Running title: Sex differences in the aging brain and episodic memory

Sex differences in the neural correlates of age-related episodic memory decline

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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. Here, we used task fMRI to investigate sex differences in neural correlates of episodic encoding and retrieval of spatial contextual details, and whether the effect of age on memory-related brain function was similar in women compared to men. We obtained fMRI scans in 41 women and 41 men, between the ages of 21 to 76 years, during spatial context encoding and retrieval. We observed no significant sex difference in retrieval accuracy. We conducted a brain-behaviour multivariate PLS analysis of the fMRI data. Both sexes activated dorsal and lateral prefrontal cortex (PFC), inferior parietal cortex (IPC) and left parahippocampal gyrus (PHG) at encoding and this supported subsequent memory performance. There were sex differences in retrieval activity in these same regions, and in lateral occipital-temporal and ventrolateral PFC. In addition, sex differentially impact the effect of age on PFC, IPC, PHG, lateral occipital-temporal and ventrolateral PFC activity. Overall, our findings suggest that the neural correlates of age-related spatial context memory decline differ in women compared to men.

Key words: aging, fMRI, PLS, sex differences

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., Cansino, 2009; Dulas & Duarte, 2012; Glisky, Polster, & Routhieaux, 1995; Rajah, Languay, & Valiquette, 2010; Schacter, Kaszniak, Kihlstrom, & Valdiserri, 1991; Spencer & Raz, 1995; Trott, Friedman, Ritter, & Fabiani, 1997). 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), prefrontal cortex (PFC), and inferior parietal cortex (IPC) (Grady et al., 2010; Hayama, Vilberg, & Rugg, 2012; Johnson & Rugg, 2007; Rajah, Crane, Maillet, & Floden, 2011; Rajah, McIntosh, & Grady, 1999; Spaniol et al., 2009). 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 of context memory, we found age-related deficits in context memory starting as early as midlife, which were associated with altered recruitment of bilateral fusiform gyrus, anterior PFC and ventrolateral PFC (Kwon et al., 2016). With advanced age context memory decline was more severe and was associated with alterations in dorsolateral PFC, MTL and IPC activity (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; Cansino, Hernández-Ramos, & Trejo-Morales, 2012; Cansino, Trejo-Morales, & Hernández-Ramos, 2010; Dennis et al., 2008; K. J. Mitchell, Ankudowich, Durbin, Greene, & Johnson, 2013, but see Cabeza, Anderson, Locantore, &

McIntosh, 2002 for functional similarities in context memory with aging). Therefore, the growing consensus is age-related declines in context memory are linked to differences in frontoparietal, medial temporal and ventral visual function with age.

However, the majority of fMRI studies that investigated age-related differences in brain activity during episodic memory pooled male and female participants. This assumes the neural correlates of age-related episodic memory decline are similar in women and men. Yet, there is evidence for sex differences in brain structure and function in adulthood (see Gur & Gur, 2002 for review), and evidence that women and men may perform differently on specific episodic memory tasks, depending on the experimental stimuli and design. For example, behavioural studies demonstrate that females perform better on episodic memory tasks for verbal stimuli (Gur & Gur, 2002; Herlitz, Nilsson, & Bäckman, 1997; Kimura & Harshman, 1984; Ragland, Coleman, Gur, Glahn, & Gur, 2000), negative emotional stimuli (Young, Bellgowan, Bodurka, & Drevets, 2013), face stimuli (Keightley, Winocur, Burianova, Hongwanishkul, & Grady, 2006; Sommer, Hildebrandt, Kunina-Habenicht, Schacht, & Wilhelm, 2013; J. E. Yonker, Eriksson, Nilsson, & Herlitz, 2003), and verbal paired associated memory (Bender, Naveh-Benjamin, & Raz, 2010). In contrast, on average, males have shown greater performance compared to females on object-location associative memory tasks (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, since 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, women are more at risk of developing late-onset Alzheimer's Disease, compared to

men (Alzheimer's Association, 2015; Mielke, Vemuri, & Rocca, 2014). Therefore, it is critical to develop a working model of healthy aging in both sexes in order to understand how the interaction of biological sex and age can lead to pathological aging 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/behavioural strategic preferences between the sexes. Thus, sex differences in brain structure and function may be observed, even when sex differences in cognitive/behavioural performance are not. For example, Nyberg et al (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 men; 17 women) (Nyberg, Habib, & Herlitz, 2000). In this study, subjects responded yes/no in a recognition paradigm for words, sentences, and landscape images. No sex differences in recognition memory were reported and a multivariate partial least squares (PLS) analysis of the O^{15} positron emission tomography (PET) data revealed that both women and men 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). Interestingly, despite similar memory performance sex differences in retrieval-related activity were observed. Women showed greater retrieval-related activity in the anterior cingulate gyrus, right inferior frontal gyrus, right fusiform, parietal cortex and cerebellum compared to men. Men showed greater activity compared to women at retrieval in bilateral inferior frontal cortex (BA44, 45), bilateral inferior temporal and parietal cortex, and in posterior cingulate cortex. Similarly, previous work have reported functional sex differences during memory tasks, albeit with a greater focus on investigating autobiographical memory (St Jacques, Conway, & Cabeza, 2011;

