Sex Differences in the Neural Correlates of Spatial Context Memory Decline in Healthy Aging

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Abstract

■ Aging is associated with episodic memory decline and alterations in memory-related brain function. However, it remains unclear if age-related memory decline is associated with similar patterns of brain aging in women and men. In the current task fMRI study, we tested the hypothesis that there are sex differences in the effect of age and memory performance on brain activity during episodic encoding and retrieval of face–location associations (spatial context memory). Forty-one women and 41 men between the ages of 21 and 76 years participated in this study. Between-group multivariate partial least squares analysis of the fMRI data was conducted to directly test for sex differences and similarities in age-related and performance-related patterns of brain activity. Our behavioral analysis indicated no significant sex differences in retrieval accuracy on the fMRI tasks. In relation to performance effects, we observed similarities and differences in how retrieval accuracy related to brain activity in women and men. Both sexes activated dorsal and lateral PFC, inferior parietal cortex, and left parahippocampal gyrus at encoding, and this supported subsequent memory performance. However, there were sex differences in retrieval activity in these same regions and in lateral occipital-temporal and ventrolateral PFC. In relation to age effects, we observed sex differences in the effect of age on memory-related activity within PFC, inferior parietal cortex, parahippocampal gyrus, and lateral occipital-temporal cortices. Overall, our findings suggest that the neural correlates of age-related spatial context memory decline differ in women compared with men. ■

INTRODUCTION

Episodic memory is our ability to encode, store, and retrieve personally experienced events in rich contextual detail (Tulving, 1984). The ability to encode and retrieve contextual details of episodic memories diminishes with age and impacts adult quality of life (e.g., Dulas & Duarte, 2012; Rajah, Languay, & Valiquette, 2010; Cansino, 2009; Trott, Friedman, Ritter, & Fabiani, 1997; Glisky, Polster, & Routhieaux, 1995; Spencer & Raz, 1995; Schacter, Kaszniak, Kihlstrom, & Valdiserri, 1991). Neuroimaging studies have shown that encoding and recollecting item–context associations relies on the function of a distributed network of brain regions including the medial-temporal lobe (MTL), PFC, and inferior parietal cortex (IPC; Hayama, Vilberg, & Rugg, 2012; Rajah, Crane, Maillet, & Floden, 2011; Grady et al., 2010; Spaniol et al., 2009; Johnson & Rugg, 2007; Rajah, McIntosh, & Grady, 1999). As such, age-related declines in episodic memory for contextual details (context memory) have been attributed to structural and functional differences in these brain regions. For example, in our previous adult lifespan fMRI study, we found that age-related deficits in context memory started in early midlife and were associated with differences in bilateral fusiform gyrus, anterior PFC, and ventrolateral PFC (VLPFC) activity in middle-aged adults, compared with young adults (Kwon et al., 2016). In older adults, context memory decline was more severe and was associated with added differences in dorsolateral PFC (DLPFC), MTL, and IPC activity, compared with middle-aged and young adults (Ankudowich, Pasvanis, & Rajah, 2016, 2017). Previous fMRI studies have also reported age-related differences in context memory with corresponding functional differences in PFC, MTL, and parietal areas (Cansino, Estrada-Manilla, et al., 2015; Cansino, Trejo-Morales, et al., 2015; Mitchell, Ankudowich, Durbin, Greene, & Johnson, 2013; Cansino, Hernández-Ramos, & Trejo-Morales, 2012; Cansino, Trejo-Morales, & Hernández-Ramos, 2010; Dennis et al., 2008, but see Cabeza, Anderson, Locantore, & McIntosh, 2002 for functional similarities in context memory among younger adults and low performing older adults). Therefore, there is growing consensus that age-related declines in context memory for visually presented stimuli are linked to differences in frontoparietal, medial-temporal and ventral visual function with age.

However, the majority of fMRI studies that have investigated age-related differences in brain activity during episodic memory have pooled participants. This assumes the neural correlates of age-related episodic memory decline are similar in female and male individuals. Yet, there

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is evidence for sex differences in brain structure and function in adulthood (see Gur & Gur, 2002, for a review) and evidence that females and males may perform differently on specific episodic memory tasks, depending on the experimental stimuli and design. For example, behavioral studies demonstrate that females perform better on episodic memory tasks for verbal stimuli (Gur & Gur, 2002; Ragland, Coleman, Gur, Glahn, & Gur, 2000; Herlitz, Nilsson, & Bäckman, 1997), negative emotional stimuli (Young, Bellgowan, Bodurka, & Drevets, 2013), face stimuli (Sommer, Hildebrandt, Kunina-Habenicht, Schacht, & Wilhelm, 2013; Yonker, Eriksson, Nilsson, & Herlitz, 2003), and verbal paired associative memory (Bender, Naveh-Benjamin, & Raz, 2010), compared with males. In contrast, on average, males have performed better than females on object–location associative memory tasks during encoding of positional information (Postma, Izendoorn, & De Haan, 1998) and memory tasks assessing visuospatial ability (e.g., De Frias, Nilsson, & Herlitz, 2006; Weiss, Kemmler, Deisenhammer, Fleischhacker, & Delazer, 2003).

Exploring the origins of sex differences in brain aging and episodic memory function is important clinically, because studies have reported sex differences in the incidence and risk for memory-related disorders (Azad, Al Bugami, & Loy-English, 2007; Jorm & Dolley, 1998). For example, females are more at risk of developing late-onset Alzheimer disease (AD), compared with males (Alzheimer's Association, 2019; Mielke, Vemuri, & Rocca, 2014). Therefore, it is critical to develop a working model of healthy aging in both sexes to better understand why there are sex differences in the prevalence of specific age-related diseases (i.e., AD).

However, a feature of sex differences in episodic memory and brain structure/function is that sociological and environmental factors influence brain development and cognitive/behavioral strategic preferences between the sexes. Thus, sex differences in brain structure and function may be observed, even when sex differences in cognitive/behavioral performance are not. For example, Nyberg, Habib, and Herlitz (2000) found both similarities and differences between sexes when they investigated sex differences in the neural correlates of episodic memory retrieval in a younger adult sample (17 males, 17 females; Nyberg et al., 2000). In this study, participants responded yes/no in a recognition paradigm for words, sentences, and landscape images. No sex differences in recognition memory were reported. A multivariate partial least squares (PLS) analysis of the O^{15} PET data revealed both similarities and differences in memory-related brain activity between females and males. Both females and males exhibited retrieval-related activity in right PFC, anterior cingulate gyrus, and midline occipital-parietal areas, which are regions typically recruited during episodic retrieval (Cabeza & Nyberg, 2000; Lepage, Ghaffar, Nyberg, & Tulving, 2000). In addition, sex differences in retrieval-related activity were observed: females showed greater retrieval-related activity in the anterior cingulate gyrus, right VLPFC, right fusiform, IPC, and cerebellum compared with males. Males showed greater activity compared with females at retrieval in bilateral dorsal VLPFC, bilateral inferior temporal cortex and IPC, and posterior cingulate cortex. Similarly, previous work has reported functional sex differences during memory tasks, albeit with a greater focus on investigating autobiographical memory (Young et al., 2013; St Jacques, Conway, & Cabeza, 2011).

Importantly, sex and age differences in PFC, IPC, MTL, and/or ventral occipitotemporal function during episodic memory studies have also been reported (Compère et al., 2016; Spalek et al., 2015; Ragland et al., 2000). Yet, it remains unclear if biological sex influences the impact of age on the neural correlates of episodic memory. In other words, we do not know if there is a Sex × Age interaction and whether the results from prior neuroimaging studies of aging and episodic memory equally reflect how age impacts brain function and episodic memory in females and males or if some results were driven by one sex. Moreover, most prior studies have been limited to testing autobiographical or recognition memory and in terms of the age range of participants tested (Compère et al., 2016; Spalek et al., 2015; Haut & Barch, 2006; Ragland et al., 2000). Given that sex differences in episodic memory remain relatively stable across the adult lifespan (De Frias et al., 2006), one may hypothesize that sex differences in the functional neural correlates of episodic memory, if present, are stable across the adult lifespan, too. However, there is a growing body of human neuroimaging studies showing that sex differences in lifetime exposure to gonadal sex hormones may differentially affect cognition and brain function in females compared to males. For example, menopause-related decline in 17-β-estradiol (e.g., Rentz et al., 2017; Jacobs et al., 2016b; Morrison, Brinton, Schmidt, & Gore, 2006) or age-related decline in testosterone (e.g., Moffat et al., 2018; Rosario, Chang, Head, Stanczyk, & Pike, 2011; Rosario & Pike, 2008; Muller, Aleman, Grobbee, de Haan, & van der Schouw, 2005) may contribute to sex differences in cognitive function. In addition, sociocultural factors, such as self-perceived gender trait possessions (Hamilton, 1995; Sharps, Price, & Williams, 1994), may also differentially influence task performance and/or strategy use during memory tasks in females, compared to males (Hamilton, 1995; Lawton, 1994; Sharps et al., 1994; Baenninger & Newcombe, 1989). Therefore, it is also possible that there are sex differences in how age impacts brain function and episodic memory. This implies that the functional neural basis of age-related memory decline may differ in females, compared with males. Such an observation would have important clinical implications because it would suggest that specific interventions may be required in females, compared with males, to support the maintenance of memory function in late life. We test this possibility in the current study.

The goal of the current cross-sectional fMRI study is to investigate how biological sex impacts the neural correlates of episodic memory encoding and retrieval of

face–location associations (spatial context memory) in an adult lifespan sample. A subsample of females and males from a previously collected fMRI data set, who were closely matched between groups on age and educational attainment, were used (Ankudowich et al., 2016). Because of prior studies highlighting the impact of menopausal transition on episodic memory-related brain regions PFC and MTL (Rentz et al., 2017; Jacobs et al., 2016a, 2016b) and our limited sample size for this subsample, we excluded middle-aged females who self-reported being in menopausal transition. We used a between-group multivariate behavior PLS (B-PLS) statistical analysis to examine sex differences in the effect of age and memory performance on brain activity during episodic encoding and retrieval (McIntosh, Chau, & Protzner, 2004). The rationale for choosing this method of analysis, in comparison with more traditional univariate contrast-based approaches, was to use a data-driven method to objectively assess if there were patterns of whole-brain activity that differentiated how age impacted memory-related brain activity in females, compared with males. Although a contrast-based method could also be used to test this hypothesis, by not using a priori contrasts we are able to observe what the strongest effects in our data set were and whether sex differences were one of them. Furthermore, B-PLS allows for a direct assessment of sex differences in how age, memory performance, and Age × Memory Performance interaction may impact brain activity. Thus, it is a powerful and parsimonious multivariate method that allows researchers to capture the complex relationship between whole-brain patterns of brain activity and multiple exogenous variables of interest in one mathematical step (Andersen, Rayens, Liu, & Smith, 2012; McIntosh, Bookstein, Haxby, & Grady, 1996). In addition, statistical significance of B-PLS experimental effects was based on permutation testing at the image level, and the stability of activations at the voxel level was assessed with bootstrapping (McIntosh et al., 2004). Thus, in using B-PLS for this study, we aimed to identify functional activation patterns from fMRI data at the whole-brain level that covaried with memory performance and to further identify how these patterns differ in females compared with males across the aging lifespan. Based on prior behavioral and fMRI studies in young adults (e.g., Spaniol et al., 2009; Nyberg et al., 2000), we predicted there would be sex differences in memory-related brain activity during encoding and/or retrieval. Additionally, given the literature on age-related differences in sex hormone levels and their influence on cognition, we also predict that there will be sex differences in how age influences memory-related brain activity at both encoding and retrieval.

