Sex differences in age- and episodic memory-related effects on task-based functional connectivity

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Abstract

Healthy aging is associated with episodic memory decline. However, little is known about sex differences in the effect of normative aging on memory-related brain network dynamics. Here, we used a data-driven multivariate partial least squares (PLS) connectivity analysis to identify similarities and differences in the effect of biological sex on age- and memory-related differences in task-based fMRI connectivity during encoding and retrieval of face-location associations (spatial context memory). Aging was associated with episodic memory decline in both sexes, but there were no significant sex or sex-by-age interactions in memory performance. The connectivity results show that men exhibited greater between-network connectivity with advanced age, which was detrimental to memory performance. Women exhibited reduced connectivity between visual and higher order cognitive networks with advanced age, which was detrimental to memory performance. Therefore, there are sex differences in the effect of age on episodic memory-related connectivity.

Key words: lifespan, sex differences, context memory, encoding, retrieval, fMRI, functional connectivity

Introduction

Our ability to encode, store, and retrieve information about past events in rich spatial and temporal contextual detail (episodic memory) is critical to our identity (Tulving, 2002). If we did not remember our past, we would have a poor understanding of ourselves and the environment, which would in turn impact our ability to plan for the future (Schacter et al., 2012), establish strong interpersonal relationships (Jing, Madore, & Schacter, 2020; Mano et al., 2011), and participate in daily activities (Dong, Wilson, De Leon, & Evans, 2010). Healthy aging is associated with episodic memory decline (Grady & Craik, 2000). These memory losses impair older adults' quality of life, daily functioning, and sometimes lead to detrimental health effects (Mol et al., 2007; Mol, van Boxtel, Willems, & Jolles, 2006). Given that the proportion of elderly adults is increasing worldwide, there is an urgent need to understand how normative aging influences memory and brain function. Such knowledge provides the necessary groundwork for distinguishing normative from pathological differences in memory and brain function and can provide insight for future intervention studies aimed at supporting episodic memory function in late life.

To this aim, there has been significant research directed at understanding how normative aging affects episodic memory and associated brain function. Behavioural studies have shown that older adults experience greater deficits in their ability to recollect spatial and temporal contextual details of past events (i.e., context memory), compared to their ability to recognize previously encountered events or items (recognition memory; Old & Naveh-Benjamin, 2008; Spencer & Raz, 1995). Studies of task-based functional magnetic resonance imaging (fMRI) activity have found that age-related differences in episodic memory performance are associated with age differences in regional brain activation in a distributed set of brain regions (e.g., medial temporal lobes [MTL], prefrontal cortex [PFC], inferior parietal cortex [IPC]; Ankudowich, Pasvanis, & Rajah, 2016, 2017; Grady et al., 2010; Hayama, Vilberg, & Rugg, 2012; Johnson & Rugg, 2007; Rajah, Crane, Maillet, & Floden, 2011; Rajah, McIntosh, & Grady, 1999; Spaniol et al., 2009). Moreover, with the growing consensus that human

cognition and behaviour depends on the dynamic interactions of large-scale neural networks (Friston, 1994; McIntosh, 2000; Mesulam, 1990; Sporns & Betzel, 2016; Strother, Kanno, Rottenberg, Friston, & Ford, 1995), recent studies have increasingly focused on how age differences in inter-regional or inter-network correlations in brain activity (functional connectivity) relate to episodic memory ability.

Many studies to date have investigated functional connectivity using resting state fMRI (rsfMRI) data and have explored how temporal correlations of blood-oxygen-level-dependent (BOLD) time series between brain regions and canonical brain networks (Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995; Power et al., 2011; Yeo et al., 2011; Uddin, Yeo, & Spreng, 2019) differ with age, and how this relates to cognitive performance as assessed by neuropsychological tests or pre/post scan. In general, these rsfMRI connectivity studies have found that older adults show greater inter-network and reduced within-network functional connectivity compared to younger adults (Allen et al., 2011; Antonenko & Flöel, 2013; Betzel et al., 2014; Cao et al., 2014; Chan, Park, Savalia, Petersen, & Wig, 2014; Damoiseaux, 2017; Ferreira et al., 2016; Geerligs, Renken, Saliasi, Maurits, & Lorist, 2015; Grady, Sarraf, Saverino, & Campbell, 2016; King et al., 2018; Ng, Lo, Lim, Chee, & Zhou, 2016; Siman-Tov et al., 2017; Spreng, Stevens, Viviano, & Schacter, 2016; Stumme, Jockwitz, Hoffstaedter, Amunts, & Caspers, 2020; Tian, Li, Wang, & Yu, 2018). This loss of functional specialization with aging is thought to reflect decreases in efficient information processing (Bullmore & Sporns, 2012; Sporns, 2013), and has been linked to reduced task performance on several cognitive domains, including episodic memory (Chan et al., 2014; Damoiseaux et al., 2008; Geerligs et al., 2015; He et al., 2012; Mevel et al., 2013; Onoda, Ishihara, & Yamaguchi, 2012; Spreng et al., 2016).

Much of this research assessing functional connectivity differences with age have found an important relationship between the default mode network (DMN) and the dorsal attention network (DAN), particularly during cognitive task performance (Amer, Anderson, Campbell, Hasher, & Grady, 2016; Damoiseaux, 2017; Dixon et al., 2017; Esposito et al., 2018; Spreng et al., 2016). The DMN is commonly involved in internally directed cognitive processes, and thus typically suppressed during

externally directed cognitive tasks, when more task-relevant networks (i.e., DAN) are recruited (Andrews-Hanna, Smallwood, & Spreng, 2014). Importantly, the frontoparietal network (FPN) is thought to regulate the interaction between the DAN and DMN by switching these networks on and off to support cognition (Avelar-Pereira, Bäckman, Wåhlin, Nyberg, & Salami, 2017; Dixon et al., 2017; Grady et al., 2016). Task-based and rsfMRI analyses have revealed that reduced DAN-DMN anticorrelations, possibly as a consequence of disrupted FPN engagement, is generally associated with worse cognitive performance and greater distractibility, particularly among older adults (Amer, Campbell, & Hasher, 2016; Avelar-Pereira et al., 2017; Dixon et al., 2017; Esposito et al., 2018; Fox et al., 2005; Grady et al., 2016; Prakash, Heo, Voss, Patterson, & Kramer, 2012; Sala-Llonch et al., 2012; Spreng et al., 2016).

This pattern of age-related increases in coupling of default and cognitive control networks is consistent with the default-executive coupling hypothesis of aging (DECHA; Turner & Spreng, 2015), which is thought to reflect older adults' greater reliance on self-referential semantic knowledge to support cognitive performance in the face of age-related declines in fluid cognition (Spreng et al., 2018; Turner & Spreng, 2015). Crucially, if access to semantic knowledge is relevant to the ongoing task, such as during creative thought, default-executive coupling may support task performance in older adults (Adnan, Beaty, Lam, Spreng, & Turner, 2019; Spreng et al., 2014). Conversely, if retrieval of prior knowledge contributes to greater distractibility among participants, this pattern of default-executive coupling either relates to worse cognitive performance, as confirmed by task-based analyses of cognitive domains assessing planning (Tower of London task; Turner & Spreng, 2015), visuospatial judgment task, and fluid intelligence (Rieck, Rodrigue, Boylan, & Kennedy, 2017), or greater semanticized recall of autobiographical memory (Spreng et al., 2018).

Network dynamics may further be modulated by the specific cognitive domain tested (Varangis, Habeck, & Stern, 2021). For example, a recent study by Varangis and colleagues (2021) assessed participants' (20-80 years) performance across 11 in-scanner tasks of vocabulary, processing speed,

fluid reasoning, and episodic memory. Functional connectivity was measured by calculating 1) average correlations within-/between-networks, 2) segregation of the networks, and 3) global efficiency and modularity. Although older adults performed significantly worse than younger adults on the episodic memory tasks, there was very little effect of age on functional connectivity measures during performance of these memory tasks. Instead, there were more robust effects of age on functional connectivity during participants' performance of the fluid reasoning tasks. Their findings highlight that the choice of cognitive task can have a significant impact on functional connectivity differences in aging. Taken together, although both task and rsfMRI connectivity studies have shown age-related dedifferentiation in intrinsic connectivity related to cognitive performance declines, functional connectivity may differ based on the specific task involved and how these networks dynamically adapt to accomplish these tasks. However, few studies have applied functional connectivity analysis to adult lifespan task fMRI data collected while participants encoded and retrieved episodic context memories, despite research indicating that associative context memory deficits are a hallmark of aging and emerge at midlife.

In addition, past task fMRI connectivity studies of episodic memory have assumed that age-related differences in functional connectivity were the same in women and men, since data were not disaggregated by sex and/or gender. However, recent studies indicate that there may be sex differences in the effect of age on memory-related brain function (Rabipour, Rajagopal, Pasvanis, & Rajah, 2021; Subramaniapillai et al., 2019). This is not surprising given that episodic memory deficits are observed in neurodegenerative diseases that exhibit sex differences in prevalence: women are disproportionately affected by Alzheimer's (Alzheimer's Association, 2020), while greater numbers of men have Parkinson's Disease (Cerri, Mus, & Blandini, 2019). Sex differences in the prevalence of these diseases highlight the need to investigate the neural underpinnings of age-related episodic memory decline separately in women and men to inform the current models of healthy aging based on sex-aggregated

113 data, and to provide important insight into sex-specific aging processes (Subramaniapillai, Almey,
114 Rajah, & Einstein, 2021).

115 Previous studies have reported sex differences in rsfMRI intrinsic connectivity, with women
116 showing greater functional connectivity within the DMN (Allen et al., 2011; Bluhm et al., 2008; Filippi
117 et al., 2013; but see Weissman-Fogel, Moayedi, Taylor, Pope, & Davis, 2010). In contrast, some
118 evidence points to greater connectivity in sensorimotor networks in men (Filippi et al., 2013; Allen et
119 al., 2011; but see Tomasi & Volkow, 2012). One study reported sex differences in functional networks
120 across a wider age range of participants (18-65 years; Scheinost et al., 2015). Although both women
121 and men generally showed resting state functional connectivity decreases with age in the DMN, men
122 showed greater age-related deficits in this network. In contrast, men and women showed divergent age-
123 related functional connectivity differences in the FPN (Scheinost et al., 2015). These sex differences in
124 connectivity may act as important biomarkers for disorders such as Alzheimer's or Parkinson's Disease
125 (Cerri et al., 2019; Damoiseaux et al., 2012), thus emphasizing the need to clarify sex-related
126 differences in healthy aging to distinguish normal from atypical processes.

127 We have previously used Partial Least Squares (PLS) activation analyses to examine age-, sex-
128 and performance-related patterns of whole-brain *activation* across the adult lifespan (Ankudowich,
129 Pasvanis, & Rajah, 2017; Subramaniapillai et al., 2019). In brief, we found that across individuals,
130 activity in regions of lateral PFC, parietal, and ventral visual cortex supported performance, but to a
131 greater extent in young adulthood than in later stages (Ankudowich et al., 2017). Moreover, we found
132 that when older individuals showed age-related increases in task-related activity across distributed
133 areas of lateral PFC, parietal, and MTL, it did not necessarily support performance. More specifically,
134 during retrieval, age-related increases in hippocampal activity were related to worse memory
135 performance. When we explicitly investigated the role of sex differences on spatial context memory
136 performance in our adult lifespan cohort, we found that these generalized age-related increases and
137 decreases in lateral fronto-parietal cortices, medial PFC, and MTL brain activity across encoding and

retrieval were specific to women (Subramaniapillai et al., 2019). Notably, despite there being sex differences in the effect of age on memory-related brain activation, there were no behavioural sex differences in context memory accuracy. Across studies, we concluded that our findings of more diffuse, distributed task-related activity in older adulthood, particularly in women, was generally consistent with the dedifferentiation theory of aging (Geerligs et al., 2015; Li, Lindenberger, & Sikström, 2001; Park et al., 2012; St-Laurent et al., 2011).

Whereas these previous studies undertaken in our lab have aimed to identify whole-brain patterns of task-related *activity* that differ across the adult lifespan, the focus of the current study is to understand how whole-brain patterns of task-related *connectivity* directly relate to context memory performance across the adult lifespan. Although functional connectivity is typically assessed at rest, the current study proposes a method of investigating functional connectivity, which examines task-related functional connectivity after regressing the mean task-related activity from the fMRI signal to account for task-timing-driven statistical associations (Cole et al., 2019). To derive independent effects of age and performance, as these two variables might be confounded (Rugg, 2017), we orthogonalized the continuous variables of age and retrieval accuracy. We then submitted these orthogonalized terms to a multivariate PLS connectivity analysis to identify whole-brain patterns of connectivity amongst 216 parcellated regions based on the Power et al (2011) atlas during encoding and retrieval, maximally relating age and accuracy on the spatial context memory task separately in women and men across the adult lifespan.

The current methodological approach allows us to differentiate patterns of task-based memory-related connectivity that reflect both age, sex, and performance effects in a data-driven way. With this approach, we expect to find: i) similarities in performance-related task-based connectivity in both sexes (Subramaniapillai et al., 2019), ii) age-related decreases in within-network connectivity and increases in between-network connectivity that will be associated with poorer memory performance (Geerligs et al., 2015), and indicative of a generalization and/or dedifferentiation of function in the aging brain (Li

et al., 2001), and iii) there will be sex differences in the networks exhibiting age-related increases in between-network connectivity that relate to poorer memory performance. We also predict that there will be sex differences in age-related patterns of task-based functional connectivity that also support memory performance with advanced age, which may be indicative of compensation in the aging brain (Subramaniapillai et al., 2019). Importantly, this investigation allows us to compare functional activation at the brain regional level (Subramaniapillai et al., 2019) with respect to task-related functional connectivity at the network level to determine whether these findings complement each other at these different scales of analysis.

Methods

The original cohort consisted of 161 community-dwelling cognitively normal participants between the ages of 19-76 years. We excluded middle-aged women who self-reported having irregular periods, symptoms of menopausal transition, and who had undergone hormone replacement therapy (HRT; n=20) since menopause transition and HRT influences memory-related brain activity (Henderson, 2010; R. Li, Cui, & Shen, 2014; Rentz et al., 2017; Yonker et al., 2006). Our final cohort consisted of 141 participants (65% women) between the ages of 19-76 years (mean age = 47.11, SE = 1.41, mean education = 15.73 years, SE = 0.18). Participants reported no history of neurological or psychological illness, or serious cardiovascular disease. All participants were right-handed, as confirmed by the Edinburgh Inventory for Handedness.