Young et al., 2013)

Importantly, sex *and* age differences in PFC, parietal, MTL and/or ventral occipito-temporal function during episodic memory studies have also been reported (Compère et al., 2016; Haut & Barch, 2006; Ragland et al., 2000; Spalek et al., 2015). 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-by-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 women and men, or if some results were driven by one sex. Given that sex differences in episodic memory remain relatively stable across the adult lifespan (De Frias et al., 2006; Jack et al., 2015), one may hypothesize that sex differences in the functional neural correlates of episodic memory, if present, are stable across the adult lifespan. However, there is a growing body of human neuroimaging studies showing sex hormone levels in women and men differ across the lifespan, and accordingly affects brain function and cognition. For example, menopause-related decline in 17-beta-estradiol (e.g., Jacobs et al., 2016b; Morrison, Brinton, Schmidt, & Gore, 2006; Rentz et al., 2017) or age-related decline in testosterone (e.g., Moffat et al., 2018; Muller, Aleman, Grobbee, de Haan, & van der Schouw, 2005; Rosario, Chang, Head, Stanczyk, & Pike, 2011; Rosario & Pike, 2008), may contribute to differences in cognitive function. In addition, sociocultural factors, such as self-perceived gender trait possessions (Hamilton, 1995; Sharps, Price, & Williams, 1994), may also influence task performance (Baenninger & Newcombe, 1989; Hamilton, 1995; Lawton, 1994; Sharps et al., 1994). 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 women, compared to men. Such an observation would have

important clinical implications since it would suggest that specific interventions may be required in women, compared to men, 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 association (spatial context memory) in an adult lifespan sample. A subsample of age- and education-matched women and men from a previously collected fMRI data sample were used (Ankudowich et al., 2016). Due to prior studies highlighting the impact of menopausal transition on episodic memory-related brain regions PFC and MTL (Jacobs et al., 2016a, 2016b; Rentz et al., 2017), and our limited sample size for this subsample (N = 10), we excluded middle-aged women who self-reported being in menopausal transition or being in the early stages of post-menopause in the current study. We used a between group multivariate behaviour partial least squares (B-PLS) statistical analysis to examine the relationship between fMRI activity and age and accuracy in women, compared to men (McIntosh et al., 2004). Based on prior behavioural and fMRI studies in young adults (e.g., Nyberg, Habib, & Herlitz, 2000; Spaniol et al., 2009), we predicted there would be sex differences in brain activity during encoding and 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.

Materials and Methods

Participants

Participants were 41 men and 41 women between the ages of 21-76 years (M = 47.1, SE = 2.03). Thirty participants could be classed as younger adults (age range: 21-35, M = 26.3, SE = 0.60), 20 as middle-aged (age range: 40 – 58, 45.8, SE = 1.17), and 32 as older adults (age range: 60-76, M = 67.3, SE = 0.66). In each age group, we had an equal number of men and women that were 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). We included middle-aged women who self-reported as pre-menopausal (excluding N = 18 currently menopausal MA women), and excluded female participants who had undergone hormone replacement therapy (HRT) (excluding N = 10 females) since menopausal transition and HRT influence brain function and episodic memory abilities (Henderson, 2010; Li, Cui, & Shen, 2014; Rentz et al., 2017; Yonker et al., 2006). Finally, we matched the male sample (N = 43) to the existing subsample of females according to age and education level, in order to use a balanced sample of males and females. Analysis of the data revealed two outliers which were subsequently removed to obtain the final matched sample.

All participants had at least a high school education (mean education = 16.1 yrs, 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 prior to participating in the study. Table 1 summarizes participant demographic and neuropsychological information by Sex within each Age Group. Post-hoc analyses revealed no significant differences in sex and education level between men and women among each age group ($p > 0.05$). Participants were recruited via newspaper and online advertisements in Montréal, Canada.

Behavioural Methods

Experimental details of this study have been previously published (Ankudowich et al., 2016). All testing was done at the Douglas Institute Brain Imaging Center. There were two testing sessions in the experiment. The first session involved medical and neuropsychological testing to ensure participants met inclusion and exclusion criteria to participate in the study. This included completing the Mini Mental Status Exam (MMSE, exclusion cut-off score < 27, (Folstein, Folstein, & McHugh, 1975), the Beck Depression Inventory (BDI) (inclusion cut-off < 15 (Beck & Steer, 1987), the American National Adult Reading Test (NART) (inclusion cut-off ≤ 2.5 SD (Strauss, Sherman, & Spreen, 2006). 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, BMI > 30, or were currently diagnosed with high cholesterol levels and/or high blood pressure that was untreated or had only been treated for less than six months. Participants also completed the California Verbal Learning Task (CVLT) which was used to assess verbal item memory. All the aforementioned participants met the cut-off 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, blood-oxygen-level-dependent (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 x Performance interactions. 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 behavioural and fMRI data collected during spatial context memory tasks to reduce the complexity of the fMRI analysis conducted. 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 behavioural tasks were designed and implemented using E-Prime (Psychology Software Tools, Inc.; Pittsburgh, PA, USA), and accuracy (% correct) and reaction time (RT, msec) was collected. Below we explain the experimental details for spatial context encoding and retrieval.

