Generalization of memory-related brain function in asymptomatic older women with a family history of late onset Alzheimer's Disease: Results from the PREVENT-AD Cohort

Sheida Rabipour[1,2], Sricharana Rajagopal[1], Stamatoula Pasvanis[1], PREVENT-AD Research Group*, and M. Natasha Rajah[1,2]

[1]Centre for Cerebral Imaging, Douglas Hospital Research Centre, Montreal, Canada
[2]Department of Psychiatry, McGill University, Montreal, Canada

**Data used in preparation of this article were obtained from the Pre-symptomatic Evaluation of Novel or Experimental Treatments for Alzheimer's Disease (PREVENT-AD) program (https://douglas.research.mcgill.ca/stop-ad-centre), data release 5.0 (November 30, 2017). A complete listing of PREVENT-AD Research Group can be found in the PREVENT-AD database: https://preventad.loris.ca/acknowledgements/acknowledgements.php?date=[2019-06-03]. The investigators of the PREVENT-AD program contributed to the design and implementation of PREVENT-AD and/or provided data but did not participate in analysis or writing of this report.*

Corresponding Author: M. Natasha Rajah, Ph.D.
Room 2114, CIC Pavilion
Douglas Hospital Research Centre
Verdun, QC, H4H 1R3
Maria.rajah@mcgill.ca

Abstract

Late-onset Alzheimer's disease (AD) disproportionately affects women compared to men. Episodic memory decline is one of the earliest and most pronounced deficits observed in AD. However, it remains unclear whether sex influences episodic memory-related brain function in cognitively intact older adults at risk of developing AD. Here we used task-based multivariate partial least squares analysis to examine sex differences in episodic memory-related brain activity and brain activity-behavior correlations in a matched sample of cognitively intact older women and men with a family history of AD from the PREVENT-AD cohort study in Montreal, Canada (M_{age}=63.03±3.78; $M_{education}$=15.41±3.40). We observed sex differences in task-related brain activity and brain activity-behavior correlations during the encoding of object-location associative memories and object-only item memory, and the retrieval of object only item memories. Our findings suggest functional dedifferentiation of episodic memory-related brain activation and performance in women compared to men. Follow up analyses should test for sex differences in the relationship between brain activity patterns and performance longitudinally, in association with risk factors for AD development.

Keywords:

Apolipoprotein E ε4 polymorphism, Alzheimer's disease, Associative learning, Brain-behavior relationships, Dedifferentiation, Episodic memory, Familial history, Partial least squares analysis, Sex differences, Task-related functional MRI.

1. Introduction

Late-onset sporadic Alzheimer's Disease (AD) accounts for an estimated 70% of dementia cases worldwide and disproportionately affects women compared to men (World Health Organization, 2019). In the United States, 65% of AD cases are in women (Alzheimer's Association, 2020; World Health Organization, 2019). Compared to men, women demonstrate elevated incidence and lifelong risk of AD even after accounting for sex and/or gender (sex/gender) differences in life expectancy, and exhibit more rapid cognitive decline and brain atrophy in the presence of AD-related neuropathology (Gamache, Yun, & Chiba-Falek, 2020). Despite advances in our overall understanding of AD neuropathophysiology, little is known about why there is this sex/gender difference in AD prevalence (Nebel et al., 2018).

One of the earliest and most pronounced deficits observed in AD is episodic memory decline (Buckner, 2004; McKhann et al., 2011). Behavioral studies have reported that females perform better than males on episodic memory tasks for verbal stimuli (Bleecker, Bolla-Wilson, Agnew, & Meyers, 1988; Bremner et al., 2001; Herlitz, Nilsson, & Backman, 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; W. Sommer, Hildebrandt, Kunina-Habenicht, Schacht, & Wilhelm, 2013; Yonker, Eriksson, Nilsson, & Herlitz, 2003) and verbal paired associative memory (Bender, Naveh-Benjamin, & Raz, 2010). In contrast, males appear to perform better than females on spatial navigation (Astur, Purton, Zaniewski, Cimadevilla, & Markus, 2016; Astur, Tropp, Sava, Constable, & Markus, 2004; Driscoll, Hamilton, Yeo, Brooks, & Sutherland, 2005) and object-location associative memory tasks (Postma, Izendoorn, & De Haan, 1998). In contrast, several studies have also found no sex differences in

episodic memory abilities. For example, in our prior adult lifespan study of episodic memory, we observed no significant sex difference in face-location associative source memory, nor did we observe any sex-by-age interaction in memory retrieval across the adult lifespan (Subramaniapillai et al., 2019). Similarly, Nyberg et al (2000) also reported no sex difference in recognition memory for objects and for words in young adults. However, when sex differences in episodic memory tasks are reported, behavioral studies suggest these sex differences are stable across the adult lifespan (de Frias, Nilsson, & Herlitz, 2006; Jack et al., 2015). Yet, little research has explored whether and how sex and/or gender may interact with the effect of age and AD risk factors on episodic memory-related brain function – despite the; higher reported prevalence, incidence, and burden of AD in women compared to men (Beam et al., 2018; Mazure & Swendsen, 2016).

Prior studies provide evidence that sex and/or gender influences age-related differences in the neural correlates of episodic memory (Gur & Gur, 2002; McCarrey, An, Kitner-Triolo, Ferrucci, & Resnick, 2016; Subramaniapillai et al., 2019). These differences are even more pronounced in AD (Irvine, Laws, Gale, & Kondel, 2012). For example, although behavioral studies suggest that women score higher on verbal episodic memory tasks than men in normative aging and in clinical samples with preserved memory function, this pattern appears to shift in advanced stages of AD pathology, where women with AD tend to perform worse than men with AD (Brunet, Caldwell, Brandt, & Miller, 2020; Chapman et al., 2011). This effect may result from sex differences in the rate of clinical progression and brain atrophy in memory-related regions such as the medial temporal lobes, where women appear to decline more rapidly – independent of other risk factors (e.g., APOE4) – in healthy aging and at various stages of AD progression (Holland, Desikan, Dale, McEvoy, & Alzheimer's Disease

Neuroimaging, 2013; Lin et al., 2015). Similarly, hippocampal atrophy appears to progress more steeply in women, compared to men, in the presence of higher tau and lower amyloid-beta (Aβ) levels in the cerebrospinal fluid (Koran, Wagener, & Hohman, 2017). Such findings suggest a complex relationship between aging, sex, and AD-related neuropathology on memory.

To elucidate neural and behavioural processes underlying episodic memory changes related to healthy vs. pathological aging, studies increasingly focus on examining asymptomatic adults at higher risk of developing AD (Frankish & Horton, 2017). Such work suggests that early neural biomarkers or cognitive indices of AD development – e.g., *APOE4* carrier status, circulating tau and Aβ levels (Brookmeyer, Abdalla, Kawas, & Corrada, 2018; Kern et al., 2018; Leoutsakos, Gross, Jones, Albert, & Breitner, 2016; Molinuevo et al., 2016; Rabipour et al., 2020; Weiner & Veitch, 2015) – may exert different influences on neural processes in men and women (Buckley et al., 2020; Caldwell, Berg, Cummings, & Banks, 2017). For example, female *APOE4* carriers show greater brain hypometabolism and cortical thinning than male carriers, suggesting that women may be more susceptible to the metabolic effects of *APOE4* (Sampedro et al., 2015). Similarly, at low levels of Aβ and high levels of tau, women appear to have more rapid hippocampal atrophy as well as cognitive decline – a relationship that appears mediated, to some extent, by *APOE4* carrier status (Koran et al., 2017). Despite the influence of sex and gender on cognitive aging, relatively few studies have examined the effects of these factors on AD risk and development. Examining sex and gender in populations likely experiencing neurological changes associated with AD, before symptoms emerge, may help identify early markers or indices that contribute to differential AD development in men and women.

Because declines in episodic memory are among the earliest manifestations of AD (Bateman et al., 2012; Gardiner, 2001), tasks that differentially probe recognition and recall of contextual details associated with a past event are particularly well suited to detect early AD-related changes. For example, adults in prodromal states of AD, such as mild cognitive impairment, demonstrate poorer retrieval accuracy of object-location source associations as well as decreased volumes in AD-related brain regions such as medial temporal lobe, compared to controls (Hampstead, Towler, Stringer, & Sathian, 2018). Similarly, our previous work demonstrated different relationships between episodic memory performance and underlying neural processes in people at higher risk of AD, even when group differences in task performance are not observed (Rabipour et al., 2020; Rajah et al., 2017). Therefore, in the current study we use an object-location associative memory paradigm that allows us to differentiate brain activity during encoding and retrieval of objects and object-location association to determine if there are sex differences in episodic memory-related brain function in older adults with elevated AD risk, including family history of AD.

The present Study

Here we evaluated sex/gender differences – via self-reported sex – in the behavioral and neural correlates of episodic memory in older adults who participated in the PREVENT-AD program (https://douglas.research.mcgill.ca/stop-ad-centre). Because our sample uniformly contained older adults with first-degree family history of AD, we aimed to examine the potential influence of self-reported sex on episodic memory performance and related brain activity over and above the influence of family history. Based on the prevalence of +*APOE4* genotype – 14% globally and 34-50% (Alzforum, 2010; Heffernan, Chidgey, Peng, Masters, & Roberts, 2016) in

adults with a first degree relative with late-onset AD – we further sought to investigate whether *APOE4* carrier status would interact with sex on brain-behavior correlations.

Specifically, women and men were scanned during the encoding and retrieval phases of an object-location source memory paradigm. The experimental design was such that it allowed us to dissociated event-related activation related to successful encoding and retrieval of object-location associative memories (source hits) and object-only item memory (source failures).

Multivariate task partial least squares (T- PLS) and behavior PLS (B-PLS) were used to test the hypotheses that: i) sex differences exist in mean levels of brain activity during successful encoding and retrieval of object-location spatial context associations using T-PLS, and ii) sex differences exist in brain activity-memory performance correlations at encoding (subsequent memory effect) and retrieval of object-location association (source hits) using B-PLS. We further explored whether any apparent sex differences in task-related activity or activity-performance correlations differed in older adults with an apolipoprotein E ε4 allele (+*APOE4*), compared to adults without this genetic risk for AD (-*APOE4*).

We selected PLS, a powerful data-driven method, due to its ability to identify whole-brain spatially and temporally distributed patterns of brain activity that differ across experimental conditions and/or relate to a specific behavioral measure (McIntosh, Chau, & Protzner, 2004). This analytic approach is ideal for understanding subtle group differences in brain activity and brain activity-behavior correlations as a function of sex and *APOE4* carrier status in asymptomatic older adults at higher risk for AD. Details on PLS have been published elsewhere (Krishnan, Williams, McIntosh, & Abdi, 2011; McIntosh & Lobaugh, 2004).

The goal of this work is to help elucidate how AD risk differentially affects memory systems in women compared to men. Given the reportedly greater impact of AD on women

compared to men (Gamache et al., 2020; Irvine et al., 2012), we hypothesized that women and men would exhibit distinct brain activation patterns related to the retrieval of object-location association, as well as different brain activity-behavior correlations during episodic retrieval. Importantly, in this study men and women were matched in age, body mass index (BMI), years of education, proximity to the age of parental AD onset (estimated years to AD onset; EYO), and motion during the fMRI scans, to help identify sex differences in brain activity and/or brain activity – memory performance correlations, after controlling for these confounds.

2. Methods

2.1 Participants: PREVENT-AD Cohort

Participants were recruited for the longitudinal PRe-symptomatic EValuation of Experimental or Novel Treatments for Alzheimer's Disease (PREVENT-AD) program, an observational cohort study of asymptomatic older adults with first-degree family history of AD in Montreal, Canada (Breitner, Poirier, Etienne, & Leoutsakos, 2016). We evaluated baseline data in 88 age- and education-matched healthy older adults with elevated risk of AD due to family history who were enrolled up to August 31st, 2017 (i.e., data release 5.0) and participated in the task fMRI portion of the study (see below). From the full sample, we excluded participants based on confounding genetic factors (i.e., *APOE2* carriers, n=34; *APOE44* homozygotes, n=7; unavailable genotype, n=3); having below-chance performance or fewer than eight trials per response type in the task fMRI protocol (n= 95); and poor fMRI image resolution (n=32). Because this sample was heavily unbalanced with respect to sex (43 men compared to 128 women), we selected a subset of 43 women matched in age, education, and *APOE4* carrier status to the original sample of men. After excluding age outliers, our final sample comprised 80 older adults (40 men and 40 women; M_{age}=63.03±3.78; $M_{education}$=15.41±3.40).