Since this sample did not comprise a balanced sex ratio and was limited by the smaller proportion of men (35%) who participated in the study, we used the cohort of 48 men and matched them with a cohort of women based on age and educational attainment to have a balanced sample of women and men. Closely matching women and men by their education level also accounts for its strong involvement as a reserve contributor in driving sex differences in performance (see Subramaniapillai et al., 2021 for gendered contribution of education as a reserve contributor).

Therefore, this matched subsample consisted of 96 participants between the ages of 19-76 years (mean age = 46.92 [SE, 1.77], mean education = 16 years [SE, 2.0]). This sample comprised 32 young adults (19-35 years, mean age = 26.34, [SE, 0.56], mean education = 16.59 [SE, 0.26] years), 32 middle-aged adults (40 – 58 years, mean age = 47.09 [SE, 0.92], mean education = 15.63 [SE, 0.32] years), and 32 older adults (60 – 76 years, mean age = 67.34 [SE, 0.66], mean education = 15.78 [SE, 0.42] years).

Participation in the study involved two separate testing sessions, conducted on different days. During an initial session, participants underwent neuropsychological assessment (Mini-International Neuropsychiatric Interview [MINI], inclusion cutoff =/< 2; the Folstein Mini Mental State Examination [MMSE], exclusion cutoff < 27; the Beck Depression Inventory [BDI], exclusion cutoff < 15; California Verbal Learning Task [CVLT], exclusion cut-off based on recommendations by Norman, Evans, Miller, & Heaton (2000). Only participants who met the above neuropsychological criteria and performed above chance on the practice context memory task returned to the testing center to complete the fMRI scanning portion of the study. All participants gave their informed consent and were paid, and the ethics board of the Faculty of Medicine at McGill University approved the study protocol.

Behavioural Methods

Stimuli and Procedure

The task stimulus set has been used in previous studies and has been independently rated for pleasantness (Kwon et al., 2016; Rajah, Languay, & Valiquette, 2010). Stimuli consisted of black-and-white photographs of faces that were varied in age and balanced for age and sex across experimental conditions. Each face presented during initial encoding was tested during subsequent retrieval, and participants were scanned during both encoding and retrieval memory phases. A detailed description of the task paradigm used in the current study can be found in previous studies from our lab (Ankudowich et al., 2016, 2017).

Using a mixed rapid event-related design, participants were scanned across 12 experimental runs while they encoded and retrieved the spatial and temporal details of faces. Each run consisted of an 'easy' temporal context memory task (TE) and an 'easy' spatial context memory task (SE), and either a 'hard' temporal context memory task (TH) or a 'hard' spatial context memory task (SH). Easy and hard tasks differed in the number of stimuli to be encoded: 6 encoding stimuli for 'easy' tasks and 12 encoding stimuli for 'hard' tasks. Encoding was intentional, and at the start of each encoding phase, participants were cued (9 sec) to memorize either the spatial location (whether a face appeared on the *LEFT* or the *RIGHT* during encoding) or the temporal order (whether a face appeared *LEAST* or *MOST* recently during encoding) of the faces and to the level of task difficulty. At encoding, each face was presented (2 sec) on either the left or the right of a central fixation cross. There was a variable inter-trial interval (ITI) of 2.2 – 8.8 sec. During encoding, participants were instructed to rate the pleasantness of each face during encoding. Participants pressed a button with their right thumb to indicate a pleasant response and a button with their left thumb to indicate a neutral response using an MRI-compatible fiber optic response box. Between encoding and retrieval memory phases, participants performed a one-minute distractor task in which they were required to reverse alphabetize two words presented centrally on the computer screen. The distractor task was used to deter participants from actively rehearsing the encoding stimuli.

Following the distractor task, participants were presented with task instructions for retrieval (9 sec) to remind participants of the temporal and/or spatial context task demands. During retrieval, participants were presented with pairs of previously encoded faces for 6 sec. One of the faces was presented above a central fixation cross, and the other was presented below. During the easy versions of the retrieval task, participants viewed 3 pairs of faces, and during the hard versions of the retrieval task they viewed 6 pairs of faces. There was a variable ITI of 2.2 – 8.8 sec between retrieval events. For the spatial task, participants were asked to indicate which of the two faces was originally presented on the *LEFT/RIGHT*. For the temporal task, participants were asked to indicate which of the two faces

238 was originally presented *LEAST/MOST* recently. Participants pressed a button under their right thumb
239 to indicate a face at the top of the screen and they pressed a button under their left thumb to indicate a
240 face at the bottom of the screen. Therefore, fMRI task-related activation was collected for 8 different
241 event-types in this experiment: encoding spatial easy (eSE), encoding temporal easy (eTE), encoding
242 spatial hard (eSH), encoding temporal hard (eTH), retrieval spatial easy (rSE), retrieval temporal easy
243 (rTE), retrieval spatial hard (rSH), retrieval temporal hard (rTH).
244
245 ***Task fMRI Imaging methods***
246 Structural and functional magnetic resonance imaging data were collected at the Douglas
247 Institute Brain Imaging Centre. Participants lied supine in a 3T Siemens Magnetom Trio scanner and
248 wore a standard 12-channel head coil. T1-weighted anatomical images were first acquired for each
249 participant at the start of the scanning session using a 3D gradient echo MPRAGE sequence (TR =
250 2300 msec, TE = 2.98 msec, flip angle = 9°, FOV = 256, 176 1 mm sagittal slices, 1 × 1 × 1 mm
251 voxels). Blood-oxygen-level-dependent (BOLD) images were acquired with a single-shot T2*-
252 weighted gradient echo-planar imaging (EPI) pulse sequence (TR = 2000 msec, TE = 30 msec, FOV =
253 256, matrix size = 64 × 64, in-plane resolution 4 × 4 mm, 32 oblique slices per whole-brain volume)
254 while participants performed the context memory tasks. Visual task stimuli were back-projected onto a
255 screen in the scanner bore using E-Prime software, and participants requiring correction for visual
256 acuity wore plastic corrective lenses. A variable ITI (2.2 – 8.8 sec) was introduced to add jitter to
257 event-related acquisitions.
258
259 *fMRI Basic Preprocessing*
260 Reconstructed images were preprocessed in SPM version 8 software. The first 5 scans
261 (approximately 10 seconds) were discarded in order to allow for steady state magnetization of tissue.
262 For each participant, the origin of functional images was reoriented to the anterior commissure of that

individual's acquired T1-weighted structural image. All functional images were then realigned to the first image, and motion artifacts were corrected using a 6-degree rigid-body transformation (three translation and three rotational parameters). Any experimental run in which within-run motion exceeded 1.5 mm was excluded from analysis. Functional images were then normalized to an MNI EPI template and resliced at 4 × 4 × 4 mm voxel resolution and smoothed with an 8 mm full-width at half maximum (FWHM) isotropic Gaussian kernel. ArtRepair toolbox for SPM8 (http://cibsr.stanford.edu/tools/human-brain-project/artrepair- software.html) was used to correct slice artifacts prior to realignment and volume artifacts after normalization and smoothing (<5% interpolated data). Any run in which interpolated data exceeded 5% was excluded from analysis.

Analysis

We focused our analysis on the behavioural and fMRI data collected during spatial context memory tasks in order to contextualize our findings in the framework of the established literature on sex differences in spatial episodic memory (Herlitz, Nilsson, & Bäckman, 1997; A. Herlitz & Rehnman, 2008; Lewin, Wolgers, & Herlitz, 2001). Furthermore, we were motivated to compare current study findings using task functional connectivity with our published study investigating sex differences and similarities in age-related and performance-related patterns of brain *functional activity* also using the same spatial context memory paradigm (Subramaniapillai et al., 2019).

<u>*Behavioural Data Analysis*</u>

Spatial Context Retrieval Accuracy and Reaction Time

Using R (R Core Team, 2013), we conducted robust linear mixed-effects regression (rlmer) models (using the robustlmm package; Koller, 2016) in the matched cohort to test the three-way interaction between age, sex (2: male, female), and task difficulty (2: easy, hard) on retrieval accuracy (% correct) and reaction time (milliseconds), respectively. The rlmer model is similar to the lmer

model (Bates, Mächler, Bolker, & Walker, 2015 for the lme4 package details) but additionally, it is robust to outliers by down-weighting the impact of extreme measures on the model performance (Koller 2016). The models contained the random effect of participants to account for the variability of participants' performance between the easy and hard versions of the spatial context task. The models used in terms of R syntax for spatial retrieval accuracy and reaction time, respectively, were:

Spatial Retrieval Accuracy ~ Age x Sex x Task Difficulty + (1|Participant)

Spatial Retrieval Reaction Time ~ Age x Sex x Task Difficulty + (1|Participant)

The continuous variable of age was standardized using a Z-score transformation, while the variables of sex and task difficulty were treated as categorical variables through deviation coding (-1, 1).

Image Analysis

fMRI Preprocessing Steps

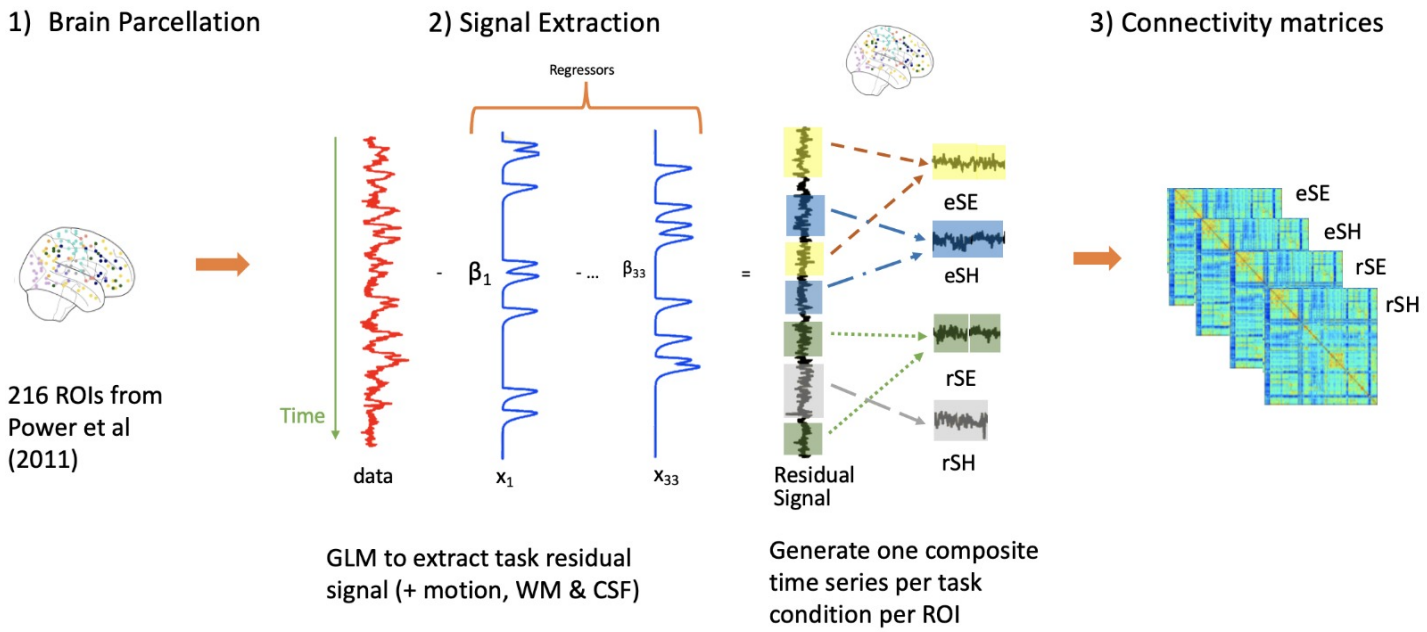


Figure 1. The fMRI preprocessing steps involved (1) functional parcellation of each subject across the 216 unique ROIs from the Power et al. atlas; (2) applying a GLM to extract the task residual signal after regressing 33 regressors to generate one composite time series per task condition for each ROI; (3) generating four connectivity matrices for each task condition for every participant.

fMRI Preprocessing for PLS Connectivity Analysis

Brain Parcellation

Using SPM's MarsBaR toolbox, the average time series for 264 regions of interest (ROIs) defined by the Power et al. (2011) functional parcellation atlas were extracted for each subject for all task-related event-types across the full experiment. Each ROI was registered from the 2x2x2 mm^3 Power atlas to the $4 \times 4 \times 4$ mm^3 voxel resolution of our functional scans. In order to do this, we took each ROI's central coordinates from the Power et al (2011) ROIs and identified a 7-voxel sphere surrounding the central coordinates. During this process of scaling down to the 4x4x4mm^3 voxel resolution, we eliminated ROIs with voxels that were not common to all participants and/or overlapped with other ROIs. We also excluded cerebellar ROIs because our fMRI acquisition did not completely acquire these regions, and the uncertain network ROIs because they did not belong to a major functional system in the brain. We additionally combined the memory retrieval network with the default mode network because the few nodes belonging to the memory retrieval network are activated in cognitive functions (e.g., memory, imagination) commonly attributed to the default mode network (Huo, Li, Wang, Zheng, & Li, 2018). Thus, we identified a total of 216 unique ROIs assigned to 9 brain networks: Auditory, Cingulo-opercular Task Control (CON), Default Mode Network (DMN), Dorsal Attention Network (DAN), Fronto-parietal Task Control Network (FPN), Salience, Sensory/Somatomotor Network (SSM), Visual Attention Network (VAN), Visual (see Supplementary Table 1 for list of coordinates and network affiliation). Figure 1 illustrates the preprocessing steps used to generate the connectivity matrices for participants across the four task conditions, which were subsequently submitted to the PLS analysis.

fMRI Signal Extraction

In order to examine task-related functional connectivity it is recommended that first the mean task/event-related activity across the full experiment be regressed out of the fMRI signal. This accounts

for the confound of task-timing-driven statistical associations (Cole et al., 2019). To this aim, event-related task activation for all 216 ROIs was estimated using SPM's General Linear Model (GLM) with an ordinary least squares (OLS) approach (i.e., with AR(1) off), using a high pass filter set at 200 sec. This GLM consisted of 12 task-related regressors: correct subsequent memory events for SE, SH, TE and TH tasks (4), correct context retrieval events for SE, SH, TE, and TH tasks (4), incorrect subsequent memory responses for all encoding tasks, incorrect context retrieval responses for all retrieval tasks, encoding and retrieval task instructions, and distraction task. In addition, the 6 movement regressors generated by SPM during motion correction, the mean white matter and the cerebrospinal fluid signals were also included as regressors in the GLM to correct for physiological noise (Birn et al., 2014). Finally, the 12 temporal derivatives of the hemodynamic response function for each of the task-related regressors and the constant (i.e., intercept) resulted in a total of 33 regressors used in the GLM. Thus, this one GLM model was used to extract the mean residual time series for each ROI per event-type using the MarsBaR toolbox in SPM (http://marsbar.sourceforge.net/). To allow readers to compare our findings with and without regressing task-related activation, we re-ran our analysis using connectivity matrices that did not regress mean task-related activity and found a similar pattern of findings (Supplementary Figure 1).