Spatial Context Encoding

Prior to 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, subjects were asked to rate each face as being pleasant or neutral using a 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). After the encoding instructions were presented, participants were shown a series of faces, one at a time, for 2 sec/stimulus with a variable inter-trial interval (ITI) 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, 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 6 blocks of SH encoding tasks).

Encoding was followed by a one-minute 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 prior to 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 ITI (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 was a total of 36 retrieval events per task type across the experiment.

MRI methods

The fMRI scanning took place at the Douglas Institute Brain Imaging Center, using a 3T Siemens Magnetom Trio scanner. Participants laid in a supine position in the scanner wearing a standard head coil. First, the T1-weighted anatomical image using a 3D gradient echo MPRAGE sequence (TR= 2300 msec, TE= 2.98 msec, flip angle = 9°, 176 1 mm sagittal slices, 1x 1 x 1 mm voxels, FOV = 256 mm^2, GRAPPA of 2, acquisition time = 5 min) was acquired. After the structural scan, functional BOLD MRI images were collected using a single-shot T2*-weighted gradient echo-planar imaging (EPI) pulse sequence (matrix size = 64 x 64, 32 oblique slices with no slice gap, in-plane resolution of 4x4 mm, TR = 2000 ms, TE = 30 ms, 4 mm^3 isotropic, FOV = 256 mm^2) while subjects performed the aforementioned behavioural task. The memory task was initiated on a computer using E-prime software, which was 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 4-button response box. Participants requiring correction for visual acuity wore corrective plastic lenses. Twelve fMRI runs were conducted, as outlined in the behavioural methods; each run was approximately 9 minutes long and yielded 278 whole-brain volumes per run. Total time in the scanner, with setup, was approximately two hours.

Preprocessing

Raw 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, 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 6-parameter rigid-body spatial transform. Participants with greater than 4mm of movement within a run were removed from the analysis. None of the participants in the current study moved > 4 mm. The data were then normalized to the MNI EPI template (4x4x4 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.

Behavioural Data Analysis

Spatial Context Retrieval Accuracy & RT

Using SPSS, we conducted two 3-way [Age Group(3), Sex(2), Task Difficulty(2)] repeated measures ANOVAs on retrieval accuracy (% correct) and reaction time (msec). Both Age Group (3: younger, middle-aged, and older adults) and Sex (2: females, males) were treated as between-subject factors, whereas Task Difficulty (2: easy, hard) was used as a within-subject factor (significance thresholded at $p < 0.05$). Post hoc Tukey's HSD tests were conducted as needed to deconstruct significant effects and interactions.

Multivariate Behavioural-Partial Least Squares Analysis

We used between group multivariate Behavioural-Partial Least Squares (B-PLS; (McIntosh & Lobaugh, 2004) to assesses the relationship between event-related brain activity (as measured by fMRI), age and retrieval accuracy in females, compared to males. B-PLS is a powerful method that permits analysis of large datasets (e.g., neuroimaging data) in order to assess the spatiotemporal distribution of whole-brain patterns of task-related activity and behaviour. 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).

In order to run a B-PLS analysis, first, the event-related brain activity and the behavioural 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 seconds). Importantly, we only analyzed fMRI activity for correctly remembered events during encoding and retrieval. There were four event types, which were encoding spatial easy (eSE), encoding spatial hard (eSH), retrieval spatial easy (rSE), and retrieval spatial hard (rSH). The whole brain BOLD fMRI activity for these event-types were stacked according to sex, where male and female groups were stacked above one another. In order to create the *behavioural matrix*, the behavioural 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 used because age and accuracy variables are highly correlated and using the age residual (which is uncorrelated to retrieval accuracy) would minimize collinearity of the two behavioural measures. The age residual and retrieval accuracy measures were stored in the final behavioural matrix, similarly to how the brain matrix was structured.