2.2 Protocol

Enrolment criteria for the PREVENT-AD trial (Breitner et al., 2016) as well as a description of the baseline task (Rabipour et al., 2020) are described elsewhere. Briefly, all participants had at least one parent or multiple siblings diagnosed with sporadic AD or a condition suggesting Alzheimer's-like dementia within 15 years (Tschanz, Norton, Zandi, & Lyketsos, 2013). At baseline and during each subsequent follow-up assessment, participants performed neuropsychological tests as well as an object-location memory task in the scanner, described below. Here we focus on baseline analyses of the task-related fMRI based on self-identified biological sex. For more information on PREVENT-AD, see: douglas.qc.ca/page/prevent-alzheimer-the-centre.

2.3 Determination of Family History of AD

A brief questionnaire from the Cache County Study on Memory Health and Aging (Utah, USA) determined that all participants had a parent or multiple siblings: i) who had troubles with memory or concentration that was sufficiently severe to cause disability or loss of function; ii) for whom the condition had insidious onset or gradual progression and was not an obvious consequence of a stroke or other sudden insult.

2.4 APOE Genotyping

Genetic characterization was completed via blood draw, as previously described (Gosselin et al., 2016). DNA was isolated from 200 µl of the blood sample using QIASymphony and the DNA Blood Mini QIA kit (Qiagen, Valencia, CA, USA). *APOE* gene variant was determined using pyrosequencing with PyroMark Q96 (Qiagen, Toronto, ON, Canada). We defined -*APOE4* as *APOE* e3/3 genotype and +*APOE4* as *APOE* e3/4 genotype.

2.5 Neuropsychological Testing

Neuropsychological assessments took approximately 40 minutes to administer and were completed prior to every testing session. The test battery included:

The Alzheimer-Dementia Eight Scale (AD8), an eight-item screening tool. The AD8 items index memory, orientation, judgment, and function. A score of two or above suggests impaired cognitive function (Galvin et al., 2005).

The Clinical Dementia Rating (CDR), a five-point scale used to characterize memory, orientation, judgment & problem solving, community affairs, home & hobbies, and personal care (Berg, 1984). The information for each rating is obtained through a semi-structured interview of the patient and a reliable informant or collateral source (e.g., family member).

The Montreal Cognitive Assessment (MoCA), a brief cognitive screening tool sensitive to mild declines in cognitive function (Nasreddine et al., 2004).

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), a battery of neuropsychological assessments aiming to identify abnormal cognitive decline in older adults (Randolph, Tierney, Mohr, & Chase, 1998). The RBANS provides scaled scores for five cognitive indices: immediate memory, visuospatial construct, language, attention, and delayed memory. We included these scaled scores, as well as the total score, in our analyses. Different versions of the RBANS were used in follow-up sessions to prevent practice effects.

2.6 Task fMRI: Behavioral Protocol

Participants were instructed to lie supine in a 3T Siemens Trio scanner (see below), while performing a source memory task programmed in E-Prime version 1.0 (Psychology Software Tools, Inc). The task comprised an initial encoding phase followed by a subsequent retrieval (test) phase.

During the initial encoding phase, participants were cued (10s) to memorize a series of 48 colored line drawings of common objects from the BOSS database (Brodeur, Guerard, & Bouras, 2014) in their spatial location (i.e., to the left or right of a central fixation cross). Each object was presented for 2000ms followed by a variable inter-trial interval (ITI; durations of 2200, 4400, or 8800ms; mean ITI = 5.13s) to add jitter to the fMRI data collection (Dale & Buckner, 1997). Following the encoding phase, there was a 20-min delay during which participants received structural MRI scans.

Following the 20-minute delay, a cue (10s) alerted participants to the beginning of the retrieval phase. During retrieval, participants were presented with 96 colored drawings of common objects: 48 'old' (i.e., previously encoded) stimuli and 48 novel objects, in randomized order. Each object was presented in the center of the screen for 3000ms, with variable ITI (2200, 4400, or 8800ms). All participants used a fiber-optic 4-button response box to make task-related responses, and had an opportunity to familiarize themselves with the response choices during a practice session prior to testing. For each retrieval object, participants made a forced-choice between four-alternative answers: i) *"The object is FAMILIAR but you don't remember the location"*; ii) *"You remember the object and it was previously on the LEFT"*; iii) *"You remember the object and it was previously on the RIGHT"*; and iv) *"The object is NEW"*. Thus (i) responses reflected object recognition and associative source memory failure (object only retrieval), (ii) and (iii) responses reflect associative recollection of object-location associations (i.e., source hits) *if* the location endorsed was correct, or source misattributions (i.e., source failures) *if* the location endorsed was incorrect and (iv) responses reflected either correct rejections of novel objects or failed retrieval ("misses"). Responding (i)-(iii) to new objects reflected false alarms.

2.7 fMRI data acquisition

Functional magnetic resonance images were acquired with a 3T Siemens Trio scanner using the standard 12-channel head coil, located at the Douglas Institute Brain Imaging Centre in Montreal, Canada. T1-weighted anatomical images were acquired after the encoding phase of the fMRI task using a 3D gradient echo MPRAGE sequence (TR=2300 msec, TE=2.98 msec, flip angle=9^{o}, 176 1mm sagittal slices, 1x1x1 mm voxels, FOV=256 mm). Blood Oxygenated Level Dependent (BOLD) images were acquired using a single-shot T2* -weighted gradient echo-planar imaging (EPI) pulse sequence with TR=2000 msec, TE=30 msec, FOV=256 mm. Brain volumes with 32 oblique slices of 4mm thickness (with no slice gap) were acquired along the anterior-posterior commissural plane with in-plane resolution of 4x4 mm.

A mixed rapid event-related design was employed to collect task-related blood oxygen level dependent (BOLD) activation during performance of the memory task (see above). Visual task stimuli were generated on a computer and back-projected onto a screen in the scanner bore. The screen was visible to participants lying in the scanner via a mirror mounted within the standard head coil. Participants requiring correlation for visual acuity wore plastic corrective glasses.

2.8 Data Analysis

2.8.1 *Preprocessing of fMRI data*.

We converted reconstructed images to NIfTI format and preprocessed them using in Statistical Parametric Mapping software version 12 (SPM12). Images from the first 10s of scanning were discarded to allow equilibration of the magnetic field. All functional images were realigned to the first image and corrected for movement artifacts using a 6-parameter rigid body spatial transform and a partial least squares approach. Functional images were then spatially

normalized to the MNI EPI-template using the "Old Normalize" method in SPM12 at 4x4x4 mm voxel resolution, and smoothed using an 8 mm full-width half-maximum (FWHM) isotropic Gaussian kernel. Participants with head motion exceeding 4mm in the x, y, or z axis during encoding and retrieval were excluded from further analyses. Participants with movements that could not be sufficiently repaired, resulting in distorted brain images as judged by an examiner, were excluded from further analysis. To be included in further analyses, all participants were required to have a minimum of eight observations per event type (i.e., object recognition and source recollection).

2.8.2 *Behavioral analyses*

We performed behavioral data analyses on neuropsychological tests and episodic memory task performance using JASP version 0.9.2, R version 3.4.1, and Psychometrica (available via: www.psychometrica.de). We used a significance threshold of p=0.05 with Greenhouse-Geisser corrections for sphericity and Holm-Bonferroni corrections for multiple comparisons, where applicable.

2.8.2.1 *Neuropsychological tests*.

We tested for sex differences in AD8, MoCA, and CDR scores using independent samples t-tests, and RBANS subscale scores using multivariate analysis of variance (MANOVA). We included self-reported sex (female, male) as the independent factor and test scores as the dependent variables.

2.8.2.2 *Episodic memory task*.

We calculated performance scores and mean reaction time (RT) for men and women, for the following event/response types: (i) correct object-only recognition with source failure (referred to as source failure) when participants correctly recognized old objects but could not

recollect the spatial source (endorsed 'familiar') and/or when they correctly recognized an object but endorsed the wrong spatial source (source misattribution); (ii) correct object-location source retrieval , which we refer to as source hits; (iii) false alarms (incorrectly identifying new objects as old); (iv) misses (incorrectly identifying old objects as new); and (v) correct rejections (correctly identifying new objects). We computed total hits using the sum of source hits + source failures, and then calculated the proportion of source hits/total hits and proportion of source failures/total hits. We further examined d', computed as overall standardized hit rate minus standardized false alarm rate, as a measure of sensitivity, and c, computed by multiplying the average of the standardized hit and false alarm rates by -1, to measure response bias (Stanislaw & Todorov, 1999). We used MANOVA to evaluate sex differences on raw accuracy and response time (RT) measures, and as well as the proportion of total hits that were correct object-location source associations (i.e., source hits) vs. object-only recognitions (i.e., source failures).

2.8.3 fMRI analyses

We performed spatio-temporal partial least squares (PLS) analyses using PLSGUI software (https://www.rotman-baycrest.on.ca/index.php?section=84) to identify whole-brain spatially and temporally distributed patterns of brain activity across experimental conditions and related to performance (McIntosh, Chau, & Protzner, 2004; see description of PLS advantages above). We conducted mean-centered task partial least squares (T-PLS) to identify group similarities and differences in event-related activity during successful object-location associative encoding and retrieval, and behavior partial least squares (B-PLS) to examine group similarities and differences in the correlations between event-related activity and the proportion of total hits that were correct object-location source associations vs. object-only recognitions. Details on PLS

have been published elsewhere (Krishnan, Williams, McIntosh, & Abdi, 2011; McIntosh & Lobaugh, 2004).

As previously described (Rabipour et al., 2020), for both T-PLS and B-PLS we averaged the event-related data for each participant across the entire time series and integrated these with task phase (i.e., encoding vs. retrieval). PLS fMRI data were stacked into a between group data matrix wherein participants were nested within event-types; event-types were nested within group; and data for the group of Men were stacked above data for the group of Women. The following five event/response-types were stacked as follows: i) encoding events in which participants subsequently remembered object-location source associations (ENC-Source Hit); ii) encoding events in which participants subsequently remembered only the object identified, but failed to recall spatial source information *or* endorsed the wrong spatial source (ENC-Source Fail); iii) retrieval events for which participants correctly recalled object-location source associations (RET-Source Hit); iv) retrieval events for which participants correctly recalled only the object identity, but failed to recall spatial source association or endorsed the wrong spatial source (RET-Source Fail); and v) events where subjects correctly identified 'new' stimuli as 'new' at retrieval (Correct Rejections). This fifth task condition was only represented in the fMRI data matrix used in the Task PLS analysis. The stacked data matrix contained the fMRI data for each event onset (time lag = 0) with seven subsequent time lags, representing a total of 14s of activation after event onset (TR = 2s $*$ 7 = 14 s). All participants analyzed had a minimum of eight correct events per event (condition) type. There was no signal at lag 0 because data were baseline corrected to the event onset. Therefore, signal in subsequent lags was expressed as percentage deviation from event onset.

2.8.3.1 *Task PLS (T-PLS)*

We mean centered the fMRI data column-wise during the encoding and retrieval phases of the episodic memory task, to evaluate whole-brain similarities and differences in brain activity related to encoding and retrieval of object-location associations in men compared to women. PLS performs singular value decomposition on the stacked data matrix to express the cross-covariance between the fMRI data and each condition into a set of mutually orthogonal latent variables (LVs). The number of LVs produced is equivalent to the number of event- types included in the analysis. Thus, this analysis yielded eight LVs (4 event-types * 2 groups). Each mean-centered LV comprises: i) a singular value reflecting the amount of covariance accounted for by the LV; ii) a design salience, depicted as a set of contrasts in the design salience plots (see results) that represent the relationship between tasks in each group and the pattern of brain activation; and iii) a singular image representing the numerical weights or "brain saliences" assigned to each voxel at each TR/time lag (i.e., the contribution of a region at each TR), yielding a spatio-temporal pattern of whole-brain activity that corresponds to the contrast effect identified by the design salience plot. Design saliences and brain saliences can be either positive or negative: positive brain saliences (depicted as warm-colored regions in the singular images) are positively correlated to *positive* design saliences, whereas negative brain saliences (depicted as cool-colored regions in the singular images) are positively correlated with *negative* design saliences (and vice-versa; Krishnan et al., 2011; McIntosh & Lobaugh, 2004). Thus, the pattern of whole brain activity shown in the singular image is symmetrically associated with the contrast effect identified by the design salience plot.

2.8.3.2 *Behavior PLS (B-PLS)*

We used B-PLS to analyze whole-brain similarities and differences in brain activity directly correlated with source hits and source failures during encoding and retrieval between

men and women. We stacked the behavioral vector containing source hits vs. failures as a proportion of total hits in the same order as the fMRI data matrix (i.e., participant within group). As in the T-PLS, B-PLS performed singular value decomposition of the stacked cross-correlation matrix to yield eight LVs. However, rather than design saliences, B-PLS analysis yields: i) a singular value, reflecting the amount of covariance explained by the LV; ii) a singular image consisting of positive and negative brain saliences, and iii) a correlation profile depicting how participants' retrieval accuracy (proportion of source hits vs. failures) correlates with the pattern of brain activity identified in the singular image. The correlation profile and brain saliences represent a symmetrical pairing of brain-behavior correlation patterns for each group to a pattern of brain activity, respectively. As with the T-PLS analysis, brain saliences can have positive or negative values, and reflect whether activity in a given voxel is positively or negatively associated with the correlation profile depicted. Thus, negative correlations on the correlation plot indicate a negative correlation between performance and *positive* brain saliences (depicted as warm-colored regions in the singular image), but a *positive* correlation between performance and negative brain saliences (depicted as cool-colored regions in the singular image). Conversely, positive correlations indicate a positive correlation between performance and *positive* brain saliences, but a *negative* correlation between performance and negative brain saliences.

