 2005; Zanto and Gazzaley, 2019).

Table 4
Significance of the loadings of the CCA Model 2.

CCA Component	Description	Loadings Scores			
		Mean	SD	95% CI	p value
X (Grey Matter Volume)	Inferior frontal gyrus - Pars opercularis	0.8595	0.0535	[0.8578, 0.8609]	*0.011
	Inferior frontal gyrus - Pars orbitalis	0.4447	0.0900	[0.4421, 0.4472]	0.311
	Inferior frontal gyrus - Pars triangularis	0.5252	0.0915	[0.5226, 0.5277]	0.215
	Middle frontal gyrus	0.7507	0.0567	[0.7491, 0.7523]	*0.044
	Superior frontal gyrus	0.8031	0.0559	[0.8015, 0.8046]	*0.027
	Orbital sulci (H-shaped sulci)	0.6001	0.0855	[0.5977, 0.6024]	0.153
Y (Memory Scores)	Item Mem. – Positive Background	0.7561	0.0594	[0.7545, 0.7578]	0.064
	Item Mem. – Neutral Background	0.7921	0.0555	[0.7906, 0.7937]	*0.043
	Item Mem. – Negative Background	0.7952	0.0543	[0.7937, 0.7967]	*0.028
	Associative Mem. – Positive Background	0.9049	0.0379	[0.9039, 0.9060]	*0.002
	Associative Mem. – Neutral Background	0.8721	0.0447	[0.8708, 0.8733]	*0.004
	Associative Mem. – Negative Background	0.9542	0.0244	[0.9535, 0.9549]	*< 0.001

Table 5
Moderation analyses.

Outcome	Predictors	B	Std. Error	t	Sig.
Y - Cognitive Performance Profile (Memory Scores)	X - Grey Matter Volume Profile (Frontal Lobe Structures)	0.118	0.059	2.007	*0.046
	Age	−0.545	0.055	- 9.83	*< 0.001
	Sex	0.115	0.039	2.989	*0.003
	Volume Profile * Age	- 0.017	0.041	- 0.429	0.668
	Sex * Age	0.022	0.041	0.540	0.590
	Education	0.170	0.041	4.166	<0.001

Among the regions of interest in the PFC, our results show memory performance related most strongly to the inferior frontal gyrus - pars opercularis, followed by the superior frontal gyrus, and finally the middle frontal gyrus.[3] In addition to executive functions (e.g., working memory, inhibitory control, reorienting attention, etc.) and language, these regions have also been associated with semantic retrieval, episodic retrieval, and spatial processing (Boisgueheneuc et al., 2006; Natasha Rajah et al., 2011; Vatansever et al., 2021). Becker et al. (2015) found that both dorsolateral and ventrolateral regions of the PFC, which include all PFC regions of interest in our study, significantly accounted for individual differences in associative memory. In contrast, Brehmer et al. (2020) found the inferior frontal gyrus - pars triangularis and inferior frontal gyrus - pars orbitalis related to associative memory performance. Methodological differences might explain the differences across studies, including the age range of participants (a lifespan sample in our case vs. just older adults in these previous studies), memory task used (object-scene associations in our case vs. word-word, face-name, and object-scene in these previous studies), and statistical models employed. Despite these differences, it is interesting to note that in all cases, grey matter volume in the PFC was a stronger predictor of associative memory than that in the MTL.

Nevertheless, we *know* that the MTL is critical for associative memory, as suggested by multiple animal studies and brain damage work with humans (Mayes et al., 2007; Olsen et al., 2012), and one of the primary goals of this study was to examine the role of specific subregions within the MTL. Thus, we also evaluated the loadings from the MTL-only model (i.e., Model 1). Interestingly, the only region of the MTL with significant loading values was the parahippocampal cortex (PHC). The PHC encompasses a large area of the MTL and has reciprocal connections within the MTL, in addition to providing a major source of input to the entorhinal cortex and direct connections with the hippocampus (Aminoff et al., 2013). The parahippocampal cortex is also highly connected with the frontal cortex (which includes connections with the medial prefrontal cortex, dorsolateral prefrontal cortex, and orbitofrontal cortex) and the insula (Aminoff et al., 2013). The relationship between anatomical integrity of the PHC and episodic performance in older adults has previously been shown (Gorbach et al., 2017; Köhncke et al., 2021; Snytte et al., 2022). Functional neuroimaging studies also demonstrate the engagement of the PHC in associative memory tasks (Li et al., 2016), and in tasks involving spatial information about the environment, including viewing pictures of scenes and landmarks (Epstein and Kanwisher, 1998). Given that our study assessed associative memory for background scenes that were cued by associated objects at retrieval, it seems sensible that grey matter integrity in this region critical for scene processing predicted performance.