Both brain and behavioural matrices were cross-correlated to create the covariance matrix. This matrix was submitted to singular value decomposition (SVD), which generates latent variables (i.e., orthogonal singular vectors) that maximally captures the relationship between brain activity and behaviour. For each latent variable (LV), PLS outputs 1) a singular value, 2) a correlation profile, and 3) a singular image. The singular value represents the covariance accounted for by that particular LV; all LVs are ranked (i.e., highest to lowest)

according to the amount of covariance that the singular image explains out of the brain-behaviour relation. The correlation profile shows brain-behaviour relations between fMRI activity and the two behavioural measures of interest (i.e., age residual and accuracy). The correlation profile shows how subjects' age and retrieval accuracy correlates with the pattern of brain activity shown in the singular image. Finally, the singular image of brain saliences contains positive and/or negative voxel salience regions which reflects the different relationships between brain activity and the behavioural measures of interest (age, accuracy). Importantly, the brain-behaviour correlation profile and brain saliences reflect a symmetrical (relationship) pairing, where the positive/negative brain saliences represent whether activity in a voxel is positively or negatively associated with the correlation profile associated with that singular image.

Statistical significance of the LV was assessed using permutation tests (assessing LV effect) and bootstrap tests (assessing stability of voxel saliences). The significance of the LV effect was assessed using permutation testing, by testing whether a signal was significantly different from noise. Each permutation involves reassigning the fMRI data (event/condition) and behavioural measures (age, retrieval accuracy) within subject by resampling, without replacement. A PLS was rerun for each resampled dataset and the probability that the permuted singular values exceed the observed singular value for a given LV was used to determine significance at $p < 0.05$ (McIntosh & Lobaugh, 2004).

After permutation testing, bootstrap tests were conducted to calculate the reliability of the voxel saliences in contributing to the singular image for each LV. Thus, the bootstrap procedure identifies voxel saliences with the most reliable patterns of positive and negative brain saliences shown in the singular image. We used 500 bootstrap samples to calculate the standard errors of

brain saliences for each LV. In this case, the assignment of the experimental conditions for all observations were maintained while each bootstrap was generated with replacement, i.e., the subject data were dropped one at a time and PLS was recalculated for each bootstrap sample. The confidence intervals are derived through bootstrap estimation, which is depicted in the LV brain-behaviour correlation profiles. The bootstrap ratio for each voxel is calculated as the voxel's bootstrapped mean salience divided by its estimated standard error. Thus, higher BSR value represent more stable voxel saliences related to a given LV. In the present study, a bootstrap ratio (BSR) threshold of 3.00 (for a significance of $p < 0.01$) with a minimum spatial cluster size of 10 voxels was considered significant. We 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 for 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 area 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.

Results

Behavioural Results

Table 1 shows mean and standard error values for demographic and fMRI behavioural measures, separated by Age Group and Sex. This includes group means for the CVLT, years of education, and retrieval accuracy scores (% correct) and reaction times (msec) for each event type. Repeated measures 3-way ANOVA (Group (3), Sex(2), Task Difficulty(2)) using spatial context retrieval accuracy as the dependent variable revealed a significant effect of Task Difficulty (i.e., spatial easy vs. spatial hard) , $F(1,76) = 15.8$, $p < 0.001$ and of Age Group, $F(2,76) = 13.3$, $p < 0.001$. No other main effects or interactions were significant. The difficulty effect revealed that participants performed with significantly greater accuracy on the SE as compared to the SH task. Posthoc pairwise comparisons using Tukey HSD to deconstruct the significant Age Group effect revealed that older adults performed significantly worse on accuracy than YA and MA adults ($p < 0.05$). YA and MA adults did not significantly differ in performance.

Repeated measures 3-way ANOVA (Group, Sex, Task Difficulty) on Accuracy RT indicated a significant effect of Task Difficulty, $F(1,76) = 12.5$, $p = 0.001$, such that on average, participants took longer to respond to the SH task compared to the SE task. In addition, there was a significant effect of Age Group, $F(2,76) = 11.5$, $p < 0.001$. A post-hoc Tukey HSD analysis revealed that older adults had significantly longer RT compared to YA and MA adults ($p < 0.05$). There was no significant difference in RT between YA and MA. No other main effects or interactions were significant.

fMRI Results

The B-PLS analysis identified four significant latent variables (LVs; $p < 0.05$). Briefly, LV 1 (16.3% crossblock covariance), LV 3 (11.4%), and LV 4 (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, LV 2 (14.2%) identified brain regions in which activity increased or decreased with age in both men and women, across encoding and retrieval (Age main effect). LV2 (Supplementary Table 1 & Supplementary Figure 1) identified a main effect of Age in both sexes, an effect that may be confounded by factors other than age-related changes in cognitive function (e.g., changes in CBF, CBV, vascular reactivity, and/or metabolism with age). Thus, this LV will not be further discussed because of the difficulties in disentangling all these factors that can impact the neurovascular coupling and subsequently affect the BOLD signal (D'Esposito, Deouell, & Gazzaley, 2003; C. L. Grady & Garrett, 2014; Handwerker, Gazzaley, Inglis, & D'Esposito, 2007; Kannurpatti, Motes, Rypma, & Biswal, 2010; Liu et al., 2013). Therefore, our results and discussion will focus specifically on Age Group interactions rather than main effects of Age. In the following sections, we present the results from LVs 1, 3, and 4 in detail.