In addition, we computed temporal brain scores for each significant LV of the T-PLS and B-PLS. Similar to factor scores, temporal brain scores determine how strongly each participant's data reflect the pattern of brain activity expressed in the singular image in relation to its paired design salience (T-PLS) or correlation profile (B-PLS), at each time lag (McIntosh et al., 2004). The brain scores are plotted with standard error of the mean (SEM) for each task condition

alongside the paired singular image for each significant LV and are used to interpret the LV effects. For each significant LV, we also report peak coordinates from time lags at which the temporal brain score profiles maximally differentiated the effects identified each LV (lags 2-5 post event/condition onset, or 4-10s after event onset). We converted these peak coordinates to Talairach space using the icbm2tal transform (Lancaster et al., 2007) as implemented in GingerAle 2.3 (Eickhoff et al., 2009). Because our acquisition incompletely acquired the cerebellum, peak coordinates from this region are not reported. We used the Talairach and Tournoux atlas (Talairach & Tournoux, 1998) to identify the Brodmann area (BA) localizations of significant activations.

2.8.3.3 *Significance Assessment of PLS*

We assessed the significance of each LV in the T-PLS and B-PLS through 1000 permutations involving resampling without replacement from the data matrix to reassign the order of task conditions within participant. We determined the stability of the brain saliences using 500 bootstrap samples to calculate standard errors of voxel saliences for each LV, sampling participants with replacement while maintaining the order of task conditions for all participants. Significant voxels were those with bootstrap ratios ≥ 3.28 (positive salience brain regions) or ≤ -3.28 (negative salience brain regions), corresponding to $p<0.001$, with a minimum spatial extent of 10 contiguous voxels.

2.8.3.4 *Post hoc analyses*

To validate our interpretations of the T-PLS effects observed, we conducted post-hoc between sex (2: men, women) – by – phase (2: encoding, retrieval) – by event/response type (2: source hit, source failure) repeated measures ANOVAs on the brain scores of significant LVs. Brain scores represent the weighted contribution of each participant to

the LV effects identified. In addition, since the task PLS analysis included a fifth conditions (correct rejections) we also conducted a post-hoc between sex 2 – by – 5 event/response type repeated ANOVAs for T-PLS LVs if correct rejections contributed to the effect identified. For B-PLS, we explored differences in the correlations between brain scores and performance scores based on sex, at each task condition. We used a significance threshold of p=0.05, and applied Greenhouse-Geisser corrections for sphericity and Bonferroni corrections for multiple comparisons, where applicable.

We also investigated the potential influence of *APOE4* genotype on task-related brain activity and brain-behavior correlations in women compared to men. We performed exploratory post hoc between sex and *APOE4* carrier status (i.e., *-APOE4* vs. *+APOE4*) 2 x 2 repeated measures ANOVAs and MANOVAs, on brain scores as described above for T-PLS. For B-PLS, we explored differences in the correlations between brain scores and performance scores based on sex and *APOE4* carrier status, at each task condition. We used a significance threshold of p=0.05, and applied Greenhouse-Geisser corrections for sphericity and Bonferroni corrections for multiple comparisons, where applicable. Because of our limited sample size (16 +APOE4 out of 40 men, and 21 +APOE4 out of 40 women), these results are reported as Supplemental Results.

3 **Results**

3.1 Behavioral Performance

Women and men were matched in demographics, including age and years of education. (Table 1a). In addition, we found no significant sex differences in body mass index (BMI), proximity to the age of parental AD onset (estimated years to AD onset; EYO), presence of AD-related biomarkers including the ratio of tau:Aβ in the cerebrospinal fluid, number of participants

undergoing hormone replacement therapy, and motion during the fMRI scans ($t_{(77.5)} \leq 1.53$, $p \geq 0.13$).

Insert Table 1 about here

3.1 .1 Neuropsychological Performance

Table 1b shows participant scores on the neuropsychological tests. We found a significant main effect of sex on MoCA total score, whereby women performed better than men ($t_{(78)}=3.17$, $p=0.002$, Cohen's $d=0.71$). Following up on this effect revealed that six men – but no women – scored below the clinical cutoff of 26 ($X^2=6.49$, $p=0.01$). We found no significant effect of sex on AD8 or CDR scores ($p>0.05$). Similarly, MANOVA on RBANS subscales revealed no significant sex differences in RBANS performance (Wilk's $\lambda=0.96$, $F_{(6,71)}=0.54$, $p=0.77$). Overall, women and men demonstrated largely comparable neuropsychological performance.

3.1.2 Task fMRI: Episodic Memory Task Performance

The behavioral results from the object-location associative memory task are presented in Table 1c. The MANOVA revealed no significant sex differences in task performance (Wilk's $\lambda=0.94$, $F_{(5,74)}=0.95$, $p=0.45$) or RT (Wilk's $\lambda=0.89$, $F_{(6,71)}=1.80$, $p=0.11$). Between-groups (i.e., sex) repeated measures ANOVA examining differences in RT by response type revealed significant response type differences in RT ($F_{(3.94,295.3)}=67.73$, $p<0.0001$, $\eta_p^2=.48$;). Both men and women had significantly longer RT for FA trials compared to source hits, source misattributions, misses, and correct rejections ($t_{(79)} \geq 6.95$, $p \leq 0.0001$, Cohen's $d \geq 0.79$), and significantly faster RT for correct rejections compared to all other trials ($t_{(79)} \geq 7.27$, $p \leq 0.0001$, Cohen's $d \geq 0.83$), with the exception of correct source hits. Of trials presenting "old" (i.e., previously viewed) objects,

participants had the fastest RT for source hits ($t_{(79)} \geq 5.73$, $p \leq 0.0001$, Cohen's $d \geq 0.65$). Thus, women and men exhibited similar performance on the behavioral task and made significantly faster source hits and correct rejection decisions than other decision types.

Insert Figure 1 (proportion source hits vs. failures) about here

3.2 fMRI results

3.2.1 Task PLS Results

The Task PLS (T-PLS) analysis yielded four significant LVs ($p \leq 0.04$). The first significant LV (LV1, $p < 0.001$) accounted for 48.16% of the cross-block covariance and identified brain regions in which activity significantly differed during correct rejections and encoding, compared to retrieval, in both groups (Figure 2A). The brain scores plot with SEM indicates that LV1 identified brain regions that were differentially activated during the successful encoding of object-location associations and objects only (source hits and source failures, respectively) and the perception of novel objects (correct rejections), compared to the successful retrieval of previously seen object-location associations and objects only, in both sexes. The post-hoc 2x2x2 repeated measures ANOVA of brain scores for LV1 confirmed significant phase ($F_{(1,78)} = 142.64$ $p < 0.001$) and task ($F_{(1,78)} = 5.45$ $p = 0.02$) effects, consistent with our interpretation. Table 2 lists the local maxima from LV1. In both men and women, the positive salience brain regions were more active during retrieval, compared to encoding and correct rejections, whereas the negative salience brain regions were more active during encoding and correct rejections, compared to retrieval. Positive salience regions included bilateral medial and lateral prefrontal cortex (PFC), posterior cingulate and precuneus, inferior parietal, medial temporal, and lateral occipital cortices. Negative salience regions included bilateral

ventromedial/orbital and superior PFC and lateral middle temporal cortices, and right fusiform cortex.

Insert Figure 2 (TPLS) about here

Insert Table 2 (local maxima for LV1) about here

LV2 of the T-PLS accounted for 18.64% of the cross-block covariance (p<0.001). The brain score plot and singular image presented in Figure 2B indicate that this LV identified brain regions differentially activated during the successful encoding of both object-location associations and objects only (source hits and source failures, negative salience brain regions), compared to correct rejections of new items (positive salience brain regions), in both sexes. The post-hoc 2 x 5 repeated measures ANOVA with pair-wise comparisons confirm a significant effect of task condition ($F_{(4, 312)} = 64.21$, $p<0.001$) due to the brain scores associated with correct rejections being significantly different from all other task conditions ($p<0.001$). The local maxima for LV2 are presented in Table 3. Positive salience regions included bilateral precentral gyrus, occipital gyrus and right ventrolateral PFC. Negative salience brain regions included bilateral medial, orbital and dorsal/superior PFC, middle temporal, temporo-parietal, and medial occipital cortices, and the right parahippocampal cortex.

Insert Table 3 about here (local maxima for LV2)

LV3 of the T-PLS accounted for 10.52% of the cross-block covariance (p=0.004). The brain scores plot indicates that LV3 identified sex differences in event-related activity during encoding and retrieval (Figure 2C). Specifically, positive salience brain regions were more active during the encoding and retrieval of object-location associations (source hits) compared to the

encoding and retrieval of objects only (source failures) (negative salience brain regions) in men. Women exhibited the same pattern of increased activity in positive salience brain regions only during object-location associative source retrieval. The post-hoc 2x2x2 repeated measures ANOVA of brain scores confirmed a significant sex-by-task condition interaction ($F_{(1,78)} = 22.73$ $p<0.001$) and a significant memory phase – by – task condition interaction ($F_{(1,78)} = 22.61$, $p<0.001$). The local maxima for LV3 are presented in Table 4. Positive salience brain regions included caudate, bilateral superior and middle temporal cortex, dorsal occipital cortex, medial cingulate, inferior parietal cortex, and precuneus. The few negative salience brain regions included bilateral ventrolateral PFC and insula. Thus, this LV identified activations related to encoding and object-only retrieval that were specific to men.

Insert Table 4 about here (local maxima for LV3)

LV4 of the T-PLS accounted for 7.49% of the cross-block covariance (p=0.04). Because this LV accounted for so little variance and identified few significant activations, we present this LV in the Supplementary Results section of this paper.

To summarize, LV1 and LV2 from the T-PLS results identified similarities in brain activity during memory encoding and retrieval in women and men. LV3 identified sex differences in brain activity and indicated that men activated different brain regions during the encoding and retrieval of object-location associations (source hits), compared to objects only (source failures).

3.2.2 Behavior PLS Results

The Behavior PLS (B-PLS) yielded one significant LV (p=0.02), which accounted for 21.56% of the cross-block covariance and identified sex differences in brain-behavior correlations (Figure 3). Table 5 lists the local maxima for the significant brain regions. The brain-behavior correlation plot indicates that, in women, activity in positive salience brain regions during encoding correlated with better subsequent retrieval of both object-location associations and object-only information. In contrast, activity in negative salience brain regions during retrieval correlated with better retrieval of both source and object-only information. In men, this LV identified brain regions in which activity during retrieval was differentially correlated with the retrieval of source information, compared to the retrieval of object-only information with source failures. Specifically, in men, activity in positive salience brain regions correlated with better source retrieval and activity in negative salience brain regions correlated with better object-only retrieval. Positive salience brain regions included bilateral insula, and posterior cingulate and/or retrosplenial cortex. Negative salience brain regions included medial prefrontal/anterior cingulate, parahippocampal and medial occipital cortices. The post hoc analysis of the B-PLS indicated a significant sex-by-event-type interaction during retrieval of object-location associations. Specifically, women demonstrated a negative correlation between performance and positive brain salience regions (r=-0.51), whereas men showed a positive correlation between performance and positive brain salience regions (r=0.62; Z=5.54, p<0.001).

Therefore, the B-PLS analysis revealed sex differences in brain-behavior correlations. In women, better encoding of object-location association and of objects alone was correlated with greater activity in the same positive salience brain regions; and better retrieval of object-location associations and of object information alone was correlated with greater activity in the same

negative salience brain regions. In men, better retrieval of object-location associations engaged distinct brain regions, compared to retrieval of objects alone.

Insert Figure 3 (BPLS) about here

Insert Table 5 (local maxima for BPLS LV1) about here

4 Discussion

Late onset AD disproportionately affects women, compared to men (Gamache et al., 2020; Irvine et al., 2012; Mazure & Swendsen, 2016). Episodic memory decline is one of the most consistent early signs of AD (Reisa A. Sperling et al., 2010). Determining whether there are sex differences in the neural correlates of episodic memory in cognitively intact older adults with risk factors for AD may help advance our understanding of why more women are diagnosed with AD, compared to men. Drawing on baseline data from the PREVENT-AD dataset (Breitner et al., 2016), here we examined sex differences in the neural correlates of episodic memory performance in a sample of older adults who all had first-degree family history of AD. Building on our previous work (Rabipour et al., 2020), we assessed the relationship between self-reported biological sex and brain activity from the whole-brain perspective using PLS, a data-driven multivariate approach, and a novel episodic memory task distinguishing object-location source association from recognition. To account for the limited sample of men compared to women, we analyzed a partial sample wherein women were matched to men with respect to age, years of education, BMI, and estimated years to symptom onset.

