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Structural and functional sex differences in medial temporal lobe subregions at midlife

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Abstract

Background Research has increasingly recognized sex differences in aging and Alzheimer's Disease (AD) susceptibility. However, sex effects on the medial temporal lobe (MTL), a crucial region affected by aging and AD, remain poorly understood when it comes to the intricacies of morphology and functional connectivity. This study aimed to systematically analyze structural and functional connectivity among MTL subregions, which are known to exhibit documented morphological sex differences, during midlife, occurring before the putative pivotal age of cerebral decline. The study sought to explore the hypothesis that these differences in MTL subregion volumes would manifest in sex-related functional distinctions within the broader brain network.

Methods 201 cognitively unimpaired adults were included and stratified into four groups according to age and sex (i.e., Women and Men aged 40–50 and 50–60). These participants underwent comprehensive high-resolution structural MRI as well as resting-state functional MRI (rsfMRI). Utilizing established automated segmentation, we delineated MTL subregions and assessed morphological differences through an ANOVA. Subsequently, the CONN toolbox was employed for conducting ROI-to-ROI and Fractional Amplitude of Low-Frequency Fluctuations (fALFF) analyses to investigate functional connectivity within the specific MTL subregions among these distinct groups.

Results Significant differences in volumetric measurements were found primarily between women aged 40–50 and men of all ages, in the posterior hippocampus (pHPC) and the parahippocampal (PHC) cortex ($p < 0.001$), and, to a lesser extent, between women aged 50–60 and men of all ages ($p < 0.05$). Other distinctions were observed, but no significant differences in connectivity patterns or fALFF scores were detected between these groups.

Discussion Despite notable sex-related morphological differences in the posterior HPC and PHC regions, women and men appear to share a common pattern of brain connectivity at midlife. Longitudinal analyses are necessary to assess if midlife morphological sex differences in the MTL produce functional changes over time and thus, their potential role in cerebral decline.

Clinical trial number Not applicable.

Keywords Medial temporal lobe (MTL), Sex differences, Midlife, Volumetry, Connectivity

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Introduction

In recent years, the recognition of sex as a crucial biological variable has significantly shaped our understanding of both normative and pathological aging processes. Women and men exhibit notable disparities in disease prevalence, onset and manifestation of symptoms, as well as treatment responses [1]. For instance, even after accounting for the longer life expectancy of women, women are twice as susceptible to Alzheimer's Disease (AD) compared to men [2–4]. This heightened vulnerability has spurred extensive research into the structural variation within the medial temporal lobe (MTL) subregions, which are particularly and precociously affected in aging and AD [5], as a potential physiological explanation of this increased risk. Notably, sex differences have been documented in these regions, with studies indicating that women typically have larger hippocampal volumes, especially in the posterior hippocampus, compared to men when normalized for total intracranial volume [6]. Similar differences are observed in the parahippocampal cortex, where women often exhibit greater volumes than men [7]. However, findings have been inconclusive. While some studies have reported larger hippocampal volumes in men compared to women (for a meta-analysis, see [8]), this difference dissipates, or even reverses, when these volumes are adjusted for Total Intracranial Volume (TIV) [1, 9, 10]. Thus, it may be necessary to refine our assessment of the hippocampal region by examining the hippocampal subfields and surrounding cortex individually. Although our study does not directly measure AD markers, understanding these sex differences in MTL structure and connectivity may reveal early changes linked to aging and AD risk. Doing so would allow us to understand the distinct functional connectivity of these areas, which support various cognitive functions that are affected differently by AD.

In research on aging and AD, structural magnetic resonance imaging (MRI) is commonly used to study changes in the MTL, which can serve as one of the markers for tracking the disease's progression [11, 12]. Essential areas of the MTL include the hippocampus (HPC), the entorhinal cortex (ERC), the perirhinal cortex (PRC), and the parahippocampal cortex (PHC) [13, 14]. These areas play pivotal roles in cognitive functions such as memory and spatial navigation [6, 7]. The hippocampus is frequently studied as a unified structure, despite an increasing body of literature highlighting substantial differences in terms of morphology and connectivity between its anterior and posterior Sects. [14–17]. Furthermore, the focus has predominantly been on the hippocampus and entorhinal cortex (for a meta-analysis, see [5]), and particularly in older populations (those aged about 60 and above). This age demarcation indicates a significant shift towards a stronger negative correlation between age and aspects of cerebral morphology, such as cortical surface area [18], brain volume [19], and particularly hippocampal volume [20]. Considering that age is the most significant risk factor for the late onset of Alzheimer's disease, examining typical markers of this condition, like the volume of MTL subregions in the pre-senescence period (between 40 and 60 years), is critical. Such investigation in middle-aged individuals is key to identifying the earliest indicators of neurodegenerative processes. The time period between the ages of 40 and 60 is also especially critical for women as it coincides with major hormonal shifts and a number of related biological changes accompanying menopause [21–23], making this a critical transitional phase for in-depth examination.