LV1

Figure 1A-B shows the singular image and correlation profiles for age and retrieval accuracy in men and women. Table 2 shows the local maxima for this LV. This LV only identified significant negative salience regions at the thresholds specified within bilateral inferior parietal cortex (IPC, peaking in left hemisphere), bilateral lateral prefrontal cortex (peaking in ventrolateral PFC [VLPFC]), right anterior-medial PFC and left parahippocampal gyrus (PHG). The correlation profile for age indicates that in men, age was not significantly correlated with activity in areas identified by this LV. In contrast, in women, advanced age was positively correlated with activity in negative salience regions at encoding and negatively correlated with activity in these regions during SH retrieval. Therefore, this LV identified an Age x Phase (encoding/retrieval) interaction in women.

In relation to performance, increased encoding activity in negative salience regions was correlated with better subsequent retrieval accuracy for both SE and SH tasks in men and in SH tasks for women. In women, increased activity in negative salience regions during both retrieval tasks was positively correlated with retrieval accuracy.

Therefore, in women age-related increases in left PHG, bilateral lateral PFC, right anterior PFC and parietal activity during SH encoding tasks was associated with subsequent memory. However, age-related decreases in activity within negative salience regions during SH retrieval in women was associated with worse retrieval accuracy. In men, increased activity in these same regions at encoding was related to better subsequent memory for both tasks and was unrelated to age.

LV3

Figure 1C-D shows the singular image and correlation profile for LV 3. Table 3 shows the local maxima of the regions involved in this LV. In men, advanced age was positively correlated with activity in negative salience regions, and negatively correlated with activity in positive salience brain regions during retrieval. Specifically, older, compared to younger, men, exhibited greater activity in bilateral posterior cingulate (BA 31), and right postcentral gyrus extending into the temporoparietal junction – negative salience regions – at retrieval. In contrast, older, compared to younger, men exhibited *less* activity in bilateral lateral occipital, middle and superior-temporal cortices, bilateral VLPFC, and anterior cingulate (positive salience regions) at retrieval. In women, the inverse pattern of age-related activity was observed across encoding and retrieval phases of SE tasks. Thus, in women, advanced aged was related to greater activity in positive salience regions and decreased activity in negative salience regions during SE encoding and retrieval.

In relation to performance, in women, increased activity in negative salience regions, and decreased activity in positive salience regions, during encoding, was related to better subsequent memory. The same pattern of performance-related correlations were observed in men at encoding, but only for the SE task; however, the inverse pattern of performance-related correlations were observed in men at retrieval, for the SH task.

In summary, in both sexes, the age-related differences in brain activity were negatively associated with retrieval accuracy. For example, in men, increased retrieval activity in positive salience regions and decreased retrieval activity in negative salience regions during SH tasks was related to better retrieval accuracy. However, with advanced age, men exhibited the opposite pattern of age-related differences in brain activity, which would have been related to poorer retrieval performance. In women, increased encoding-related activity in negative salience regions, and decreased encoding-related activity in positive salience-regions was related to better subsequent memory effects. Yet, older, compared to younger women, exhibited the opposite pattern of activity during SE encoding and retrieval tasks. Therefore, the observed sex difference in how age correlated with memory-related brain activity, was negatively associated with memory performance in both sexes. Thus, older men and women's poorer memory performance may be related to distinct differences in brain function with advance age.

LV4

Figure 1E-F shows the singular image and correlation profile for LV 4. Table 4 shows the local maxima of the regions involved in this LV. The correlation profile indicates that in men, increasing age was positively correlated with increased encoding-related activity in negative salience regions, including activity in anterior cingulate and right DLPFC. In contrast, in men, increasing age was *negatively* correlated with encoding-related activity in positive salience

regions, including: bilateral lateral occipital and temporal cortices, and bilateral parahippocampal gyrus (PHG) extending to right hippocampus. In women, a main effect of age was observed across encoding and retrieval that was in the opposite direction of that observed in men. Specifically, in women, increasing age was positively correlated with activity in positive salience regions and negatively correlated with activity in negative salience regions during encoding and retrieval.

In relation to retrieval accuracy, the correlation profile indicates that in both men and women 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) was related to better retrieval accuracy. Thus, in women, age-related increases in brain activity in positive salience regions during retrieval was related to lower retrieval accuracy, particularly during SH retrieval tasks. Since men did not exhibit age-related differences in activity at retrieval, the brain-performance accuracy correlations observed at retrieval, were unrelated to age in men.