4.2 Few Sex Differences in Behavior and Brain Activity Related to Encoding and Retrieval of Old vs. Novel Objects

Our analyses identified few sex differences in behavioral performance. Both women and men performed generally well on neuropsychological tests and in line with previously reported trends in this population (Larouche et al., 2016). We found no significant sex differences in performance on the episodic memory task, including in the accuracy and RT associated with object-location associations and object-only recognition. This comparability of behavioral performance between women and men is unsurprising given our prior findings in the larger PREVENT-AD baseline analysis (Rabipour et al., 2020).

The data-driven mean-centered T-PLS analysis identified general patterns of object-only and object-location associative encoding and retrieval activity that were common to both sexes (LV1, LV2) and supported the task-related brain activation patterns we previously found in this cohort (Rabipour et al., 2020). Women and men exhibited similar patterns of event-related brain activity during successful encoding vs. retrieval of object-only and associative information (LV1). Both groups demonstrated greater activity in bilateral ventromedial/orbital and superior PFC as well as lateral middle temporal cortices and right fusiform cortex during encoding, compared to broad bilateral activity in medial and lateral PFC, posterior cingulate and precuneus, inferior parietal, medial temporal, and lateral occipital cortices at retrieval. In addition, brain activation patterns were consistent across both sexes for the encoding of old objects compared to novelty detection (LV2). Women and men exhibited more activity in bilateral medial, orbital, and dorsal/superior PFC, middle temporal, temporo-parietal, medial occipital regions, and right parahippocampal cortex during the encoding of object-location associations and object-only information. Conversely, novelty detection associated with more activity in bilateral precentral and occipital regions and right ventrolateral PFC in both sexes.

The episodic memory-related brain activity patterns identified in T-PLS LV1 and LV2 are consistent with those previously reported for the encoding and retrieval of associative information in older adults (Maillet & Rajah, 2014; Salami, Eriksson, & Nyberg, 2012). In particular, our results support greater engagement of medial orbitofrontal and dorsal/superior PFC, lateral middle temporal, as well as primary and secondary sensory cortices (e.g., prefrontal and ventral occipito-temporal areas) and parahippocampal cortex during visual associative encoding (de Chastelaine, Mattson, Wang, Donley, & Rugg, 2015, 2016; Dennis et al., 2019; T. Sommer, Rose, Weiller, & Buchel, 2005) and of dorsal precuneus during visuospatial associative encoding (Rami et al., 2012; Schott et al., 2019). In comparison, during episodic retrieval we found activation of medial temporal, fronto-parietal control, and default-mode network regions such as the posterior cingulate and inferior parietal cortices (Huo, Li, Wang, Zheng, & Li, 2018; Sestieri, Corbetta, Romani, & Shulman, 2011). These patterns are consistent with the Retrieval, Experience, and Decision (RED) model (Kim, 2020), suggesting multi-stage engagement of these networks during episodic retrieval. Together, findings from LV1 and LV2 of our T-PLS analysis indicate that older women and men at risk of AD engage similar brain regions during the encoding and retrieval of old vs. novel objects, and that these regions are comparable to episodic memory-related activity in cognitively healthy older adults.

4.3 *Sex Differences in Task-related Brain Activity and Brain Activity-Behavior Correlations*

In addition to similarities in task-related brain activation patterns in women and men during episodic encoding and retrieval (T-PLS LV1, LV2), our analyses also identified sex differences in task-related activation and in brain-behavior correlations. For example, in men, LV3 from the T-PLS identified brain regions that were differentially activated during the encoding and retrieval of object-location associations (source hits), compared to the encoding

and retrieval of object-only information (source failures). Also, in men, LV1 from the B-PLS identified distinct patterns of retrieval-related activity that correlated with better associative retrieval (source hits), compared to object-only retrieval (source failures) in men. Therefore, distinct brain regions supported object-location associative memory, compared to object only memory in older +FH men.

In contrast, older +FH women did not exhibit different patterns of brain activity during the encoding and retrieval of object-location associative memory, compared to object only memory. For example, T-PLS LV3 demonstrated no distinct activation patterns in women at encoding, and general activation of positive salience areas for object-location retrieval that were common to women and men. Also, in women, LV1 from the B-PLS identified a general pattern of encoding-related activity that correlated with better subsequent retrieval of object-location associations and object only information; and a general pattern of retrieval-related activity that correlated with better associative and object retrieval accuracy. Therefore, older +FH women exhibited less distinct patterns of memory-related brain activity during encoding and retrieval, compared to older +FH men. In other words, the same set of brain regions that support object-location encoding and retrieval also supported object only encoding retrieval. These findings corroborate our previous findings from adult lifespan sample consisting of adults with no family history of AD (Subramaniapillai et al., 2019), which also identified more generalized patterns of brain activity in women across memory conditions.

In this prior fMRI study, adults aged 18 to 76 yrs of age with no family history of AD, were scanned while encoding and retrieving face-location associations (Subramaniapillai et al., 2019). The B-PLS analysis in this study identified generalized age-related increases and decreases in brain activity across encoding and/or retrieval in women only. These age-related

differences in activation were observed in lateral fronto-parietal cortices, medial PFC, cingulate, precuneus, retrosplenial and medial temporal regions; and, exhibited similar patterns of brain-behavior correlations across memory conditions at encoding and retrieval.

In the current B-PLS analysis of older adults with a family history of AD (+FH), we again observed generalized patterns of activity across different memory conditions in women only. Interestingly, in both studies, similar midline brain regions, *i.e.* medial PFC, cingulate, retrosplenial and medial temporal cortex, are implicated. This implies, that the generalized activation of these brain regions across memory conditions may not relate to FH status in women (since this was observed in -FH and +FH women across studies). However, this does to preclude the possibility that this generalization of midline cortical activation across memory conditions in older women may be an early sign of memory-related brain pathology, since having a -FH status does not mean one is protected from developing AD.

Generalized patterns of brain function across task domains is widely reported with increasing age (Koen & Rugg, 2019). For example, studies have demonstrated age-related reductions in the functional specificity of parahippocampal and inferior temporal regions (Park et al., 2004) and episodic memory-related changes in the connections between the caudate and default-mode network (Rieckmann, Johnson, Sperling, Buckner, & Hedden, 2018). Previous research has further suggested that generalization of brain activity across task domains is associated with reduced task performance (La Fleur, Meyer, & Dodson, 2018; Wilson, Segawa, Hizel, Boyle, & Bennett, 2012). Here we provide evidence for the first time that such generalization of brain function across memory conditions is specific to women and was observed in the absence of sex differences or deficits in episodic memory performance.

It is possible that the observed generalization of brain activity across memory conditions reflects greater age-related dedifferentiation of function in women, compared to men. Within the context of the cognitive neuroscience of aging, dedifferentiation of function has been defined as an age-related reduction in task-specific brain activations *across task domains* due to decreases in signal-to-noise and less distinctive neural representations (Li, Lindenberger, & Sikstrom, 2001; Park & Reuter-Lorenz, 2009; Rajah & D'Esposito, 2005). Longitudinal studies in cognitively healthy older adults and AD converters suggest that cognitive dedifferentiation relates more strongly to terminal cognitive decline than to advancing age, and may be attributable to increasing neural pathology in late life stages (e.g., Batterham, Christensen, & Mackinnon, 2011; Hulur, Ram, Willis, Schaie, & Gerstorf, 2015; Wilson et al., 2012). Similarly, older adults in early stages of AD-related cognitive impairment exhibit generalized patterns of brain activity during associative memory task performance (Oedekoven, Jansen, Keidel, Kircher, & Leube, 2015) and rest (Bai et al., 2008), as well as memory-related hyperactivation of hippocampal and default mode regions (Dickerson et al., 2005; Nyberg, Andersson, Lundquist, Salami, & Wahlin, 2019). Resting and memory task-related hyperactivation of these regions also appears in young and older adults with increased genetic risk (i.e., family history or *APOE4* allele) of AD (Bookheimer et al., 2000; Filippini et al., 2009; Machulda et al., 2011; Quiroz et al., 2010) and may represent an early sign of pathological Aβ accumulation (Busche & Konnerth, 2016; R. A. Sperling et al., 2009). However, given that in our study women exhibited generalized patterns of brain activity, but *within a specific task domain* – episodic memory – it is arguable that our result is not indicative of dedifferentiation. Instead, it is possible that this generalization of brain activation reflects a fundamental neurocognitive shift in how women

approached our memory task, compared to men. Whether this shift is an early indication of AD-related neuropathology is unclear since all adults in the current study were cognitively intact.

5 Limitations and Future Directions

In addition to limitations noted in our previous work (Rabipour et al., 2020), the number of men enrolled in PREVENT-AD limited our sample size. Analyzing a larger sample may have revealed different behavioral and brain activity patterns. Another caveat in the present analyses is the categorization of groups (i.e., men vs. women) based on a single, binary male/female self-report. Such limited questioning fails to capture possible nuances in sex and gender, including transsexual or transgender individuals whose self-identified sex/gender might not fit under the traditional binary categorization. Moreover, increasing evidence suggests a prominent impact of reproductive history and hormonal state (e.g., level of circulating estrogen, history of hormone replacement therapy, etc.) on episodic memory (Jacobs et al., 2016). Such information therefore represents an important consideration in any analysis of sex differences in memory function, and may contribute to episodic memory processes in healthy and pathological aging (Irvine et al., 2012); unfortunately, these data were incompletely available in the PREVENT-AD cohort. As the influence of sex on cognitive aging and AD risk becomes more apparent, studies are increasingly collecting these data to include as analytic variables.

It is possible that some of the sex differences in memory-related brain function observed in the current study may be due to underlying sex differences in regional brain structure (Forde et al., 2020; Ritchie et al., 2018). Two prior structural analyses of the baseline PREVENT-AD cohort included sex/gender as a covariate of no interest (Pichet Binette et al., 2020; Tardif et al., 2018), thus it is unclear if sex/gender effects were observed in these studies. We report significant sex differences in overall gray matter volume after controlling for total intracranial

volumes, with women exhibiting greater total gray matter volumes compared to men. Therefore, it is possible that some of the sex differences in memory-related activations may reflect functional compensation or alterations in memory-related brain function due to differences in underlying structural differences. However, this assumes that underlying structural differences drive activation effects; yet it is possible that sex differences in regional BOLD activation, variability and/or brain activation-behavior correlation precede the structural volume effects reported in prior work. It is not possible to know the direction of the influence between structure-function with the baseline PREVENT-AD data. Our future work will examine whether and how biological sex may influence these relationships longitudinally, including the potential role of brain structure and genotype in mediating these effects.

6 Conclusions

Our findings are among the first to identify sex differences in episodic memory-related brain activity and brain-behavior correlations in older adults with elevated genetic risk for AD. The evidence we present here is notable for several reasons. The PREVENT-AD cohort comprises a unique dataset of behavioral and task fMRI data in cognitively healthy older adults with first-degree (i.e., at least one parent or multiple sibling) history of AD. In addition, we carefully selected our female sample to match the available male sample based on age, years of education, and *APOE4* carrier status. Our resulting sample was further balanced in BMI, EYO, and other factors including raw task performance scores. Moreover, the present sample included both women and men with relatively high levels of education, a factor traditionally confounded with sex/gender effects on cognition (Angrisani, Lee, & Meijer, 2020; Tucker & Stern, 2011). Historically, women have had different educational and occupational opportunities than men, and engaged in different lifestyle habits including levels of physical activity and participation in

caregiver roles – factors that influence memory processes in normative aging and AD (Andrew & Tierney, 2018; Laws, Irvine, & Gale, 2018). The sex differences we observed in brain activation patterns are therefore unlikely to result from these factors, which are often confounded in studies of sex differences and of AD risk. Finally, given the greater number of older women compared to men diagnosed with AD (Beam et al., 2018), it is possible that our sample included more women, compared to men, at prodromal stages of AD. The identified generalization of brain function in women – i.e., failure of activation of a source-specific set of regions leading to object-only recognition – may therefore represent a sex-specific preclinical marker of AD-related functional neuropathology.

Acknowledgments

We thank members of the Rajah lab, the Cerebral Imaging Centre, and the StoP-AD Centre at the Douglas Hospital Research Centre for their helpful feedback on this work. We also acknowledge the Fonds de Recherche Québec – Santé Postdoctoral Fellowship Awarded to SR, Natural Sciences and Engineering Research Council (NSERC) Discovery Grant RGPIN-2018-05761, and Canadian Institutes of Health Research (CIHR) Project Grant 153321 and CIHR Sex and Gender Chair Awarded to MNR.