METHODS

Participants

Participants were 41 males and 41 females between the ages of 21 and 76 years (M = 47.1, SE = 2.03). Thirty participants could be classed as younger adults (age range = 21–32 years, M = 26.3, SE = 0.60), 20 as middle-aged adults (age range = 40–56 years, M = 45.8, SE = 1.17), and 32 as older adults (age range = 61–76 years, M = 67.3, SE = 0.66). In each age group, we had an equal number of males and females who were closely matched according to age and level of education. This sample was obtained from a larger cohort sample (N = 128) primarily used for the investigation of episodic memory across the aging lifespan (e.g., Ankudowich et al., 2016).

Our sample size was restricted by the number of males (n = 43) who participated in our study. We used this male sample and matched females closest in age and level of educational attainment to have an equivalent sample size of males and females who were balanced in age and educational attainment. In selecting our middle-aged females to match our male sample, we included middle-aged females who self-reported as being in either pre- or postmenopausal reproductive stages. We excluded middle-aged females who self-reported having irregular periods and experiencing symptoms of menopausal transition (n = 18) and who had undergone hormone replacement therapy (HRT; n = 10), because menopausal transition and HRT influence brain function and episodic memory abilities (Rentz et al., 2017; Li, Cui, & Shen, 2014; Henderson, 2010; Yonker et al., 2006). Thus, the youngest woman in the middle-aged group was 40 years old and premenopausal, and the oldest woman in the middle-aged group was 56 years old and postmenopausal. Analysis of the data revealed two brain score–behavior correlation outliers based on the correlation profiles that were subsequently removed (and their matched pairs) to obtain the final matched sample (n = 82). All participants had at least a high school education (mean education = 16.1 years, SE = 0.22). Everyone was right-handed as assessed using the Edinburgh Inventory for Handedness (Oldfield, 1971) and met the inclusion/exclusion criteria (listed below). The study was approved by the institutional review board of the Faculty of Medicine, McGill University, and all participants signed a consent form before participating in the study. Participants were recruited via newspaper and online advertisements in Montréal, Canada.

Table 1 summarizes participant demographic and neuropsychological information by sex within each age group. Post hoc analyses revealed no significant differences in education level between males and females within each age group (p > .05), confirming that we successfully balanced our two samples on this variable.

Behavioral Methods

Experimental details of this study have been published (Ankudowich et al., 2016). All tests were done at the Douglas Institute Brain Imaging Center. There were two testing sessions in the experiment. The first session involved medical and neuropsychological testing. The neuropsychological tests completed by each participant included the Mini-Mental Status Exam (Folstein, Folstein, & McHugh,

Table 1. Mean Demographic and fMRI Behavioral Measures (and Standard Errors) by Age Group and Sex

	Younger Adults (YA)		*Middle-aged Adults (MA)*		*Older Adults (OA)*		
	Males	*Females*	*Males*	*Females*	*Males*	*Females*	*p*
Sample size (*n*)	15	15	10	10	16	16	
Age (years)	26.53 (0.89)	26.13 (0.82)	45.50 (1.67)	46.00 (1.73)	67.12 (1.04)	67.56 (0.85)	$p < .001$
Education (years)	16.47 (0.36)	16.87 (0.41)	16.00 (0.54)	15.70 (0.70)	16.19 (0.61)	15.38 (0.57)	*ns*
Predicted full-scale IQ	120.10 (1.38)	118.70 (1.47)	118.70 (2.10)	119.04 (1.57)	119.73 (1.04)	120.65 (1.08)	*ns*
BDI	4.07 (0.91)	2.27 (0.94)	1.70 (0.75)	3.50 (0.92)	4.25 (1.04)	3.19 (0.74)	*ns*
CVLT-LFR	13.33 (0.50)	13.53 (0.43)	12.10 (1.15)	13.60 (0.50)	12.00 (0.56)	13.19 (0.56)	*ns*
CVLT-LCR	13.47 (0.42)	13.67 (0.47)	12.70 (0.91)	13.80 (0.61)	12.50 (0.47)	13.25 (0.46)	*ns*
CVLT-RG	15.40 (0.19)	15.20 (0.20)	15.40 (0.27)	15.10 (0.35)	15.12 (0.18)	14.94 (0.23)	*ns*
BMI (kg/m^2)	23.85 (0.69)	22.31 (0.69)	26.13 (0.72)	23.97 (1.25)	24.37 (0.57)	25.10 (0.86)	$p < .05$
Smoking history	1.07 (0.07)	1.20 (0.14)	1.33 (0.24)	1.00 (0.00)	1.88 (0.18)	1.69 (0.15)	$p < .05$
SE retrieval accuracy (%correct)	0.87 (0.03)	0.91 (0.02)	0.91 (0.02)	0.89 (0.02)	0.80 (0.02)	0.84 (0.02)	$p < .001$
Spatial hard retrieval accuracy (%correct)	0.86 (0.03)	0.90 (0.02)	0.85 (0.03)	0.85 (0.03)	0.73 (0.03)	0.78 (0.02)	$p < .001$
SE retrieval RT (msec)	2286.28 (107.41)	2073.71 (138.29)	2178.30 (130.05)	2439.54 (189.85)	2633.79 (138.26)	2894.03 (92.98)	$p < .001$
Spatial hard retrieval RT (msec)	2455.03 (96.93)	2165.73 (139.18)	2276.82 (115.16)	2554.16 (177.63)	2765.84 (154.00)	2874.13 (93.05)	$p < .001$

A two-way ANOVA of Age Group (3: YA, MA, OA) × Sex (2: males, females) were performed on each of the measures, except smoking history, for which chi-square analyses were conducted separately for sex and age group (significance of $p < .05$ used). All significant outcomes only show a significant main effect of Age Group. Tukey's honestly significant difference post hoc between-group tests on fMRI behavioral measures revealed OA participants performed significantly worse than YA and MA participants and with significantly greater RT to complete the task in both conditions of the task ($p < .05$). YA had significantly lower BMI compared with middle-aged and older adults. Chi-square analyses on smoking history revealed significant age group differences (i.e., OA had greater smoking use patterns compared with YA and MA), but no significant sex differences. Smoking history: 0 = *never*, 1 = *past smoker*, 2 = *current smoker*. BDI = Beck Depression Inventory; LFR = Long-form Free Recall; LCR = Long-form Cued Recall; RG = Recognition; BMI = body mass index.

1975), with exclusion cutoff score of <27; the Beck Depression Inventory (Beck & Steer, 1987), with inclusion cutoff of <15; and the 50-word National Adult Reading Test (NART; Nelson, 1982) or the 40-word French NART (fNART; Mackinnon & Mulligan, 2005)—depending on the participant's language preference, given that Montreal is an English/French bilingual city. We used participants' NART or fNART score to calculate their predicted full-scale IQ using the standard formulas provided in Nelson (1982) for the NART and in Mackinnon and Mulligan (2005) for the fNART. We excluded any adult with a predicted full-scale IQ of ≤1 *SD* below the mean standardized IQ = 100, where 1 *SD* = 15 IQ points (exclusion criteria ≤ 85 predicted full-scale IQ). To calculate these NART-derived predicted IQ scores, we calibrated the English NART scores against the WAIS-IV full-scale IQ and the French NART scores against the WAIS-R verbal for the French version (see Mackinnon & Mulligan, 2005; Nelson, 1982).

Participants were additionally excluded from the study if they self-reported as having a history of neurological insult, psychiatric illness, substance abuse, smoking > 40 cigarettes/day, diabetes, or body mass index of >30 kg/m^2 or were currently diagnosed with high cholesterol levels and/or high blood pressure that was untreated or had only been treated for less than 6 months. Participants also completed the California Verbal Learning Test (CVLT), which was used to assess verbal item memory. All the aforementioned participants met the cutoff criteria for the neuropsychological tests and were able to perform above chance on a mock fMRI session of the context memory tasks employed in our fMRI study (detailed below) and were invited to the second fMRI scanning session. The stimuli used in the mock scanning session did not overlap with stimuli used in the fMRI session.

During the fMRI session, BOLD fMRI scans were obtained while participants performed easy and difficult versions of spatial and temporal context memory tasks for photographs of age-variant face stimuli of multiple ethnicities. Scans were obtained during both encoding and retrieval phases of the memory tasks. The difficulty manipulation was included to help differentiate brain activity related to main effects of Sex and Performance and Sex × Performance interaction. Details of the difficulty manipulation are presented below. A mixed rapid event-related fMRI design with 12 experimental runs was employed (Dale & Buckner, 1997). Each run contained a spatial easy (SE), temporal easy (TE), and a hard version of either a spatial (SH) or temporal (TH) memory task. In total, the SE and TE tasks were performed 12 times and the SH and TH tasks were performed six times. The results herein only examined the behavioral and fMRI data collected during spatial context memory tasks to reduce the complexity of the fMRI analysis conducted. Moreover, we focused specifically on the spatial context memory tasks to facilitate the interpretations of our findings in light of the considerable literature investigating sex differences in spatial episodic memory (Herlitz & Rehnman, 2008; Lewin, Wolgers, & Herlitz, 2001; Herlitz, Airaksinen, & Nordström, 1999; Herlitz et al., 1997). Thus, only details pertaining to these tasks are presented below. For details about the temporal context memory tasks, refer to Ankudowich et al. (2016, 2017). The behavioral tasks were designed and implemented using E-Prime (Psychology Software Tools, Inc.), and accuracy (% correct) and RT (msec) were collected. Below, we explain the experimental details for spatial context encoding and retrieval.