Discussion

In the current fMRI study, we investigated how age and biological sex were associated with brain activity during the encoding and retrieval of spatial context memory. We examined whether age-related differences in brain activity during a memory task were similar among women and men. To this aim, we used multivariate B-PLS to test for the main effects of biological sex, age, and for an age-by-sex interaction in brain activity. The behavioural analysis of retrieval accuracy and RT measures obtained during fMRI tasks indicated there was a main effect of age: 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; M. K. Johnson, Hashtroudi, & Lindsay, 1993). In addition, participants took longer and performance accuracy declined on the hard vs. easy version of the task, demonstrating an effect of task load on performance with aging, again, replicating previous findings (Ankudowich et al., 2016; Kwon et al., 2016; Spaniol & Grady, 2012). 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 behavioural results are in contrast to prior studies that have shown women outperform men on a variety of episodic memory tasks: such as, verbal stimuli (Herlitz et al., 1997; Kimura & Harshman, 1984; Ragland et al., 2000), negative emotional stimuli (Young et al., 2013), face stimuli (Keightley et al., 2006; Sommer et al., 2013; Yonker et al., 2003) and verbal paired associated memory (Bender et al., 2010). The absence of an effect of sex, nor an age-by-sex interaction, in memory performance may be explained by the nature of the episodic memory task we used. 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, men outperform women on spatial tasks, and women perform better than men on face and emotional memory tasks (Herlitz et al., 1997; Lejbak, Crossley, & Vrbancic, 2011; Sommer et al., 2013; Weiss et al., 2003). Thus, the null effect of sex on spatial context memory performance for face-location associations may have emerged because the stimuli used were non-verbal and required both spatial and facial/emotional stimuli processing. Alternatively, it is possible that when female and male participants are matched on education and neuropsychological test measures, 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. Overall, performance-related activation during encoding and retrieval were similar between the sexes, consistent with the behavioural findings; however, there were some sex differences in performance-related contributions of lateral prefrontal and occipito-temporal cortices at retrieval. Our findings suggest that the neural correlates of age-related spatial context memory decline differ in women compared to men. 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 women and men engaged similar brain regions at encoding and retrieval to support memory performance. This observation is consistent with the behavioural 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 dorsolateral PFC (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 (Blumenfeld & Ranganath, 2007; Hayama & Rugg, 2009; Murray & Ranganath, 2007; Simons & Spiers, 2003; Staresina, 2006).

LV1 also indicated that increased inferior parietal activity, extending into PFC, was positively related to memory performance. Previously, we examined age and performance-related differences in brain activity using a larger lifespan cohort where sample size for the two

sexes were 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 women. 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 (Cabeza et al., 2003; Cabeza, Dolcos, Graham, & Nyberg, 2002; Dulas & Duarte, 2014; Grady, 2008; Mitchell & Johnson, 2009). 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 women.

We also found that activity in bilateral lateral temporal cortices, posterior lateral occipital cortices, anterior cingulate and ventrolateral PFC (VLPFC) during encoding (LV3), was negatively correlated with subsequent memory in both sexes. In addition, activity in similar 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 women (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 (Demb et al., 1995; Kirchhoff, Anderson, Barch, & Jacoby, 2012). 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 subjects 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, LV3 also indicated that only in men, increased activity in lateral occipital, lateral temporal, and VLPFC at retrieval supported retrieval accuracy on hard spatial context memory tasks.

In general, our findings suggest that sex differences in performance-related activity were present at retrieval compared to encoding. In women, 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 men 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 subtly 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 to females at retrieval. However, their sex difference findings

in bilateral inferior parietal cortex are contrary to what we observed in our results. Specifically, Nyberg et al found that women had reduced inferior parietal cortical activity compared to men. This contradicts our findings of sex differences at retrieval, where men and women 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 women exhibited increased activity in lateral occipital-temporal cortices across encoding and retrieval (LV3; LV4); particularly for easy spatial context memory tasks. Women also exhibited age-related increases in right PHG during encoding and retrieval (LV4), and age-related increases in frontal-parietal

and left PHG during encoding (LV1). Thus, with advanced age women exhibited a general increase in brain activity in a variety of regions at encoding and retrieval.

In contrast, women 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 women, age-related reductions in spatial context memory may be related to differences in PFC, parietal and medial temporal activity at retrieval.

Also, in women, activity in lateral occipital-temporal at encoding and retrieval, in VLPFC at encoding was negatively correlated with memory performance. Thus, the observation that with advanced age, women increased activity in these brain regions suggests that older women may have engaged in sub-optimal 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 women; the age-related increase in these regions at encoding may reflect functional compensation (Cabeza et al., 2018). In men, 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 men, these sex specific decreases in lateral occipital-temporal and VLPFC activity suggests there may be functional deficits in these regions in older men. In contrast, men 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 men. Therefore, in men 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. In both men and women, activation of right DLPFC during retrieval supported memory and activation of lateral occipital-temporal and VLPFC at retrieval support memory only in men. However, the pattern of age-related activation in these regions at encoding and retrieval was not beneficial to memory performance.