It is widely acknowledged that anatomical changes in the MTL have significant implications for its functional connectivity with the broader brain network [14, 24, 25]. Specifically, anatomical changes in the MTL notably influence its functional connectivity, which correlates with episodic memory performance and may serve as an early marker for predicting cognitive aging trajectories. It has been documented that as individuals age, the hippocampal connectivity network established before the age of 30 undergoes a shift in the course of aging (after the age of 60), reflecting a functional reorganization of cerebral connectivity [26]. The precise timing of this shift remains to be elucidated, underscoring a crucial gap in our understanding of the hippocampal function across the adult lifespan.

It has also been demonstrated that sex has a substantial impact, not only on the anatomical and cognitive aspects related to the hippocampus [1, 27], but also on the configuration of connectivity patterns across the brain [3, 28], independent of age [15]. Considering that the functional organization of hippocampal networks is intricate and extends across major brain networks [14], and thereby significantly impacts a wide range of cognitive functions that may potentially decline with age [29], investigating whether sex-specific morphological differences could exert an influence on these connectivity patterns during midlife holds considerable importance. This study aims to provide valuable insights into identifying early markers of brain vulnerability, unraveling potential mechanisms that contribute to age-related cognitive vulnerability, and laying the foundation for the development of early interventions.

Therefore, this study was designed to systematically analyze the fine-grained functional connectivity (FC) among MTL subregions known to exhibit documented morphological sex differences and the broader brain network in a cohort of middle-aged adults. We hypothesize that disparities in the volumes of MTL subregions between women and men would indeed manifest in their functional organization with the rest of the brain

and that differences in functional organization will emerge between women and men, as well as between the younger and older women within our cohort. To test these hypotheses, we conducted a comprehensive examination of the structural and functional distinctions based on sex during midlife by employing a refined and precise segmentation technique, along with an analysis of resting-state fMRI.

Materials and methods

Participants

A total of 409 adults, ranging in age from 40 to 62, were enrolled in a study investigating the neural impacts of metabolic syndrome, with the prevalence of cardiometabolic disorders in the cohort closely resembling that of the general population. Among them, this study included 201 cognitively unimpaired participants, consisting of 134 women and 133 men, who were categorized into four groups: Women 1 and Men 1 (40–50 years) and Women 2 and Men 2 (50–60 years), as detailed in Table 1. The age stratification was chosen to better capture potential age-related specificities and differences, particularly considering menopause in women (with an average onset age of slightly over 50 in white women from industrialized countries; [22, 23, 30]). Although a questionnaire was used to assess menopausal status, we based the groupings on the average predictive age of menopause from the literature due to the known limitations of self-reported data. Details on the questionnaire are provided in Supplementary Table 1. The selection of these participants was based on specific inclusion criteria: (1) age range from 40 to 60; (2) absence of MRI contraindications; (3) a Mini-Mental State Examination (MMSE [31]), score of >24, ensuring intact cognitive function. Participants with any neurological (such as Parkinson's Disease, Epilepsy, Huntington's Disease, etc.), major psychiatric diseases, or history of substance abuse were excluded from the study. Participants provided their medical history information via self-report questionnaires, and they underwent a neuropsychological evaluation, brain imaging, and a general health assessment. The assessments and imaging sessions were conducted in separate visits, with most participants completing the entire study within a month. Prior to enrollment, all participants provided written informed consent, and the Institutional Review Board at the University of Texas at Austin granted approval for all study procedures (#2011-07-0025).

Table 1 Summary of the demographics of the study participants

	Women 1 (40–50)	Women 2 (50–60)	Men 1 (40–50)	Men 2 (50–60)
N	53	47	57	44
Age	43.4 ± 2.8 [40, 49]	54.6 ± 3.1 [50, 60]	44.6 ± 2.9 [40, 49]	55.6 ± 2.9 [50, 60]
Education (Years)	16.2 ± 2.6 [10, 22]	15.7 ± 2.3 [10, 21]	15.9 ± 2.6 [12, 24]	16.4 ± 2.7 [10, 24]
MMSE (/30)	28.6 ± 1.7 [24, 30]	28.5 ± 1.6 [25, 30]	28.6 ± 1.4 [25, 30]	28.8 ± 1.4 [24, 30]
Race, *n* (%)				
Non-Hispanic White	27 (51%)	32 (68%)	33 (58%)	29 (66%)
Hispanic	12 (23%)	8 (17%)	11 (19%)	7 (16%)
African American	7 (13%)	5 (11%)	5 (9%)	2 (5%)
Multi-racial	0 (0%)	0 (0%)	1 (2%)	1 (2%)
Other	7 (13%)	2 (4%)	7 (12%)	5 (11%)

Note. Values are mean ± standard deviation and ranges. Race/ethnicity data are presented as n (%)

MRI data acquisition

Participants underwent a high-resolution scan using a SIEMENS 3T Skyra MRI scanner equipped with a 32-channel head coil. This scan included a structural scan (MPRAGE) with a 256×256 matrix, a 7° flip angle, a field-of-view (FOV) of 24×24 cm^2, 1 mm slice thickness, and no gap. Additionally, participants completed a 6-minute resting-state functional MRI scan, characterized by a repetition time (TR) of 3000 ms, a time to echo (TE) of 30 ms, a FOV of 24×24 cm^2, a 64×64 matrix, 42 axial slices, a 3 mm slice thickness, and a 0.3 mm gap. During this functional MRI scan, participants were instructed to keep their eyes open and fixate on a central crosshair.