Generating Functional Connectivity Matrices

Since the focus of our current analysis is the spatial version of the task, we only generated functional connectivity matrices for each event-type of the spatial task. Each participant's residual time series were concatenated across similar event-types in order to generate composite time series for each event-type that roughly had the length of ~ 30 sec, which has previously been shown to be reliably sufficient for task-based connectivity analyses (e.g., Mohr et al., 2016). As a measure of functional connectivity, Pearson correlations were conducted, and a correlation coefficient was computed for each ROI with every other ROI. Connectivity matrices were created for each participant and event-type from

the correlation coefficients, which then underwent Fisher z-transformation. Thus, in total, each subject had four connectivity matrices, one for each of the four event-types (i.e., eSE, eSH, rSE, rSH) of size 216 x 216. Since the matrix is symmetrical around the diagonal, there were a total of 23,220 unique connections or edges.

PLS Functional connectivity analysis

Behavioural multivariate partial least squares (B-PLS) connectivity analysis was used to identify patterns of task-based functional connectivity (Anthony R. McIntosh & Mišić, 2013), due to its ability to simultaneously detect distributed patterns of whole-brain connectivity that differ based on participants' age, sex, and memory performance. Connectivity matrices for each individual were organized by participant sex and task event-type and then stored in a data matrix that was stacked similarly across participants. Since we were interested in how patterns of task-based functional connectivity differed in women and men across the lifespan and related to memory performance on our tasks, we conducted a PLS using participant age and retrieval accuracy as behavioural measures of interest. We orthogonalized our behavioural vectors of age and accuracy to assess independent effects of age and performance (consistent with Subramaniapillai et al., 2019; see also Ankudowich et al., 2017). That is, outside of PLS, we conducted a regression analysis where task-specific retrieval accuracy was used to predict age to obtain an age-residual vector that would be uncorrelated with retrieval accuracy. These age-residual and retrieval accuracy vectors were then stacked in the same manner as the fMRI data matrix by participant sex and by event-type. Given that the retrieval accuracy behavioural vector did not have age regressed from it, it allowed us to assess connectivity associated with age-related performance effects, whilst the age-residual allowed us to assess age effects orthogonal to performance effects. The stacked fMRI data matrix was then cross-correlated with the similarly stacked behavioural vectors.

The resulting cross-correlation matrix was submitted to singular value decomposition (SVD). SVD re-expresses the matrix as a set of orthogonal singular vectors or latent variables (LV). Each LV consists of a singular value that reflects the proportion of matrix accounted for by that LV, and a pair of vectors (a left singular vector consisting of the behavioural weights and a right singular vector consisting of the connectivity weights) that reflect a symmetrical relationship between the pattern of whole-brain connectivity and the experimental design/behaviour measures. The profile of behavioural weights shows how the behavioural vectors of age and retrieval accuracy are correlated to the pattern of whole-brain connectivity identified in the singular vector of connectivity weights. The connectivity weights identify the collection of edges that, as a group, are maximally related to the behavioural weights.

Significance testing for the LVs was done using 500 permutations ($p < 0.05$). The permutation test assesses whether the functional networks and behavioural profiles are more strongly associated with one another than expected by chance. Bootstrap resampling was performed to assess the reliability of each of the edges (500 bootstraps, bootstrap ratio [BSR] threshold was set at 95th percentile, $p < 0.001$). Connectivity edge contribution was estimated with edge loadings, which is calculated as the correlation of the participants' PLS-derived brain score pattern with their stacked connectivity matrices. The pattern of edge loadings (i.e., correlations) is referred to as the loading matrix and reflects whether edges are more positively or negatively associated with the behavioural weights. A positive correlation coefficient in the loading matrix indicates a positive association with positive behavioural weights. Conversely, a negative correlation coefficient in the loading matrix is positively associated with the negative behavioural weights. Since the relationship between the behavioural weights and the loading matrix (i.e., connectivity weights) is symmetric, the inverse is also true. That is, a positive correlation coefficient indicates a negative association with negative behavioural weights and vice versa.

Post-Hoc Analyses

We conducted two post-hoc analyses to determine whether findings from the primary matched sample analysis applied to the cohort of women that were not used (i.e., hold-out cohort; see Supplementary Table 2 for the demographic summary of this cohort). First, we computed predicted brain scores on the remaining cohort of women (n = 43) to determine the robustness and generalizability of the primary PLS findings. Predicted brain scores were calculated by multiplying the brain saliences of the primary analysis to the stacked connectivity matrices of the hold-out cohort of women. We then computed an rlmer model to determine whether the brain scores of the hold-out women were significantly different to the brain scores of the women in the primary analysis across the three significant LVs. The model used in terms of R syntax was:

```
rlmer(LV ~ Data_Source+ (1|ID) + (1|Task_EventType))
```

Three models were run in total, one for each of the three significant LVs. The Data_Source was whether women were from the original 'matched' cohort or the 'holdout' cohort. The Task_EventType represents the four task event-types of the study (eSE, eSH, rSE, rSH). No significant difference in brain scores between the groups would confirm that the brain-behaviour findings correspond to the cohort of women excluded from the original age- and education-matched cohort.

In our second post-hoc analysis, we ran a within-sex partial least squares analysis using the full cohort of women from the primary and hold-out cohorts (n= 91) to determine whether the within-sex PLS findings were similar to the primary between-sex PLS findings (see Supplementary Table 3 for demographic summary of this cohort of women).

Since our findings could be driven by sex differences in intracranial volume (ICV) with men having larger ICV than women, we ran a supplementary analysis using a sub-cohort (n =50) of women

and men matched according to age, education, and ICV to determine whether this pattern of LV findings were similar to the primary analysis (see Supplementary Figure 2).

Results

Behavioural Results

Tables 1 and 2 summarizes the participant demographic and neuropsychological information across the age groups for the full (n=141) and matched cohort (n=96), respectively. Within the matched cohort, post hoc analyses revealed no significant differences in age and education between women and men within each age group ($p>.05$), confirming the successful age- and sex-matching of participants. Behaviourally, the rlmer model investigating the effects of age, sex, and task difficulty on memory accuracy showed a main effect of age ($\beta = -0.03$ [SE, 0.01]; $t = -2.35$, $p < .05$) and task difficulty ($\beta = -0.04$ [SE, 0.01]; $t = -3.00$, $p < .05$). Younger adults had greater accuracy than older adults on the tasks, and generally, participants performed worse on the SH task compared to the SE task. No other main effects or interactions were significant.

There were also significant main effects of age ($\beta = 145.60$ [SE = 68.71]; $t = 2.12$, $p < .05$) and task difficulty ($\beta = 130.23$, [SE = 36.71]; $t = 3.55$, $p < .05$) on reaction time. Young adults were faster than older adults across SE and SH tasks, and participants took longer to respond to the SH task than the SE task. No other main effects or interactions were significant. The behavioural results for the spatial task results were consistent between the full and matched cohorts.

Table 1. Mean Demographic and Behavioural Measures (and Standard Errors) according to Age Group and Sex (N = 141)

	Younger Adults (YA)		Middle Aged Adults (MA)		Older Adults (OA)		
	Males	Females	Males	Females	Males	Females	*p*
Sample size (n)	16	29	17	35	16	28	
Age (years)	26.56 (0.84)	25.90 (0.72)	47.18 (1.31)	49.69 (0.90)	67.13 (1.04)	66.14 (0.65)	
Educations (years)	16.44 (0.34)	15.90 (0.42)	15.59 (0.41)	15.66 (0.36)	16.19 (0.61)	15.07 (0.42)	ns
Predicted full-scale IQ	119.72 (1.34)	118.84 (1.02)	119.54 (1.43)	119.44 (0.85)	119.73 (1.04)	120.03 (1.06)	ns
BDI	4.06 (0.87)	3.32 (0.74)*	3.12 (0.87)	4.54 (0.72)	4.38 (1.04)	3.79 (0.57)	ns
CVLT-LFR	13.25 (0.48)	14.14 (0.28)	11.82 (0.76)	13.46 (0.27)	12.00 (0.56)	13.25 (0.44)	$p < .05^{\%\#}$
CVLT-LCR	13.38 (0.41)	14.24 (0.33)	12.41 (0.62)	13.71 (0.30)	12.50 (0.47)	13.39 (0.39)	$p < .05^{\%\#}$
CVLT-RG	15.38 (0.18)	15.55 (0.13)	15.35 (0.21)	15.34 (0.15)	15.13 (0.18)	15.20 (0.17)	ns
BMI (kg/m^2)	23.93 (0.65)	22.03 (0.68)	25.15 (0.78)	24.60 (0.67)	24.37 (0.57)	25.80 (0.72)*	ns
SE retrieval accuracy (%correct)	0.85 (0.03)	0.90 (0.01)	0.88 (0.02)	0.86 (0.02)	0.80 (0.02)	0.83 (0.02)	$p < .01^{\#}$
SH retrieval accuracy (%correct)	0.84 (0.03)	0.89 (0.09)	0.83 (0.03)	0.84 (0.02)	0.73 (0.03)	0.78 (0.02)	$p < .01^{\#}$
SE retrieval RT (msec)	2270.69 (101.68)	2194.72 (104.90)	2353.35 (122.95)	2464.396 (93.95)	2633.79 (138.26)	2878.14 (83.98)	$p < .01^{\#}$
SH retrieval RT (msec)	2422.47 (96.33)	2267.92 (100.09)	2467.69 (109.12)	2610.75 (77.30)	2765.84 (154.00)	2871.45 (82.69)	$p < .01^{\#}$

*One participant had missing BDI (n=28) or BMI (n=29) information. Values in brackets represent the standard error. A linear regression of Age x Sex was performed on each of the measures (significance of $p < .05$ used). % The linear regression produced a significant effect of Sex, such that women outperformed men on this score. # The linear regression produced a significant main effect of Age. The fMRI behavioural measures revealed that OA participants performed significantly worse than younger and middle-aged participants and with significantly greater RT to complete the spatial tasks. BDI = Beck Depression Inventory; LFR = Long-form Free Recall; LCR = Long-form Cued Recall; RG = Recognition; BMI = body mass index.

Table 2. Mean Demographic and Behavioural Measures (and Standard Errors) according to Age Group and Sex (N = 96)

	Younger Adults (YA)		Middle Aged Adults (MA)		Older Adults (OA)		
	Males	Females	Males	Females	Males	Females	*p*
Sample size (n)	16	16	16	16	16	16	
Age (years)	26.56 (0.84)	26.13 (0.76)	46.94 (1.37)	47.25 (1.28)	67.13 (1.04)	67.56(0.85)	
Educations (years)	16.44 (0.34)	16.75 (0.40)	15.44 (0.41)	15.81 (0.49)	16.19 (0.61)	15.38 (0.57)	ns
Predicted full-scale IQ	119.72 (1.34)	118.49 (1.33)	120.42 (1.21)	120.76 (1.25)	119.73 (1.04)	120.65 (1.08)	ns
BDI	4.06 (0.87)	3.53 (1.08)*	3.25 (0.92)	4.31 (1.12)	4.38 (1.04)	3.25 (0.73)	ns
CVLT-LFR	13.25 (0.48)	13.50 (0.41)	11.81 (0.81)	13.19 (0.43)	12.00 (0.56)	13.19 (0.56)	$p < .05^{\%}$
CVLT-LCR	13.38 (0.41)	13.69 (0.45)	12.44 (0.66)	13.44 (0.51)	12.50 (0.47)	13.25 (0.46)	ns
CVLT-RG	15.38 (0.18)	15.31 (0.20)	15.44 (0.20)	15.31 (0.24)	15.13 (0.18)	14.94 (0.23)	ns
BMI (kg/m^2)	23.93 (0.65)	22.01 (0.70)	24.85 (0.76)	23.63 (0.78)	24.37 (0.57)	25.10 (0.86)	$p < 0.05^{\wedge}$
SE retrieval accuracy (%correct)	0.85 (0.03)	0.90 (0.02)	0.88 (0.02)	0.87 (0.02)	0.80 (0.02)	0.84 (0.02)	$p < .01^{\#}$
SH retrieval accuracy (%correct)	0.84 (0.03)	0.89 (0.03)	0.83 (0.03)	0.86 (0.02)	0.73 (0.03)	0.78 (0.02)	$p < .01^{\#}$
SE retrieval RT (msec)	2270.69 (101.68)	2105.18 (141.44)	2393.30 (123.78)	2448.30 (160.42)	2633.79 (138.26)	2894.03 (92.98)	$p < .01^{\#}$
SH retrieval RT (msec)	2422.47 (96.33)	2218.69 (144.57)	2514.95 (104.71)	2596.62 (132.19)	2765.84 (154.00)	2874.13 (93.05)	$p < .01^{\#}$

*One participant had missing BDI information (n=15). Values in brackets represent the standard error. A linear regression of Age x Sex was performed on each of the measures (significance of $p < .05$ used). % The linear regression produced a significant effect of Sex, such that women outperformed men on this score. ^ Age x Sex interaction of BMI: age-related increase in BMI; younger and middle-aged adult men had higher BMI than their female counterparts; and older men had higher BMI than older women. # The linear regression produced a significant main effect of Age. The fMRI behavioural measures revealed that OA participants performed significantly worse than younger and middle-aged participants and with significantly greater RT to complete the spatial tasks. BDI = Beck Depression Inventory; LFR = Long-form Free Recall; LCR = Long-form Cued Recall; RG = Recognition; BMI = body mass index.

Functional connectivity results

The PLS analysis of the fMRI data identified three significant LVs at $p < 0.05$. LV1 (42% cross-block covariance) identified sex differences in how age impacted memory-related brain connectivity and how brain connectivity related to memory accuracy. LV2 and LV3 (26.50% and 9.41% cross-block covariance respectively) demonstrated sex similarities in how brain connectivity related to memory performance but differences in how age impacted memory-related brain connectivity. These findings were consistent with PLS findings that matched women and men by ICV (Supplementary Figure 2).