Spatial Context Encoding

Before each encoding session, participants were presented with a 9-sec instruction screen, which informed them that the following task was a spatial context memory task and that they were required to memorize each face and its left/right spatial location on the screen. In addition, participants were asked to rate each face as being pleasant or neutral using a two-alternative button press. We have found that making such a social–emotional evaluation of stimuli at encoding improves subsequent memory (Maillet & Rajah, 2013, but also see Harvey, Fossati, & Lepage, 2007; Mitchell, Macrae, & Banaji, 2004). In addition, this balanced the motor demands of the encoding and retrieval tasks employed, as both tasks required two-alternative decisions.

After the encoding instructions were presented, participants were shown a series of faces, one at a time, for 2 sec/stimulus with a variable intertrial interval of 2.2–8.8 sec, which served to add jitter to the event-related fMRI data acquisition (Dale & Buckner, 1997). Each face was presented either on the left or right side of a central fixation. During SE tasks, six faces were presented at encoding, and during SH tasks, 12 faces were presented. Therefore, an encoding load manipulation was used to modulate task difficulty. In total, there were 72 encoding stimuli per task (12 blocks of SE encoding tasks and six blocks of SH encoding tasks).

Encoding was followed by a 1-min distraction phase where participants performed a verbal alphabetization task, which required participants to identify which one of two words came first in the alphabet. The goal of this part of the experiment was to prevent participants from actively rehearsing the face stimuli.

Spatial Context Retrieval

After the distraction phase, participants entered the retrieval phase of the task. There was a 9-sec instruction screen that appeared before retrieval events to orient participants to their task. Participants were instructed they would see a series of two previously encoded faces during each retrieval event and were required to select which of the two faces were originally presented on the left of the screen (for half the retrieval tasks) or on the right of screen (for half the retrieval tasks). After the instructions, participants were presented with three consecutive retrieval events, 6 sec/event, with a variable intertrial interval (as

stated above) during SE tasks and with six consecutive retrieval events for SH tasks. Participants made their responses using a button press with an MRI-compatible response box. There were 36 retrieval events per task type across the experiment.

MRI Methods

The fMRI scanning took place while participants lay in supine position in a 3T Siemens Magnetom Trio scanner wearing a standard 12-channel head coil. First, the T1-weighted anatomical image was acquired using a 3-D gradient-echo MPRAGE sequence (repetition time [TR] = 2300 msec, echo time = 2.98 msec, flip angle = 9°, 176 1 mm sagittal slices, 1 × 1 × 1 mm voxels, field of view = 256 mm^2, GRAPPA of 2, acquisition time = 5 min). After the structural scan, functional BOLD MRI images were collected while participants performed the aforementioned behavioral task using a single-shot T2*-weighted gradient EPI pulse sequence (matrix size = 64 × 64, 32 oblique slices with no slice gap, in-plane resolution of 4 × 4 mm, TR = 2000 msec, echo time = 30 msec, 4 mm^3 isotropic, field of view = 256 mm^2). The memory task was initiated on a computer using E-Prime software; the visual stimuli were back-projected onto a screen in the scanner bore and made visible to participants via a mirror mounted within the head coil. Participants were able to make task-related responses using a fiber-optic four-button response box. Participants requiring correction for visual acuity wore corrective plastic lenses. Twelve fMRI runs were conducted, as outlined in the behavioral methods; each run was approximately 9 min long and yielded 278 whole-brain volumes per run. Total time in the scanner, with setup, was approximately 2 hr.

Preprocessing

DICOM files were converted to ANALYZE format. The first five functional images were removed to ensure that tissue had reached a steady state magnetization. The fMRI data were preprocessed using Statistical Parametric Mapping (Version 8). ArtRepair from SPM8 Toolbox was used for noise filtering to correct for bad slices and voxel spike noise using linear interpolation for up to 5% of the fMRI data and elimination of data outside the head. After correction for bad slices, images were realigned to the first acquired functional image and corrected for movement using a six-parameter rigid-body spatial transform. Participants with greater than 4 mm of movement within a run were removed from the analysis. Maximum movement observed within a run by participants was 0.65 mm. Therefore, none of the subjects was excluded for excess motion. The data were then normalized to the MNI EPI template (4 × 4 × 4 mm voxel resolution) using a 12-parameter affine transformation with default settings and then smoothed using an 8-mm FWHM isotropic Gaussian kernel. Finally, ArtRepair (SPM8) was again used to correct for bad volumes using a standard of <5% interpolated data.

Behavioral Data Analysis

Spatial Context Retrieval Accuracy and RT

Using R (R Core Team, 2016), we conducted a linear mixed-effects regression (LMER) model (using the *lme4* package in R; Bates, Mächler, Bolker, & Walker, 2015) to test the three-way interaction between age, sex (2: male, female), and task difficulty (2: easy, hard) on retrieval accuracy (% correct) and RT (msec). In addition, the model contained the random effect of participants to account for the variability of participant performance between the two difficulty conditions of the spatial task. Thus, in terms of R syntax, the specific model that was fitted was:

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

The age variable was standardized using a *Z*-score transformation and treated as a continuous variable. The variables of sex and task difficulty were treated as categorical variables through deviation coding (−1, 1). Significance was computed via the Satterthwaite approximations (at $p \leq .05$; using the R "lmerTest" package; Kuznetsova, Brockhoff, & Christensen, 2017).

Multivariate B-PLS Analysis

We conducted between-group (i.e., sex) multivariate B-PLS (McIntosh & Lobaugh, 2004) analysis to assesses the relationship between event-related brain activity (as measured by fMRI), age and retrieval accuracy in females, compared with males using the open source plsgui software (https://www.rotman-baycrest.on.ca/index.php?section=345), implemented in Matlab R2012a (https://www.mathworks.com/help/matlab/release-notes-R2014a.html). B-PLS is a powerful method that permits analysis of large data sets (e.g., neuroimaging data) to assess the spatiotemporal distribution of whole-brain patterns of task-related activity and behavior. Importantly, this analysis does not make any assumptions about the shape of the hemodynamic response function and makes use of permutation testing and bootstrap resampling methods to identify statistically robust multivoxel patterns of brain activity over time (McIntosh & Lobaugh, 2004). Detailed PLS methods are presented in McIntosh and Lobaugh (2004) and McIntosh et al. (2004).

To run a B-PLS analysis, first, the event-related brain activity and the behavioral measures must be stored in separate matrices. The brain activity matrix consists of the BOLD signal at each voxel (columns of the matrix) for each participant (rows of the matrix, ordered by event type) across the voxel time series (time lags 0–7 with a TR = 2 sec for a total of 16 sec). Importantly, we only analyzed fMRI activity for correctly remembered events during encoding and retrieval. There were four event types, which were: encoding SE (eSE), encoding SH

(eSH), retrieval SE (rSE), and retrieval SH (rSH). The whole-brain BOLD fMRI activity for these event-types was stacked according to sex, where the male group was stacked above the female group. To create the behavioral matrix, the behavioral measures of age and retrieval accuracy were used. The age variable was first submitted to a regression analysis in which retrieval accuracy was used to predict age. The age residual was then used in the B-PLS analysis as a covariate, instead of raw age, because age and accuracy variables are highly correlated. Thus, using the age residual (which is uncorrelated to retrieval accuracy) would minimize collinearity of the two behavioral measures. Therefore, the behavioral matrix consists of the age residual and retrieval accuracy measures stacked in the same order as the brain activity matrix.

The brain and behavioral matrices were cross-correlated to create a covariance matrix. This matrix was submitted to singular value decomposition, which generates latent variables (LVs; i.e., orthogonal singular vectors) that maximally captures the relationship between brain activity and behavior. For each LV, PLS outputs (1) a singular value, (2) a singular image, and (3) a correlation profile. The singular value represents the covariance accounted for by each LV. The PLS ranks LVs according to the amount of covariance each LV explains (i.e., highest to lowest). The singular image contains positive and/or negative saliences that identify brain voxels in which activity, at a given lag, was correlated with the behavioral measures of interest (age residual and accuracy). The PLS also calculates individual participant's brain scores, which is the dot product of the voxel saliences identified in the singular image and each participant's functional image volumes. Brain scores represent how strongly each participant expressed the given LV for each of the task conditions. The correlation profile reflects the correlation between participants' brain scores and corresponding behavioral measure. In the current study, the correlation profile shows how participants' age (residual) and retrieval accuracy correlated with the pattern of brain activity shown in the singular image.

Ninety-five percent confidence intervals are calculated for the brain score–behavior correlations as an assessment of the reliability of the correlations. Importantly, the correlation profiles and singular images reflect a symmetrical pairing. Thus, the positive and negative voxel saliences of given singular images indicate whether activity in the associated voxels are positively or negatively associated with the correlation profile. For example, a correlation profile in which retrieval accuracy was positively correlated with participants' brain scores at encoding would be interpreted as indicating that higher subsequent retrieval accuracy was positively correlated to brain activity in positive voxel salience regions (warm color regions showing the singular image) and negatively correlated to brain activity in the negative voxel salience regions (blue-colored regions shown in the singular image). In contrast, if retrieval accuracy was negatively correlated to participants' brain scores at encoding, this would mean that higher subsequent retrieval accuracy was negatively correlated to brain activity in positive voxel salience regions (warm color regions showing the singular image) and positively correlated to brain activity in the negative voxel salience regions (blue-colored regions shown in the singular image).

The significance of LVs identified by the PLS was assessed with permutation testing (Edgington, 1980). We conducted 1000 permutations. Each permutation involved reassigning the fMRI data (event/condition) and behavioral measures (age, retrieval accuracy) within participant by resampling without replacement. A PLS was rerun for each resampled data set, and the probability that the permuted singular values exceed the observed singular value for a given LV was used to determine significance ($p < .05$; McIntosh et al., 2004; McIntosh & Lobaugh, 2004).

After permutation testing, we conducted 500 bootstraps to assess the stability of the voxel saliences identified by the LVs (Efron & Tibshirani, 1986). We calculated the standard errors of brain saliences for each LV for 500 bootstrap samples generated using sampling with replacement. In resampling, the assignment of the experimental conditions for all observations was maintained. A PLS is recalculated after each resampling. The bootstrap ratio (BSR) for each voxel is calculated as the voxel's bootstrapped mean salience divided by its estimated standard error. Thus, higher BSR values represent more stable voxel saliences related to a given LV. In this study, a BSR threshold of 3.00 (for a significance of $p < .01$) with a minimum spatial cluster size of 10 voxels was considered significant. The confidence intervals depicted in the correlation profiles are derived through bootstrap estimation.