MTL structural processing

Automatic segmentation of MTL subregions

We used ITK-SNAP version 3.8.0, an automated segmentation tool available at www.itksnap.org, to delineate various MTL subregions [32]. These subregions included the aHPC and pHPC (anterior and posterior HPC), the ERC, the PHC, and the Brodmann areas 35 and 36 (as components of the PRC). Including Brodmann areas 35 and 36 allowed us to target specific regions of the PRC involved in memory, enhancing the interpretability of our findings. The segmentation process was conducted using a specific atlas known as ASHS-PMC-T1 1.0.0, which was tailored for Hippocampus and MTL cortex (ERC, PRC, PHC) segmentation in 3 Tesla T1-weighted MRI scans. Following automated segmentation, rigorous quality control was conducted by visually evaluating the segmentation of each subregion for all participants. Independent reviews were performed by two experienced researchers, and segmentations were cross-referenced with neuroanatomical atlases to ensure accuracy (see Fig. 1 for an example, Supplementary material). The TIV was also calculated via ITK-SNAP (sum of the volumes of gray matter, white matter, and cerebrospinal fluid).

Volumetric statistical analyses

All statistical analyses were conducted using R (version 4.2.1; R Core Team, 2022). Morphological differences in volumes of MTL subregions among the four groups

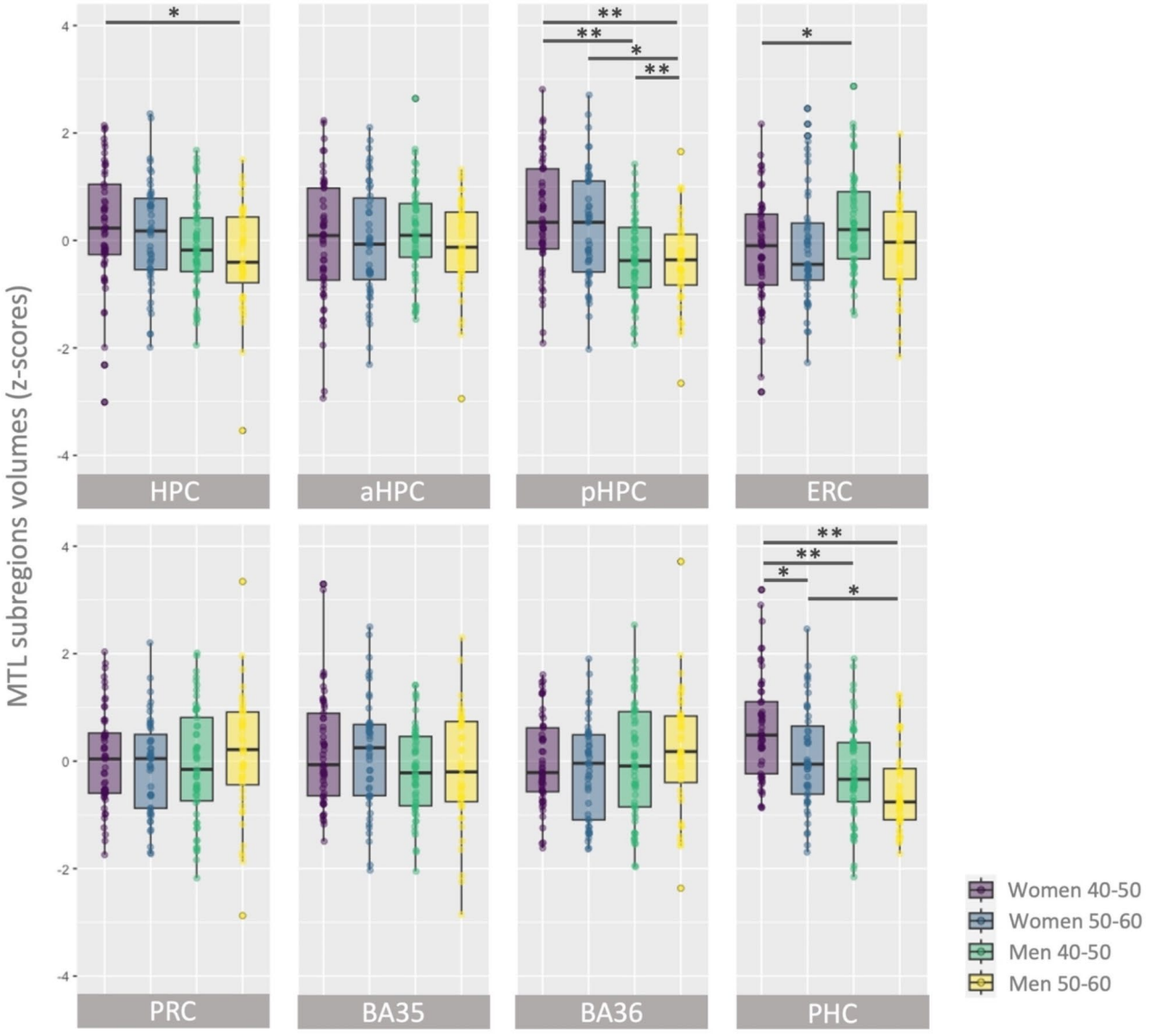

Fig. 1 Comparison of Medial Temporal Lobe subregions, illustrating z-transformed TIV-normalized volumes. Note. Significance levels indicated as $^{**}p < 0.001$ and $^{*}p < 0.05$ (Bonferroni-adjusted post-hoc t-tests). HPC: Hippocampus; aHPC: anterior; pHPC: posterior; ERC: Entorhinal Cortex; PRC: Perirhinal Cortex; BA: Brodmann Area; PHC: Parahippocampal Cortex

(Women 1, Women 2, Men 1, and Men 2) were assessed via analysis of variance (ANOVA) corrected with a Bonferroni adjustment. To streamline the analysis and enhance statistical robustness, volumes from both the left and right hemispheres within each subregion were averaged. The total volume of the entire HPC was determined by summing the volumes of the anterior and posterior HPC subregions. Similarly, the volumes of Brodmann areas 35 and 36 were aggregated to estimate the PRC volume. For standardization and to account for individual variations in head size, the raw bilateral volumes were normalized by the TIV. This normalization involved dividing the raw volume by TIV and subsequently applying a z-transformation to enhance comparability among the various MTL subregions. ANOVA analyses were also conducted on the Education and MMSE variables to ensure comparability among the four groups. ANOVA was conducted to compare all groups comprehensively, but our primary focus was on the specific comparisons most relevant to our hypotheses.

MTL connectivity processing

Functional and structural image data were preprocessed and analyzed using the CONN toolbox [33] in SPM (version 12.7771, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). The preprocessing of functional Magnetic