Figures 2-4 depict the relevant LV information for LVs 1-3, respectively. The subplots include the 1) behavioural weights, 2) thresholded loading matrix, 3) network density matrix, and the 4) brain figure representing the highly involved nodes. The behavioural weights (1) indicate how the loading

matrix relates to the behavioural vectors of age and accuracy in women and men. The thresholded connectivity matrix (2) represents the 95th percentile of the z-score values of correlation coefficients. The network density matrix (3) represents the sum of the unthresholded significant edges divided by the total number of possible edges between any two networks (or within a network). Each LV generated two density plots because calculations were done separately on the positive and negative correlation coefficients. LV1 and LV2 did not produce any significant negative correlations, so only the network density matrix for the negative correlations in LV3 is presented (Figure 4D). Finally, the brain figures (4) identify the most highly contributing nodes from the thresholded loading matrix, as determined by the ranked sum of the correlation values from most to least involved.

Due to the larger cohort of women in the original cohort, we sought out two methods for determining if findings from the PLS corresponded to the hold-out cohort of women (n =43). First, the rlmer models determined that the hold-out cohort of womens' brain scores did not significantly differ with the brain scores of the women used in the primary analysis. Second, a within-sex PLS of the full cohort of women (n = 91) produced two significant LVs that produced findings consistent to the primary PLS findings (see Supplementary Figure 3). We present LV1 of this within-sex analysis in conjunction with LV1 of the primary analysis since there were some effects that reached significance in the full cohort of women that were marginal in the primary analysis. Since the behavioural weights of LV2 was identical to LV3 of the primary analysis, we present LV2 findings of this within-sex analysis in Supplementary Figure 3.

LV1: Sex differences in age- and accuracy-related task connectivity

The first LV (LV1) accounted for 42.1% crossblock covariance and identified significant positive correlation coefficients between several networks. The loading matrix and density matrix for LV1 (Figures 1C and 1D) indicates there were dense patterns of positive correlations observed between the Visual and CON, DAN, FPN, Salience, and SSM networks. DAN also had significant positive

correlations with the SSM, Salience, and CON networks, in addition to within-network connectivity. The loading matrix (Figure 2C) and behavioural weights (Figure 2A) together indicate that in women, this pattern of positive brain connectivity during encoding and retrieval was negatively correlated with age and was positively correlated with memory performance for the SH task. Of note, women showed a trending effect of memory-related brain connectivity with task performance in the original matched analysis, which was significant in the larger within-sex analysis of women (Figure 2B). Conversely, men did not show any age-related differences in the pattern of task-based connectivity identified in LV1. In addition, in men, increased positive connectivity in these same networks during encoding and retrieval, was related to *poorer* memory performance across all tasks. The network density matrix (Figure 2D) and brain figure (Figure 2E) corroborate the loading matrix findings. The thresholded connectivity matrix representing the 95th percentile of the z-score values of correlation coefficients for LV1 (Figure 2C) is available online https://github.com/sivaniya/M48F48_conn_matrix.

LV1: Sex differences in age- and accuracy-related task connectivity

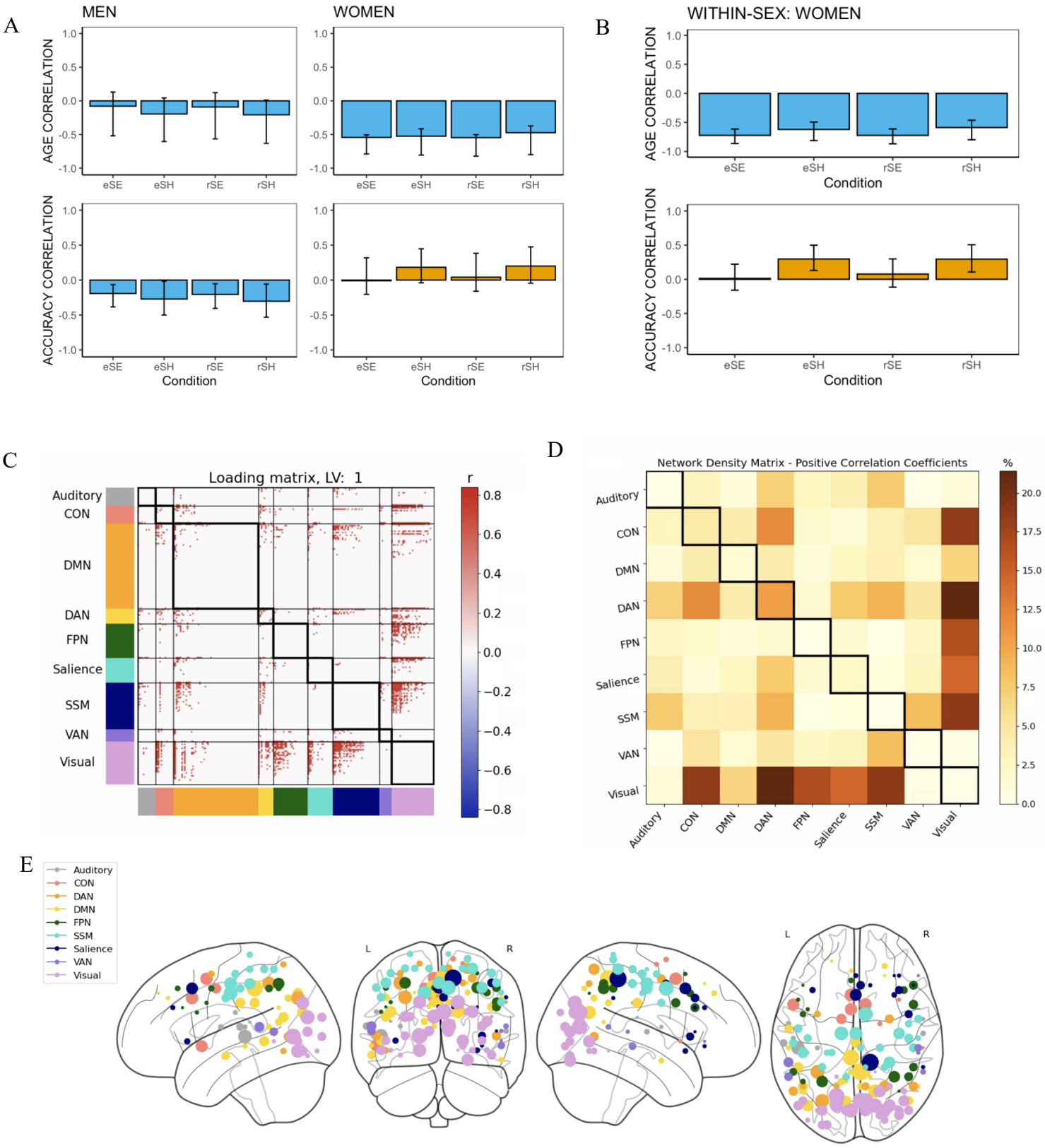


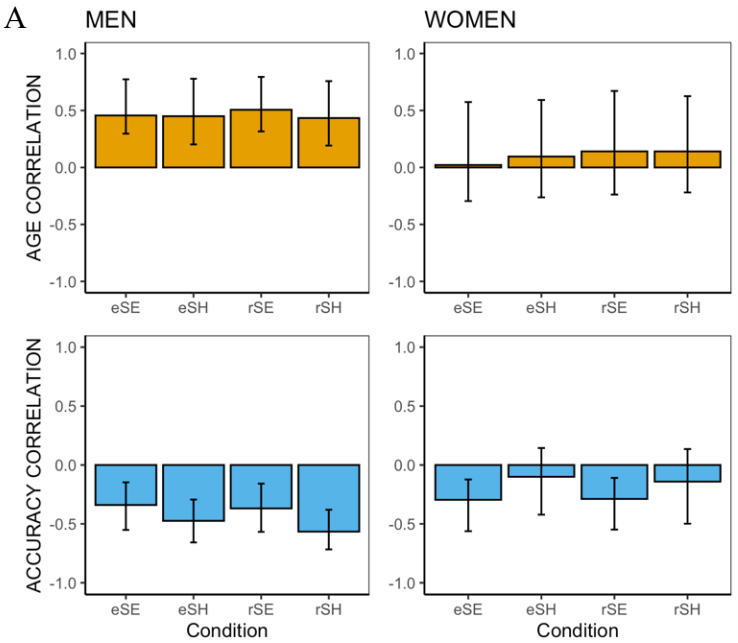
Figure 2. LV1 reflects sex differences in age- and memory-related brain connectivity. Correlation between the behavioural

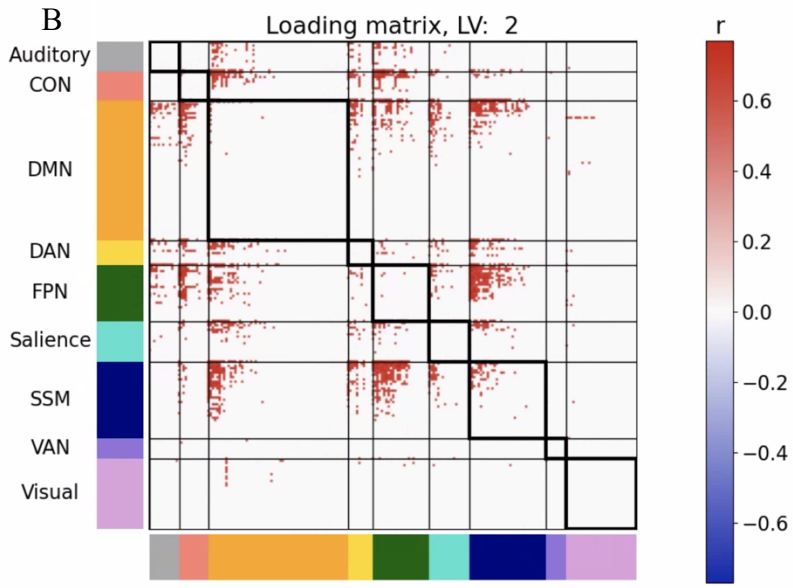
vectors of age and accuracy with the task fMRI connectivity of participants for the **(A)** primary analysis and **(B)** within-sex sample (LV1). Error bars represent bootstrapped standard deviations. **(C)** Thresholded 95th percentile of correlations between participants' task fMRI data and behavioural profile indicated in A. **(D)** The density plot for the positive correlation coefficients (i.e., sum of the significant correlation coefficients after thresholding, divided by the total number of edges between any two networks). The density matrix for the negative correlation coefficients is not presented because there were no significant edges. **(E)** Most densely connected nodes from the positive salience loading matrix as represented by the rank sum of the correlation coefficients of the thresholded matrix. Greater node size represents greater node involvement. eSE = encoding spatial easy; eSH = encoding spatial hard; rSE = retrieval spatial easy; rSH = retrieval spatial hard; CON = cingulo-opercular network; DMN = default mode network; DAN = dorsal attention network; FPN = frontoparietal network; SSM = somatomotor network; VAN = ventral attention network.

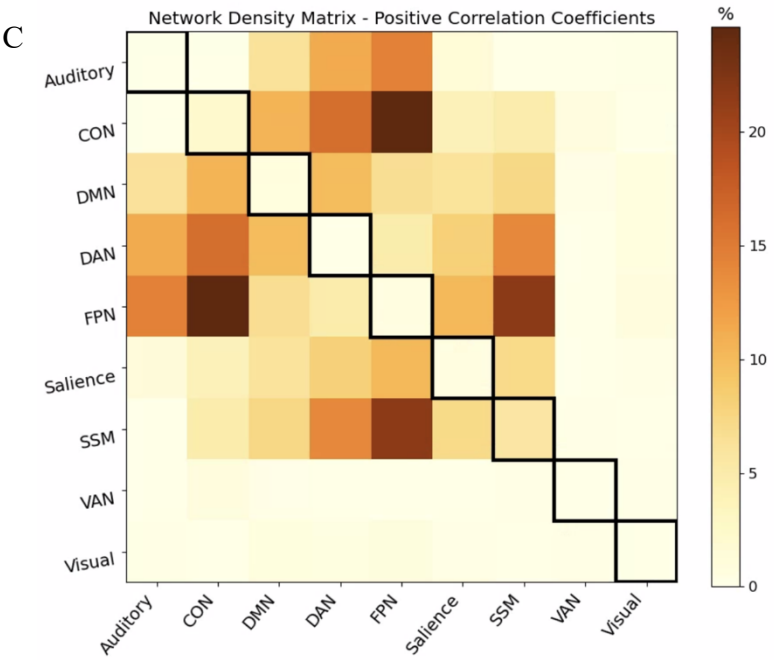
LV2: Sex differences in age-, but not accuracy-, related task connectivity

The second LV (LV2) accounted for 26.50% of the cross-block covariance and identified significant positive correlation coefficients amongst most networks, with few significant correlations between VAN and Visual networks and other networks. The loading matrix and density matrix for LV2 (Figures 3B and 3C) indicates there were a significant number of positive correlations between the Auditory network and DMN, DAN, FPN; between CON and DMN, DAN, FPN; and between SSM and DAN, FPN. Taken together, the loading matrix (Figure 3B) and behavioural weights (Figure 3A) demonstrate that there were age-related increases in task-related connectivity in the aforementioned networks for men and that increased connectivity in these networks during encoding and retrieval was associated with worse memory accuracy during both SE and SH tasks in men. Similarly, in women, greater functional connectivity in these networks during encoding and retrieval was associated with poorer memory performance during SE tasks. However, in women, there were no significant age-related differences in these connectivity patterns. The thresholded connectivity matrix representing the 95th percentile of the z-score values of correlation coefficients for LV2 (Figure 3B) is available online: https://github.com/sivaniya/M48F48_conn_matrix.