As expected, age was largely associated with a decrease in episodic memory performance in both men and women (Duarte and Dulas, 2020). However, our results showed that the age-related differences in associative memory were greater in men. This result is supported by previous work showing sex differences in episodic memory, with the magnitude of that difference varying based on the material to be remembered. Women usually outperform men on tasks that require verbal processing, while men outperform women on tasks requiring spatial processing (Asperholm et al., 2019). During the study phase of the current task, participants had to elaborate a story that linked the object to the scene, which relies on verbal processing. Thus, our finding that women outperformed men on this task fits with the general pattern in the literature. Sex differences in the age-related decline in episodic memory have also been attributed to sex difference in hippocampal volume (Zheng et al., 2017). In our study however, we did not observe sex differences in either the relationship between age and grey matter volume or the relationship between grey matter volume and memory performance. Thus, the observed age × sex interaction in predicting associative memory might have been due to some other factor, such as functional differences between men and women. For example, recent functional MRI work found sex differences in the effect of age on neural activity within several regions (including the PFC and parahippocampal gyrus) during the encoding and retrieval of face–location associations (Subramaniapillai et al., 2022). This is consistent with studies showing increasing reliance on functional network integrity to maintain performance despite progressive atrophy in aging (Bethlehem et al., 2020; Guardia et al., 2021; Liu et al., 2022; Tsvetanov et al., 2016, 2018) and neurodegeneration (Passamonti et al., 2019; Tsvetanov et al., 2020). Future studies should further examine the distinct contribution of regional grey matter differences, functional activity and connectivity to sex differences in associative memory across the lifespan.

Some limitations to the current study should be noted. First, we recognize that our cross-sectional design is not ideal for capturing the

[3] These regions are quite similar to the regions identified by Model 3, which also controlled for volumes in the MTL. The only additional regions identified by Model 3 were the orbital sulci and parahippocampal cortex.

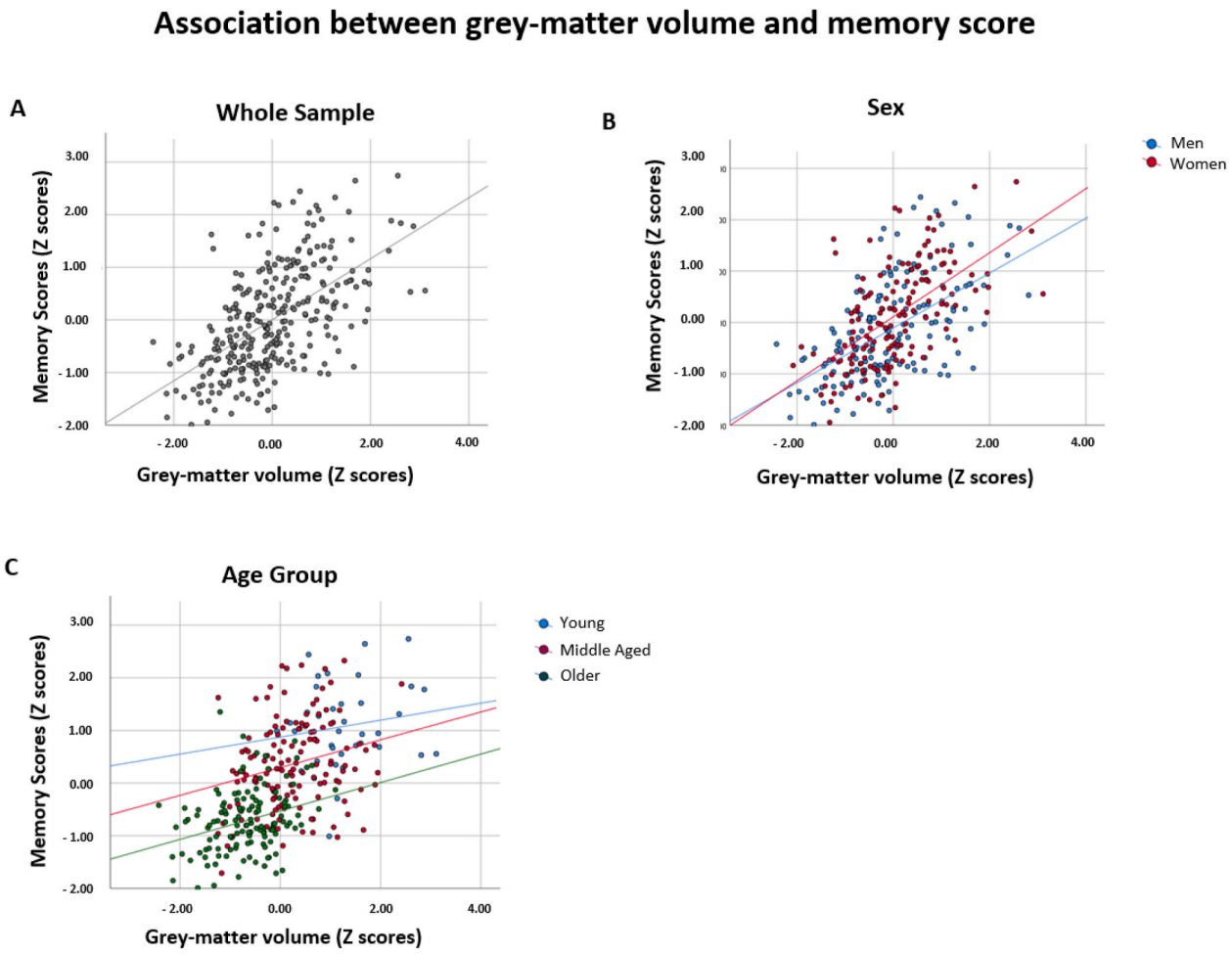

Fig. 2. Association between grey matter volume in frontal lobes (X) and memory scores (Y) (values expressed in Z scores) for A) Whole sample. B) Whole sample split by sex. C) Whole sample split by age groups (for illustrative purposes only; age was used as a continuous variable in the moderation model).