Resonance Imaging (fMRI) data included the following steps: realignment with correction for susceptibility distortion interactions, slice timing correction, outlier detection, direct segmentation, MNI-space normalization, and smoothing with gaussian filter kernel (full width at half maximum=6 mm). Functional data underwent denoising through a standard denoising pipeline where noise components from white matter and cerebral spinal fluid, head motion, and scrubbing effects were identified and removed separately for each voxel and each subject scan. Connectivity was calculated using Pearson correlation, with partial correlation employed to control for confounding factors such as head motion and physiological noise. Significant connectivity patterns were identified using a statistical threshold ($p<0.001$ voxel-level, p-FDR<0.05 cluster-size). The comprehensive procedural details, distributed under a Public Domain Dedication license (CC0 1.0) are available on the CONN toolbox website (https://web.conn-toolbox.org/resources/citing-conn; refer to the Document 1 in Supplementary Material 1).

ROI-to-ROI (Region Of Interest) and fALFF (Fractional Amplitude of Low-Frequency Fluctuations) analyses were performed on this toolbox.

ROI-to-ROI analyses

This approach involves assessing how the ROIs interact and communicate with each other, providing insights into neural networks [34]. At the first-level analysis, ROI-to-ROI connectivity matrices were estimated to characterize functional connectivity patterns. We conducted a specific ROI-to-ROI analysis to explore functional connectivity between distinct MTL subregions and the entire brain. We pre-defined four ROIs based on their relevance to the research question and their prior segmentation using automated techniques. Specifically, these ROIs were defined as the bilateral PHC and posterior HPC. These ROIs were obtained from https://neurovault.org/collections/3731/ [35] and closely approximated the segmentations acquired during our automated segmentation for these subregions (refer to Fig. 2 in the Supplementary material). We used NeuroVault ROIs to ensure consistency with validated atlases, enhancing comparability and reducing biases across studies. Group-level analyses were subsequently conducted using a General Linear Model (GLM). To assess the effects comprehensively, we estimated F-statistics for our ROIs using a GLM that covered the entire brain. Our analyses included comparisons among the four groups (Women 1, Women 2, Men 1, and Men 2), as well as separate analyses for each group. Results were thresholded using a combination of a cluster-forming threshold at $p<0.001$ (voxel-level) and a familywise corrected p-FDR<0.05 (cluster-size threshold).

fALFF analyses

The fALFF technique quantifies low-frequency fluctuations in brain signals and measures the fraction of the fMRI signal within the range of slow waves [36]. Motion and noise correction were applied using a comprehensive denoising pipeline to ensure accurate fALFF measurements. This method offers insights into intrinsic brain activity that complement traditional functional connectivity analyses. At the first-level, the fALFF was calculated for each voxel. This is the ratio of the amplitude of low-frequency fluctuations to the total amplitude across a defined frequency range, typically in the low-frequency band. The fALFF values were computed on all the participants and extracted for our specific MTL ROIs to conduct group-level analyses in R. We averaged fALFF values from the left and right hemispheres within each subregion. We performed an ANOVA to compare the fALFF values among the four groups within the two regions of interest, the PHC and the posterior HPC. A Bonferroni correction was applied.