LV2: Sex differences in age-, but not accuracy-, related task connectivity







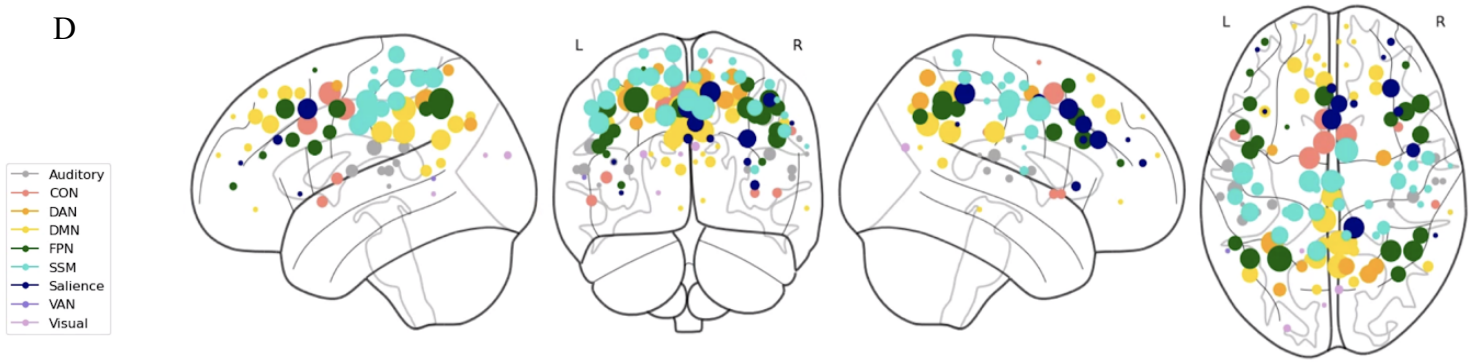


Figure 3. LV2 reflects sex similarities in memory-related brain connectivity, but differences in age-related brain connectivity. **(A)** Correlation between the behavioural vectors of age and accuracy with the task fMRI connectivity of participants. Error bars represent bootstrapped standard deviations. **(B)** Thresholded 95th percentile of correlations between participants' task fMRI data and behavioural profile indicated in A. **(C)** The density plot for the positive correlation coefficients (i.e., sum of the significant correlation coefficients after thresholding, divided by the total number of edges between any two networks). The density matrix for the negative correlation coefficients is not presented because there were no significant edges. **(D)** Most densely connected nodes from the positive salience loading matrix as represented by the rank sum of the correlation coefficients of the thresholded matrix. Greater node size represents greater node involvement. eSE = encoding spatial easy; eSH = encoding spatial hard; rSE = retrieval spatial easy; rSH = retrieval spatial hard; CON = cingulo-opercular network; DMN = default mode network; DAN = dorsal attention network; FPN = frontoparietal network; SSM = somatomotor network; VAN = ventral attention network.

LV3: Sex similarities in accuracy-related, but differences in age-related, task connectivity

LV3 accounted for 9.41% of the cross-block covariance and identified significant positive correlation coefficients between several networks. The loading and density matrices (Figure 4B and 4C) indicate that there was greatest density of positive correlations between the FPN and Salience networks, and between the Visual network and VAN. In addition, there were dense within-network positive correlations in the Salience, VAN, and Visual networks. The loading matrix (Figure 4B) and behavioural weights (Figure 4A) indicate that in men, age was negatively correlated with increased connectivity in the aforementioned networks, and memory performance during SE tasks was also negatively correlated with increased functional connectivity in these networks. In women, age was not significantly correlated with connectivity amongst these networks, and memory performance for both SE and SH tasks was negatively correlated with increased functional connectivity in these networks. LV3 also identified negative correlations within DAN and between DAN, FPN and Salience networks; and, between Visual-FPN and Salience, and VAN-FPN (Figure 4D). These patterns of within- and between-network connectivity were correlated with advanced age in men, better memory performance during SE tasks for men, and better memory performance during both tasks in women. Thus, both LV2 and LV3 demonstrated similar performance effects in both sexes but identified age-effects in only men. Thus, both LV2 and LV3 demonstrated similar performance effects in both sexes but identified age-effects in only men. The thresholded connectivity matrix representing the 95th percentile of the z-score values of correlation coefficients for LV3 (Figure 4B) is available online https://github.com/sivaniya/M48F48_conn_matrix.

LV3: Sex similarities in accuracy-related, but differences in age-related, task connectivity

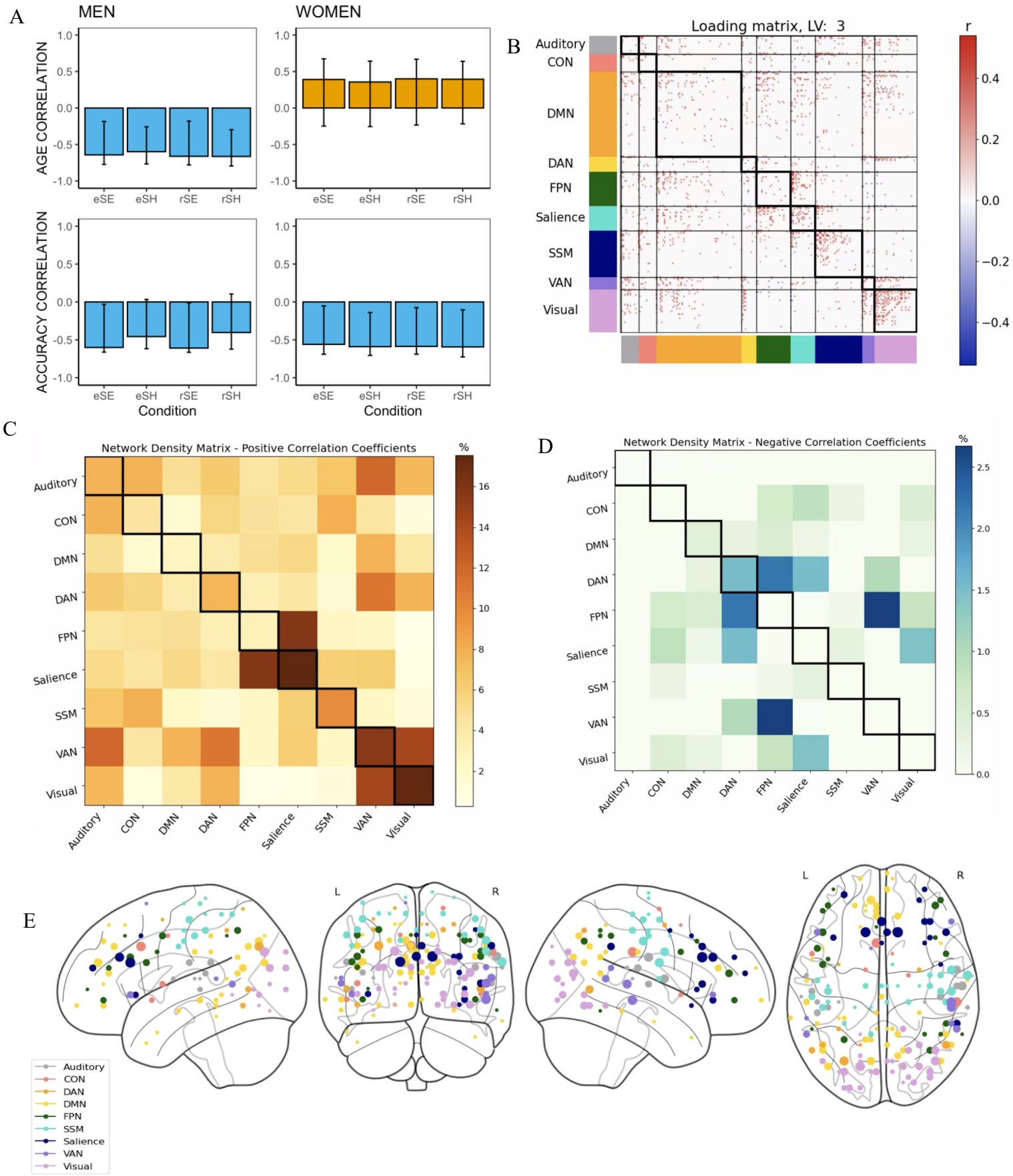


Figure 4. LV3 reflects sex similarities in memory-related brain connectivity, but differences in age-related brain connectivity. **(A)** Correlation between the behavioural vectors of age and accuracy with the task fMRI connectivity of participants. Error bars represent bootstrapped standard deviations. **(B)** Thresholded 95th percentile of correlations between participants' task fMRI data and behavioural profile indicated in A. **(C)** The density plot for the positive correlation coefficients (i.e., sum of the significant correlation coefficients after thresholding, divided by the total number of edges between any two networks). **(D)** The density matrix for the negative correlation coefficients. **(E)** Most densely connected nodes from the positive salience loading matrix as represented by the rank sum of the correlation coefficients of the thresholded matrix. Greater node size represents greater node involvement. eSE = encoding spatial easy; eSH = encoding spatial hard; rSE = retrieval spatial easy; rSH = retrieval spatial hard; CON = cingulo-opercular network; DMN = default mode network; DAN = dorsal attention network; FPN = frontoparietal network; SSM = somatomotor network; VAN = ventral attention network.

Discussion

The current study investigated sex differences in the effects of age and retrieval accuracy (memory performance) on memory-related task functional connectivity. The behavioural results were consistent with our prior findings (Ankudowich, Pasvanis, & Rajah, 2017; Subramaniapillai et al., 2019). We found significant main effects of age and task difficulty on spatial context memory accuracy and reaction time. Older adults performed worse than younger adults on retrieval accuracy and experienced slower processing speeds to complete the spatial context tasks. A main effect of task difficulty showed that participants, independent of age, generally performed worse on the spatial hard context tasks than the easy version of the task. Moreover, we found no significant effect of sex on accuracy and reaction time, nor any significant interactions of age and sex. Therefore, the sample included in this connectivity analysis parallels that used in our prior study examining sex differences in the effect of age and memory performance on spatial context memory activation (Subramaniapillai et al., 2019). These behavioural findings counter some prior work indicating women and men differ on episodic memory (Astur, Purton, Zaniewski, Cimadevilla, & Markus, 2016; Bremner et al., 2001; Keightley, Winocur, Burianova, Hongwanishkul, & Grady, 2006; Ragland, Coleman, Gur, Glahn, & Gur, 2000). However, closer examination of studies revealing sex differences in episodic memory demonstrate considerable range of outcomes even within-sex, with small to medium effect sizes across the studies (Asperholm, Van Leuven, & Herlitz, 2020; Herlitz & Rehnman, 2008). Thus, straying away from average-based group analyses and towards understanding individual differences may be a more

fruitful approach that appropriately considers the range of diversity observed within- and between-sexes.

Despite there being no significant sex-differences in task performance, our task-based functional connectivity analysis revealed a more detailed picture of how women's and men's memory performance was related to task-based connectivity across the adult lifespan. Specifically, by using PLS functional connectivity analysis, we were able to consider both within- and between-sex differences in memory accuracy and age in relation to task-based connectivity. In general, using this approach we found three main findings. First, consistent with our prediction, women and men largely showed similar performance-related patterns of functional connectivity. Second, consistent with our prediction, we observed age-related decreases in within-network connectivity and increases in between-network connectivity that was also related to poorer memory performance in advanced age; however, counter to our prediction, this was only observed in men. Women showed age-related *decreases* in functional connectivity associated with worse memory performance. Below, we detail our PLS connectivity findings and further describe how they complement our previous investigations of brain-behaviour relations in functional activity in a similar cohort.

Sex similarities and differences in the effect of accuracy on memory-related brain connectivity

Consistent with our behavioural findings indicating no significant sex differences in memory performance, we observed similarities in performance-related functional connectivity patterns in women and men in LV2 and LV3. LV2 indicated that during episodic encoding and retrieval, increased between-network connectivity of DMN, FPN and DAN networks with CON, Auditory and SSM networks, respectively, was associated with poorer memory performance for both SE and SH tasks in men, and poorer memory accuracy for SE tasks in women. LV2 also indicated that poorer performance in both sexes was associated with no connectivity of Visual and VAN with other networks. LV3

indicated that greater connectivity within visual, VAN and Salience networks, and between visual-VAN and Salience-FPN networks were related to poorer memory performance for the SE tasks in men and across both task conditions in women. In contrast, the negative correlations from LV3 (Figure 4D) indicates that greater connectivity within DAN, and between DAN-FPN and Salience, Visual-FPN and Salience, VAN-FPN, was correlated with better task performance for SE task in men and both tasks in women. However, these negative correlations were sparse compared to the positive correlations observed in LV3.

Previous task-based functional connectivity analysis of visual episodic memory tasks has indicated that greater connectivity between higher-order cognitive networks, i.e., FPN, DMN and the DAN, with task-relevant visual processing networks, i.e., Visual and VAN, is associated with recollection (Bowen & Kensinger, 2017; King, Chastelaine, Elward, Wang, & Rugg, 2015). In contrast, Sneve et al. (2017) found that greater intrinsic connectivity between task-*irrelevant* perceptual networks and cognitive networks during rest, was associated with poorer performance on an associative encoding task performed outside of the scanner. In the current visual spatial context memory study, we found that between-network connectivity of cognitive networks, i.e., DMN, DAN and FPN, with CON and task-irrelevant sensory networks, i.e., Auditory and SSM, during encoding and retrieval was associated with poorer memory performance across all tasks for men, and SE tasks for women. Poorer memory performance was also associated with weak/absent connections between these cognitive networks and Visual and VAN (LV2), and greater connectivity within and between Visual and VAN (LV3). Interestingly, connectivity between the CON, a network hypothesized to be critical for establishing and maintaining task-related performance demands (Dosenbach et al., 2006), with other cognitive networks, i.e., FPN, was not associated with better task performance. This is contrary to prior results highlighting the importance of CON connectivity with other cognitive networks, particularly the FPN, for support for cognitive task performance (Shen et al., 2018). One possibility is that when CON-cognitive network connectivity is paralleled by increased connectivity between these same cognitive

networks and task-irrelevant sensory networks, performance is negatively impacted (LV2). Therefore, our results support the hypothesis that successful associative encoding and retrieval in women and men was correlated with the degree to which higher order cognitive networks were functionally connected with task-irrelevant, compared to task-relevant, sensory networks, and highlight the importance of neural context in determining whether between-network integration of CON with other higher order cognitive networks was beneficial to task performance or not (McIntosh, 2004).

Prior studies of visual episodic memory tasks have also indicated that FPN connectivity with DAN supports episodic memory retrieval (Benoit & Schacter, 2015; Cabeza & St Jacques, 2007; Kim, 2012; Spreng et al., 2016). Our results from LV3, support the hypothesis that greater FPN-DAN connectivity during encoding and retrieval was beneficial for memory performance in both sexes. We also found that memory performance in women and men was differentially correlated to distinct patterns of Salience network connectivity in LV3. It has been hypothesized that connectivity between Salience network and FPN supports externally oriented task performance (Uddin, 2015). Here we found that successful memory performance was associated with Salience network connectivity with DAN; and with VAN and Visual network connectivity with FPN and Salience, respectively. However, the loading and density matrices for LV3 negative correlations indicate the negative correlations were sparse, suggesting segregated patterns of connections involving FPN and Salience with visual systems were important for successful memory performance.