PREVENT-AD was launched in 2011 as a $13.5 million, 7-year public-private partnership using funds provided by McGill University, the Fonds de Recherche du Québec – Santé, an unrestricted research grant from Pfizer Canada, the Levesque Foundation, the Douglas Hospital Research Centre and Foundation, the Government of Canada, and the Canada Fund for Innovation. Private sector contributions are facilitated by the Development Office of the McGill University Faculty of Medicine and by the Douglas Hospital Research Centre Foundation (http://www.douglas.qc.ca/).

Author Contributions

Data creation was a collaborative effort from the PREVENT-AD Research Group. SR and MNR analyzed and interpreted the data with help from SR and SP. SR wrote the manuscript with editorial and written contributions from MNR. All authors approved the final version of the manuscript.

Declaration of interest

The authors declare no financial or personal relationships with other people or organizations that could inappropriately influence this work.

References

Alzforum. (2010). ALZGENE - META-ANALYSIS OF ALL PUBLISHED AD ASSOCIATION STUDIES (CASE-CONTROL ONLY) APOE_E2/3/4. Retrieved from http://www.alzgene.org/meta.asp?geneID=83. from Biomedical Research Forum, LLC. http://www.alzgene.org/meta.asp?geneID=83

Alzheimer's Association. (2020). 2020 Alzheimer's disease facts and figures. *Alzheimers Dement, 16*, 391-460. doi:10.1002/alz.12068

Astur, R. S., Purton, A. J., Zaniewski, M. J., Cimadevilla, J., & Markus, E. J. (2016). Human sex differences in solving a virtual navigation problem. *Behav Brain Res, 308*, 236-243. doi:10.1016/j.bbr.2016.04.037

Astur, R. S., Tropp, J., Sava, S., Constable, R. T., & Markus, E. J. (2004). Sex differences and correlations in a virtual Morris water task, a virtual radial arm maze, and mental rotation. *Behav Brain Res, 151*(1-2), 103-115. doi:10.1016/j.bbr.2003.08.024

Aubert-Broche, B., Fonov, V. S., Garcia-Lorenzo, D., Mouiha, A., Guizard, N., Coupe, P., . . . Collins, D. L. (2013). A new method for structural volume analysis of longitudinal brain MRI data and its application in studying the growth trajectories of anatomical brain structures in childhood. *Neuroimage, 82*, 393-402. doi:10.1016/j.neuroimage.2013.05.065

Bai, F., Zhang, Z. J., Yu, H., Shi, Y. M., Yuan, Y. G., Zhu, W. L., . . . Qian, Y. (2008). Default-mode network activity distinguishes amnestic type mild cognitive impairment from healthy aging: A combined structural and resting-state functional MRI study. *Neuroscience Letters, 438*(1), 111-115. doi:10.1016/j.neulet.2008.04.021

Bateman, R. J., Xiong, C., Benzinger, T. L., Fagan, A. M., Goate, A., Fox, N. C., . . . Dominantly Inherited Alzheimer, N. (2012). Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med, 367*(9), 795-804. doi:10.1056/NEJMoa1202753

Batterham, P. J., Christensen, H., & Mackinnon, A. J. (2011). Comparison of Age and Time-to-Death in the Dedifferentiation of Late-Life Cognitive Abilities. *Psychology and Aging, 26*(4), 844-851. doi:10.1037/a0023300

Beam, C. R., Kaneshiro, C., Jang, J. Y., Reynolds, C. A., Pedersen, N. L., & Gatz, M. (2018). Differences Between Women and Men in Incidence Rates of Dementia and Alzheimer's Disease. *J Alzheimers Dis, 64*(4), 1077-1083. doi:10.3233/JAD-180141

Bender, A. R., Naveh-Benjamin, M., & Raz, N. (2010). Associative deficit in recognition memory in a lifespan sample of healthy adults. *Psychol Aging, 25*(4), 940-948. doi:10.1037/a0020595

Bleecker, M. L., Bolla-Wilson, K., Agnew, J., & Meyers, D. A. (1988). Age-related sex differences in verbal memory. *J Clin Psychol, 44*(3), 403-411. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/3384968

Bookheimer, S. Y., Strojwas, M. H., Cohen, M. S., Saunders, A. M., Pericak-Vance, M. A., Mazziotta, J. C., & Small, G. W. (2000). Patterns of brain activation in people at risk for Alzheimer's disease. *New England Journal of Medicine, 343*(7), 450-456. doi:Doi 10.1056/Nejm200008173430701

Breitner, J. C. S., Poirier, J., Etienne, P. E., & Leoutsakos, J. M. (2016). Rationale and Structure for a New Center for Studies on Prevention of Alzheimer's Disease (StoP-AD). *J Prev Alzheimers Dis, 3*(4), 236-242. doi:10.14283/jpad.2016.121

Bremner, J. D., Soufer, R., McCarthy, G., Delaney, R., Staib, L. H., Duncan, J. S., & Charney, D. S. (2001). Gender differences in cognitive and neural correlates of remembrance of emotional words. *Psychopharmacol Bull, 35*(3), 55-78. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12397879

Brookmeyer, R., Abdalla, N., Kawas, C. H., & Corrada, M. M. (2018). Forecasting the prevalence of preclinical and clinical Alzheimer's disease in the United States. *Alzheimers Dement, 14*(2), 121-129. doi:10.1016/j.jalz.2017.10.009

Brunet, H. E., Caldwell, J. Z. K., Brandt, J., & Miller, J. B. (2020). Influence of sex differences in interpreting learning and memory within a clinical sample of older adults. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn, 27*(1), 18-39. doi:10.1080/13825585.2019.1566433

Buckley, R. F., Scott, M. R., Jacobs, H. I. L., Schultz, A. P., Properzi, M. J., Amariglio, R. E., . . . Sperling, R. A. (2020). Sex Mediates Relationships Between Regional Tau Pathology and Cognitive Decline. *Ann Neurol*. doi:10.1002/ana.25878

Buckner, R. L. (2004). Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron, 44*(1), 195-208. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15450170

Busche, M. A., & Konnerth, A. (2016). Impairments of neural circuit function in Alzheimer's disease. *Philos Trans R Soc Lond B Biol Sci, 371*(1700). doi:10.1098/rstb.2015.0429

Caldwell, J. Z. K., Berg, J. L., Cummings, J. L., & Banks, S. J. (2017). Moderating effects of sex on the impact of diagnosis and amyloid positivity on verbal memory and hippocampal volume. *Alzheimers Res Ther, 9*(1), 72. doi:10.1186/s13195-017-0300-8

Chapman, R. M., Mapstone, M., Gardner, M. N., Sandoval, T. C., McCrary, J. W., Guillily, M. D., . . . DeGrush, E. (2011). Women have farther to fall: gender differences between normal elderly and Alzheimer's disease in verbal memory engender better detection of Alzheimer's disease in women. *J Int Neuropsychol Soc, 17*(4), 654-662. doi:10.1017/S1355617711000452

de Chastelaine, M., Mattson, J. T., Wang, T. H., Donley, B. E., & Rugg, M. D. (2015). Sensitivity of negative subsequent memory and task-negative effects to age and associative memory performance. *Brain Res, 1612*, 16-29. doi:10.1016/j.brainres.2014.09.045

de Chastelaine, M., Mattson, J. T., Wang, T. H., Donley, B. E., & Rugg, M. D. (2016). The relationships between age, associative memory performance, and the neural correlates of successful associative memory encoding. *Neurobiol Aging, 42*, 163-176. doi:10.1016/j.neurobiolaging.2016.03.015

de Frias, C. M., Nilsson, L. G., & Herlitz, A. (2006). Sex differences in cognition are stable over a 10-year period in adulthood and old age. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn, 13*(3-4), 574-587. doi:10.1080/13825580600678418

Dennis, N. A., Overman, A. A., Gerver, C. R., McGraw, K. E., Rowley, M. A., & Salerno, J. M. (2019). Different types of associative encoding evoke differential processing in both younger and older adults: Evidence from univariate and multivariate analyses. *Neuropsychologia, 135*, 107240. doi:10.1016/j.neuropsychologia.2019.107240

Dickerson, B. C., Salat, D. H., Greve, D. N., Chua, E. F., Rand-Giovannetti, E., Rentz, D. M., . . . Sperling, R. A. (2005). Increased hippocampal activation in mild cognitive impairment

compared to normal aging and AD. *Neurology, 65*(3), 404-411. doi:10.1212/01.wnl.0000171450.97464.49
Driscoll, I., Hamilton, D. A., Yeo, R. A., Brooks, W. M., & Sutherland, R. J. (2005). Virtual navigation in humans: the impact of age, sex, and hormones on place learning. *Horm Behav, 47*(3), 326-335. doi:10.1016/j.yhbeh.2004.11.013
Filippini, N., MacIntosh, B. J., Hough, M. G., Goodwin, G. M., Frisoni, G. B., Smith, S. M., . . . Mackay, C. E. (2009). Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. *Proc Natl Acad Sci U S A, 106*(17), 7209-7214. doi:10.1073/pnas.0811879106
Forde, N. J., Jeyachandra, J., Joseph, M., Jacobs, G. R., Dickie, E., Satterthwaite, T. D., . . . Voineskos, A. N. (2020). Sex Differences in Variability of Brain Structure Across the Lifespan. *Cereb Cortex, 30*(10), 5420-5430. doi:10.1093/cercor/bhaa123
Frankish, H., & Horton, R. (2017). Prevention and management of dementia: a priority for public health. *Lancet, 390*(10113), 2614-2615. doi:10.1016/S0140-6736(17)31756-7
Gamache, J., Yun, Y., & Chiba-Falek, O. (2020). Sex-dependent effect of APOE on Alzheimer's disease and other age-related neurodegenerative disorders. *Disease Models & Mechanisms, 13*. doi:10.1242/dmm.045211
Gardiner, J. M. (2001). Episodic memory and autonoetic consciousness: a first-person approach. *Philos Trans R Soc Lond B Biol Sci, 356*(1413), 1351-1361. doi:10.1098/rstb.2001.0955
Gur, R. E., & Gur, R. C. (2002). Gender differences in aging: cognition, emotions, and neuroimaging studies. *Dialogues Clin Neurosci, 4*(2), 197-210. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22033483
Hampstead, B. M., Towler, S., Stringer, A. Y., & Sathian, K. (2018). Continuous measurement of object location memory is sensitive to effects of age and mild cognitive impairment and related to medial temporal lobe volume. *Alzheimers Dement (Amst), 10*, 76-85. doi:10.1016/j.dadm.2017.10.007
Heffernan, A. L., Chidgey, C., Peng, P., Masters, C. L., & Roberts, B. R. (2016). The Neurobiology and Age-Related Prevalence of the epsilon4 Allele of Apolipoprotein E in Alzheimer's Disease Cohorts. *J Mol Neurosci, 60*(3), 316-324. doi:10.1007/s12031-016-0804-x
Herlitz, A., Nilsson, L. G., & Backman, L. (1997). Gender differences in episodic memory. *Mem Cognit, 25*(6), 801-811. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9421566
Holland, D., Desikan, R. S., Dale, A. M., McEvoy, L. K., & Alzheimer's Disease Neuroimaging, I. (2013). Higher rates of decline for women and apolipoprotein E epsilon4 carriers. *AJNR Am J Neuroradiol, 34*(12), 2287-2293. doi:10.3174/ajnr.A3601
Hulur, G., Ram, N., Willis, S. L., Schaie, K. W., & Gerstorf, D. (2015). Cognitive Dedifferentiation With Increasing Age and Proximity of Death: Within-Person Evidence From the Seattle Longitudinal Study. *Psychology and Aging, 30*(2), 311-323. doi:10.1037/a0039260
Huo, L., Li, R., Wang, P., Zheng, Z., & Li, J. (2018). The Default Mode Network Supports Episodic Memory in Cognitively Unimpaired Elderly Individuals: Different Contributions to Immediate Recall and Delayed Recall. *Front Aging Neurosci, 10*, 6. doi:10.3389/fnagi.2018.00006
Irvine, K., Laws, K. R., Gale, T. M., & Kondel, T. K. (2012). Greater cognitive deterioration in women than men with Alzheimer's disease: a meta analysis. *J Clin Exp Neuropsychol, 34*(9), 989-998. doi:10.1080/13803395.2012.712676

Jack, C. R., Jr., Wiste, H. J., Weigand, S. D., Knopman, D. S., Vemuri, P., Mielke, M. M., . . . Petersen, R. C. (2015). Age, Sex, and APOE epsilon4 Effects on Memory, Brain Structure, and beta-Amyloid Across the Adult Life Span. *JAMA Neurol, 72*(5), 511-519. doi:10.1001/jamaneurol.2014.4821

Jacobs, E. G., Weiss, B. K., Makris, N., Whitfield-Gabrieli, S., Buka, S. L., Klibanski, A., & Goldstein, J. M. (2016). Impact of Sex and Menopausal Status on Episodic Memory Circuitry in Early Midlife. *J Neurosci, 36*(39), 10163-10173. doi:10.1523/JNEUROSCI.0951-16.2016