We also computed temporal brain scores to determine which time lags the task differences in a given LV were strongest (i.e., Lags 2–5). Thus, it was these peak voxel coordinates, which demonstrated maximal task differences, that were converted from MNI to Talairach space using the icbm2tal transform (Lancaster et al., 2007) as used in GingerAle 2.3 (Eickhoff et al., 2009). The cluster report for each LV was generated, which lists the brain regions involved in that particular LV, which meet the BSR and spatial cluster size threshold criteria. The cluster report also reveals additional ROI characteristics, including its BSR value, spatial extent, and the Brodmann's area (BA) the coordinate falls under. Each ROI in the cluster report shows the peak coordinate of activation within the cluster. Peak coordinates from cerebellum and brainstem areas were removed from the cluster report because our fMRI acquisition did not completely acquire these regions.

Lastly, to verify our interpretations of the brain–behavior patterns observed in each LV, we tested specific post hoc LMER models of the participants' brain scores. The fixed effects were the variables of age, sex, and retrieval accuracy. In addition, to account for interindividual variability within participants tested across task conditions (i.e., eSE, eSH, rSE, rSH), we used participant and task condition as

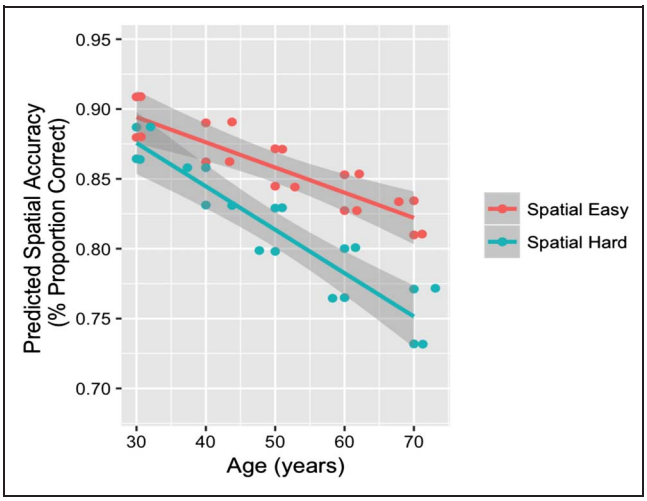

Figure 1. The partial effects plot demonstrating the two-way interaction of age and task difficulty against spatial retrieval accuracy, showing worsening of memory performance with age. Accuracy was higher for the SE task compared with the SH task. The shaded error bands represent the 95% confidence interval limits.

random effects variables within the model. Significance was computed via the Satterthwaite approximation (at $p \leq .05$; using the R "lmerTest" package; Kuznetsova et al., 2017).

RESULTS

Behavioral Results

Table 1 shows mean and standard error values for demographic and fMRI behavioral measures separated by age group and sex. This includes group means for the CVLT, years of education, and retrieval accuracy scores (% correct) and RTs (msec) for each event type. The LMER model testing the three-way interaction of Age, Sex, and Task Difficulty using spatial context retrieval accuracy as the dependent variable revealed a significant main effect of Age ($\beta = -0.03$, $SE = 0.01$, $t(123.73) = -2.21$, $p < .05$), Task Difficulty ($\beta = -0.04$, $SE = 0.01$, $t(78) = -2.98$, $p < .05$), and a significant interaction of Age × Task Difficulty ($\beta = -0.03$, $SE = 0.01$, $t(78) = -2.01$, $p < .05$). This interaction was due to participants performing significantly worse on the SH task, compared with the SE task, with advanced age (Figure 1).

The LMER model testing the three-way interaction of Age, Sex, and Task Difficulty on RT (msec) identified significant main effects of Age ($\beta = 177.219$, $SE = 75.69$, $t(88.58) = 2.34$, $p < .05$) and Task Difficulty ($\beta = 137.15$, $SE = 37.82$, $t(78.0) = 3.63$, $p < .05$). The main effect of Age was due to increased age being associated with longer RT. The main effect of Task Difficulty was due to participants taking longer to respond during SH tasks compared with the SE tasks.

fMRI Results

The B-PLS analysis identified four significant LVs ($p < .05$). Briefly, LV1 (16.3% crossblock covariance), LV3 (11.4%), and LV4 (8.9%) identified sex differences in how age impacted memory-related brain activity at encoding and/or retrieval and in how brain activity related to performance. In contrast, LV2 (14.2%) identified brain regions in which activity increased or decreased with age in both

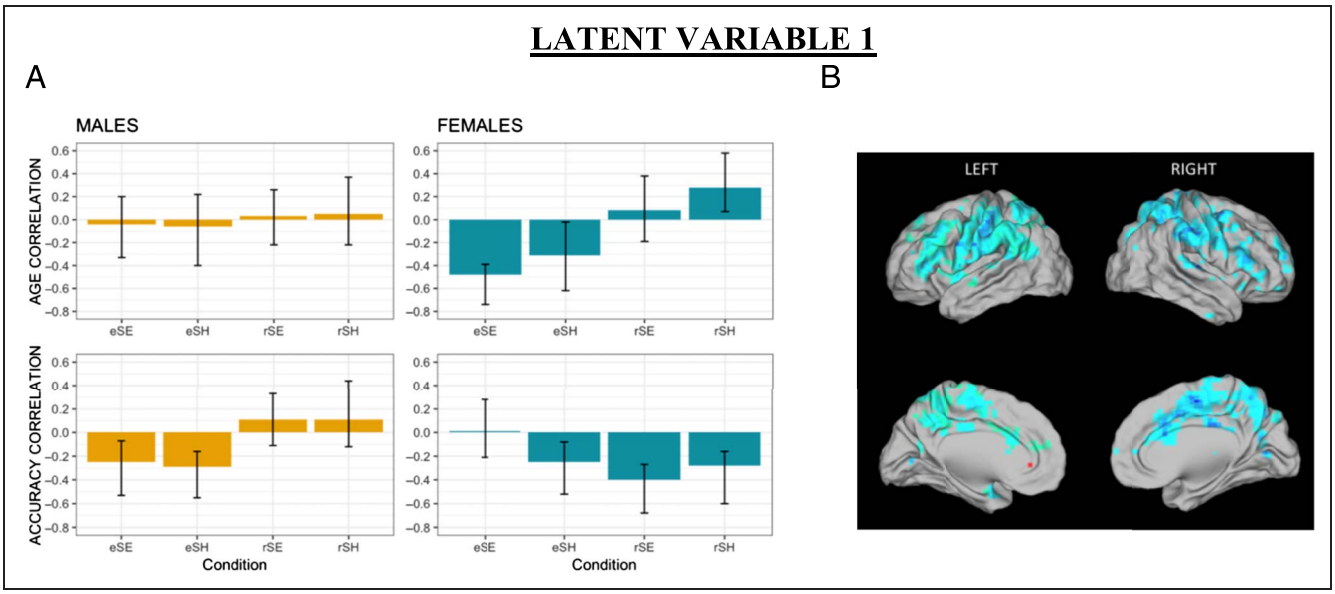

Figure 2. LV1. (A) The brain–behavior correlation profiles for LV1 for age and accuracy. (B) The singular image for B-PLS LV1, threshold BSR of ±3.00, $p < .001$. Red regions reflect positive brain saliences, and blue regions reflect negative brain saliences. Activations are presented on template images of the lateral and medial surfaces of the left and right hemispheres of the brain using Caret software (brainvis.wustl.edu/wiki/index.php/Caret:Download). eSE = encoding spatial easy; eSH = encoding spatial hard; rSE = retrieved spatial easy; rSH = retrieval spatial hard.

Table 2. Local Maxima for LV1

Temporal Lag	BSR	Cluster Size (Voxel)	Talairach Coordinates			Gyral Location of Peak Coordinate	BA
			x	*y*	*z*		
Negative saliences							
Left hemisphere							
2	−4.49	276	−2	−13	46	Paracentral lobule	31
2, 3	−5.96	1187	−42	−28	48	Inferior parietal lobule	40
3	−6.17	1078	−61	−19	27	Postcentral gyrus extending to frontal gyri	2
4	−3.56	16	−13	−69	34	Cuneus	7
4	−3.69	90	−38	−59	9	Middle temporal gyrus	39
4	−3.76	35	−53	−8	31	Precentral gyrus	6
4	−4.00	80	−53	28	6	Inferior frontal gyrus	45
4, 5	−4.42	29	−57	−2	10	Precentral gyrus	6
5	−4.09	20	−38	−19	−13	Caudate	Caudate Tail
5	−4.39	26	−13	31	54	Superior frontal gyrus	6
5	−5.42	583	−64	−38	32	Inferior parietal lobule	40
5	−6.51	38	−27	4	−17	Parahippocampal gyrus	34
Right hemisphere							
2	−3.31	18	28	4	56	Medial frontal gyrus	6
2	−3.59	19	14	53	24	Superior frontal gyrus	9
2, 4	−4.13	72	10	14	35	Cingulate gyrus	24, 32
3	−3.49	10	29	13	10	Claustrum	*
3	−3.85	28	50	−24	35	Postcentral gyrus	2
3	−4.01	57	35	−56	54	Superior parietal lobule	7
3	−4.31	10	10	57	17	Medial frontal gyrus	10
3	−5.45	147	54	−18	14	Transverse temporal gyrus	41
4	−3.29	20	54	−25	6	Superior temporal gyrus	41
4	−3.47	10	54	−1	34	Precentral gyrus	6
4	−3.91	26	17	41	26	Medial frontal gyrus	9
5	−3.75	27	62	−26	14	Superior temporal gyrus	42
3, 4, 5	−3.95	19	25	53	24	Superior frontal gyrus	9, 10
4, 5	−3.97	25	21	−67	20	Precuneus	7, 31
4, 5	−3.89	18	2	−66	9	Cuneus	30
4, 5	−5.60	2819	54	27	19	Inferior frontal gyrus	45

Temporal lag represents the time after event onset when a cluster of voxels showed an effect of interest. The BSR threshold was set to ± >3.00 ($p <$ .001) and identified dominant and stable activation clusters. The spatial extent refers to the total number of voxels included in the voxel cluster (threshold = 10). The stereotaxic coordinates (measured in millimeters), gyral location, and BAs were determined by referring to Talairach and Tournoux (1988). Hemishphere = cerebral hemisphere in which the activation of interest occurred.