Results

Demographics

Summary of the demographics of the study participants can be found in Table 1. There was a significant age difference between our young and old groups ($p<0.001$) based on ANOVA, which was the intended categorization of our study. However, no significant age differences existed between men and women within the same age groups. ANOVA comparison was non-significant for the Education ($p=0.574$) and MMSE (0.823) variables.

Sex related structural differences in MTL subregions

MTL raw volumes, TIV and comparison of MTL volumes adjusted for TIV can be found in Table 2. Comparison of MTL subregions (z-transformed TIV-normalized volumes) can be seen in Fig. 1. ANOVA analyses comparing the volumetric measurements of MTL subregions among our four groups yielded significant differences ($p<0.001$) for the pHPC and the PHC between Women 1 and Men 1, Women 1 and Men 2. Additionally, significant differences ($p<0.05$) were observed for the pHPC between Women 2 and Men 1, Women 2 and Men 2, and for the PHC between Women 2 and Men 2. Notably, a significant difference was also detected between Women 1 and Women 2 for the PHC ($p=0.02$). Women 1 and Men 2 also exhibited significant differences in the total volume of the HPC ($p=0.034$). The subgroups of women consistently differed significantly ($p<0.001$) in terms of TIV from the subgroups of men (women having a smaller TIV). In all other comparisons, no significant differences were observed (Table 2).

Table 2 Medial Temporal Lobe raw volumes, total intracranial volume and comparison of medial temporal lobe volumes adjusted for total intracranial volume

	Women 1	**Women 2**	**Men 1**	**Men 2**	***P* values**					
	(40-50)	**(50-60)**	**(40-50)**	**(50-60)**	**W1 vs. W2**	**W1 vs. M1**	**W1 vs. M2**	**W2 vs. M1**	**W2 vs. M2**	**M1 vs. M2**
Mediotemporal subregions volumetry										
HPC (total)	1652.2 ± 188.8	1701.2 ± 145.4	1780.2 ± 160.3	1791 ± 221.3	1	0.342	0.034*	1	0.249	1
	[1118.4, 2151.8]	[1393.9, 2002.9]	[1422.2, 2283.9]	[1305.3, 2247.9]						
Anterior HPC	1695.4 ± 248.6	1783.8 ± 250.8	1920.3 ± 247.3	1904.4 ± 284.8	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*
	[1031.5, 2379.8]	[1205.3, 2316.3]	[1447.8.5, 2710.5]	[1290.3, 2530.8]						
Posterior HPC	1637.7 ± 227	1672.3 ± 160.5	1691.5 ± 166.7	1728.9 ± 200.9	1	<0.001**	<0.001**	0.011*	0.007*	1
	[1142.8, 2275.8]	[1292.8, 2029.8]	[1343.5, 2174]	[1282.3, 2127]						
ERC	543.1±75.4	577.1±85.3	629.4±77	604.9±83	1	0.041*	1	0.127	1	0.193
	[390.5, 712.8]	[418.5, 752]	[488.3, 854.5]	[425.8, 799.3]						
PRC (total)	1637.7 ± 227	1672.3 ± 160.5	1691.5±166.7	1728.9 ±200.9	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*
	[1142.8, 2275.8]	[1292.8, 2029.8]	[1343.5, 2174]	[1282.3, 2127]						
BA35	599.3 ± 99.3	620.4 ± 111.1	619.3 ± 78.9	629 ± 96.7	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*
	[387.8, 862]	[371.3, 921 0.5]	[428, 802.3]	[393.5, 860.5]						
BA36	1735.4 ± 245.7	1809.3 ± 287	1994.9 ± 390.2	2045.8 ± 401.4	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*
	[1193.3, 2246.8]	[1167.5, 2523.8]	[1142.8, 2904.8]	[1416, 3602.3]						
PHC	1056.3 ± 139.4	1031 ± 125.7	1054.8 ± 141.9	1049.7 ± 117.1	0.02*	<0. 001**	<0.001**	0.657	0.018*	0.705
	[796.5, 1376.5]	[757.5, 1296.8]	[753.3, 1357.8]	[835.3, 1423.5]						
Total Intracranial Volume										
TIV	1.4e+6 ± 114,077	1.4e+6 ± 116,603	1.5e+6±115,468	1.6e+6 ± 140,148	0.084	<0.001**	<0.001 **	<0.001**	<0.001**	0.876
	[1.1e+6, 1.6e+6]	[1.1e+6, 1.7e+6]	[1.3e+6, 1.8e+6]	[1.3e+6, 1.8e+6]						

Note. Values are mean ± standard deviation and ranges.