Keightley, M. L., Winocur, G., Burianova, H., Hongwanishkul, D., & Grady, C. L. (2006). Age effects on social cognition: faces tell a different story. *Psychol Aging, 21*(3), 558-572. doi:10.1037/0882-7974.21.3.558

Kern, S., Zetterberg, H., Kern, J., Zettergren, A., Waern, M., Hoglund, K., . . . Skoog, I. (2018). Prevalence of preclinical Alzheimer disease: Comparison of current classification systems. *Neurology, 90*(19), e1682-e1691. doi:10.1212/WNL.0000000000005476

Kim, H. (2020). An integrative model of network activity during episodic memory retrieval and a meta-analysis of fMRI studies on source memory retrieval. *Brain Research, 1747*. doi:ARTN 147049

10.1016/j.brainres.2020.147049

Kimura, D., & Harshman, R. A. (1984). Sex differences in brain organization for verbal and non-verbal functions. *Prog Brain Res, 61*, 423-441. doi:10.1016/S0079-6123(08)64452-0

Koen, J. D., & Rugg, M. D. (2019). Neural Dedifferentiation in the Aging Brain. *Trends Cogn Sci, 23*(7), 547-559. doi:10.1016/j.tics.2019.04.012

Koran, M. E. I., Wagener, M., & Hohman, T. J. (2017). Sex differences in the association between AD biomarkers and cognitive decline. *Brain Imaging and Behavior, 11*(1), 205-213. doi:10.1007/s11682-016-9523-8

Krishnan, A., Williams, L. J., McIntosh, A. R., & Abdi, H. (2011). Partial Least Squares (PLS) methods for neuroimaging: a tutorial and review. *Neuroimage, 56*(2), 455-475. doi:S1053-8119(10)01007-4 [pii]

10.1016/j.neuroimage.2010.07.034

La Fleur, C. G., Meyer, M. J., & Dodson, C. (2018). Exploring Dedifferentiation Across the Adult Lifespan. *Psychology and Aging, 33*(5), 855-870. doi:10.1037/pag0000274

Larouche, E., Tremblay, M. P., Potvin, O., Laforest, S., Bergeron, D., Laforce, R., . . . Hudon, C. (2016). Normative Data for the Montreal Cognitive Assessment in Middle-Aged and Elderly Quebec-French People. *Archives of Clinical Neuropsychology, 31*(7), 819-826. doi:10.1093/arclin/acw076

Leoutsakos, J. M., Gross, A. L., Jones, R. N., Albert, M. S., & Breitner, J. C. S. (2016). 'Alzheimer's Progression Score': Development of a Biomarker Summary Outcome for AD Prevention Trials. *J Prev Alzheimers Dis, 3*(4), 229-235. doi:10.14283/jpad.2016.120

Li, S. C., Lindenberger, U., & Sikstrom, S. (2001). Aging cognition: from neuromodulation to representation. *Trends Cogn Sci, 5*(11), 479-486. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11684480

Lin, K. A., Choudhury, K. R., Rathakrishnan, B. G., Marks, D. M., Petrella, J. R., Doraiswamy, P. M., & Alzheimer's Disease Neuroimaging, I. (2015). Marked gender differences in progression of mild cognitive impairment over 8 years. *Alzheimers Dement (N Y), 1*(2), 103-110. doi:10.1016/j.trci.2015.07.001

Machulda, M. M., Jones, D. T., Vemuri, P., McDade, E., Avula, R., Przybelski, S., . . . Jack, C. R., Jr. (2011). Effect of APOE epsilon4 status on intrinsic network connectivity in cognitively normal elderly subjects. *Arch Neurol, 68*(9), 1131-1136. doi:10.1001/archneurol.2011.108

Maillet, D., & Rajah, M. N. (2014). Age-related differences in brain activity in the subsequent memory paradigm: a meta-analysis. *Neurosci Biobehav Rev, 45*, 246-257. doi:10.1016/j.neubiorev.2014.06.006

Mazure, C. M., & Swendsen, J. (2016). Sex differences in Alzheimer's disease and other dementias. *Lancet Neurol, 15*(5), 451-452. doi:10.1016/S1474-4422(16)00067-3

McCarrey, A. C., An, Y., Kitner-Triolo, M. H., Ferrucci, L., & Resnick, S. M. (2016). Sex differences in cognitive trajectories in clinically normal older adults. *Psychol Aging, 31*(2), 166-175. doi:10.1037/pag0000070

McIntosh, A. R., Chau, W. K., & Protzner, A. B. (2004). Spatiotemporal analysis of event-related fMRI data using partial least squares. *Neuroimage, 23*(2), 764-775. doi:10.1016/j.neuroimage.2004.05.018

McIntosh, A. R., & Lobaugh, N. J. (2004). Partial least squares analysis of neuroimaging data: applications and advances. *Neuroimage, 23 Suppl 1*, S250-263. doi:10.1016/j.neuroimage.2004.07.020

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr., Kawas, C. H., . . . Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 263-269. doi:10.1016/j.jalz.2011.03.005

Molinuevo, J. L., Gramunt, N., Gispert, J. D., Fauria, K., Esteller, M., Minguillon, C., . . . Cami, J. (2016). The ALFA project: A research platform to identify early pathophysiological features of Alzheimer's disease. *Alzheimers Dement (N Y), 2*(2), 82-92. doi:10.1016/j.trci.2016.02.003

Nebel, R. A., Aggarwal, N. T., Barnes, L. L., Gallagher, A., Goldstein, J. M., Kantarci, K., . . . Mielke, M. M. (2018). Understanding the impact of sex and gender in Alzheimer's disease: A call to action. *Alzheimers Dement, 14*(9), 1171-1183. doi:10.1016/j.jalz.2018.04.008

Nyberg, L., Andersson, M., Lundquist, A., Salami, A., & Wahlin, A. (2019). Frontal Contribution to Hippocampal Hyperactivity During Memory Encoding in Aging. *Frontiers in Molecular Neuroscience, 12*. doi:ARTN 229
10.3389/fnmol.2019.00229

Oedekoven, C. S. H., Jansen, A., Keidel, J. L., Kircher, T., & Leube, D. (2015). The influence of age and mild cognitive impairment on associative memory performance and underlying brain networks. *Brain Imaging and Behavior, 9*(4), 776-789. doi:10.1007/s11682-014-9335-7

Park, D. C., Polk, T. A., Park, R., Minear, M., Savage, A., & Smith, M. R. (2004). Aging reduces neural specialization in ventral visual cortex. *Proc Natl Acad Sci U S A, 101*(35), 13091-13095. doi:10.1073/pnas.0405148101

Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: aging and neurocognitive scaffolding. *Annu Rev Psychol, 60*, 173-196. doi:10.1146/annurev.psych.59.103006.093656

Pichet Binette, A., Gonneaud, J., Vogel, J. W., La Joie, R., Rosa-Neto, P., Collins, D. L., . . . Group, P.-A. R. (2020). Morphometric network differences in ageing versus Alzheimer's disease dementia. *Brain, 143*(2), 635-649. doi:10.1093/brain/awz414

Postma, A., Izendoorn, R., & De Haan, E. H. (1998). Sex differences in object location memory. *Brain Cogn, 36*(3), 334-345. doi:10.1006/brcg.1997.0974

Quiroz, Y. T., Budson, A. E., Celone, K., Ruiz, A., Newmark, R., Castrillon, G., . . . Stern, C. E. (2010). Hippocampal hyperactivation in presymptomatic familial Alzheimer's disease. *Ann Neurol, 68*(6), 865-875. doi:10.1002/ana.22105

Rabipour, S., Rajagopal, S., Yu, E., Pasvanis, S., Lafaille-Magnan, M. E., Breitner, J., . . . Rajah, M. N. (2020). APOE4 Status is Related to Differences in Memory-Related Brain Function in Asymptomatic Older Adults with Family History of Alzheimer's Disease: Baseline Analysis of the PREVENT-AD Task Functional MRI Dataset. *Journal of Alzheimer Disease, 76*(1), 97-119. doi:10.3233/JAD-191292

Ragland, J. D., Coleman, A. R., Gur, R. C., Glahn, D. C., & Gur, R. E. (2000). Sex differences in brain-behavior relationships between verbal episodic memory and resting regional cerebral blood flow. *Neuropsychologia, 38*(4), 451-461. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10683395

Rajah, M. N., & D'Esposito, M. (2005). Region-specific changes in prefrontal function with age: a review of PET and fMRI studies on working and episodic memory. *Brain, 128*, 1964-1983. doi:10.1093/brain/awh608

Rajah, M. N., Wallaceb, L. M. K., Ankudowich, Yu, E. H., Swierkot, A., Patel, R., . . . Pasvanis, S. (2017). Family history and APOE4 risk for Alzheimer's disease impact the neural correlates of episodic memory by early midlife. *Neuroimage Clinical, 14*, 760-774.

Rami, L., Sala-Llonch, R., Sole-Padulles, C., Fortea, J., Olives, J., Llado, A., . . . Molinuevo, J. L. (2012). Distinct functional activity of the precuneus and posterior cingulate cortex during encoding in the preclinical stage of Alzheimer's disease. *J Alzheimers Dis, 31*(3), 517-526. doi:10.3233/JAD-2012-120223

Rieckmann, A., Johnson, K. A., Sperling, R. A., Buckner, R. L., & Hedden, T. (2018). Dedifferentiation of caudate functional connectivity and striatal dopamine transporter density predict memory change in normal aging. *Proc Natl Acad Sci U S A, 115*(40), 10160-10165. doi:10.1073/pnas.1804641115

Ritchie, S. J., Cox, S. R., Shen, X., Lombardo, M. V., Reus, L. M., Alloza, C., . . . Deary, I. J. (2018). Sex Differences in the Adult Human Brain: Evidence from 5216 UK Biobank Participants. *Cereb Cortex, 28*(8), 2959-2975. doi:10.1093/cercor/bhy109

Salami, A., Eriksson, J., & Nyberg, L. (2012). Opposing effects of aging on large-scale brain systems for memory encoding and cognitive control. *J Neurosci, 32*(31), 10749-10757. doi:32/31/10749 [pii]

10.1523/JNEUROSCI.0278-12.2012

Sampedro, F., Vilaplana, E., de Leon, M. J., Alcolea, D., Pegueroles, J., Montal, V., . . . Alzheimer's Disease Neuroimaging, I. (2015). APOE-by-sex interactions on brain structure and metabolism in healthy elderly controls. *Oncotarget, 6*(29), 26663-26674. doi:10.18632/oncotarget.5185

Schott, B. H., Wustenberg, T., Lucke, E., Pohl, I. M., Richter, A., Seidenbecher, C. I., . . . Richardson-Klavehn, A. (2019). Gradual acquisition of visuospatial associative memory representations via the dorsal precuneus. *Hum Brain Mapp, 40*(5), 1554-1570. doi:10.1002/hbm.24467

Sestieri, C., Corbetta, M., Romani, G. L., & Shulman, G. L. (2011). Episodic memory retrieval, parietal cortex, and the default mode network: functional and topographic analyses. *J Neurosci, 31*(12), 4407-4420. doi:31/12/4407 [pii]
10.1523/JNEUROSCI.3335-10.2011
Sommer, T., Rose, M., Weiller, C., & Buchel, C. (2005). Contributions of occipital, parietal and parahippocampal cortex to encoding of object-location associations. *Neuropsychologia, 43*(5), 732-743. doi:10.1016/j.neuropsychologia.2004.08.002
Sommer, W., Hildebrandt, A., Kunina-Habenicht, O., Schacht, A., & Wilhelm, O. (2013). Sex differences in face cognition. *Acta Psychol (Amst), 142*(1), 62-73. doi:10.1016/j.actpsy.2012.11.001
Sperling, R. A., Dickerson, B. C., Pihlajamaki, M., Vannini, P., Laviolette, P. S., Vitolo, O. V., . . . Johnson, K. A. (2010). Functional Alterations in Memory Networks in Early Alzheimer's Disease. *NeuroMolecular Medicine, 12*(1), 27-43. doi:10.1007/s12017-009-8109-7
Sperling, R. A., LaViolette, P. S., O'Keefe, K., O'Brien, J., Rentz, D. M., Pihlajamaki, M., . . . Johnson, K. A. (2009). Amyloid Deposition Is Associated with Impaired Default Network Function in Older Persons without Dementia. *Neuron, 63*(2), 178-188. doi:10.1016/j.neuron.2009.07.003
Subramaniapillai, S., Rajagopal, S., Elshiekh, A., Pasvanis, S., Ankudowich, E., & Rajah, M. N. (2019). Sex Differences in the Neural Correlates of Spatial Context Memory Decline in Healthy Aging. *J Cogn Neurosci, 31*(12), 1895-1916. doi:10.1162/jocn_a_01455
Tardif, C. L., Devenyi, G. A., Amaral, R. S. C., Pelleieux, S., Poirier, J., Rosa-Neto, P., . . . Group, P.-A. R. (2018). Regionally specific changes in the hippocampal circuitry accompany progression of cerebrospinal fluid biomarkers in preclinical Alzheimer's disease. *Hum Brain Mapp, 39*(2), 971-984. doi:10.1002/hbm.23897
Tschanz, J. T., Norton, M. C., Zandi, P. P., & Lyketsos, C. G. (2013). The Cache County Study on Memory in Aging: factors affecting risk of Alzheimer's disease and its progression after onset. *Int Rev Psychiatry, 25*(6), 673-685. doi:10.3109/09540261.2013.849663
Weiner, M. W., & Veitch, D. P. (2015). Introduction to special issue: Overview of Alzheimer's Disease Neuroimaging Initiative. *Alzheimers Dement, 11*(7), 730-733. doi:10.1016/j.jalz.2015.05.007
Wilson, R. S., Segawa, E., Hizel, L. P., Boyle, P. A., & Bennett, D. A. (2012). Terminal dedifferentiation of cognitive abilities. *Neurology, 78*(15), 1116-1122. doi:10.1212/WNL.0b013e31824f7ff2
World Health Organization. (2019). Dementia. Retrieved from https://www.who.int/news-room/fact-sheets/detail/dementia
Yonker, J. E., Eriksson, E., Nilsson, L. G., & Herlitz, A. (2003). Sex differences in episodic memory: minimal influence of estradiol. *Brain Cogn, 52*(2), 231-238. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12821106
Young, K. D., Bellgowan, P. S., Bodurka, J., & Drevets, W. C. (2013). Functional neuroimaging of sex differences in autobiographical memory recall. *Hum Brain Mapp, 34*(12), 3320-3332. doi:10.1002/hbm.22144

Tables

Table 1

a) Participant demographics represented as mean values ± standard deviation.