Although we observed significant evidence of similarities in performance-based connectivity in women and men, we also observed some sex differences (LV1). We found that between-network connectivity of the Visual network with DAN, CON, FPN, Salience and SSM during encoding and retrieval was associated with better memory performance during SH tasks in women, and poorer memory performance across all tasks in men. Interestingly, LV3 had a similar pattern of negative correlations between Visual and the aforementioned brain networks and was associated with better memory performance on all tasks in women, and better performance on SE tasks in men. But, in LV3

647 the Visual network was not densely connected to DAN. Moreover, LV3 indicated Visual-VAN
648 connectivity was negatively correlated with performance in both sexes. The VAN responds to
649 unexpected stimuli (Corbetta and Shulman, 2002; Macaluso et al., 2002; Vossel et al., 2006; 2009),
650 while the DAN regulates perceptual attention for goal-directed task completion and is more relevant to
651 the current task demands (Dixon et al., 2018). Thus, in women, spatial context memory task
652 performance was differentially related to the specific attentional network the Visual network was
653 functionally connected to during encoding and retrieval; with Visual network connectivity to DAN and
654 other higher cognitive networks being associated with better during the more challenging SH task. This
655 pattern of task-based connectivity in women is generally consistent with our previous study looking at
656 fMRI activation, which showed that dorsolateral prefrontal and parietal activation during encoding was
657 correlated with better subsequent performance for SH tasks in women (Subramaniapillai et al., 2019).
658 Importantly, although women did not directly recruit FPN networks, they did recruit the DAN, which is
659 connected with the FPN to regulate perceptual attention for successful task completion (Dixon et al.,
660 2018). Therefore, our results indicate that Visual network integration with other cognitive networks
661 was more relevant to memory performance in women compared to men.
662
663 *Sex differences in the effect of age on memory-related connectivity*
664 Although successful memory performance was correlated with similar patterns of brain
665 connectivity during encoding and retrieval in women and men, there were sex differences in the effect
666 of age on memory-related functional connectivity. This suggests that age-related spatial context
667 memory decline was associated with altered task-based connectivity in distinct brain networks in
668 women, compared to men. In women, spatial context memory performance across all tasks was
669 correlated with greater integration of the Visual network with other cognitive networks (LV1 and LV3)
670 and DAN-FPN connectivity (LV3), and performance on the more difficult SH tasks was related to
671 greater integration of the Visual network with DAN and other cognitive networks (LV1). With age,

women generally showed age-related decreases in these patterns of connectivity. Thus, while older women's reduced ability to engage these networks was not associated with worse task performance during the SE task, it did result in worse SH task performance, suggesting a failure to externally direct attention and engage in spatial processing, particularly with increasing task demands (Corbetta, Patel, & Shulman, 2008; Grigg & Grady, 2010; Gusnard, Akbudak, Shulman, & Raichle, 2001; Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010). In sum, worse memory performance in older women was associated with their inability to successfully integrate task-relevant sensory and cognitive networks to support their performance.

In men, spatial context memory performance was positively correlated with *decreased* functional connectivity between task-irrelevant Auditory and SSM networks (LV2) and task-relevant Visual network (LV1) with higher order cognitive networks (i.e., CON, DMN, DAN, FPN). However, increased age was correlated with greater connectivity between task-irrelevant sensory networks and higher cognitive networks (LV2). Age-related increases in between-network connectivity (integration) has been reported in prior fMRI studies in which biological sex and gender was not used to disaggregate connectivity analyses (Chan et al., 2014; Geerligs et al., 2015; King et al., 2018; Onoda et al., 2012). These age-related differences in functional connectivity are generally associated with age-related cognitive decline and are consistent with theories of age-related neural dedifferentiation that propose neural representations of specific cognitive functions become less distinct with increased age. In the current study, by disaggregating our data by biological sex, we found that these age-related patterns of increased between-network connectivity were specific to men. However, it is notable, that in men advanced age was also associated with reduced within-network connectivity (Salience, VAN, Visual), increased within-network connectivity of DAN, and greater between-network connectivity of DAN-FPN and Salience, which was associated with better performance on the spatial context task at lower task demands (i.e., SE tasks in LV3). This highlights how age-related segregation of brain networks may be modulated by task difficulty.

The current connectivity results both complement and extend our previous activation study findings (Subramaniapillai et al., 2019). Both studies interrogate sex differences with age and memory accuracy at different levels of scale in the brain (i.e., regional- vs network-level) using different analyses (activity vs. connectivity), so findings may not completely corroborate with each other. For example, our previous study found age-related deficits in spatial context memory that were primarily associated with altered brain activity at encoding in both women and men, although the pattern of activation differed in both sexes. Interestingly, in our prior activation analyses of these data (Subramaniapillai et al., 2019) and another fMRI study of spatial context memory in older adults at risk of Alzheimer's Disease, we observed greater activation in women, compared to men, in task-relevant sensory networks and higher-order cognitive brain regions that supported memory function (Rabipour et al., 2021). We interpreted these results as potentially reflecting age-related generalization of cognitive function. The current findings indicate that patterns observed in activation and connectivity analyses may be complementary in the sexes. Such that, activation and connectivity increase in task-relevant sensory networks with cognitive networks benefit memory performance in women, and age-related decreases in memory function in women is related to decreases in these patterns of connectivity but complementary increases in activation – perhaps to compensate for connectivity deficits. In contrast, in our prior work we did not observed strong patterns of age-related increases in activation in men, but we did see age-related decreases in brain activation. Successful performance was related to distinct/segregated and task-specific patterns of activation. Here, we see that men exhibited age-related increases in between-network integration of task-irrelevant sensory networks with control networks and this was associated with age-related decreases in memory performance. Therefore, in men we observed more generalized patterns of connectivity but not activation with age. In sum, the nature of our current investigation enables an overview of whole brain functional networks on a much broader level in both sexes, while our previous functional activation studies permitted more region-specific understanding of sex differences in age and brain activity, and how these differences directly relate to performance.

Caveats

The present study examined sex similarities and differences in episodic/context memory across the lifespan using a novel functional connectivity methodological approach. However, our study has several limitations that future work should address. First and foremost, a comprehensive data collection approach was not used when collecting participants' biological sex. Our current study acquired participants' biological sex through self-report, although it could also be ascertained through other means, including participants' sex hormone measurements. Hormone collection is especially relevant when investigating major life transitions, such as menopause, which is associated with age-related differences in women's hormonal profiles. As a consequence of women's greater menopause-related hormonal changes and the established literature of memory effects during this transition (Henderson, 2010; Li et al., 2014; Rentz et al., 2017; Yonker et al., 2006), we decided to omit our cohort of women transitioning through menopause and those who underwent hormone replacement therapy. Although our small cohort size of women in the menopause transition prevented us from including them in our primary analysis, it is essential that future research integrate important life transitions to better inform our understanding of healthy aging models in women and men. Lastly, given that we did not collect information about participants' sociocultural gender, it is further challenging to disentangle the effects of biological sex and sociocultural gender on age- and memory-related connectivity differences.

Our relatively small cohort size constituted another limitation of the current study. Despite the small cohort, our findings complement our previous activation studies, both at the behavioural and functional level, using the same lifespan cohort (Subramaniapillai et al., 2019) and including the larger cohort (n>100; Ankudowich et al., 2016; 2017). Moreover, we found that our PLS connectivity findings were robust to several methodological confounds. First, one challenge that we foresaw was that sex differences in intracranial volume (ICV), with men typically having greater ICV than women, may be driving our functional connectivity results. However, when we ran our analysis on a smaller cohort of participants matched on ICV (and age and education), our findings corroborate our primary

747 analysis (Supplementary Figure 2). However, we recognize that this supplementary analysis was
748 conducted on a subcohort of participants with a smaller sample size. Although our primary analysis
749 used a subcohort of participants from the full lifespan cohort, our sample was limited by the smaller
750 cohort of male participants. Strategies are needed to motivate male participants, particularly middle-
751 aged men, to participate in research studies. However, we addressed our concerns of not integrating the
752 larger cohort of women through two additional supplementary analyses, findings of which corroborated
753 our primary analysis.

754 Finally, although we have theoretical justification for regressing task mean activity from the
755 fMRI signal, one might rightfully ask what the error term actually means, in terms of functional
756 relevance. When we ran the PLS connectivity analysis without regressing mean task-related activity,
757 the analysis generated the same exact LV results and functional network connectivity with minimal
758 differences observed in connectivity at the nodal rather than network level. This enabled us to conclude
759 that the level of interpretation we used for the current study (i.e., at the network level) would have
760 resulted in the same interpretations of findings, whether or not we chose to regress mean task-related
761 activity or not. Future work should endeavour to understand what these minute differences mean at the
762 node level, both theoretically and conceptually. Thus, although there was the possibility of several
763 confounds, our supplementary analyses findings demonstrate our primary analysis was robust to
764 different preprocessing strategies and methodological confounds.

765

766 *Conclusions*

767 Our results highlight similarities in performance-related patterns of task-based connectivity
768 during spatial context encoding and retrieval in women and men, and sex differences in how age
769 impacts memory-related brain connectivity. Aging was correlated with increased between-network
770 connectivity of task-irrelevant (Auditory and SSM) sensory networks and cognitive networks in men
771 that were detrimental to task performance. In women, aging was correlated decreased connectivity

between task-relevant Visual network and higher order cognitive networks, including DAN. This suggests that the neural basis of age-related episodic memory decline differs in women and men. Evidently, task-based connectivity and resting state connectivity both have an important and complementary role in studying sex differences in healthy aging and cognition. Our findings further cement the importance of separately understand healthy aging models for women and men to understand how healthy aging that eventually lead to neurodegenerative disorders, such as Alzheimer's or Parkinson's, that differentially impact women and men.

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Competing Interests*:* The authors have no conflict of interest to declare.

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Supplementary Materials

Supplementary Table 1. Power atlas ROI network nodes (n=216) used in the analysis

			MNI Coordinates		
Network	Talaraich Daemon Label	Brodmann_Area	X	Y	Z
Auditory	Insula	13	32	-28	12
Auditory	Insula	13	64	-32	20
Auditory	Transverse Temporal	41	56	-16	8
Auditory	STG	42	-40	-32	16
Auditory	STG	41	-60	-24	12
Auditory	STG	41	-48	-28	4
Auditory	Insula	13	44	-24	20
Auditory	Insula	13	-48	-36	24
Auditory	Insula	13	-52	-20	24
Auditory	PreCent	43	-56	-8	12
Auditory	PreCent	43	56	-4	12
Auditory	PostCent	2	60	-16	28
Auditory	Insula	13	-32	-28	12
CON	mFG	6	-4	4	52
CON	IPL	40	56	-28	32
CON	SFG	6	20	-8	64
CON	SFG	6	-16	-4	72
CON	CG	24	-12	-4	44
CON	LN	Putamen	36	0	-4
CON	SFG	6	12	0	68
CON	mFG	6	8	8	52
CON	Insula	13	-44	0	8
CON	Insula	13	48	8	0
CON	STG	22	-52	8	-4
CON	CG	32	-4	16	36
CON	Claustrum	*	36	12	0
DMN	MTG	19	-40	-76	24
DMN	mFG	10	4	68	-4
DMN	mFG	10	8	48	-16
DMN	PHG	30	-12	-40	0
DMN	mFG	10	-16	64	-8
DMN	MTG	19	-44	-60	20
DMN	MTG	39	44	-72	28
DMN	STG	38	-44	12	-36
DMN	STG	38	44	16	-32
DMN	MTG	21	-68	-24	-16
DMN	MTG	39	-44	-64	36
DMN	PrCu	19	-40	-76	44
DMN	PostCing	31	-8	-56	28

DMN	PrCu	7	4	-60	36
DMN	PostCing	30	-12	-56	16
DMN	PostCing	29	-4	-48	12
DMN	CG	31	8	-48	32
DMN	PrCu	31	16	-64	24
DMN	CG	31	-4	-36	44
DMN	PostCing	30	12	-52	16
DMN	STG	39	52	-60	36
DMN	SFG	8	24	32	48
DMN	SFG	6	-12	40	52
DMN	SFG	6	-16	28	52
DMN	MFG	6	-36	20	52
DMN	MFG	8	24	40	40
DMN	SFG	8	12	56	40
DMN	SFG	8	-12	56	40
DMN	SFG	8	-20	44	40
DMN	mFG	9	4	56	16
DMN	SFG	9	8	64	20
DMN	mFG	10	-8	52	0
DMN	mFG	10	8	56	4
DMN	ACC	32	-4	44	-8
DMN	ACC	32	8	44	-4
DMN	mFG	9	-12	44	8
DMN	mFG	8	-4	36	36
DMN	ACC	32	-4	40	16
DMN	SFG	9	-20	64	20
DMN	mFG	9	-8	48	24
DMN	ITG	21	64	-12	-20
DMN	MTG	21	-56	-12	-12
DMN	MTG	21	-56	-28	-4
DMN	MTG	21	64	-32	-8
DMN	MTG	21	-68	-40	-4
DMN	SFG	6	12	28	60
DMN	ACC	32	12	36	20
DMN	Sub-Gyral	21	52	-4	-16
DMN	PHG	36	-28	-40	-8
DMN	PHG	36	28	-36	-12
DMN	FFG	37	-32	-40	-16
DMN	STG	38	52	8	-28
DMN	MTG	21	-52	4	-28
DMN	STG	39	48	-52	28
DMN	MTG	21	-48	-44	0
DMN	IFG	47	-48	32	-12
DMN	MFG	47	48	36	-12