P values refer to significant analysis of variance (ANOVA) of Medial Temporal Lobe (MTL) subregions volumes adjusted for Total Intracranial Volume (TIV), followed by post hoc pairwise comparisons with Bonferroni correction; ns: non-significant analysis before post hoc comparisons; *$p < 0.05$, **$p < 0.001$;

W1: Women 1, 40–50; W2: Women 2, 50–60; M1: Men 1, 40–50; M2: Men 2, 50–60; HPC: Hippocampus; aHPC: anterior; pHPC: posterior; ERC: Entorhinal Cortex; PRC: Perirhinal Cortex; PHC: Parahippocampal Cortex.

Common connectivity pattern based on sex and age in ROI-to-ROI analyses

Results from our ROI-to-ROI connectivity analyses, the inter-group comparisons (W1, W2, M1, and M2) did not withstand a False Discovery Rate (FDR) correction. This suggests that the observed differences in connectivity patterns between these groups, although visually notable, did not reach statistical significance after adjusting for multiple comparisons.

When examining the connectivity of our ROIs, PHC and pHPC, with the rest of the brain in each group, we consistently found a similar pattern of connections (Fig. 2). These connections are extensive and involve various brain regions (see Tables 2, 3, 4 and 5, Supplementary material), including the Default Mode Network (DMN; pHPC, PHC, precuneous cortex, bilateral inferior temporal gyrus and medial frontal cortex), the visual network (the bilateral lingual gyrus, lateral occipital, occipital fusiform gyrus, and Heschl's gyrus), and the salience network (the bilateral supramarginal gyrus, insular cortex, frontal operculum cortex, and anterior cingulate cortex).

No group differentiation in fALFF analyses

Results from our ANOVA comparisons of fALFF scores across the four groups within our two regions of interest (PHC and pHPC) revealed no statistically significant differences (Fig. 3).

Discussion

This study investigated sex-specific differences in brain volumetry and connectivity at midlife in key regions associated with aging and AD, focusing on the critical age ranges marking the transition to cerebral aging. Our study revealed morphological distinctions in the pHPC and PHC between women and men at midlife. Notably, these differences in brain structure did not translate into differences in the connectivity patterns of these regions with the entire brain in our sample.

A detailed analysis and comparison of MTL subregion volumetrics revealed significant differences between women aged 40 to 50 and men, and, to a lesser extent, between women aged 50 to 60 and men, in key regions that have been previously described as sex-dependent in the literature [6, 10, 37]. Specifically, when adjusting for TIV, the posterior HPC and PHC showed larger volumes in women compared to men, highlighting the importance of adjusting raw brain region values when working with a mixed-sex sample of participants, due to the significant disparity in TIV between sexes.

The observed volumetric differences in the pHPC are particularly interesting due to their implications for network dynamics. Furthermore, previous studies with conflicting or inconsistent results regarding sex differences in total HPC volume may find a potential explanation in the anterior-posterior distinction of this structure, both in terms of volume and functionality [6, 10]. These results underscore the importance of using suitable