Conclusions

Our results point to several significant sex differences in how age impacts memory-related brain function. First, that age-related increases in lateral frontal-parietal and left PHG activity at encoding were specific to women 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 were similarly detrimental to task performance. In other words, although women exhibited a generalized age-related increase in brain activity in these areas across encoding and retrieval, and men 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 that age-related differences in activation was not the same in women and men. This implies that the neural correlates of spatial context memory decline with age differs in men and women, and the brain regions that support successful memory function in late life also differ in women and men. In conclusion, our study showed that men and women 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 biological sex effects on memory and aging. First, it is important to consider how hormonal differences between men and women 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) have significantly contributed to differences in spatial memory performance in women (Doreen Kimura & Hampson, 1994). In addition, midlife in women is associated with declines in 17β -estradiol, a known neurocognitive hormone that might contribute to performance differences in midlife compared to other age groups (e.g., Jacobs et al., 2016b; Morrison, Brinton, Schmidt, & Gore, 2006; Rentz et al., 2017). To minimize our variability, we removed MA women with HRT in the present study design (see Methods). However, an understanding of hormonal changes in aging is important given that women 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, the influence of societal gender roles in addition to stress differences (e.g., Pruessner, 2018) will meaningfully contribute to our understanding of sex differences in memory

and aging. Thus, a more holistic approach in understanding sex differences in memory and aging, which takes into consideration biological and sociocultural differences, might shed more light on why women are at greater risk for memory-related disorders, such as AD.

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

	Younger Adults (YA)		Middle Aged Adults (MA)		Older Adults (OA)		p-value
	Males	Females	Males	Females	Males	Females	
Sample size (n)	15	15	10	10	16	16	
Age (Years)	26.53(1.05)	26.13(1.05)	45.50(1.29)	46.00(1.29)	67.13(1.02)	67.56(1.02)	$p < 0.001$
Education (Years)	16.47(0.51)	16.87(0.51)	16(0.63)	15.7(0.63)	16.19(0.50)	15.38(0.50)	ns
BDI	4.07(0.88)	2.27(0.88)	1.70(1.07)	3.50(1.07)	4.25(0.85)	3.19(0.85)	ns
CVLT-LFR	13.33(0.58)	13.53(0.58)	12.10(0.71)	13.60(0.71)	12.00(0.56)	13.19(0.56)	ns
CVLT-LCR	13.47(0.51)	13.67(0.51)	12.70(0.63)	13.80(0.63)	12.50(0.50)	13.25(0.50)	ns
CVLT-RG	15.40(0.22)	15.20(0.22)	15.40(0.27)	15.10(0.27)	15.13(0.21)	14.94(0.21)	ns
Spatial Easy Retrieval Accuracy (%correct)	0.87(0.02)	0.91(0.02)	0.91(0.03)	0.89(0.03)	0.80(0.02)	0.84(0.02)	$p < 0.001$
Spatial Hard Retrieval Accuracy (%correct)	0.86(0.03)	0.90(0.03)	0.85(0.03)	0.85(0.03)	0.73(0.03)	0.78(0.03)	$p < 0.001$

Spatial Easy Retrieval RT (msec)	2286.28(125.19)	2073.71(125.19)	2178.30(153.33)	2439.54(153.33)	2633.79(121.22)	2894.03(121.22)	$p < 0.001$
Spatial Hard Retrieval RT (msec)	2455.03(125.11)	2165.73(125.11)	2276.82(153.23)	2554.16(153.23)	2765.84(121.14)	2874.13(121.14)	$p < 0.001$

Note: BDI = Beck Depression Inventory; CVLT = California Verbal Learning Test; LFR = Long-form Free Recall; LCR = Long-form Cued Recall; RG = Recognition; RT = Reaction Time. A two-way ANOVA of Age Group(3: YA, MA, OA) by Sex(2: Males, Females) were performed on each of the neuropsychological and fMRI behavioural measures (significance of $p < 0.05$ used). All significant outcomes show only a significant main effect of Age Group. Tukey's HSD post-hoc between-group tests on fMRI behavioural 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 ($p < 0.05$).

Table 2.

Local maxima for LV1

			Talaraich Coordinates				
Temporal Lag	Bootstrap Ratio	Cluster Size(voxel)	x	y	z	Gyral Location of Peak Coordinate	Brodmann Area
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

Note: Temporal lag represents the time after event onset when a cluster of voxels showed an effect of interest. The bootstrap ratio (BSR) threshold was set to ± > 3.00 ($p < 0.001$) 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 Brodmann areas (BAs) were determined by referring to Talaraich and Tournoux (1998). HEM = Cerebral hemisphere in which the activation of interest occurred.

Table 3.

Local maxima for LV3

Temporal Lag	Bootstrap Ratio	Cluster Size (voxels)	Talaraich Coordinates x	y	z	Gyral Location	Brodmann Area
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
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

Note: Temporal lag represents the time after event onset when a cluster of voxels showed an effect of interest. The bootstrap ratio (BSR) threshold was set to ± > 3.00 ($p < 0.001$) 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 Brodmann areas (BAs) were determined by referring to Talaraich and Tournoux (1998). HEM = Cerebral hemisphere in which the activation of interest occurred.