effects of causality; thus, our results should be interpreted with caution. Second, due to our large sample size, we used automated segmentation tools to obtain measures of grey matter volume in the MTL and PFC. Although such tools have been widely used, especially in large-scalebrain imaging initiatives, and have been reported to have competitive accuracy and reliability when compared to manual segmentation (Sederevičius et al., 2021; Yushkevich et al., 2015), we acknowledge the possibility of potential bias in these segmentation algorithms. Differences across segmentation protocols, especially regarding the localization of anatomical boundaries among structures, might also lead to differences across studies (Snytte et al., 2022; Xie et al., 2016; Yushkevich et al., 2015). In terms of sex differences, we only measured self-reported sex, but this fails to capture any independent effects of gender. The term "sex" refers to the biological characteristic of an individual assigned at birth (e.g., chromosomes, anatomy), while "gender" involves self-identity and is associated social roles (e.g., societal expectations for education, caregiver responsibilities, etc.) (Heidari et al., 2016). Future studies should ask about both sex at birth and gender-related social roles separately to better characterize their potential independent contributions to neurocognitive aging.

In conclusion, many factors contribute to age-related differences in episodic memory. Our findings suggest that structural differences within the frontal lobes in particular may be one of the critical factors.

Data and Code Availability Statement

The MRI dataset used in this work was acquired from the Cambridge Centre for Ageing and Neuroscience (Cam-CAN). Access to the Cam-CAM database can be requested at https://www.cam-can.org/. Analysis code currently being uploaded to GitHub (will be available by time of publication).

Declaration of competing interest

All authors declare no competing interests to disclose.

Data availability

Data and Code Availability Statement has been provided

Acknowledgements

The Cambridge Centre for Ageing and Neuroscience (Cam-CAN) was supported by the Biotechnology and Biological Sciences Research Council (grant number B/H008217/1). The authors are grateful to the Cam-CAN respondents and their primary care teams in Cambridge for their participation in this study. The authors also thank colleagues at the MRC Cognition and Brain Sciences Unit MEG and MRI facilities for their assistance.

Further, Tiago Guardia was supported by an Ontario Trillium Scholarship; Kamen A. Tsvetanov by the Guarantors of Brain (G101149); Rosanna Olsen by Canadian Institutes of Health Research (PJT 162292) and Natural Sciences and Engineering Research Council of Canada (RGPIN- 2017–06178) and Karen L. Campbell by the Canadian Institutes

of Health Research (PJT 180591), the Natural Sciences and Engineering Research Council of Canada (Grant RGPIN-2017-03804) and the Canada Research Chairs program.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynirp.2023.100168.

References

Aminoff, E.M., Kveraga, K., Bar, M., 2013. The role of the parahippocampal cortex in cognition. Trends Cognit. Sci. 17 (8), 379–390. https://doi.org/10.1016/j.tics.2013.06.009.

Asperholm, M., Högman, N., Rafi, J., Herlitz, A., 2019. What did you do yesterday? A meta-analysis of sex differences in episodic memory. Psychol. Bull. 145 (8), 785–821. https://doi.org/10.1037/bul0000197.

Bagarinao, E., Watanabe, H., Maesawa, S., Mori, D., Hara, K., Kawabata, K., Yoneyama, N., Ohdake, R., Imai, K., Masuda, M., Yokoi, T., Ogura, A., Taoka, T., Koyama, S., Tanabe, H.C., Katsuno, M., Wakabayashi, T., Kuzuya, M., Ozaki, N., et al., 2019. Reorganization of brain networks and its association with general cognitive performance over the adult lifespan. Sci. Rep. 9 (1), 11352 https://doi.org/10.1038/s41598-019-47922-x.

Becker, N., Laukka, E.J., Kalpouzos, G., Naveh-Benjamin, M., Bäckman, L., Brehmer, Y., 2015. Structural brain correlates of associative memory in older adults. Neuroimage 118, 146–153. https://doi.org/10.1016/j.neuroimage.2015.06.002.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false Discovery rate: a practical and powerful approach to multiple testing. J. Roy. Stat. Soc. B 57 (1), 289–300. http://www.jstor.org/stable/2346101.

Bethlehem, R.A.I., Paquola, C., Seidlitz, J., Ronan, L., Bernhardt, B., Consortium, C.-C., Tsvetanov, K.A., 2020. Dispersion of functional gradients across the adult lifespan. Neuroimage, 117299. https://doi.org/10.1016/j.neuroimage.2020.117299.

Boisgueheneuc, F. du, Levy, R., Volle, E., Seassau, M., Duffau, H., Kinkingnehun, S., Samson, Y., Zhang, S., Dubois, B., 2006. Functions of the left superior frontal gyrus in humans: a lesion study. Brain 129 (12), 3315–3328. https://doi.org/10.1093/BRAIN/AWL244.

Brehmer, Y., Nilsson, J., Berggren, R., Schmiedek, F., Lövdén, M., 2020. The importance of the ventromedial prefrontal cortex for associative memory in older adults: a latent structural equation analysis. Neuroimage 209, 116475. https://doi.org/10.1016/j.neuroimage.2019.116475.