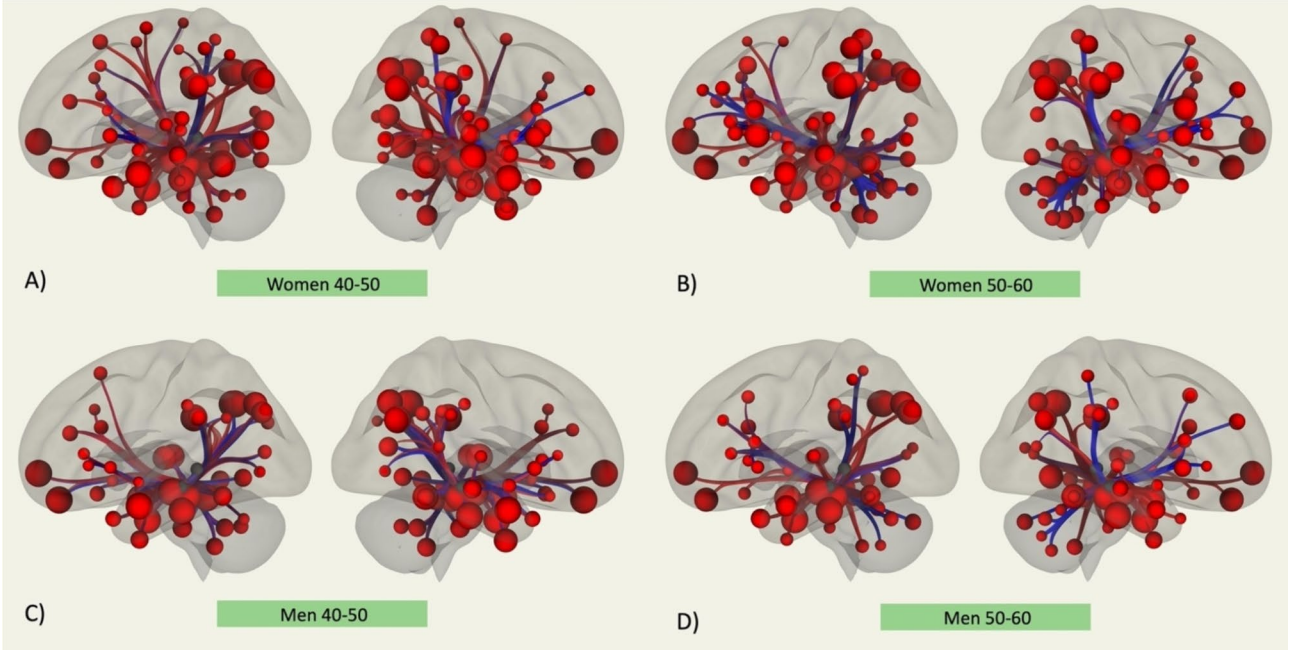

Fig. 2 Common connectivity patterns based on sex and age in ROI-to-ROI analyses. Note. F-statistic with threshold at $p < 0.001$ (voxel-level) and a familywise corrected p-FDR < 0.05 (cluster-size threshold). Networks involved include the Default Mode Network, Visual Network, and Salience Network. The corresponding statistics are depicted in Supplementary material, Tables 2, 3, 4 and 5

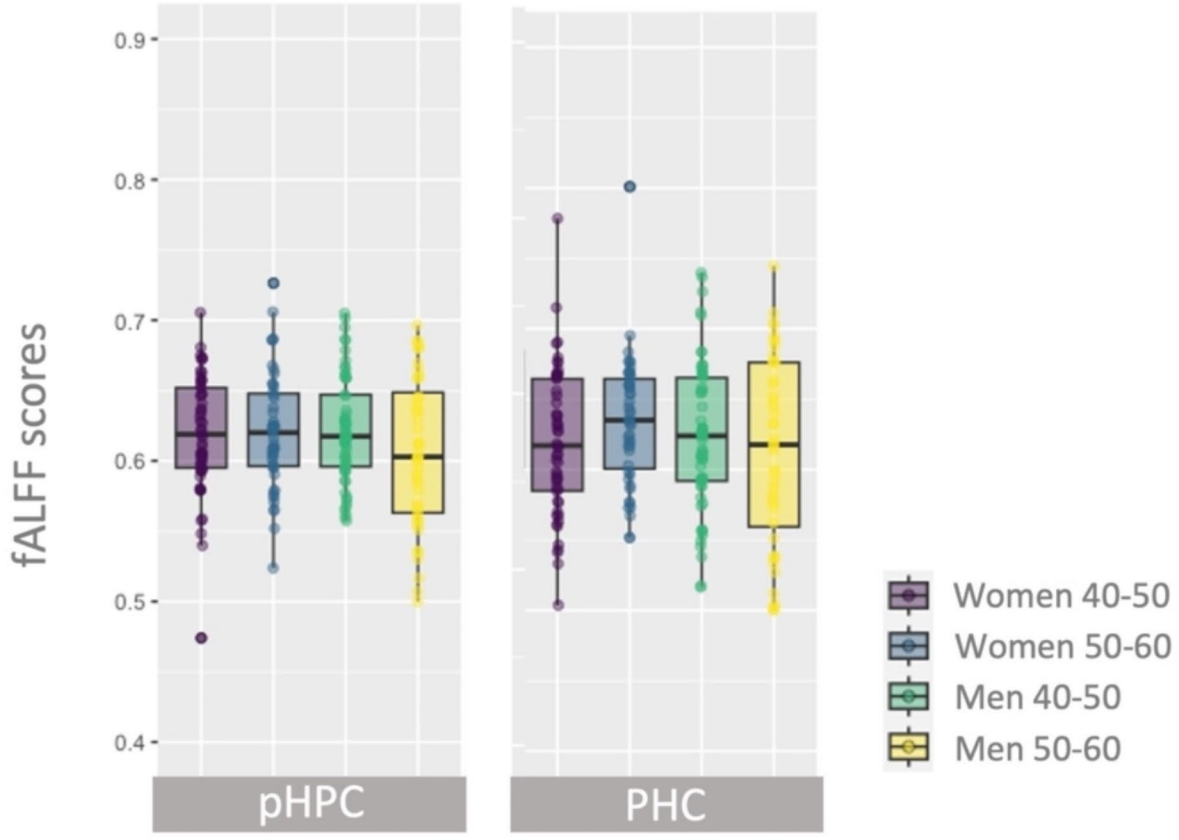

Fig. 3 Absence of significant differences in fractional Amplitude of Low-Frequency Fluctuations (fALFF) scores across the four groups within the two regions of interest. Note. Bonferroni-adjusted post-hoc t-tests. pHPC: posterior Hippocampus; PHC: Parahippocampal cortex

neuroimaging tools to segment the HPC accurately to obtain values for both the anterior and posterior portions of the HPC, rather than studying it as a whole [38]. Although hormonal changes during menopause are recognized to impact cognition, brain structure, and function in mid-life women [25], our study did not find any differences between our groups of younger (40–50) and older (50–60) women regarding this subregion.