DMN	CG	31	-4	-36	32
DMN	PrCu	7	-8	-72	40
DMN	PrCu	7	12	-68	44
DMN	PrCu	7	4	-48	52
DMN	CG	23	0	-24	32
DAN	PrCu	7	8	-60	60
DAN	MTG	37	-52	-64	4
DAN	PrCu	7	20	-64	48
DAN	MTG	37	48	-60	4
DAN	SPL	7	24	-60	60
DAN	IPL	40	-32	-48	48
DAN	PrCu	19	-28	-72	36
DAN	MFG	6	-32	0	56
DAN	FFG	37	-44	-60	-8
DAN	SPL	7	-16	-60	64
DAN	MFG	6	28	-4	52
FPN	PreCent	6	-44	0	44
FPN	MFG	9	48	24	28
FPN	IFG	9	-48	12	24
FPN	IPL	40	-52	-48	44
FPN	SFG	6	-24	12	64
FPN	ITG	20	60	-52	-12
FPN	ACC	10	24	44	-16
FPN	MFG	10	32	56	-12
FPN	PreCent	6	48	8	32
FPN	PreCent	6	-40	4	32
FPN	MFG	46	-44	40	20
FPN	MFG	10	40	44	16
FPN	IPL	40	48	-44	44
FPN	SPL	7	-28	-56	48
FPN	IPL	40	44	-52	48
FPN	MFG	6	32	16	56
FPN	PrCu	39	36	-64	40
FPN	IPL	40	-44	-56	44
FPN	MFG	6	40	20	40
FPN	MFG	10	-36	56	4
FPN	IFG	10	-40	44	-4
FPN	SPL	7	32	-52	44
FPN	MFG	46	44	48	-4
FPN	MFG	9	-44	24	28
FPN	mFG	8	-4	28	44
Salience	PrCu	7	12	-40	52
Salience	Supramarginal	40	56	-44	36
Salience	MFG	6	44	0	48

Salience	MFG	9	32	32	28
Salience	IFG	45	48	24	8
Salience	Insula	13	-36	20	0
Salience	Insula	13	36	20	4
Salience	IFG	47	36	32	-4
Salience	Claustrum	*	32	16	-8
Salience	CG	32	-12	24	24
Salience	mFG	32	0	16	44
Salience	SFG	10	-28	52	20
Salience	CG	32	0	32	28
Salience	CG	32	4	24	36
Salience	CG	32	12	24	28
Salience	SFG	10	32	56	16
Salience	SFG	9	28	48	28
Salience	MFG	10	-40	52	16
SSM	PrCu	7	-8	-52	60
SSM	CG	24	-12	-16	40
SSM	ParaCent	31	0	-16	48
SSM	CG	24	8	0	44
SSM	mFG	6	-8	-20	64
SSM	ParaCent	4	-8	-32	72
SSM	ParaCent	4	12	-32	76
SSM	PostCent	2	-52	-24	44
SSM	PreCent	4	28	-16	72
SSM	PostCent	7	8	-44	72
SSM	PostCent	2	-24	-32	72
SSM	PostCent	3	-40	-20	56
SSM	Sub-Gyral	40	28	-40	60
SSM	PostCent	2	52	-20	40
SSM	PostCent	2	-40	-28	68
SSM	ParaCent	4	20	-28	60
SSM	PreCent	4	44	-8	56
SSM	Sub-Gyral	40	-28	-44	60
SSM	mFG	6	12	-16	76
SSM	SPL	7	24	-44	68
SSM	IPL	40	-44	-32	48
SSM	Sub-Gyral	40	-20	-32	60
SSM	PreCent	6	-12	-16	76
SSM	PostCent	3	44	-20	56
SSM	PreCent	4	-40	-16	68
SSM	PostCent	7	-16	-44	72
SSM	ParaCent	5	4	-28	60
SSM	mFG	6	4	-16	60
SSM	PreCent	4	36	-16	44

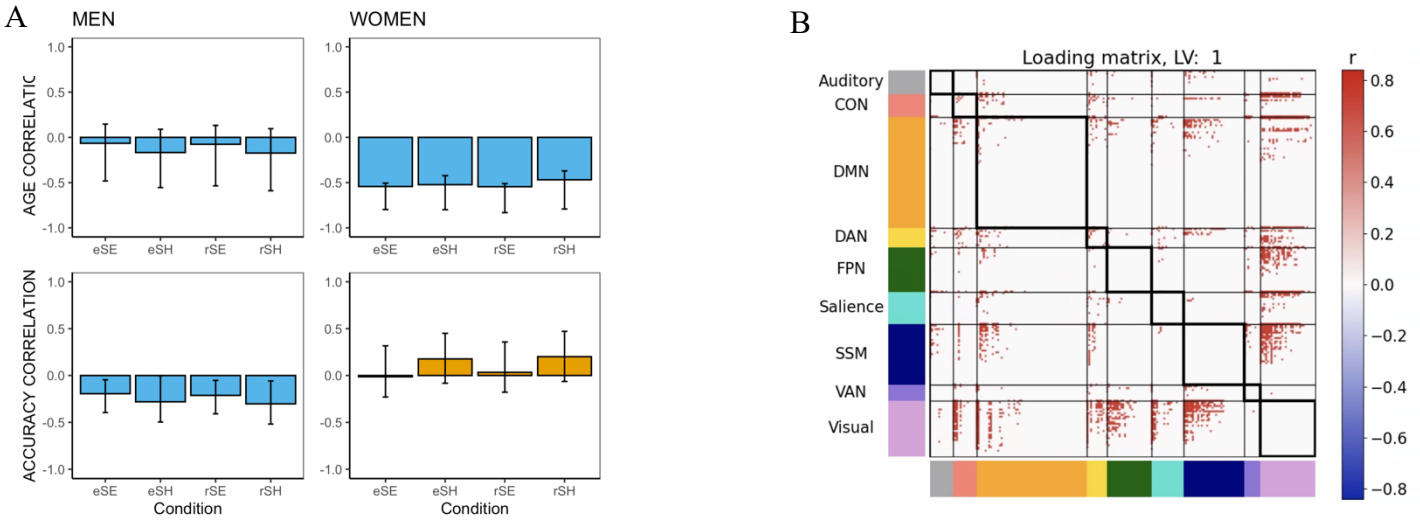
SSM	IPL	40	48	-28	48
SSM	PreCent	6	-48	-12	36
SSM	Claustrum	*	36	-8	12
SSM	PreCent	6	52	-4	32
SSM	PreCent	4	64	-8	24
VAN	SFG	6	-8	12	68
VAN	STG	13	52	-44	20
VAN	STG	22	-56	-52	8
VAN	STG	22	-56	-40	12
VAN	STG	41	52	-32	8
VAN	STG	22	52	-28	-4
VAN	STG	22	56	-48	12
VAN	IFG	45	52	32	0
VAN	IFG	45	-48	24	0
Visual	Culmen	*	16	-48	-8
Visual	MOG	19	40	-72	16
Visual	Cu	30	8	-72	12
Visual	LG	18	-8	-80	8
Visual	MOG	19	-28	-80	20
Visual	LG	19	20	-64	0
Visual	MOG	18	-24	-92	20
Visual	FFG	19	28	-60	-8
Visual	LG	18	-16	-72	-8
Visual	LG	19	-16	-68	4
Visual	FFG	19	44	-80	-12
Visual	FFG	19	-48	-76	-8
Visual	Cu	19	-16	-92	32
Visual	Cu	19	16	-88	36
Visual	PrCu	31	28	-76	24
Visual	LG	18	20	-84	-4
Visual	Cu	18	16	-76	32
Visual	LG	18	-16	-52	0
Visual	ITG	19	40	-64	-8
Visual	Cu	18	24	-88	24
Visual	Cu	18	4	-72	24
Visual	ITG	37	-44	-72	0
Visual	MOG	19	24	-80	-16
Visual	Cu	18	-16	-76	32
Visual	Cu	18	-4	-80	20
Visual	IOG	18	-40	-88	-8
Visual	MOG	19	36	-84	12
Visual	LG	18	8	-80	8
Visual	MOG	18	-28	-92	4
Visual	FFG	19	-32	-80	-12

Visual	IOG	19	36	-80	0

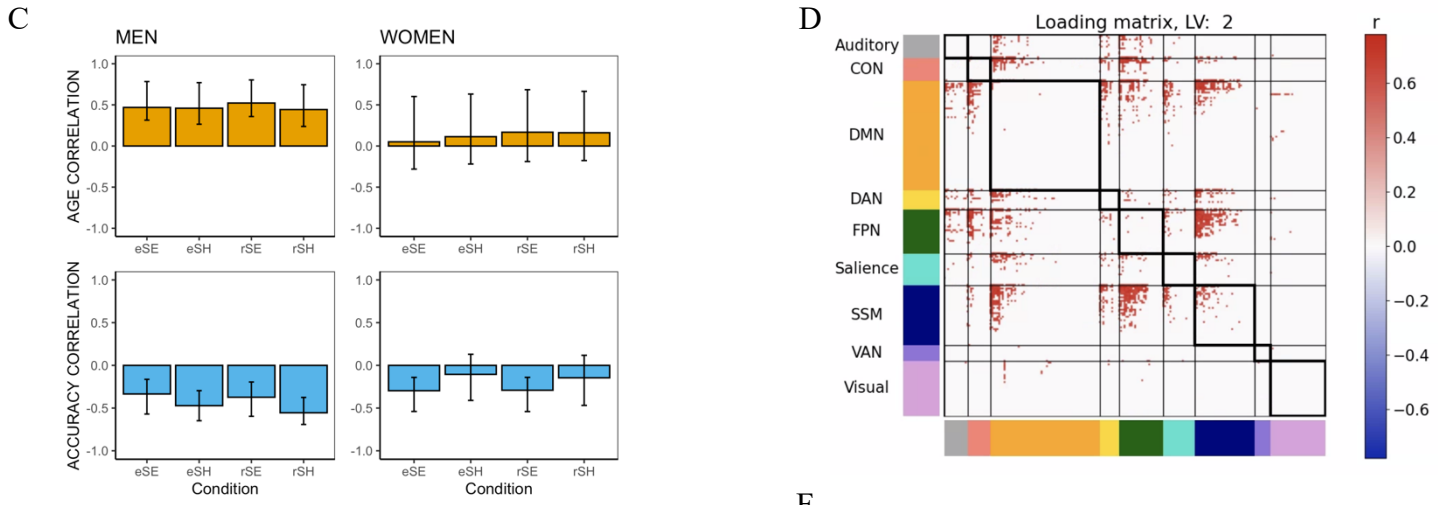
Note: CON = Cingulo-opercular Task Control; DMN = Default Mode Network; DAN = Dorsal Attention Network; FPN = Fronto-parietal Task Control Network; SSM = Sensory/Somatomotor Network

Supplementary Figure 1. BPLS without regressing mean task-related activity

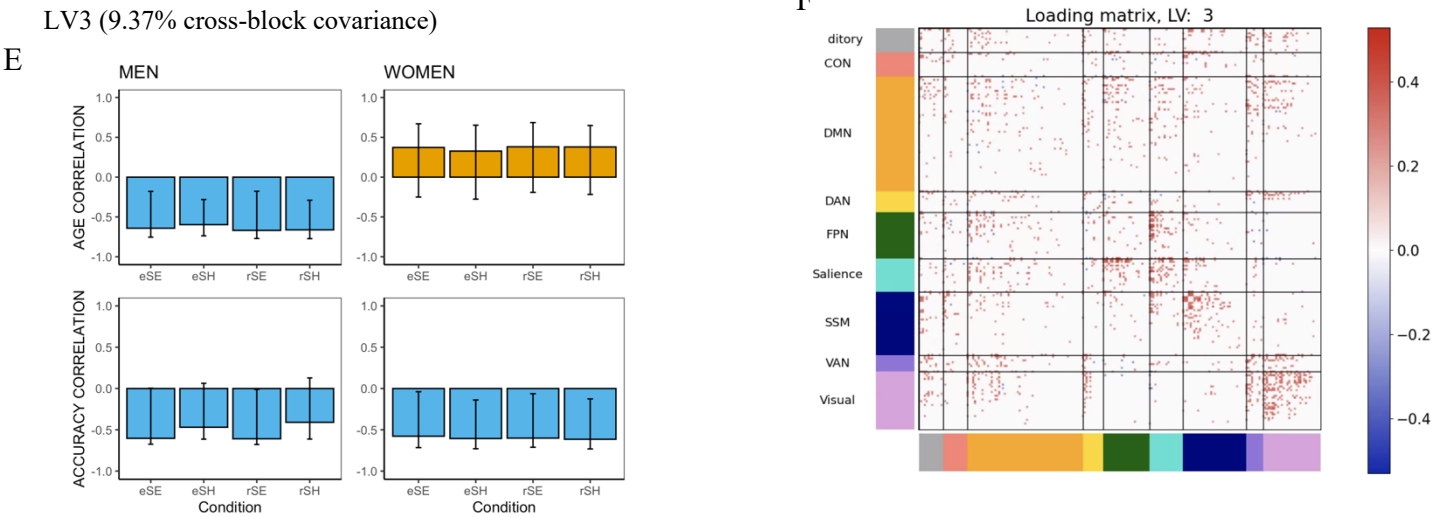
LV1 (41.45% cross-block covariance)



LV2 (26.88% cross-block covariance)



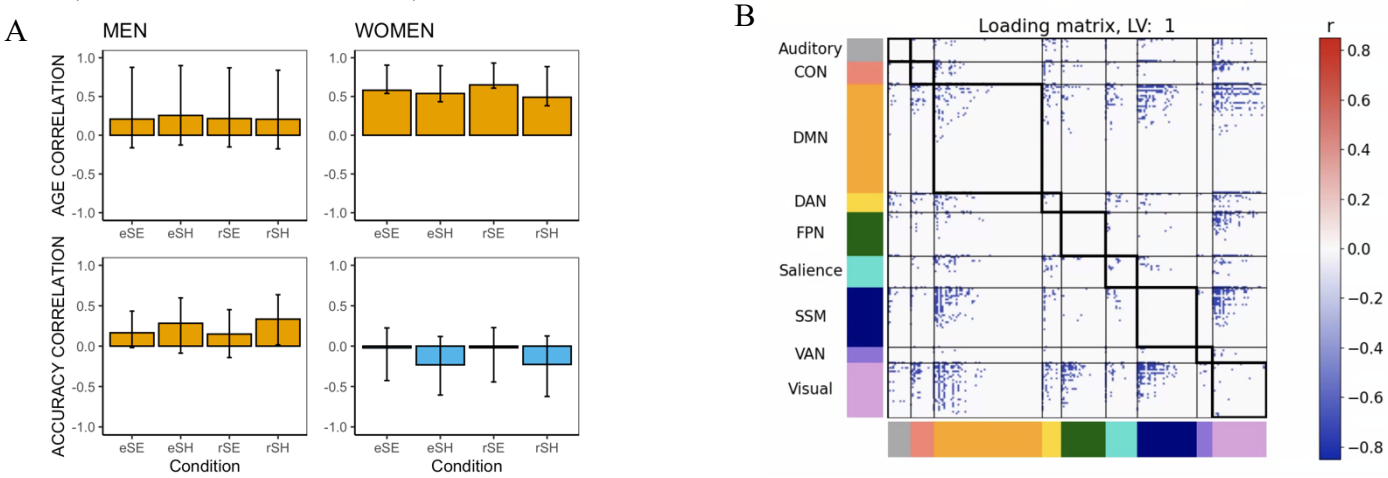
LV3 (9.37% cross-block covariance)