Cabeza, R., 2006. Prefrontal and medial temporal lobe contributions to relational memory in young and older adults. In: Zimmer, H., Mecklinger, A., Lindenberger, U. (Eds.), Handbook of Binding and Memory: Perspectives from Cognitive Neuroscience. Oxford University Press.

Campbell, K.L., Hasher, L., Thomas, R.C., 2010. Hyper-binding: a unique age effect. Psychol. Sci. 21 (3), 399–405. https://doi.org/10.1177/0956797609359910.

Carr, V.A., Bernstein, J.D., Favila, S.E., Rutt, B.K., Kerchner, G.A., Wagner, A.D., 2017. Individual differences in associative memory among older adults explained by hippocampal subfield structure and function. Proc. Natl. Acad. Sci. U. S. A 114 (45), 12075–12080. https://doi.org/10.1073/pnas.1713308114.

Castel, A.D., Craik, F.I.M., 2003. The effects of aging and divided attention on memory for item and associative information. Psychol. Aging 18 (4), 873–885. https://doi.org/10.1037/0882-7974.18.4.873.

Chalfonte, B.L., Johnson, M.K., 1996. Feature memory and binding in young and older adults. Mem. Cognit. 24, 403–416.

Cohn, M., Emrich, S.M., Moscovitch, M., 2008. Age-related deficits in associative memory: the influence of impaired strategic retrieval. Psychol. Aging 23 (1), 93–103. https://doi.org/10.1037/0882-7974.23.1.93.

Cowell, P.E., Turetsky, B.I., Gur, R.C., Grossman, R.I., Shtasel, D.L., Gur, R.E., 1994. Sex differences in aging of the human frontal and temporal lobes. J. Neurosci. 14 (8), 4748. https://doi.org/10.1523/JNEUROSCI.14-08-04748.1994.

Davis, E.E., Foy, E.A., Giovanello, K.S., Campbell, K.L., 2021. Implicit associative memory remains intact with age and extends to target-distractor pairs. Aging Neuropsychol. Cognit. 28 (3), 455–471. https://doi.org/10.1080/13825585.2020.1782827.

DeMaster, D., Pathman, T., Lee, J.K., Ghetti, S., 2014. Structural development of the Hippocampus and episodic memory: developmental differences along the anterior/posterior Axis. Cerebr. Cortex 24 (11), 3036–3045. https://doi.org/10.1093/cercor/bht160.

Dennis, N.A., McCormick-Huhn, J.M., 2018. Item and associative memory decline in healthy aging. In: Stevens' Handbook of Experimental Psychology and Cognitive Neuroscience. Wiley, pp. 1–40. https://doi.org/10.1002/9781119170174.epcn110.

Driscoll, I., Hamilton, D.A., Petropoulos, H., Yeo, R.A., Brooks, W.M., Baumgartner, R.N., Sutherland, R.J., 2003. The aging Hippocampus: cognitive, biochemical and structural findings. Cerebr. Cortex 13 (12), 1344–1351. https://doi.org/10.1093/cercor/bhg081.

Duarte, A., Dulas, M.R., 2020. Episodic memory decline in aging. In: The Cambridge Handbook of Cognitive Aging. Cambridge University Press, pp. 200–217. https://doi.org/10.1017/9781108552684.013.

Duarte, A., Graham, K.S., Henson, R.N., 2010. Age-related changes in neural activity associated with familiarity, recollection and false recognition. Neurobiol. Aging 31 (10), 1814–1830. https://doi.org/10.1016/j.neurobiolaging.2008.09.014.

Efron, B., Tibshirani, R., 1986. Bootstrap methods for standard errors, confidence intervals, and other measures of statistical accuracy. Stat. Sci. 1 (1), 54–75. https://doi.org/10.1214/ss/1177013815.

Epstein, R., Kanwisher, N., 1998. A cortical representation of the local visual environment. Nature 392 (6676), 598–601. https://doi.org/10.1038/33402.

Fandakova, Y., Hartley, C., 2020. Mechanisms of learning and plasticity in childhood and adolescence. Dev. Cogn. Neurosci. 42, 100764 https://doi.org/10.1016/j.dcn.2020.100764.

Fandakova, Y., Lindenberger, U., Shing, Y.L., 2015. Maintenance of youth-like processing protects against false memory in later adulthood. Neurobiol. Aging 36 (2), 933–941. https://doi.org/10.1016/j.neurobiolaging.2014.10.022.

Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Ségonne, F., Salat, D.H., Busa, E., Seidman, L.J., Goldstein, J., Kennedy, D., Caviness, V., Makris, N., Rosen, B., Dale, A. M., 2004. Automatically parcellating the human cerebral cortex. Cerebr. Cortex 14 (1), 11–22. https://doi.org/10.1093/cercor/bhg087.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12 (3), 189–198. https://doi.org/10.1016/0022-3956(75)90026-6.

Freund & Pettman, 2010. Structural brain changes in aging: courses, causes and cognitive consequences. Rev. Neurosci. 21 (Issue 3).