As part of the posterior medial network, crucial for spatial information and scene processing [7], the PHC's volumetric differences suggest that it may be more susceptible to age-related changes than its anterior counterpart [39]. Our data support this observation, as the sole volumetric differences detected in the MTL subregions among age groups pertain to the PHC, with significantly larger volumes in the younger women (40–50) even after adjusting for TIV. It has been suggested that volumetric changes may occur within the substructures comprising the hippocampus/parahippocampus in early menopausal women [40, 41], potentially accounting for this difference. A reduction in parahippocampal functional connectivity has even been noted in postmenopausal women [28]. Further investigations should involve linking the results with the menopausal status of the women.

In our analyses of connectivity patterns, we specifically examined the connections originating from our primary regions of interest: the pHPC and the PHC. These analyses aimed to uncover how these two crucial regions interacted among themselves and with various other brain regions. Despite bigger relative volume in these subregions in women, they did not show greater FC than men with the rest of the brain. However, within each group (women and men aged 40–50 and 50–60), our results revealed noteworthy connectivity patterns ($p<0.05$, FDR corrected). Importantly, these patterns were similar in each group and involved the PHC and pHPC, emphasizing their roles in distinct functional brain networks. Notably, the analyses identified a robust connectivity pattern with the default mode network (DMN) with strong connections to DMN key regions like the precuneous cortex, the bilateral inferior temporal gyrus and the medial frontal cortex. This suggests a significant role for the PHC and pHPC in the coordination of processes related to memory consolidation, self-reflection, and

introspective thought, all of which are prominent functions of the DMN [42, 43].

We also observed significant associations between these two subregions and networks that are related to cognitive and sensory processing, underscoring the intricate interplay of the PHC and pHPC with these broader brain networks. This includes the visual network, which plays a role in visual processing and object recognition [44], and the salience network, associated with detecting and orienting attention toward relevant stimuli [45]. These findings contribute to our understanding of how the pHPC and PHC are involve in a variety of cognitive and sensory processes and their potential implications in both typical and pathological aging.

The analyses comparing fALFF values within our four groups in the PHC and pHPC regions significantly complement our ROI-to-ROI connectivity analyses. While connectivity analyses inform us about the functional interactions between different brain regions, the fALFF analyses delve into the intrinsic characteristics of these regions by assessing low-frequency fluctuations in amplitude [36]. By combining these two approaches, we gain a more comprehensive view of the functional connectivity between brain regions and how intrinsic activity varies across different demographic groups and age ranges. Intrinsic activity in the PHC and pHPC regions, as reflected in consistent fALFF values across the groups, thus highlights enduring physiological stability. This combined analysis allows us to explore both functional connectivity and region-specific features, contributing to a deeper understanding of the underlying neurobiology in our observations. The results indicate that, in terms of fALFF, these specific brain regions do not exhibit significant variations among our distinct groups. This information is therefore valuable in understanding the stability and consistency of resting-state brain activity in these regions across our groups.

One limitation of this study pertains to the sample size. Indeed, with the categorization of our four groups specific to our study design, the group sizes are relatively constrained to detect subtle connectivity differences between the groups. Furthermore, this study would benefit from additional information, particularly regarding the menopausal status of women and their levels of estrogen and testosterone, to provide supplementary explanatory factors for the differences observed between the two age groups in women. Given that our menopause data was based on self-reported questionnaires, which are known to lack precision, we chose to rely on the predicted average age of menopause from the literature to form our groups. While this approach was appropriate, a more precise method could have enhanced the accuracy of our groupings. Additionally, although we collected data on race and ethnicity, these variables were not included in our analyses due to an imbalance in representation across the groups, which could have affected the statistical power. Lastly, this study is cross-sectional and would benefit from longitudinal data to assess whether our morphological and functional results change with the advancing age of our participants.

Conclusion

This study adds to our understanding of sex-related specificities and underscores the significance of employing appropriate analytical tools for investigating MTL subregions. These insights not only contribute valuable knowledge but also open up promising avenues for future research, particularly in delving into the intricate interplay among sex, age, and the structural-functional relationships within the brain. Conducting longitudinal analyses could provide insights into whether morphological sex differences in the MTL during midlife remain unchanged over time or ultimately lead to distinct aging patterns.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12868-024-00905-9.

Supplementary Material 1

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Author contributions

Marie Caillaud conducted the analyses, prepared the figures, generated the tables, and wrote the main manuscript text. Isabelle Gallagher contributed to the analyses and data organization. Janelle Foret participated in the theoretical discussion and data analysis. Andreana P. Haley supervised the entire project and guided the theoretical discussion. All authors reviewed the manuscript and approved its final version.

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Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki, and the Institutional Review Board at the University of Texas at Austin granted approval for all study procedures (#2011-07-0025). Written informed consent was obtained from all participants.

Consent to publish

Not applicable.

Competing interests

The authors declare no competing interests.

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