males and females, across encoding and retrieval (Age main effect; Supplementary Table 1 and Supplementary Figure 1),[1] an effect that may be confounded by factors other than age-related changes in cognitive function (e.g., changes in CBF, cerebral blood volume, vascular reactivity, and/or metabolism with age). Thus, this LV will not be further discussed because of the difficulties in disentangling task-related effects from age effects

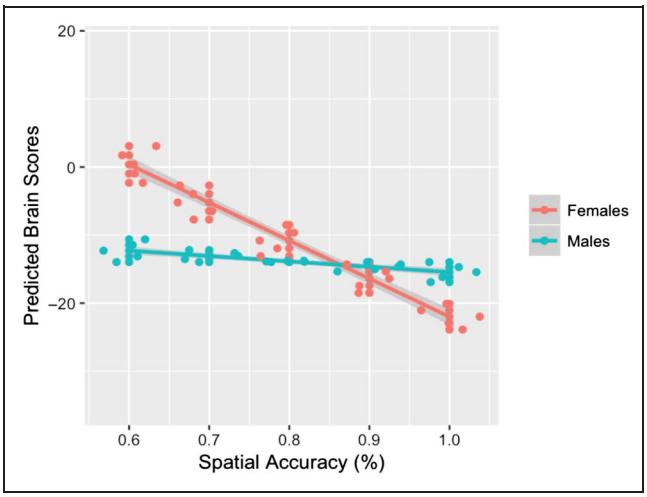

Figure 3. The partial effects plot demonstrating the interaction between spatial retrieval accuracy and sex against brain scores (LV1). This effect shows that females contributed greater to the LV pattern observed compared with males except at a higher spatial retrieval accuracy. The shaded error bands represent the 95% confidence interval limits.

associated with differences in neurovascular coupling (Grady & Garrett, 2014; Liu et al., 2013; Kannurpatti, Motes, Rypma, & Biswal, 2010; Handwerker, Gazzaley, Inglis, & D'Esposito, 2007; D'Esposito, Deouell, & Gazzaley, 2003). Therefore, our results and discussion will focus specifically on the effects of Sex, Memory Performance, and Sex × Memory Performance on memory-related brain activity. In the following sections, we present the results from LV1, LV3, and LV4 in detail.

LV1

Figure 2A–B shows the singular image and correlation profiles for age and retrieval accuracy in males and females for LV1. Table 2 shows the local maxima for this LV. This LV only identified significant negative (blue-colored regions in the singular image) salience regions at the thresholds specified within bilateral IPC (peaking in left hemisphere), bilateral lateral PFC (peaking in VLPFC), right anterior-medial PFC, and left parahippocampal gyrus (PHG). Taken together, the singular image and correlation profile for LV1 indicate that, in females, age-related increases in left PHG, bilateral lateral PFC, right anterior PFC, and parietal activity during SH encoding tasks were associated with better subsequent memory. However, age-related decreases in activity within negative salience regions during SH retrieval in females were associated with worse retrieval accuracy. Compared with females, males showed no age-related differences directly linked to subsequent memory performance. Instead, males showed increased activity in these same frontoparietal and PHG regions at encoding, which was related to better subsequent memory for both tasks and uncorrelated with age.

Specifically, the correlation profile for age indicates that, in males, age was not significantly correlated with activity in areas identified by this LV. In contrast, in females, advanced age was positively correlated with activity in negative salience regions at encoding and negatively correlated with activity in these regions during SH retrieval. Consistent with this interpretation, the post hoc within-sex LMER model of Age × Memory Phase (4: eSE, eSH, rSE, rSH) interaction against brain scores revealed an Age × Memory Phase interaction in females ($p < .05$), but not in males

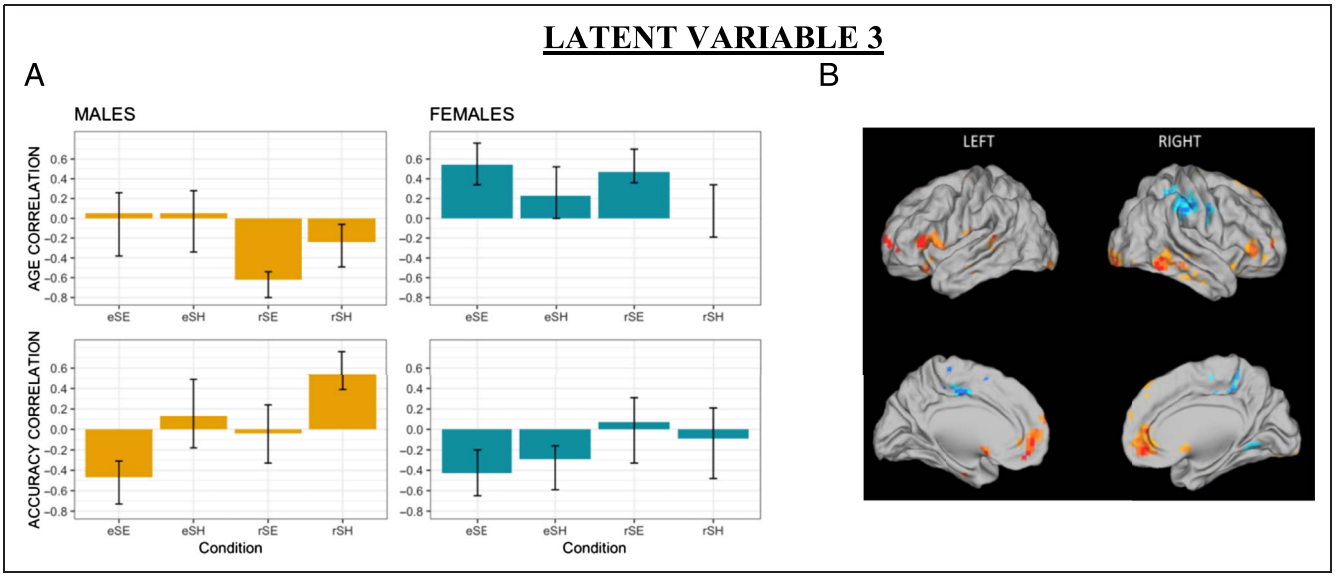

Figure 4. LV3. (A) The brain–behavior correlation profiles for LV3 for age and accuracy. (B) The singular image for B-PLS LV3, threshold BSR of ±3.00, $p < .001$. Red regions reflect positive brain saliences, and blue regions reflect negative brain saliences. Activations are presented on template images of the lateral and medial surfaces of the left and right hemispheres of the brain using Caret software (brainvis.wustl.edu/wiki/index.php/Caret:Download). eSE = encoding spatial easy; eSH = encoding spatial hard; rSE = retrieved spatial easy; rSH = retrieval spatial hard.

Table 3. Local Maxima for LV3

Temporal Lag	*BSR*	*Cluster Size (Voxel)*	*Talairach Coordinates*			*Gyral Location of Peak Coordinate*	*BA*
			x	*y*	*z*		
Positive saliences							
Left hemisphere							
2	3.78	20	−60	−57	−6	Inferior temporal gyrus	37
2, 5	4.08	21	−13	27	61	Superior frontal gyrus	6
3	4.85	17	−21	−46	72	Postcentral gyrus	7
3	3.76	21	−31	47	8	Middle frontal gyrus	10
4	3.75	15	−53	−32	8	Middle temporal gyrus	22
5	5.16	49	−1	3	−6	Anterior cingulate	25
4, 5	4.58	70	−53	22	−2	Inferior frontal gyrus	47
5	4.27	45	−34	34	−11	Middle/inferior frontal gyrus	11/47
5	4.04	19	−35	−15	67	Precentral gyrus	6
5	3.90	71	−8	44	−3	Anterior cingulate	32
5	3.86	30	−31	−94	−12	Inferior occipital gyrus	18
5	3.67	40	−42	−18	−20	Inferior temporal gyrus	20
5	3.35	10	−20	1	11	Lentiform nucleus	Putamen
Right hemisphere							
3	4.70	57	58	−46	−10	Inferior temporal gyrus	20
3	4.65	31	39	0	63	Middle frontal gyrus	6
3	4.27	17	33	33	−6	Inferior frontal gyrus	47
3	4.08	11	20	−50	72	Postcentral gyrus	7
2, 3, 5	4.80	134	17	15	64	Superior frontal gyrus	6, 8
2, 3, 4	4.72	189	7	47	5	Anterior cingulate	32
4	4.58	33	51	35	8	Inferior frontal gyrus	46
4	3.85	10	44	−12	−7	Insula	13
4, 5	5.92	93	29	−90	−15	Inferior occipital/fusiform gyrus	18
5	4.87	51	25	41	−9	Middle frontal gyrus	11
5	4.40	23	47	−20	0	Superior temporal gyrus	22
5	4.30	59	31	−19	68	Precentral gyrus	6
5	4.15	13	44	43	2	Middle/inferior frontal gyrus	46
5	3.99	13	51	−22	−19	Inferior temporal gyrus	20
Negative saliences							
Left hemisphere							
3	−4.40	61	−16	−20	42	Cingulate gyrus	31
5	−3.50	35	−20	−44	50	Paracentral lobule	5
5	−3.77	27	−13	−22	56	Medial frontal gyrus	6

Table 3. (*continued*)

Temporal Lag	BSR	Cluster Size (Voxel)	Talairach Coordinates			Gyral Location of Peak Coordinate	BA
			x	*y*	*z*		
Right hemisphere							
2, 3	−4.59	330	39	−4	26	Precentral gyrus	6
4	−3.89	53	39	−24	39	Postcentral gyrus	2
5	−3.58	17	13	−22	53	Medial frontal gyrus	6
5	−4.29	301	17	−39	40	Cingulate gyrus	31

Temporal lag represents the time after event onset when a cluster of voxels showed an effect of interest. The BSR threshold was set to ± >3.00 ($p <$ .001) and identified dominant and stable activation clusters. The spatial extent refers to the total number of voxels included in the voxel cluster (threshold = 10). The stereotaxic coordinates (measured in millimeters), gyral location, and BAs were determined by referring to Talairach and Tournoux (1988). Hemisphere = cerebral hemisphere in which the activation of interest occurred.

($p > .05$). Therefore, this LV identified an Age × Memory Phase (encoding/retrieval) interaction in females only.