	Women (N = 40)	Men (N = 40)
Proportion of the full sample that had an +*APOE4* genotype	21 (53%)	16 (40%)
Age	63.13 ± 3.90	62.94 ± 3.74
BMI	25.92 ± 4.52	27.34 ± 3.79
Years of Education	15.40 ± 3.75	15.43 ± 3.06
Age proximity to parental diagnosis (EYO)	10.77 ± 7.44	9.31 ± 8.29
Tau:Aβ Ratio	0.26 ± 0.13	0.36 ± 0.27
Hormone Replacement Therapy (n)	7	2
Hysterectomy (n)	8	-
On prescription benzodiazepine for treatment of anxiety (n)	2	1
On prescription for treatment of depression (n)	9	5
fMRI motion	0.044 ± 0.18	0.04 ± 0.10
Total Gray Matter Volumes (adj. by total intracranial volumes)	0.49 ± 0.02	0.50 ± 0.02*

Note: Welch's independent samples t-tests indicated no significant sex differences in mean demographic variables ($t_{(77.5)} \leq 1.53$, $p \geq .13$), except for total gray matter volumes after adjusting for total intracranial volume ($t_{(77)} = -2.834$, $p = .006$). Cerebrospinal fluid data not available in 22 women and 27 men. None of the participants were diagnosed with Type 1 or 2 diabetes at time of testing. Total gray matter and total intracranial volumes were calculated for baseline PREVENT-AD data using the methods described in (Aubert-Broche et al., 2013).

b) Neuropsychological performance represented as mean values ± standard deviation.

	Women	Men
MoCA	28.50* ± 1.26	27.40 ± 1.80
AD8	0.08 ± 0.27	0.25 ± 0.63
CDR	0.00 ± 0.00	0.04 ± 0.13
Immediate Memory	104.54 ± 11.98	104.64 ± 10.06
Visuospat. Constr.	95.87 ± 13.25	91.97 ± 13.27
Language	100.13 ± 9.03	99.03 ± 8.07
Attention	106.85 ± 15.54	104.31 ± 14.62
Delayed Memory	101.97 ± 9.87	103.10 ± 9.20
RBANS Total	102.10 ± 10.59	100.39 ± 9.28

Note: MoCA = Montreal Cognitive Assessment; AD8 = Alzheimer-Dementia Eight Scale; CDR= Clinical Dementia Rating; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status. RBANS data missing from one man and one woman who did not receive the test. There was a significant group difference in MoCA score *$t_{(78)}$=3.17, p=.002, Cohen's d = .71

c) Episodic memory task performance and RT represented as mean values ± standard deviation.

	Women	Men
% Total Hits	85.21 ± 10.75	82.29 ± 12.72
% Source Hits	55.37 ± 13.69	52.14 ± 16.16
% Source Failures	17.66 ± 9.83	16.35 ± 12.29
% Source Misattributions	12.19 ± 6.27	13.80 ± 5.89
% Misses	14.79 ± 10.75	17.71 ± 12.72
% False Alarms	13.97 ± 10.07	15.68 ± 12.79
% Correct Rejections	86.25 ± 10.14	84.06 ± 12.82
Proportion Source Hits	0.64 ± 0.12	0.62 ± 0.14
Proportion Source Fails	0.36 ± 0.12	0.38 ± 0.14
d'	0.17 ± 1.38	-0.26 ± 1.50
C	-0.04 ± 0.59	-0.002 ± 0.83
Source Hits (sec)	1.67 ± 0.31	1.79 ± 0.30
Source Failures (sec)	2.28 ± 0.61	2.45 ± 0.64
Source Misattributions (sec)	2.03 ± 0.50	2.17 ± 0.42
Misses (sec)	1.94 ± 0.48	2.13 ± 0.52
False Alarms (sec)	2.53 ± 0.55	2.45 ± 0.47
Correct Rejections (sec)	1.62 ± 0.28	1.68 ± 0.34

Table 2

Local maxima revealed for LV1 of the T-PLS analysis.

Temporal Lag	Bootstrap Ratio	Spatial Extent (voxels)	Talairach Coordinates			Gyral Location	Brodmann Area
			X	Y	Z		
Positive Salience Regions							
Right Hemisphere							
5	10.01	1995	2	-74	48	Precuneus	7
2	6.93	228	35	-76	34	Superior Occipital Gyrus	39
2,5	6.60	211	36	10	38	Precentral Gyrus	4,9
5	6.31	123	18	51	-1	Superior Frontal Gyrus	10
5	5.27	72	29	21	-4	Insula	47
Left Hemisphere							
3,4	12.07	10910	-31	21	6	Insula	
4	11.22	8742	-9	-69	37	Precuneus	7
2	9.28	1245	-39	-76	32	Angular Gyrus	39
2	7.62	675	-16	6	1	Putamen	
5	7.50	150	-1	-34	23	Posterior Cingulate	23
2,5	7.19	292	-38	50	16	Middle Frontal Gyrus	6,9,10
5	5.68	255	-16	-8	-4	Medial Globus Pallidus	
2,5	5.38	164	-9	13	49	Superior Frontal Gyrus	6,10
4	3.97	10	-68	-34	-7	Middle Temporal Gyrus	21
3	3.87	15	-49	-51	9	Superior Temporal Gyrus	39
Negative Salience Regions							
Right Hemisphere							
2,5	-6.66	347	47	-53	-14	Fusiform Gyrus	19,37
2	-4.73	206	6	38	55	Superior Frontal Gyrus	8
5	-4.56	11	46	-7	51	Precentral Gyrus	6
2	-4.27	17	17	-93	10	Cuneus	18
5	-4.13	39	36	-89	7	Middle Occipital Gyrus	19
3	-4.03	11	14	28	11	Caudate	
Left Hemisphere							
2,3,4,5	-8.82	409	-43	-29	58	Postcentral Gyrus	1,2,3
4,5	-8.73	170	-4	22	-12	Subcallosal Gyrus	25
2,3	-8.05	163	-4	37	-10	Anterior Cingulate	32
2	-5.57	111	-1	23	-15	Medial Frontal Gyrus	25
2	-5.23	246	-35	-91	-5	Inferior Occipital Gyrus	18
3	-4.84	37	-56	-15	-16	Inferior Temporal Gyrus	21

4,5	-4.75	28	-16	39	54	Superior Frontal Gyrus	8
5	-4.73	32	-49	-15	-12	Middle Temporal Gyrus	21
2,5	-4.37	34	-60	-1	0	Superior Temporal Gyrus	22,41
5	-3.97	17	-16	-82	14	Cuneus	17
2	-3.79	15	-20	-89	14	Middle Occipital Gyrus	18

We report only lags 2-5, and clusters with a spatial threshold of at least 10 continuous voxels with brain saliences ≥3.28 times greater than the bootstrap standard error. We converted these peak coordinates to Talairach space and used the Talairach and Tournoux atlas to identify the Brodmann area localizations of significant activations.

Table 3

Local maxima revealed for LV2 of the T-PLS analysis.

Temporal Lag	Bootstrap Ratio	Spatial Extent (voxels)	Talairach Coordinates			Gyral Location	Brodmann Area
			X	Y	Z		
Positive Salience Regions							
Right Hemisphere							
3,4	9.06	648	28	-85	4	Middle Occipital Gyrus	18
3	4.68	95	39	3	30	Precentral Gyrus	6
3,4	4.45	31	32	-10	44	Middle Frontal Gyrus	6
3	4.33	22	24	-51	43	Precuneus	7
3	4.19	14	25	29	-3	Inferior Frontal Gyrus	47
Left Hemisphere							
3	9.72	862	-35	-25	48	Precentral Gyrus	4
3	8.62	555	-38	-75	-11	Fusiform Gyrus	19
4	6.27	185	-20	-93	13	Middle Occipital Gyrus	18
2,4	6.01	192	-57	-24	44	Postcentral Gyrus	2,3
3	5.62	58	-49	-22	16	Insula	
Negative Salience Regions							
Right Hemisphere							
2,4	-8.35	1001	35	-30	60	Precentral Gyrus	4
3	-6.20	200	39	-30	56	Postcentral Gyrus	3
4	-5.36	86	40	-34	-9	Parahippocampal Gyrus	36
3,5	-5.35	493	55	-26	-22	Inferior Temporal Gyrus	20
5	-5.32	1276	10	-98	-8	Lingual Gyrus	18
4,5	-5.26	186	47	29	-7	Inferior Frontal Gyrus	10,47
3,4	-4.89	196	32	24	43	Middle Frontal Gyrus	8
2,3,5	-4.77	53	14	48	38	Superior Frontal Gyrus	8,9,10
2	-4.39	17	25	-17	3	Lentiform Nucleus	
2	-4.12	12	14	24	10	Caudate	
5	-4.08	48	3	-14	10	Thalamus	
4	-4.07	15	62	-42	-6	Middle Temporal Gyrus	21
4	-3.79	13	18	50	13	Medial Frontal Gyrus	10
Left Hemisphere							
4,5	-9.21	277	-5	-69	41	Precuneus	7,19
3	-8.12	347	-53	-56	27	Superior Temporal Gyrus	39
2	-7.47	2540	-1	-80	-7	Lingual Gyrus	18
4	-7.27	312	-46	-65	33	Angular Gyrus	39

3,4,5	-6.89	208	-56	-34	-11	Middle Temporal Gyrus	21
3,5	-6.69	194	-45	22	-9	Inferior Frontal Gyrus	47
2,3,5	-6.65	1146	-2	8	63	Superior Frontal Gyrus	6
3	-6.58	673	-5	-82	22	Cuneus	18
3,4	-6.43	1384	-35	13	52	Middle Frontal Gyrus	6
4	-5.81	325	-9	21	39	Cingulate Gyrus	32

We report only lags 2-5, and clusters with a spatial threshold of at least 10 continuous voxels with brain saliences ≥3.28 times greater than the bootstrap standard error. We converted these peak coordinates to Talairach space and used the Talairach and Tournoux atlas to identify the Brodmann area localizations of significant activations.

Table 4

Local maxima revealed for LV3 of the T-PLS analysis.

Temporal Lag	Bootstrap Ratio	Spatial Extent (voxels)	Talairach Coordinates			Gyral Location	Brodmann Area
			X	Y	Z		
Positive Salience Regions							
Right Hemisphere							
3	5.51	216	39	-48	54	Inferior Parietal Lobule	40
2,3	5.31	1024	17	-21	49	Precentral /Dorsomedial Frontal Gyrus	6
2	4.73	86	43	-72	-5	Inferior Occipital Gyrus	19
3,4	4.37	13	58	-1	-2	Superior Temporal Gyrus	22,38
4	4.10	22	6	-74	51	Precuneus	7
2	3.96	63	25	27	14	Anterior Cingulate	32
2	3.95	58	10	-80	0	Lingual Gyrus	
Left Hemisphere							
2	5.31	195	-35	-79	29	Superior Occipital Gyrus	19
2	4.40	50	-31	-84	-1	Middle Occipital Gyrus	18
3	3.90	11	-6	-49	64	Postcentral Gyrus	7
3	3.75	11	-23	29	-1	Claustrum	
4	3.61	27	-20	-15	28	Caudate	
2	3.53	10	-42	-76	-7	Inferior Occipital Gyrus	19
Negative Salience Regions							
Right Hemisphere							
5	-5.44	80	40	21	-4	Inferior Frontal Gyrus	47
4	-4.76	66	44	17	-1	Insula	
4	-4.04	16	37	13	-34	Superior Temporal Gyrus	38
Left Hemisphere							
4	-4.73	12	-64	-54	5	Middle Temporal Gyrus	21
5	-4.22	73	-5	13	45	Medial Frontal Gyrus	6
4	-3.81	33	-45	13	5	Insula	13

We report only lags 2-5, and clusters with a spatial threshold of at least 10 continuous voxels with brain saliences ≥3.28 times greater than the bootstrap standard error. We converted these peak coordinates to Talairach space and used the Talairach and Tournoux atlas to identify the Brodmann area localizations of significant activations.