Gorbach, T., Pudas, S., Lundquist, A., Orädd, G., Josefsson, M., Salami, A., de Luna, X., Nyberg, L., 2017. Longitudinal association between hippocampus atrophy and episodic-memory decline. Neurobiol. Aging 51, 167–176. https://doi.org/10.1016/j.neurobiolaging.2016.12.002.

Grady, C.L., Ryan, J.D., 2017. Age-related differences in the human Hippocampus: behavioral, structural and functional measures. In: Hannula, D.E., Duff, M.C. (Eds.), The Hippocampus from Cells to Systems: Structure, Connectivity, and Functional Contributions to Memory and Flexible Cognition. Springer International Publishing, pp. 167–208. https://doi.org/10.1007/978-3-319-50406-3_7.

Green, D.M., Swets, J.A., others, 1966. Signal Detection Theory and Psychophysics, vol. 1. Wiley, New York.

Guardia, T., Geerligs, L., Tsvetanov, K.A., Ye, R., Campbell, K.L., 2021. The role of the arousal system in age-related differences in cortical functional network architecture. Hum. Brain Mapp. https://doi.org/10.1002/HBM.25701.

Hasher, L., 2016. Inhibit. Deficit Hypoth. https://doi.org/10.1002/9781118528921.wbeaa259.

Head, D., Rodrigue, K.M., Kennedy, K.M., Raz, N., 2008. Neuroanatomical and cognitive mediators of age-related differences in episodic memory. Neuropsychology 22 (4), 491–507. https://doi.org/10.1037/0894-4105.22.4.491.

Heidari, S., Babor, T.F., de Castro, P., Tort, S., Curno, M., 2016. Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use. Res. Integrity and Peer Rev. 1 (1) https://doi.org/10.1186/s41073-016-0007-6.

Henson, R.N., Campbell, K.L., Davis, S.W., Taylor, J.R., Emery, T., Erzinclioglu, S., Tyler, L.K., Brayne, C., Bullmore, E.T., Calder, A.C., Cusack, R., Dalgleish, T., Duncan, J., Matthews, F.E., Marslen-Wilson, W.D., Rowe, J.B., Shafto, M.A., Cheung, T., Geerligs, L., et al., 2016. Multiple determinants of lifespan memory differences. Sci. Rep. 6 (1), 32527 https://doi.org/10.1038/srep32527.

Herlitz, A., Rehnman, J., 2008. Sex differences in episodic memory. Curr. Dir. Psychol. Sci. 17 (1), 52–56. https://doi.org/10.1111/j.1467-8721.2008.00547.x.

Hotelling, H., 1936. Relations between two sets of variates. Biometrika 28 (3/4), 321–377. https://doi.org/10.2307/2333955.

Karl Healey, M., Hasher, L., Campbell, K.L., 2013. The role of suppression in resolving interference: evidence for an age-related deficit. Psychol. Aging 28 (3), 721–728. https://doi.org/10.1037/a0033003.

Köhncke, Y., Düzel, S., Sander, M.C., Lindenberger, U., Kühn, S., Brandmaier, A.M., 2021. Hippocampal and parahippocampal gray matter structural integrity assessed by multimodal imaging is associated with episodic memory in old age. Cerebr. Cortex 31 (3), 1464–1477. https://doi.org/10.1093/cercor/bhaa287.

Koo, T.K., Li, M.Y., 2016. A guideline of selecting and reporting Intraclass correlation coefficients for reliability research. J. Chiropractic Med. 15 (2), 155–163. https://doi.org/10.1016/j.jcm.2016.02.012.

Lang, P.J., Bradley, M.M., Cuthbert, Greenwald, M., Dhman, A., Vaid, D., Hamm, A., Cook, E., Bertron, A., Petry, M., Bruner, R., Mcmanis, M., Zabaldo, D., Martinet, S., Cuthbert, S., Ray, D., Koller, K., Kolchakian, M., Hayden, S., 1997. International affective picture system (IAPS): technical manual and affective ratings. In: International Affective Picture System. IAPS.

Langnes, E., Vidal-Piñeiro, D., Sneve, M.H., Amlien, I.K., Walhovd, K.B., Fjell, A.M., 2019. Development and decline of the hippocampal long-Axis specialization and differentiation during encoding and retrieval of episodic memories. Cerebr. Cortex 29 (8), 3398–3414. https://doi.org/10.1093/cercor/bhy209.

Li, M., Lu, S., Zhong, N., 2016. The parahippocampal cortex mediates contextual associative memory: evidence from an fMRI study. BioMed Res. Int. 2016 https://doi.org/10.1155/2016/9860604.

Liljequist, D., Elfving, B., Roaldsen, K.S., 2019. Intraclass correlation – a discussion and demonstration of basic features. PLoS One 14 (7). https://doi.org/10.1371/journal.pone.0219854.

Liu, X., Tyler, L.K., Cam-Can, |, James, |, Rowe, B., Tsvetanov, K.A., 2022. Multimodal fusion analysis of functional, cerebrovascular and structural neuroimaging in healthy aging subjects. Hum. Brain Mapp. https://doi.org/10.1002/HBM.26025.

MacDonald, M.E., Pike, G.B., 2021. MRI of healthy brain aging: a review. In: NMR in Biomedicine, vol. 34. John Wiley and Sons Ltd. https://doi.org/10.1002/nbm.4564. Issue 9.