In relation to performance, the correlation profile revealed that males and females shared common encoding-related activity during the SH task, where increased encoding activity in negative salience regions was correlated with better subsequent retrieval accuracy. In addition, in males, increased encoding activity in these same regions was related to better subsequent retrieval accuracy for the SE task. In females only, we observed that increased activity in negative salience regions during both retrieval tasks was positively correlated with retrieval accuracy. This is consistent with the post hoc LMER model, which revealed a significant Sex × Retrieval Accuracy interaction ($\beta = -5.13$, $SE = 2.25$, $t(165.67) = -2.28$, $p < .05$), demonstrating that females contributed greater to the LV pattern compared with males (except at a higher spatial retrieval accuracy). However, overall, the LV pattern indicates that males and females showed decreasing brain scores with increasing retrieval accuracy, which suggests a similar modulation of the LV pattern in both sexes (Figure 3).

LV3

Figure 4A–B shows the singular image and correlation profile for LV3. Table 3 shows the local maxima of the regions involved in this LV. LV3 identified a distributed pattern of brain activity containing both negative and positive voxel saliences. Negative salience regions included bilateral posterior cingulate (BA 31), and right postcentral gyrus extending into the TPJ. Positive salience regions included bilateral lateral occipital, middle and superior-temporal cortices, bilateral VLPFC, and anterior cingulate. The singular image and correlation profile for LV3 identified age-related differences in brain activity at encoding in females and at retrieval in males, which were negatively associated with subsequent memory performance. In males, increased retrieval activity in positive salience regions and decreased retrieval activity in negative salience regions during SH tasks were related to better retrieval accuracy. However, with advanced age, males exhibited the opposite pattern of age-related differences in brain activity, which was related to poorer retrieval performance. In females, increased encoding-related activity in negative salience regions and decreased encoding-related activity in positive salience regions were related to better subsequent memory effects. Yet, older, compared with younger, females exhibited the opposite pattern of activity during SE encoding and retrieval tasks.

More specifically, in males, advanced age was positively correlated with activity in negative salience regions and negatively correlated with activity in positive salience brain regions during retrieval. In other words, older, compared with younger, males exhibited greater activity in bilateral posterior cingulate (BA 31) and right postcentral gyrus extending into the TPJ—negative salience regions—at retrieval. In contrast, older, compared with younger, males exhibited less activity in bilateral lateral occipital, middle,

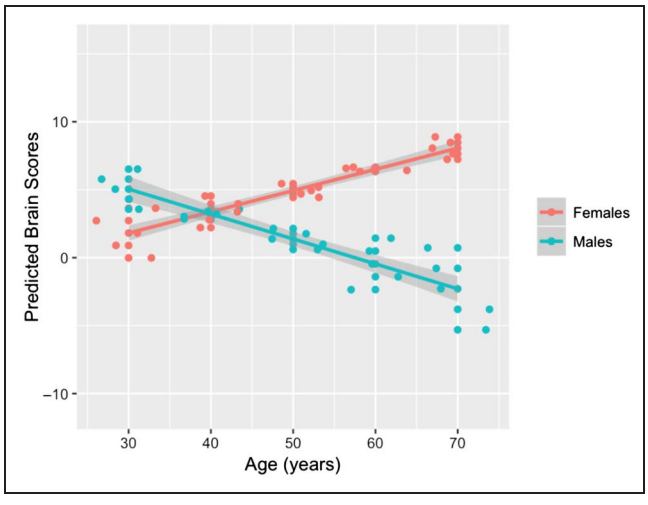

Figure 5. The partial effects plot demonstrating the interaction between Age and Sex against brain scores (LV3). This effect shows a greater age-related contribution of the LV pattern in females compared with males. The shaded error bands represent the 95% confidence interval limits.

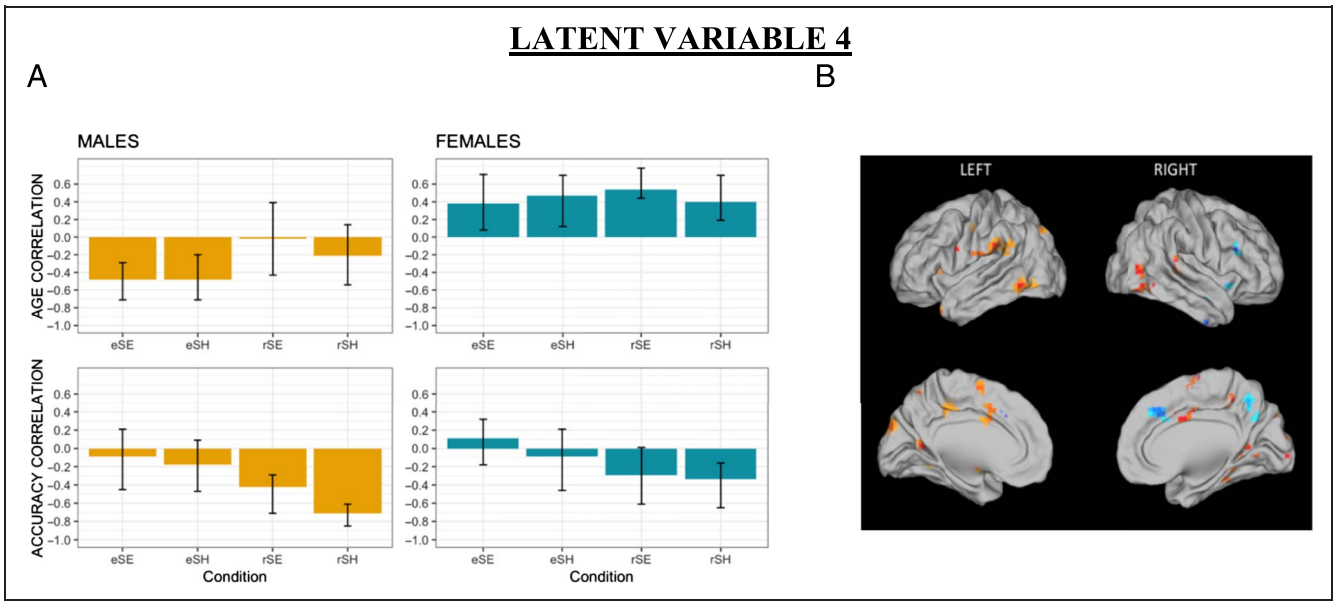

Figure 6. LV4. (A) The brain–behavior correlation profiles for LV4 for age and accuracy. (B) The singular image for B-PLS LV4, threshold BSR of ±3.00, $p < .001$. Red regions reflect positive brain saliences, and blue regions reflect negative brain saliences. Activations are presented on template images of the lateral and medial surfaces of the left and right hemispheres of the brain using Caret software (brainvis.wustl.edu/wiki/index.php/Caret:Download). eSE = encoding spatial easy; eSH = encoding spatial hard; rSE = retrieved spatial easy; rSH = retrieval spatial hard.

and superior-temporal cortices; bilateral VLPFC; and anterior cingulate (positive salience regions) at retrieval.

In females, the inverse pattern of age-related activity was observed across encoding and retrieval phases of SE tasks. Thus, in females, advanced age was related to greater activity in positive salience regions and decreased activity in negative salience regions during SE encoding and retrieval. However, when directly comparing age-related activity between both sexes as a function of task condition, males and females specifically showed the opposite pattern of brain activity during retrieval (SE task). Consistent with this interpretation, the post hoc LMER analysis on brain scores revealed a main effect of Age ($\beta = -2.91$, $SE = 1.09$, $t(91.42) = -2.67$, $p < .05$) and an Age × Sex interaction ($\beta = 6.03$, $SE = 1.52$, $t(87.87) = 3.96$, $p < .05$). Figure 5 depicts this interaction and reveals that females have an age-related increase whereas males have an age-related decrease in brain scores.

In relation to performance, in females, increased activity in negative salience regions and decreased activity in positive salience regions during encoding were related to better subsequent memory. The same pattern of performance-related correlations was observed in males during the SE encoding task. However, the inverse pattern of performance-related correlations was observed in males at retrieval for the SH task. Unlike males, females did not show significant performance-related brain–behavior correlations at retrieval. The post hoc LMER analysis found no significant effect of retrieval accuracy nor any significant interactions with Retrieval Accuracy on LV3 brain scores. However, the within-sex group post hoc LMER models testing for Age, Retrieval Accuracy, and Age × Retrieval Accuracy against brain scores yielded a significant Age × Retrieval Accuracy interaction in both sexes ($p < .05$), which is consistent with our interpretation of the LV effect.

Therefore, LV3 revealed sex differences in how age correlated with memory-related brain activity during encoding and/or retrieval. The age-related differences in brain activity identified in LV3 were related to worse memory performance in both sexes. Thus, older males and females' poorer memory performance may be related to distinct differences in brain function with advanced age.

LV4

Figure 6A–B shows the singular image and correlation profile for LV4. Table 4 shows the local maxima of the regions involved in this LV. Negative salience regions included anterior cingulate and right DLPFC. Positive salience regions included bilateral lateral occipital and temporal cortices and bilateral PHG extending to right hippocampus. LV4 revealed that, in females, age-related increases in brain activity within positive salience regions at retrieval were related to lower retrieval accuracy, particularly during SH retrieval tasks. In contrast, males did not exhibit age-related differences in activity at retrieval. Thus, in males, the correlation between retrieval-related brain activity and memory performance observed was not significantly correlated with age.