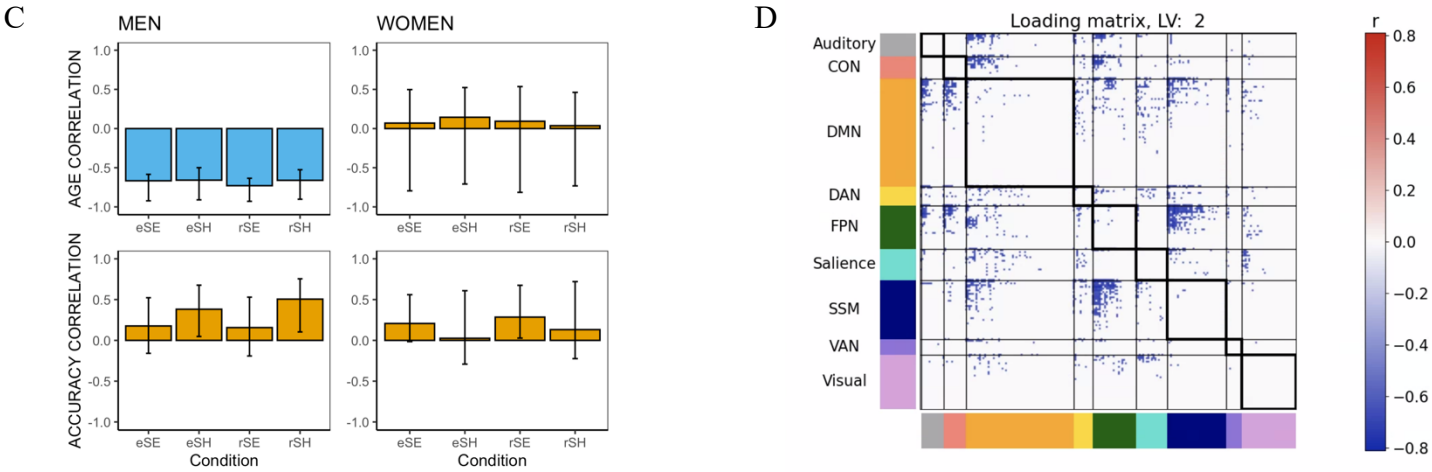
Note. The B-PLS analysis using connectivity matrices that did not regress mean-task-related activity generated 3 significant LVs, similar to the primary BPLS described in the manuscript. Supp Fig 1A, C, E reflect the correlation between the behavioural vectors of age and accuracy with the task fMRI connectivity of participants. Error bars represent bootstrapped standard deviations. Supp Fig 1B, D, F reflect the thresholded 95th percentile of correlations between participants' task fMRI data and behavioural profile.

Supplementary Figure 2. Matched Intracranial Volume Cohort Analysis

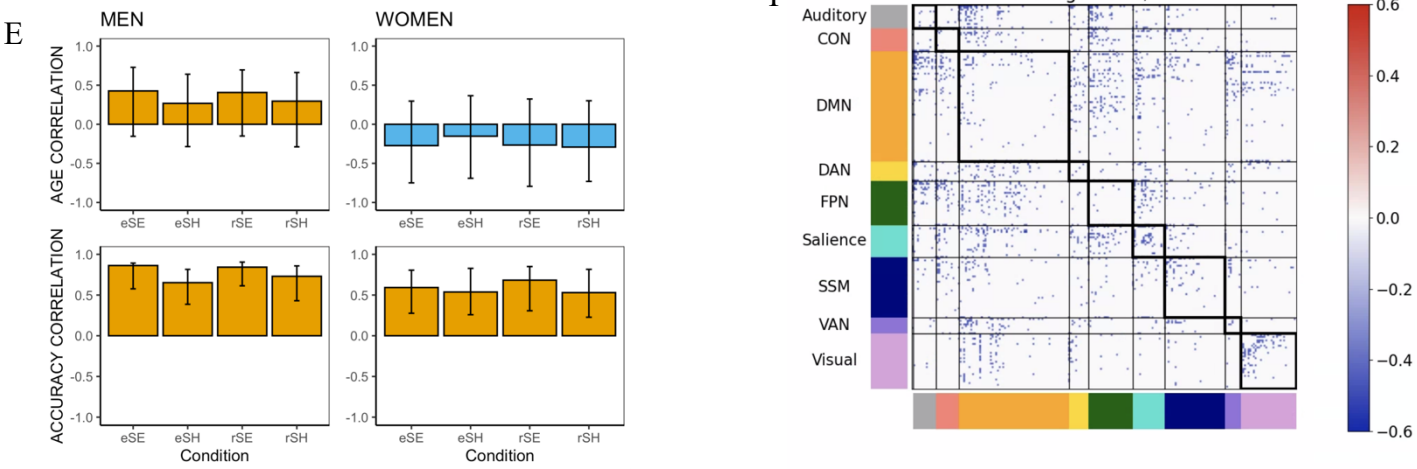
LV1 (44.17% cross-block covariance)



LV2 (19.17% cross-block covariance)



LV3 (9.92 % cross-block covariance)



Note. The BPLS analysis with a subcohort of participants matched by intracranial volume, age, and education (25 men, 25 women) determined findings similar to the original BPLS analysis described in the manuscript. Supp Fig 1A, C, E reflect the correlation between the behavioural vectors of age and accuracy with the task fMRI connectivity of participants. Error bars represent bootstrapped standard deviations. Supp Fig 1B, D, F reflect the thresholded 95th percentile of correlations between participants' task fMRI data and behavioural profile

Table 2. Mean Demographic and Behavioural Measures (and Standard Errors) in held-out Women (n = 43)

	Younger Adults (YA)	Middle Aged Adults (MA)	Older Adults (OA)	*p*
Sample size (n)	12	19	12	
Age (years)	25.75 (1.45)	51.74 (1.08)	64.25 (0.76)	
Educations (years)	14.75 (0.77)	15.53 (0.52)	14.67 (0.62)	model ns
Predicted full-scale IQ	118.84 (1.72)	118.32 (1.13)	119.22 (2.06)	model ns
BDI	3.33 (1.10	4.74 (0.96)	4.50 (0.92)	model ns
CVLT-LFR	14.92 (0.29)	13.68 (0.34)	13.33 (0.72)	$p < .05^{\#}$
CVLT-LCR	15.00 (0.44)	13.95 (0.36)	13.58 (0.69)	model ns
CVLT-RG	15.92 (0.08)	15.37 (0.19)	15.50 (0.26)	model ns
BMI (kg/m^2)	22.10 (1.40)	25.43 (1.03)	26.83 (1.23)*	$p < .01^{\#}$
SE retrieval accuracy (%correct)	0.89 (0.02)	0.86 (0.02)	0.82 (0.04)	model ns
SH retrieval accuracy (%correct)	0.90 (0.03)	0.82 (0.03)	0.78 (0.04)	$p < .01^{\#}$
SE retrieval RT (msec)	2305.06 (161.95)	2477.96 (112.40)	2856.97 (156.86)	$p < .01^{\#}$
SH retrieval RT (msec)	2360.28 (147.56)	2622.64 (92.27)	2867.88 (153.03)	$p < .01^{\#}$

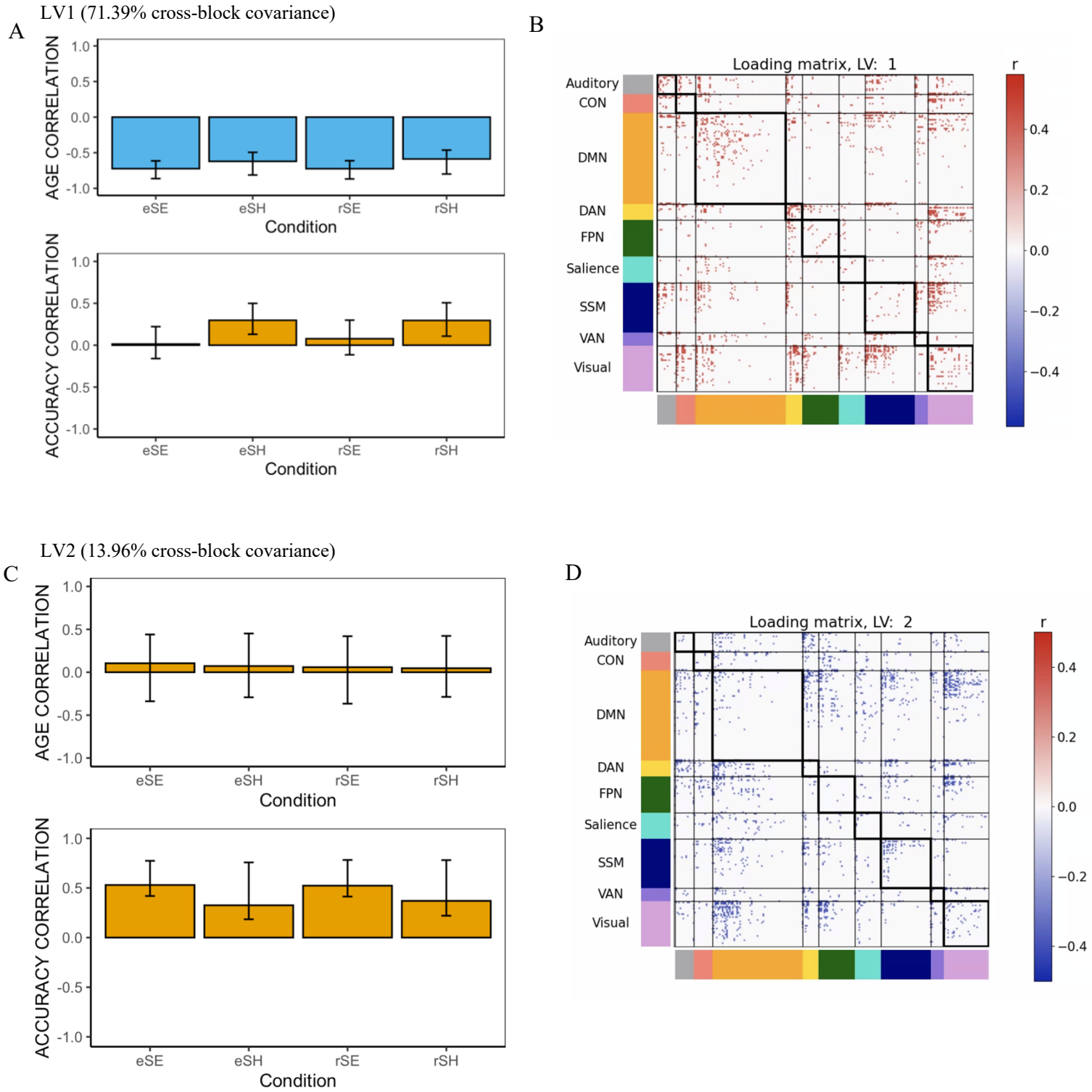
*BMI missing for one participant (n =11). Values in brackets represent the standard error. A linear regression with Age as the independent measure was performed on each of the measures (significance of $p < .05$ used). # The linear regression produced a significant main effect of Age. The fMRI behavioural measures revealed that OA participants performed significantly worse than younger and middle-aged participants and with significantly greater RT to complete the spatial tasks. BDI = Beck Depression Inventory; LFR = Long-form Free Recall; LCR = Long-form Cued Recall; RG = Recognition; BMI = body mass index.

Table 3. Mean Demographic and Behavioural Measures (and Standard Errors) in Women (n = 91)

	Younger Adults (YA)	Middle Aged Adults (MA)	Older Adults (OA)	*p*
Sample size (n)	28	35	28	
Age (years)	25.96 (0.74)	49.69 (0.90)	66.14 (0.65)	
Educations (years)	15.89 (0.44)	15.66 (0.36)	15.07 (0.42)	ns
Predicted full-scale IQ	118.64 (1.04)	119.44 (0.85)	120.04 (1.06)	ns
BDI	3.44 (3.95)*	4.54 (0.72)	3.7 9(0.57)	ns
CVLT-LFR	14.11(0.29)	13.46 (0.27)	13.25 (0.44)	ns
CVLT-LCR	14.25 (0.34)	13.71 (0.30)	13.39 (0.39)	ns
CVLT-RG	15.57 (0.13)	15.34 (0.15)	15.18 (0.18)	ns
BMI (kg/m^2)	22.05 (0.71)	24.60 (0.67)	25.80 (0.72)*	$p < .01^{\#}$
SE retrieval accuracy (%correct)	0.89 (0.01)	0.86 (0.02)	0.83 (0.02)	$p < .01^{\#}$
SH retrieval accuracy (%correct)	0.89 (0.02)	0.84 (0.02)	0.78 (0.02)	$p < .01^{\#}$
SE retrieval RT (msec)	2200.11 (105.50)	2464.40 (9.95)	2878.14 (83.98)	$p < .01^{\#}$
SH retrieval RT (msec)	2279.37(103.05)	2610.75 (77.30)	2871.45 (82.69)	$p < .01^{\#}$

*One participant had missing BDI information (n=27), and one participant had missing BMI information (n =27). Values in brackets represent the standard error. A linear regression with Age as the independent measure was performed on each of the measures (significance of $p < .05$ used). # The linear regression produced a significant main effect of Age. The fMRI behavioural measures revealed that OA participants performed significantly worse than younger and middle-aged participants and with significantly greater RT to complete the spatial tasks. BDI = Beck Depression Inventory; LFR = Long-form Free Recall; LCR = Long-form Cued Recall; RG = Recognition; BMI = body mass index.

Supplementary Figure 3. Within-Sex PLS Analysis Within Women (n=91)



Note. The within-sex B-PLS of the full cohort of women (n = 91) generated two significant LVs that produced findings consistent to the primary B-PLS findings in women. Supp Fig 1A and 1C reflect the correlation between the behavioural vectors of age and accuracy with the task fMRI connectivity of participants. Error bars represent bootstrapped standard deviations. Supp Fig 1B and 1D reflect the thresholded 95th percentile of correlations between participants' task fMRI data and behavioural profile.