Maillet, D., Rajah, M.N., 2014. Age-related differences in brain activity in the subsequent memory paradigm: a meta-analysis. In: Neuroscience and Biobehavioral Reviews, vol. 45. Elsevier Ltd, pp. 246–257. https://doi.org/10.1016/j.neubiorev.2014.06.006.

Mayes, A., Montaldi, D., Migo, E., 2007. Associative memory and the medial temporal lobes. Trends Cognit. Sci. 11 (3), 126–135. https://doi.org/10.1016/j.tics.2006.12.003.

McDougall, G.J., Pituch, K.A., Stanton, M.P., Chang, W., 2014. Memory performance and affect: are there gender differences in community-residing older adults? Issues Ment. Health Nurs. 35 (8), 620–627. https://doi.org/10.3109/01612840.2014.895071.

Mioshi, E., Dawson, K., Mitchell, J., Arnold, R., Hodges, J.R., 2006. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. Int. J. Geriatr. Psychiatr. 21 (11), 1078–1085. https://doi.org/10.1002/gps.1610.

Natasha Rajah, M., Languay, R., Grady, C.L., 2011. Age-related changes in right middle frontal gyrus volume correlate with altered episodic retrieval activity. J. Neurosci. 31 (49), 17941–17954. https://doi.org/10.1523/JNEUROSCI.1690-11.2011.

Naveh-Benjamin, M., 2000. Adult age differences in memory performance: tests of an associative deficit hypothesis. J. Exp. Psychol. Learn. Mem. Cogn. 26 (5), 1170–1187.

Naveh-Benjamin, M., Mayr, U., 2018. Age-related differences in associative memory: empirical evidence and theoretical perspectives. In: Psychology and Aging, vol. 33. American Psychological Association, pp. 1–6. https://doi.org/10.1037/pag0000235. Issue 1.

Nilssen, E.S., Doan, T.P., Nigro, M.J., Ohara, S., Witter, M.P., 2019. Neurons and networks in the entorhinal cortex: a reappraisal of the lateral and medial entorhinal subdivisions mediating parallel cortical pathways. In: Hippocampus, vol. 29. John Wiley and Sons Inc, pp. 1238–1254. https://doi.org/10.1002/hipo.23145. Issue 12.

Nordin, K., Herlitz, A., Larsson, E.M., Söderlund, H., 2017. Overlapping effects of age on associative memory and the anterior hippocampus from middle to older age. Behav. Brain Res. 317, 350–359. https://doi.org/10.1016/j.bbr.2016.10.002.

Noulhiane, M., Piolino, P., Hasboun, D., Clemenceau, S., Baulac, M., Samson, S., 2007. Autobiographical memory after temporal lobe resection: neuropsychological and MRI volumetric findings. Brain 130 (12), 3184–3199. https://doi.org/10.1093/brain/awm258.

Nyberg, L., Lövdén, M., Riklund, K., Lindenberger, U., Bäckman, L., 2012. Memory aging and brain maintenance. Trends Cognit. Sci. 16 (5), 292–305. https://doi.org/10.1016/j.tics.2012.04.005.

Old, S.R., Naveh-Benjamin, M., 2008. Differential effects of age on item and associative measures of memory: a meta-analysis. Psychol. Aging 23 (1), 104–118.

Olsen, R., Moses, S., Riggs, L., Ryan, J., 2012. The hippocampus supports multiple cognitive processes through relational binding and comparison. Front. Hum. Neurosci. 6. https://www.frontiersin.org/article/10.3389/fnhum.2012.00146.

Park, H., Kennedy, K.M., Rodrigue, K.M., Hebrank, A., Park, D.C., 2013. An fMRI study of episodic encoding across the lifespan: changes in subsequent memory effects are evident by middle-age. Neuropsychologia 51 (3), 448–456. https://doi.org/10.1016/j.neuropsychologia.2012.11.025.

Passamonti, L., Tsvetanov, K.A., Jones, P.S., Bevan-Jones, W.R., Arnold, R., Borchert, R. J., Mak, E., Su, L., O'Brien, J.T., Rowe, J.B., 2019. Neuroinflammation and functional connectivity in Alzheimer's disease: interactive influences on cognitive performance. J. Neurosci. 39 (36), 2518–2574. https://doi.org/10.1523/jneurosci.2574-18.2019.

Poppenk, J., Moscovitch, M., 2011. A hippocampal marker of recollection memory ability among healthy young adults: contributions of posterior and anterior segments. Neuron 72 (6), 931–937. https://doi.org/10.1016/j.neuron.2011.10.014.

Rajah, M.N., Kromas, M., Han, J.E., Pruessner, J.C., 2010. Group differences in anterior hippocampal volume and in the retrieval of spatial and temporal context memory in healthy young versus older adults. Neuropsychologia 48 (14), 4020–4030. https://doi.org/10.1016/j.neuropsychologia.2010.10.010.

Ranganath, C., 2010. Binding items and contexts: the cognitive neuroscience of episodic memory. Curr. Dir. Psychol. Sci. 19 (3), 131–137. http://www.jstor.org/stable/41038556.

Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., Acker, J.D., 2005. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cerebr. Cortex 15 (11), 1676–1689. https://doi.org/10.1093/cercor/bhi044.