However, in males, age was positively correlated with encoding-related activity in negative salience regions, including activity in anterior cingulate and right DLPFC. In contrast, in males, age was negatively correlated with encoding-related activity in positive salience regions,

Table 4. Local Maxima for LV4

Temporal Lag	BSR	Cluster Size (Voxel)	Talairach Coordinates			Gyral Location of Peak Coordinate	BA
			x	*y*	*z*		
Positive saliences							
Left hemisphere							
2	3.57	12	−20	11	27	Cingulate gyrus	24
2, 3	5.15	53	−53	−57	−9	Middle/inferior temporal gyrus	37, 20
3	4.45	44	−9	−86	18	Cuneus	18
3	4.38	22	−24	−76	36	Precuneus	19
3	4.21	47	−5	−39	40	Cingulate gyrus	31
3	3.85	21	−17	−26	59	Precentral gyrus	4
3	3.54	13	−16	7	26	Caudate	Caudate Body
3	3.48	12	−42	−12	38	Precentral gyrus	4
3	3.44	16	−2	−9	39	Cingulate gyrus	24
3, 4	5.38	86	−61	−33	22	Superior temporal gyrus	42
3, 4	4.08	66	−23	−39	4	Parahippocampal gyrus	30
4	3.90	14	−31	20	13	Insula	13
4	3.79	14	−16	−55	10	Posterior cingulate	30
4	3.30	16	−5	3	33	Cingulate gyrus	24
5	3.83	14	−31	15	27	Middle frontal gyrus	9
Right hemisphere							
2	3.56	10	58	−33	9	Superior temporal gyrus	42
2	3.47	18	47	−46	−10	Inferior temporal/fusiform gyrus	20, 37
3	4.82	92	25	−43	4	Parahippocampal gyrus	Hippocampus
3, 4	3.54	11	32	−34	−16	Parahippocampal/fusiform gyrus	36, 20
4	3.50	22	2	−11	64	Medial frontal gyrus	6
Negative saliences							
Right hemisphere							
2	−3.66	10	32	17	−1	Insula	13
2	−3.69	10	6	−58	42	Precuneus	7
2	−4.21	21	43	18	28	Middle frontal gyrus	9
2	−4.76	60	10	21	42	Cingulate gyrus	32

Temporal lag represents the time after event onset when a cluster of voxels showed an effect of interest. The BSR threshold was set to ± >3.00 ($p <$ .001) and identified dominant and stable activation clusters. The spatial extent refers to the total number of voxels included in the voxel cluster (threshold = 10). The stereotaxic coordinates (measured in millimeters), gyral location, and BAs were determined by referring to Talairach and Tournoux (1988). Hemisphere = cerebral hemisphere in which the activation of interest occurred.

including bilateral lateral occipital and temporal cortices and bilateral PHG extending to right hippocampus. In females, a main effect of Age was observed across encoding and retrieval that was in the opposite direction of that observed in males. Specifically, in females, age was positively correlated with activity in positive salience regions and negatively correlated with activity in negative salience regions during encoding and retrieval. The post hoc LMER analysis, which directly tested for an Age × Sex interaction against brain scores, was significant

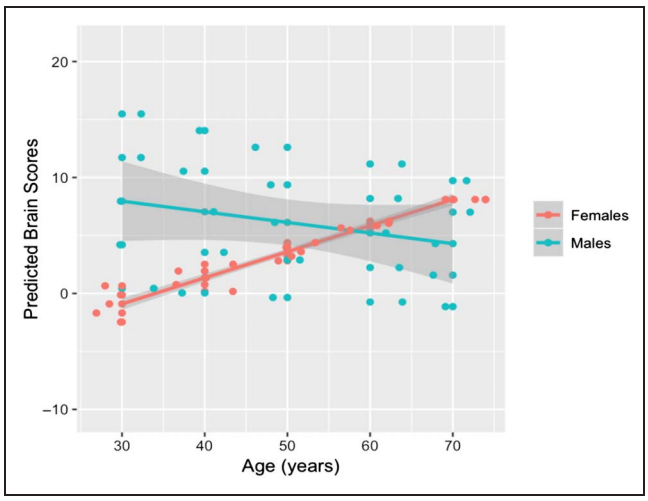

Figure 7. The partial effects plot demonstrating the significant interaction of age and sex against brain scores, indicating a greater age-related modulation of brain scores in females compared with males (LV4). The shaded error bands represent the 95% confidence interval limits.

($\beta = 3.89$, $SE = 1.30$, $t(73.94) = 2.99$, $p < .05$). Figure 7 depicts this interaction and shows that, at a younger age, males have higher brain scores compared with females, but the inverse was true in older age.

In relation to Retrieval Accuracy, the correlation profile indicates that, in both males and females, increased retrieval-related activity in negative salience regions (right DLPFC and anterior cingulate) and decreased retrieval-related activity in positive salience regions (left DLPFC, bilateral PHG, and lateral occipito-temporal cortices) were related to better retrieval accuracy. This interpretation was confirmed by our post hoc LMER analysis, which found a main effect of Retrieval Accuracy against brain scores ($\beta = -1.70$, $SE = 0.60$, $t(241.79) = -2.84$, $p < .05$).

DISCUSSION

In the current study, we tested the hypotheses that there would be sex differences in memory-related brain activity during encoding and/or retrieval and that there would also be an effect of biological sex on age-related differences in brain activity at both encoding and retrieval. To this aim, we investigated how age and biological sex were associated with memory-related brain activity during the encoding and retrieval of face–location associations (spatial context memory). We used between-group multivariate B-PLS and LMER to test for sex differences in age-related and performance-related patterns of encoding- and retrieval-related brain activity.

The behavioral analysis of retrieval accuracy and RT measures obtained during the fMRI spatial context memory tasks indicated there was a main effect of Age on both measures. Increasing age was related to declines in retrieval accuracy and increases in RT on spatial context memory tasks. This result is consistent with the prior results observed in our larger adult lifespan sample (Ankudowich et al., 2016, 2017) and with previous adult lifespan studies of context/source memory (e.g., Cansino, 2009; Johnson, Hashtroudi, & Lindsay, 1993). In addition, participants took longer on the hard compared with the easy version of the task; however, we observed an Age × Task Difficulty interaction on retrieval accuracy, indicating that older participants (compared with younger participants) performed significantly worse on the SH task, compared with the SE task, demonstrating an effect of task load on retrieval accuracy with advanced age. We did not observe a significant main effect of biological sex, nor did we observe a significant Age × Sex interaction in either retrieval accuracy or RT.

Our behavioral results are inconsistent with prior studies that have shown females outperform males on a variety of episodic memory tasks, such as verbal stimuli (Ragland et al., 2000; Herlitz et al., 1997), negative emotional stimuli (Young et al., 2013), face stimuli (Sommer et al., 2013; Yonker et al., 2003), and verbal paired associative memory (Bender et al., 2010). In the current study, we did not observe a significant effect of Sex nor an Age × Sex interaction in memory performance. This may be explained by the nature of the episodic memory task we used. Indeed, this is the first study, to our knowledge, to explore sex differences in face–location spatial context memory. Past studies have shown that, on average, males outperform females on spatial tasks, and females perform better than males on face and emotional memory tasks (Sommer et al., 2013; Lejbak, Crossley, & Vrbancic, 2011; Weiss et al., 2003; Herlitz et al., 1997). Thus, the null effect of sex on spatial context memory performance for face–location associations may have emerged because the stimuli used were nonverbal and required both spatial and facial/emotional stimuli processing. Alternatively, it is possible that when female and male participants are matched on age and education, as they were in the current study, sex differences in episodic memory are no longer apparent.

Although we did not observe a significant effect of Sex or an Age × Sex interaction on spatial context retrieval accuracy and RT, our fMRI results identified sex differences in age-related patterns of brain activity during successful spatial context encoding and retrieval and sex differences in performance-related patterns of brain activity during retrieval. Overall, our findings suggest that the neural correlates of age-related spatial context memory decline differ in females compared with males. Below, we discuss our findings in greater detail.

Performance-related Patterns of Brain Activity: Similarities and Differences between the Sexes

Our findings suggest that generally females and males engaged similar brain regions at encoding and retrieval to support memory performance. This observation is consistent with the behavioral results, indicating there were no significant sex differences in memory performance. In both sexes, activity in right anterior-medial,

bilateral dorsal and lateral PFC, and left PHG during spatial context encoding positively correlated with better subsequent memory (LV1). Similarly, activity in right DLPFC during spatial context retrieval positively correlated with retrieval accuracy (LV4). These results are consistent with prior literature showing that successful episodic encoding is associated with medial-temporal and lateral PFC activity, and successful episodic retrieval is associated with right DLPFC activity (Hayama & Rugg, 2009; Blumenfeld & Ranganath, 2007; Murray & Ranganath, 2007; Staresina & Davachi, 2006; Simons & Spiers, 2003).

LV1 also indicated that increased inferior parietal activity, extending into PFC, at retrieval was positively related to memory performance in females. Previously, we examined age and performance-related differences in brain activity using a larger lifespan cohort where sample size for the two sexes was not matched (Ankudowich et al., 2017). We did not consider biological sex in this earlier analysis. Results from this analysis indicated that inferior parietal activity during both encoding and retrieval reflected performance, rather than age, effects. Interestingly, by considering sex in the current analysis, we observe that frontal and parietal activation at encoding supported subsequent performance in both sexes, but frontal and parietal activation at retrieval was only positively correlated to memory performance in females. Prior studies have highlighted the importance of frontoparietal regions in mediating top–down cognitive control of memory-related medial-temporal functions at encoding and retrieval (Dulas & Duarte, 2014; Mitchell & Johnson, 2009; Grady, 2008; Cabeza et al., 2003; Cabeza, Dolcos, Graham, & Nyberg, 2002). The current study suggests that the controlled relational encoding of face–location associations benefitted subsequent memory in both sexes, but the recapitulation of these processes at retrieval only supported memory performance in females.

We also found that activity in bilateral lateral temporal cortices, posterior lateral occipital cortices, anterior cingulate, and VLPFC during encoding (LV3) was negatively correlated with subsequent memory in both sexes. However, in males, increased activity in anterior lateral occipital, middle and superior temporal cortices, and VLPFC at retrieval supported retrieval accuracy on hard spatial context memory tasks. In addition, we also found that activity in more posterior lateral temporal and occipital regions during retrieval (LV4) was negatively related to memory performance in both sexes. These findings are generally consistent with our prior analysis of this study, in which sex differences were not investigated (Ankudowich et al., 2017). In both the previous and current analyses, we found that activity in lateral temporal and lateral posterior occipital areas during encoding and retrieval was negatively correlated with performance and positively correlated with age. In the current study, we found that this positive correlation with age was primarily observed in females (see below).

Activity in lateral occipital-temporal cortices and VLPFC at encoding has been associated with less specific, semantic processing of visual stimuli, including faces (Kirchhoff, Anderson, Barch, & Jacoby, 2012; Demb et al., 1995). This suggests that semantic processing during the encoding of face–location associations results in poorer memory in the current study but controlled relational encoding of face–location associations (discussed above) supported subsequent memory. This observation is consistent with recent findings showing that orienting participants to semantic associations was detrimental to subsequent memory and suggests that semantically associating stimuli at encoding may interfere with successful episodic encoding (Long & Kahana, 2017). Interestingly, our LV3 retrieval effects suggest that, in males engaging VLPFC, lateral occipital (anterior) and temporal cortices supported retrieval accuracy.

In general, our findings suggest that there were sex differences in performance-related activity at retrieval, compared with encoding. In females, encoding and retrieval success was related to the engagement of lateral frontoparietal-related cognitive control processes and to relational mnemonic processes associated with the PHG (LV1 and LV4). In males, these same processes were important for successful spatial context encoding success, but successful retrieval was also related to the retrieval of semantic associations.