Table 5

Local maxima revealed by LV1 of the B-PLS analysis.

Temporal Lag	Bootstrap Ratio	Spatial Extent (voxels)	Talairach Coordinates			Gyral Location	Brodmann Area
			X	Y	Z		
Positive Salience Regions							
Right Hemisphere							
5	6.18	276	32	21	0	Insula/Inferior Frontal Gyrus	
5	4.83	52	10	-2	44	Cingulate Gyrus	24,31
5	4.58	106	35	-24	42	Postcentral Gyrus	3
5	4.16	34	35	-50	33	Supramarginal Gyrus	40
5	3.88	10	36	10	35	Precentral Gyrus	6
Left Hemisphere							
5	4.19	40	-24	-24	45	Precentral Gyrus	4
5	3.87	13	-49	-22	19	Insula/Inferior Frontal Gyrus	
5	3.71	31	-5	-41	22	Posterior Cingulate	23
Negative Salience Regionss							
Right Hemisphere							
3	-4.30	24	21	31	15	Anterior Cingulate	32
5	-4.02	13	10	24	10	Caudate	
4	-3.97	12	31	-52	58	Superior Parietal Lobule	7
4	-3.90	11	36	-33	-20	Parahippocampal Gyrus	36
Left Hemisphere							
3	-6.05	163	-9	-98	-9	Lingual Gyrus	18
2,3,5	-5.49	181	-16	29	-4	Anterior Cingulate	10,32
2,3	-5.08	37	-23	33	-7	Inferior Frontal Gyrus	47
3,5	-4.95	21	-13	-61	67	Superior Parietal Lobule	7
4	-4.82	91	-9	-64	63	Precuneus	7
3	-4.60	36	-9	5	55	Medial Frontal Gyrus	6
3	-4.24	13	-46	-2	50	Precentral Gyrus	6
3	-3.90	15	-27	-18	-20	Parahippocampal Gyrus	35

We report only lags 2-5, and clusters with a spatial threshold of at least 10 continuous voxels with brain saliences ≥3.28 times greater than the bootstrap standard error. We converted these peak coordinates to Talairach space and used the Talairach and Tournoux atlas to identify the Brodmann area localizations of significant activations.

Figures

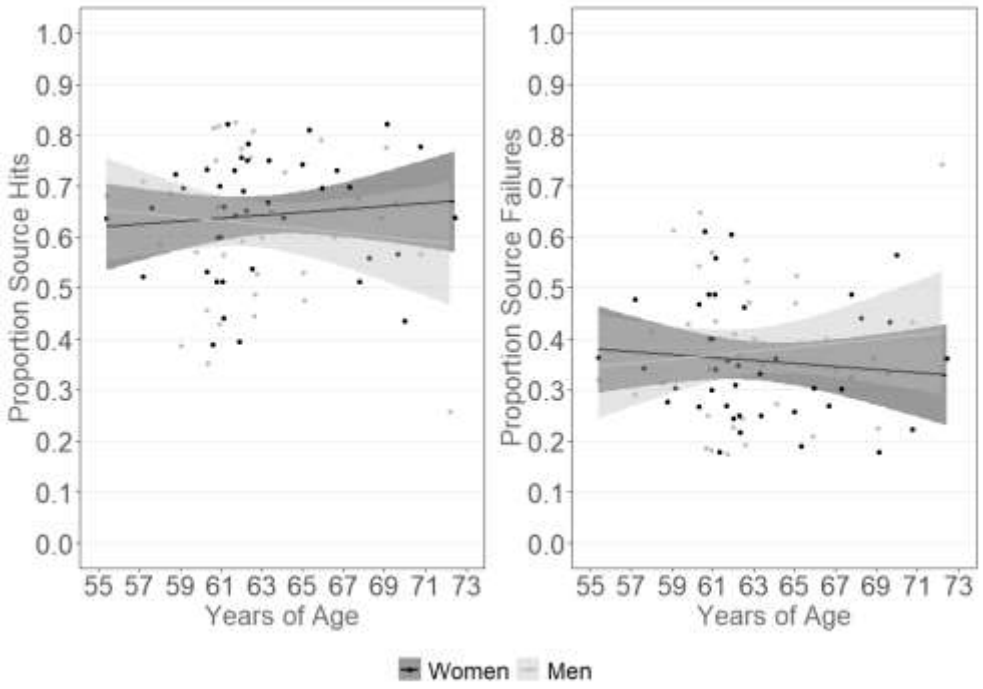

Fig. 1. Source hits and source failures, calculated as a proportion of total hits, in women and men. Shaded regions represent 95% CI.

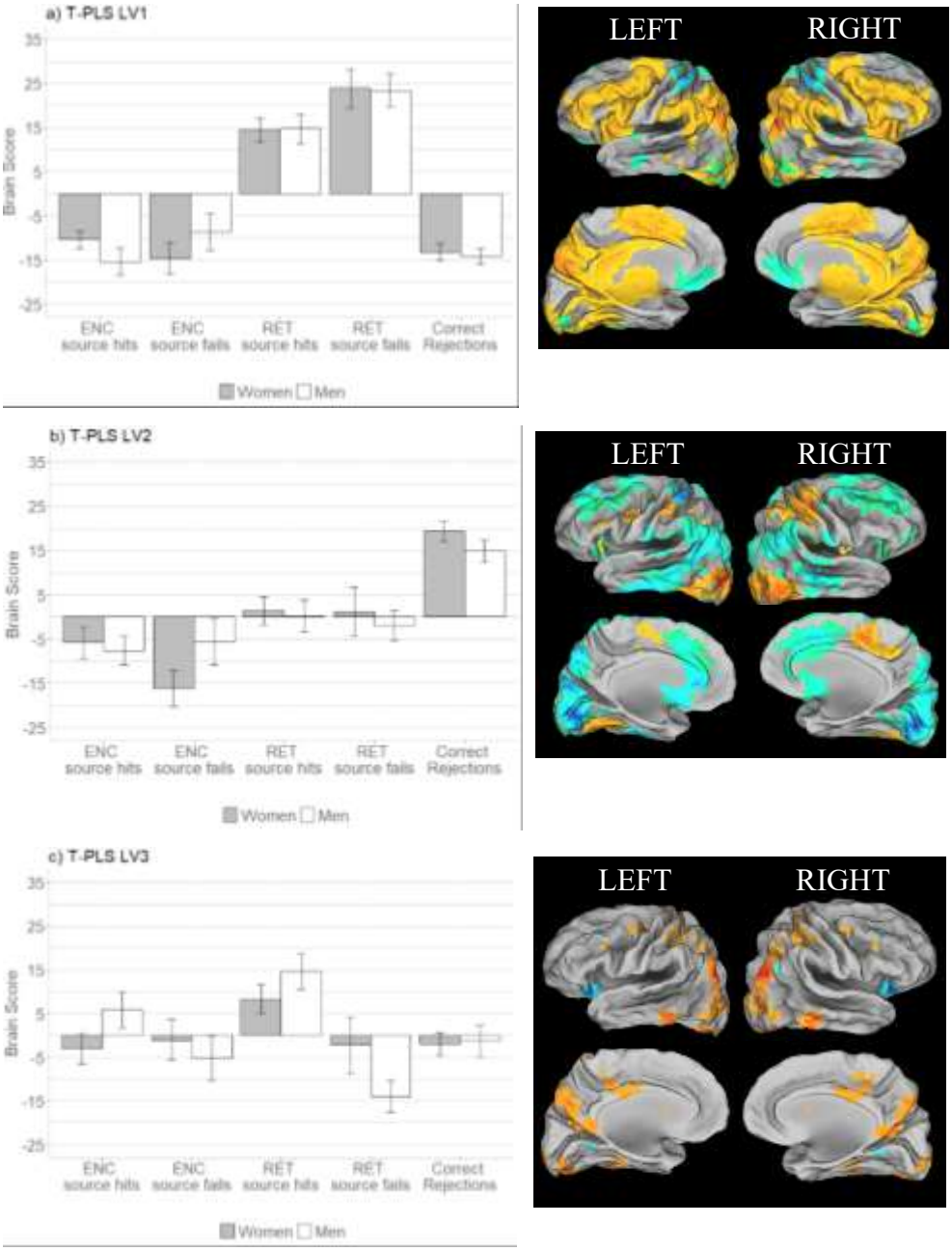

Fig. 2. Design salience plot and singular image representing brain activity patterns by condition for (a) LV1, (b) LV2, and (c) LV3 revealed by the T-PLS analysis. LEFT: Error bars on design salience plots represent standard error of the mean. Positive brain scores indicate conditions in which activity was greater in positive brain salience regions (shown in warm tones in the singular images) and vice versa. Negative brain scores indicate conditions in which activity was greater in negative brain salience regions (shown in cool tones in the singular images) and vice versa. RIGHT: Singular images representing peak coordinates thresholded at a bootrstrap ratio of ±3.28. Warm-toned brain regions represent positive brain saliences; cool-toned regions represent 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).

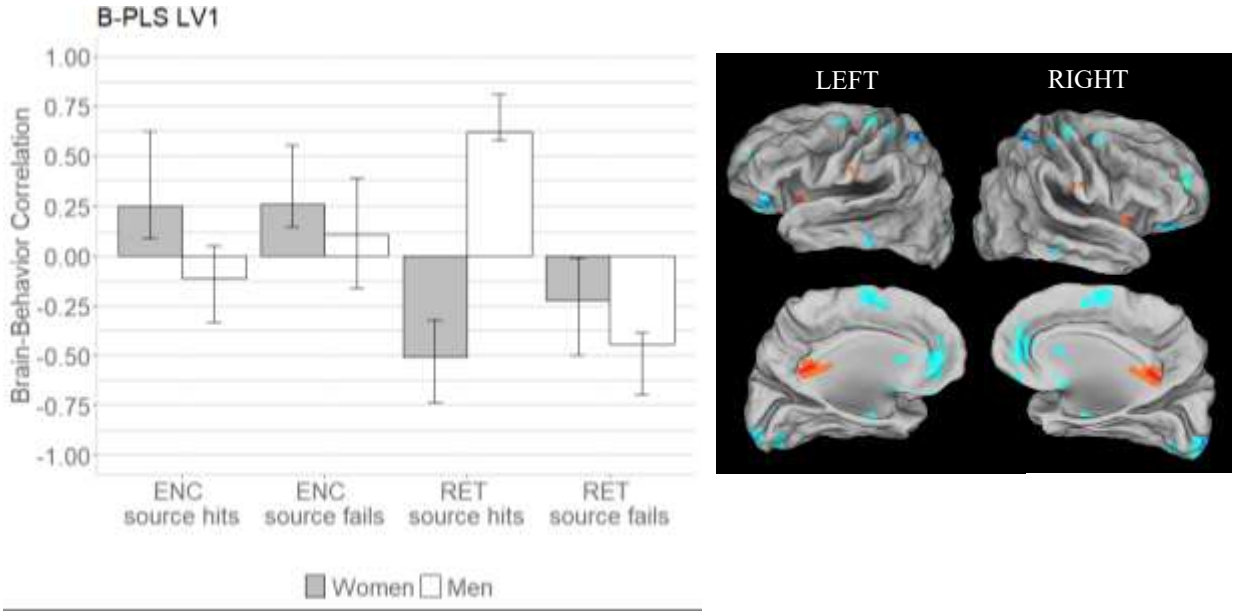

Fig. 3. Correlations between brain activity and task performance by condition, revealed by the only significant LV of the B-PLS analysis. LEFT: Bars represent brain-behavior correlations for each group, by condition. Positive correlations indicate conditions in which performance was positively associated with activity in positive brain salience regions (shown in warm tones in the singular images) and vice-versa. Negative correlations indicate conditions in which performance was positively associated with activity in negative brain salience regions (shown in cool tones in the singular images) and vice-versa. Error bars represent standard error of the mean. RIGHT: The singular image thresholded at a bootstrap ratio of ±3.28, depicting the identified negative brain saliences in cool tones. 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).