Table 4.

Local maxima for LV4

Temporal Lag	Bootstrap Ratio	Cluster Size(voxels)	Talaraich Coordinates x	y	z	Gyral Location	Brodmann Area
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

Note: Temporal lag represents the time after event onset when a cluster of voxels showed an effect of interest. The bootstrap ratio (BSR) threshold was set to ± > 3.00 ($p < 0.001$) 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 Brodmann areas (BAs) were determined by referring to Talaraich and Tournoux (1998). HEM = Cerebral hemisphere in which the activation of interest occurred.

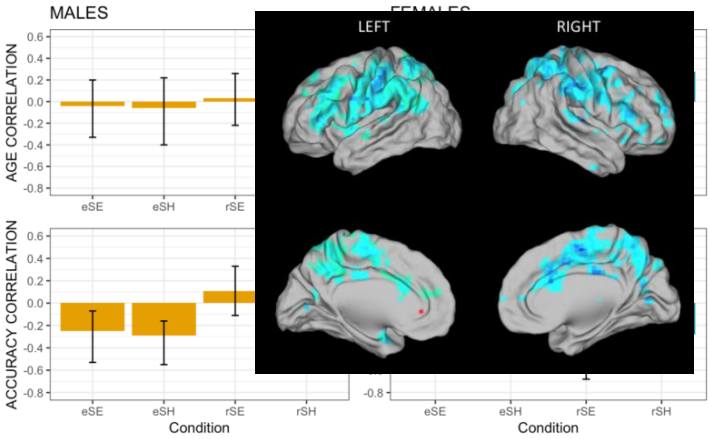
Figure Captions

Figure 1. A) The brain-behaviour correlation profiles for LV1 for age and accuracy. B) The singular image for B-PLS LV1, threshold bootstrap ratio of ± 3.00, $p < 0.001$. Red brain 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 (http://brainvis.wustl.edu/wiki/index. php/Caret:Download). C) The brain-behaviour correlation profiles for LV3 for age and accuracy. D) The singular image for B-PLS LV3, threshold bootstrap ratio of ± 3.00, $p < 0.001$. Red brain 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 (http://brainvis.wustl.edu/wiki/index. php/Caret:Download). E) The brain-behaviour correlation profiles for LV4 for age and accuracy. F) The singular image for B-PLS LV4, threshold bootstrap ratio of ± 3.00, $p < 0.001$. Red brain 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 (http://brainvis.wustl.edu/wiki/index. php/Caret:Download).

Figure 1

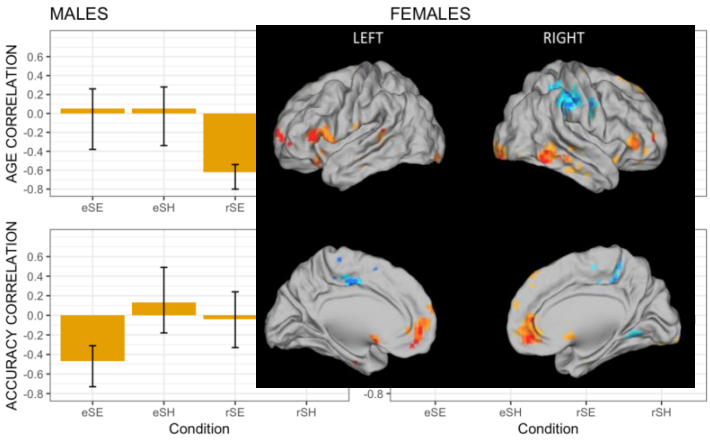
LATENT VARIABLE 1

A. **B.**



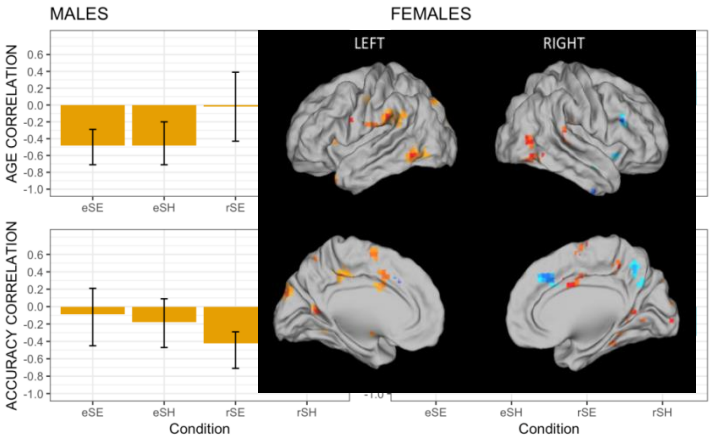
LATENT VARIABLE 3

C. **D.**



LATENT VARIABLE 4

E.


MALES
FEMALES
LEFT
RIGHT
AGE CORRELATION
ACCURACY CORRELATION
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
eSE
eSH
rSE
rSH
Condition

F.