Our findings demonstrate that both sexes engaged different sets of brain regions and related cognitive processes to support memory at retrieval. To our knowledge, very few studies have specifically explored functional sex differences at episodic retrieval. One such study by Nyberg et al. (2000) found functional sex differences at memory retrieval in a younger adult sample. Similar to our findings, Nyberg et al. found increased activity in bilateral inferior temporal cortex in males compared with females at retrieval. However, their sex difference findings in bilateral IPC are contrary to what we observed in our results. Specifically, Nyberg et al. found that females had reduced IPC activity compared with males. This contradicts our findings of sex differences at retrieval, where males and females showed the opposite pattern of results in fusiform and IPC activity. These differences may be because these studies used different experimental tasks. That is, Nyberg et al. combined data from three different episodic memory tasks, which differed in terms of the type of stimuli encoded (i.e., words, sentences, landscapes), the way in which participants had to encode the stimuli (i.e., silent reading, intentional encoding), and the modality in which the stimuli were presented at encoding (i.e., visual vs. auditory). Moreover, their retrieval task was a yes/no recognition task of the stimuli, whereas our retrieval task was more explicit in that participants had to select the face that they saw either to the left/right at encoding (depending on the retrieval cue). Taken together, these studies showed that participants recruited brain regions typically involved at retrieval and suggest that the specific experimental tasks

used might help explain differences in retrieval-related brain activity across study findings. Below, we discuss sex differences in the effect of age on memory related brain activity.

Sex Differences in the Effect of Age on Encoding and Retrieval-related Activity

We observed sex differences in the effect of age on frontal-parietal (LV1), medial-temporal activity (LV1, LV4), lateral occipital-temporal (LV3, LV4), and VLPFC (LV3) activity during encoding and retrieval. Specifically, with advanced age, females exhibited increased activity in lateral occipital-temporal cortices (LV3, LV4) and VLPFC (LV3) across encoding and retrieval, particularly for easy spatial context memory tasks. Females also exhibited age-related increases in right PHG during encoding and retrieval (LV4) and in frontal-parietal and left PHG during encoding (LV1). Thus, with advanced age, females exhibited a general increase in brain activity in a variety of regions at encoding and retrieval.

In contrast, females exhibited age-related decreases in right DLPFC activity across encoding and retrieval (LV4) and in bilateral frontal-parietal and left PHG during hard spatial context retrieval (LV1). Age-related decreases in these regions may reflect an age-related deficit in function, particularly at retrieval, given that activation of these regions at retrieval was related to better memory performance (discussed above; Rajah & D'Esposito, 2005). This suggests that, in females, age-related reductions in spatial context memory may be related to differences in PFC and parietal and medial-temporal activity at retrieval.

Also, in females, activity in lateral occipital-temporal at encoding and retrieval and in VLPFC at encoding was negatively correlated with memory performance (LV3, LV4). Thus, the observation that, with advanced age, females increased activity in these brain regions suggests that older females may have engaged in suboptimal strategies during encoding and retrieval (Mitchell & Johnson, 2009). In contrast, given that the engagement of frontal-parietal and left PHG activity at encoding and retrieval was related to better memory performance in females (LV1); the age-related increase in these regions at encoding may reflect functional compensation (Cabeza et al., 2018).

In males, advanced age was related to decreased activity in lateral occipital-temporal and right PHG at encoding (LV4) and in lateral occipital-temporal and VLPFC activity at retrieval (LV3). Given that activation of these brain regions during hard spatial context retrieval tasks was related to better memory performance in males, this indicates there may be functional deficits in these regions in older males. In contrast, males exhibited age-related increases in precentral and posterior cingulate activity during retrieval and in right DLPFC and cingulate during encoding. These patterns of age-related increase were not beneficial to performance in males. Thus, age-related differences in lateral occipital-temporal cortices, VLPFC, right DLPFC, precentral cortex, and cingulate cortex may contribute to spatial context decline particularly in males. Interestingly, we did not observe age-related differences in lateral frontal-parietal and left PHG activity (LV1), and activation of these regions at encoding supported subsequent memory across all ages. This suggests, independent of age, spatial context memory performance in males is correlated with frontal-parietal and left PHG activity.

However, aging is associated with changes in cerebrovascular structure and function, which may impair CBF (Brown et al., 2010; Yonas, Smith, Durham, Pentheny, & Johnson, 2009) and may contribute to age-related declines in memory and memory-related brain activity (e.g., Donahue et al., 2014; Restom, Bangen, Bondi, Perthen, & Liu, 2007). Moreover, there may be sex differences in the effect of Age on cerebrovascular function and/or Age × Sex interactions, which may be influencing some of our findings. Indeed, females and males differ in baseline CBF throughout the adult lifespan (Liu, Lou, & Ma, 2016; Matteis, Troisi, Monaldo, Caltagirone, & Silvestrini, 1998). For example, in a study using arterial spin labeling to measure CBF, Liu et al. (2016) found that CBF was significantly higher in young females, compared with males; but there was no significant sex difference in CBF between older postmenopausal females, compared with older males (Liu et al., 2016). The authors found that, within sex, postmenopausal females had significantly lower CBF compared with young females, but there was no significant age-related effect in males. In another study, Asllani et al. (2009) tested young and older healthy adults and examined age-related differences in CBF within females and males, after adjusting for partial volume effects to account for age-related structural decline (Asllani et al., 2009). In males, age-related CBF decline was observed in frontal (e.g., left middle frontal gyrus, bilateral superior frontal gyrus), parietal (e.g., bilateral precuneus), and cingulate areas. In females, age-related CBF decline was observed in bilateral amygdala, left hypothalamus, bilateral hippocampus, and right middle frontal gyrus. However, the authors did not test for sex differences and Age × Sex interactions in CBF because their primary goal was to determine age effects in CBF.

Unfortunately, we did not collect arterial spin labeling data in the current study to directly examine cerebrovascular changes in aging. However, we expressly excluded consideration of LV2, which identified a main effect of Age precisely because it would be difficult to disentangle age-related differences in event-related activity, from age-related differences in cerebrovascular function (see review by D'Esposito et al., 2003). Moreover, we did not observe any main effects of Sex or a general Age × Sex interaction that applied across encoding, retrieval, and different task types. Instead, we found that sex differences in the effect of age on memory-related brain function were specific to memory phase (encoding and/or retrieval) and specific event/task types. Therefore, it is unlikely that our findings were impacted by sex

differences or Age × Sex interactions in cerebrovascular functions, because this would have a more generalized influence on event-related brain activity across tasks. Nonetheless, it is possible that Age × Sex differences in CBF in specific regions (e.g., frontal-parietal areas) may partly contribute to the sex differences in the overall effect of age on memory and brain function that were observed (Asllani et al., 2009).

Conclusions

Our results point to several significant sex differences in how age impacts memory-related brain function. First, age-related increases in lateral frontal-parietal and left PHG activity at encoding were specific to females and directly impacted memory success. Second, there were pronounced sex differences in the impact of age on occipital, temporal, and VLPFC activity; however, in both sexes, the pattern of age-related difference in these regional activations was similarly detrimental to task performance. In other words, although females exhibited a generalized age-related increase in brain activity in these areas across encoding and retrieval and males exhibited age-related decreases in activity within these regions only at retrieval, in both sexes, these age-related differences negatively impacted memory performance. Third, age-related deficits in spatial context memory are primarily related to altered brain activity at retrieval in both sexes, but the nature of those age-related differences in activation was not the same in females and males. This implies that the neural correlates of spatial context memory that decline with age differ in males and females and the brain regions that support successful memory function in late life also differ in females and males. Moreover, we were able to verify the patterns observed at the LV level through post hoc LMER analyses using brain scores generated for each participant across task conditions. In conclusion, our study showed that males and females showed both functional similarities and differences, which were modulated by age, in context memory performance. Understanding these similarities and differences are critical in providing important insight as to why there are sex differences in memory-related disorders and how treatment interventions should be tailored in the realm of aging and dementia.

Caveats

The present investigation explored sex similarities and differences in episodic/context memory across the lifespan. There are limitations of the study design and methodology that prevent us from having a more comprehensive understanding of sex differences in the effect of age on memory and brain function. First, it is important to consider how hormonal differences between males and females and age-related hormonal changes within sex might influence our interpretation of the results. For example, past studies have shown the phase of the menstrual cycle (linking changes in estradiol and progesterone) has significantly contributed to differences in spatial memory performance in females (Kimura & Hampson, 1994). In addition, midlife in females is associated with declines in 17β-estradiol, a known neurocognitive hormone that might contribute to performance differences in midlife compared with other age groups (e.g., Rentz et al., 2017; Jacobs et al., 2016b; Morrison et al., 2006). Moreover, the impact of HRT at midlife may have direct impacts on cerebrovascular function by promoting vasodilation and CBF (Sherwood et al., 2007). This vasodilatory effect in response to 17β-estradiol seems to be mediated by age—older postmenopausal females are less responsive to estrogen therapy compared with younger postmenopausal females (Vitale et al., 2008; Sherwood et al., 2007). To minimize the variability in our sample, we removed middle-aged females currently undergoing the menopause transition and/or HRT in this study design (see Methods). However, an understanding of hormonal changes in aging is important given that females report subjective memory deficits particularly during menopause transition (Weber & Mapstone, 2009). Finally, it is important to consider hormonal differences, such as age-related declines in testosterone (a hormone linked to spatial memory), which may selectively impact the cognitive aging process in both sexes (Fabbri et al., 2016; Harman, Metter, Tobin, Pearson, & Blackman, 2001).

Importantly, there is strong evidence that stress affects memory and that there may be sex differences in stress levels and Age × Sex interactions on stress levels and stress responses (e.g., Pruessner, 2018). For example, a meta-analysis conducted by Otte et al. (2005) found that the stress response to a pharmacological or psychological (e.g., cognitive computer-based task) stressor is greater in older adults compared with younger adults and that this response is much stronger in females than in males. The analysis included studies that measured stress using saliva/plasma concentrations of cortisol at baseline and post-stressor challenge. Importantly, male and female participants were balanced in age among the younger and older adult groups (males: 29 years vs. 70 years, females: 30 years vs. 69 years) and the analysis controlled for variations in sex hormones (e.g., menstrual cycles, oral contraceptives, HRT). Thus, sex differences in stress levels and stress responsivity may also contribute to the observed sex differences in memory and brain function in our current study (Otte et al., 2005; Wolf, Kudielka, Helhammer, Hellhammer, & Kirschbaum, 1998).

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Note

1. Supplementary material for this paper can be retrieved from https://doi.org/10.6084/m9.figshare.9394154.v1.

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