Rodrigue, K.M., Daugherty, A.M., Haacke, E.M., Raz, N., 2013. The role of hippocampal iron concentration and hippocampal volume in age-related differences in memory. Cerebr. Cortex 23 (7), 1533–1541. https://doi.org/10.1093/cercor/bhs139.

Saygin, Z.M., Kliemann, D., Iglesias, J.E., van der Kouwe, A.J.W., Boyd, E., Reuter, M., Stevens, A., van Leemput, K., McKee, A., Frosch, M.P., Fischl, B., Augustinack, J.C., Initiative, A.D.N., 2017. High-resolution magnetic resonance imaging reveals nuclei of the human amygdala: manual segmentation to automatic atlas. Neuroimage 155, 370–382. https://doi.org/10.1016/j.neuroimage.2017.04.046.

Schlichting, M.L., Guarino, K.F., Schapiro, A.C., Turk-Browne, N.B., Preston, A.R., 2017. Hippocampal structure predicts statistical learning and associative inference abilities during development. J. Cognit. Neurosci. 29 (1), 37–51. https://doi.org/10.1162/jocn_a_01028.

Sederevičius, D., Vidal-Piñeiro, D., Sørensen, Ø., van Leemput, K., Iglesias, J.E., Dalca, A. v., Greve, D.N., Fischl, B., Bjørnerud, A., Walhovd, K.B., Fjell, A.M., 2021. Reliability and sensitivity of two whole-brain segmentation approaches included in FreeSurfer – ASEG and SAMSEG. Neuroimage 237. https://doi.org/10.1016/j.neuroimage.2021.118113.

Shafto, M.A., Tyler, L.K., Dixon, M., Taylor, J.R., Rowe, J.B., Cusack, R., Calder, A.J., Marslen-Wilson, W.D., Duncan, J., Dalgleish, T., Henson, R.N., Brayne, C., Bullmore, E., Campbell, K., Cheung, T., Davis, S., Geerligs, L., Kievit, R., McCarrey, A., et al., 2014. The Cambridge Centre for Ageing and Neuroscience (Cam-CAN) study protocol: a cross-sectional, lifespan, multidisciplinary examination of healthy cognitive ageing. BMC Neurol. 14 (1) https://doi.org/10.1186/s12883-014-0204-1.

Shing, Y.L., Werkle-Bergner, M., Brehmer, Y., Müller, V., Li, S.C., Lindenberger, U., 2010. Episodic memory across the lifespan: the contributions of associative and strategic components. Neurosci. Biobehav. Rev. 34 (7), 1080–1091. https://doi.org/10.1016/j.neubiorev.2009.11.002.

Simons, J.S., Spiers, H.J., 2003. Prefrontal and medial temporal lobe interactions in long-term memory. Nat. Rev. Neurosci. 4 (8), 637–648. https://doi.org/10.1038/nrn1178.

Snytte, J., Fenerci, C., Rajagopal, S., Beaudoin, C., Hooper, K., Sheldon, S., Olsen, R.K., Rajah, M.N., 2022. 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. Neuroimage 254, 119164. https://doi.org/10.1016/j.neuroimage.2022.119164.

Squire, L.R., 2009. The legacy of patient H.M. for neuroscience. Neuron 61 (1), 6–9. https://doi.org/10.1016/j.neuron.2008.12.023.

Subramaniapillai, S., Rajagopal, S., Ankudowich, E., Pasvanis, S., Misic, B., Rajah, M.N., 2022. Age- and episodic memory-related differences in task-based functional connectivity in women and men. J. Cognit. Neurosci. 1–21 https://doi.org/10.1162/jocn_a_01868.

Ta, A.T., Huang, S.E., Chiu, M.J., Hua, M.S., Tseng, W.Y.I., Chen, S.H.A., Qiu, A., 2012. Age-related vulnerabilities along the hippocampal longitudinal axis. Hum. Brain Mapp. 33 (10), 2415–2427. https://doi.org/10.1002/hbm.21364.

Taylor, J.R., Williams, N., Cusack, R., Auer, T., Shafto, M.A., Dixon, M., Tyler, L.K., Cam-Can, Henson, R.N., 2017. The Cambridge Centre for Ageing and Neuroscience (Cam-CAN) data repository: structural and functional MRI, MEG, and cognitive data from a cross-sectional adult lifespan sample. Neuroimage 144, 262–269. https://doi.org/10.1016/j.neuroimage.2015.09.018.

Tsvetanov, K.A., Gazzina, S., Jones, P.S., van Swieten, J., Borroni, B., Sanchez-Valle, R., Moreno, F., Laforce Jr., R., Graff, C., Synofzik, M., Galimberti, D., Masellis, M., Tartaglia, M.C., Finger, E., Vandenberghe, R., de Mendonça, A., Tagliavini, F., Santana, I., Ducharme, S., the Genetic FTD Initiative, G, 2021. Brain functional network integrity sustains cognitive function despite atrophy in presymptomatic genetic frontotemporal dementia. Alzheimer's Dementia 17 (3), 500–514. https://doi.org/10.1002/alz.12209.

Tsvetanov, K.A., Gazzina, S., Jones, S.P., Swieten, J. van, Borroni, B., Sanchez-Valle, R., Moreno, F., Laforce, R., Graff, C., Synofzik, M., Galimberti, D., Masellis, M., Tartaglia, M.C., Finger, E., Vandenberghe, R., Mendonça, A. de, Tagliavini, F., Santana, I., Ducharme, S., (GENFI), T. G. F. T. D. I., 2020. Brain functional network integrity sustains cognitive function despite atrophy in presymptomatic genetic frontotemporal dementia. Alzheimer's Dementia. https://doi.org/10.1002/alz.12209.

Tsvetanov, K.A., Henson, R.N.A., Tyler, L.K., Razi, A., Geerligs, L., Ham, T.E., Rowe, J.B., 2016. Extrinsic and intrinsic brain network connectivity maintains cognition across the lifespan despite accelerated decay of regional brain activation. J. Neurosci. 36 (11), 3115–3126. https://doi.org/10.1523/JNEUROSCI.2733-15.2016.

Tsvetanov, K.A., Spindler, L.R.B., Stamatakis, E.A., Newcombe, V.F.J., Lupson, V.C., Chatfield, D.A., Manktelow, A.E., Outtrim, J.G., Elmer, A., Kingston, N., Bradley, J. R., Bullmore, E.T., Rowe, J.B., Menon, D.K., Group, T. C. N., BioResource, T. N. C.-19, Facility, T. C. N. C. R., & Collaboration, T. C.-N. B. C.-19., 2022. Hospitalisation for COVID-19 predicts long lasting cerebrovascular impairment: a prospective observational cohort study. medRxiv. https://doi.org/10.1101/2022.02.01.22270235, 2022.02.01.22270235.

Tsvetanov, K.A., Ye, Z., Hughes, L., Samu, D., Treder, M.S., Wolpe, N., Tyler, L.K., Rowe, J.B., 2018. Activity and connectivity differences underlying inhibitory control across the adult life span. J. Neurosci. 38 (36), 7887–7900. https://doi.org/10.1523/JNEUROSCI.2919-17.2018.

Tulving, E., 2002. Episodic memory: from mind to brain. Annu. Rev. Psychol. 53 (1), 1–25. https://doi.org/10.1146/annurev.psych.53.100901.135114.

Vatansever, D., Smallwood, J., Jefferies, E., 2021. Varying demands for cognitive control reveals shared neural processes supporting semantic and episodic memory retrieval. Nat. Commun. 12 (1) https://doi.org/10.1038/s41467-021-22443-2.

Voevodskaya, O., 2014. The effects of intracranial volume adjustment approaches on multiple regional MRI volumes in healthy aging and Alzheimer's disease. Front. Aging Neurosci. 6 (OCT) https://doi.org/10.3389/fnagi.2014.00264.

Ward, A.M., Mormino, E.C., Huijbers, W., Schultz, A.P., Hedden, T., Sperling, R.A., 2015. Relationships between default-mode network connectivity, medial temporal lobe structure, and age-related memory deficits. Neurobiol. Aging 36 (1), 265–272. https://doi.org/10.1016/j.neurobiolaging.2014.06.028.

West, R., 2000. In defense of the frontal lobe hypothesis of cognitive aging. J. Int. Neuropsychol. Soc. 6 (6), 727–729.

Xie, L., Wisse, L.E.M., Das, S.R., Wang, H., Wolk, D.A., Manjón, J. v, Yushkevich, P.A., 2016. Accounting for the Confound of Meninges in segmenting entorhinal and perirhinal Cortices in T1-weighted MRI. Medical Image Computing and Computer-Assisted Intervention : MICCAI International Conference on Medical Image Computing and Computer-Assisted Intervention 9901, 564–571. https://doi.org/10.1007/978-3-319-46723-8_65.

Yeung, L.K., Olsen, R.K., Hong, B., Mihajlovic, V., D'angelo, M.C., Kacollja, A., Ryan, J. D., Barense, M.D., 2019. Object-in-place memory predicted by anterolateral entorhinal cortex and parahippocampal cortex volume in older adults. J. Cognit. Neurosci. 31 (5), 711–729. https://doi.org/10.1162/jocn_a_01385.

Yushkevich, P.A., Pluta, J.B., Wang, H., Xie, L., Ding, S.-L., Gertje, E.C., Mancuso, L., Kliot, D., Das, S.R., Wolk, D.A., 2015. Automated volumetry and regional thickness analysis of hippocampal subfields and medial temporal cortical structures in mild cognitive impairment. Hum. Brain Mapp. 36 (1), 258–287. https://doi.org/10.1002/hbm.22627.

Zanto, T.P., Gazzaley, A., 2019. Aging of the frontal lobe. In: Handbook of Clinical Neurology, vol. 163. Elsevier B.V, pp. 369–389. https://doi.org/10.1016/B978-0-12-804281-6.00020-3.

Zheng, Z., Li, R., Xiao, F., He, R., Zhang, S., Li, J., 2017. Sex matters: hippocampal volume predicts individual differences in associative memory in cognitively normal older women but not men. Front. Hum. Neurosci. 11. https://www.frontiersin.org/article/10.3389/fnhum.2017.00093.

Zhuang, X., Yang, Z., Cordes, D., 2020. A technical review of canonical correlation analysis for neuroscience applications. Hum. Brain Mapp. 41 (13), 3807–3833. https://doi.org/10.1002/hbm.25090.