


RESEARCH ARTICLE

Early midlife ovarian removal is associated with lower posterior hippocampal function

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Abstract

INTRODUCTION: Women with early bilateral salpingo-oophorectomy (BSO) have greater Alzheimer's disease (AD) risk than women with spontaneous menopause (SM), but the pathway toward this risk is understudied. Considering associative memory

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deficits may reflect early signs of AD, we studied how BSO affected brain activity underlying associative memory.

METHODS: Early midlife women with BSO (with and without 17 β -estradiol therapy [ET]) and age-matched controls (AMCs) with intact ovaries completed a face-name associative memory task during functional magnetic resonance imaging. Hippocampal activity along the anteroposterior axis during associative encoding and retrieval was compared among three groups (BSO [$n = 28$], BSO+ET [$n = 35$], AMCs [$n = 40$]).

RESULTS: Both BSO groups (with and without ET) showed lower posterior hippocampal activation during encoding compared to the AMC group. However, this difference in activation was not significantly correlated with associative memory task performance.

DISCUSSION: Early 17 β -estradiol loss may influence posterior hippocampal activity during associative encoding, possibly presaging late-life AD.

KEYWORDS

estradiol, functional magnetic resonance imaging, hippocampus, hormone therapy, menopause, oophorectomy

Highlights

- After ovarian removal, changes in hippocampal function may affect dementia risk.
- Midlife ovarian removal is associated with less activation in the posterior hippocampus.
- Estradiol therapy may ameliorate alterations in brain function during learning.

1 | BACKGROUND

Compared to healthy aging, Alzheimer's disease (AD) is characterized by difficulties with associative memory processes involving integration of inter-item relationships—identified as decreased ability to remember novel associations (e.g., between faces and names¹). Successful associative memory depends on encoding, storage, and retrieval processes binding different aspects of an event into a cohesive episode.² Associative memory processes are sensitive to AD markers (e.g., apolipoprotein E ϵ 4), pathologies (e.g., tau neurofibrillary tangles and amyloid beta [A β] accumulation), and mild cognitive impairment (MCI).³⁻⁷ Before A β accumulation, dysfunction of associative memory brain networks involving the hippocampus also occurs, suggesting changes here may be sensitive markers of early AD.⁸

Individuals with the breast cancer 1 or 2 (*BRCA1/2*) tumor suppressor gene mutation are recommended cancer risk-reducing bilateral salpingo-oophorectomy (BSO; removal of ovaries and fallopian tubes) \approx 10 years before the typical age of spontaneous menopause (SM), which is age 51.⁹ BSO before age 48 is associated with accelerated cognitive decline and greater risk of late-life AD.¹⁰⁻¹² Some of the earliest cognitive declines related to BSO involve hippocampal-dependent associative memory; 17 β -estradiol therapy (ET) among participants with BSO may ameliorate these declines.¹³⁻¹⁷ While research has

shown that within 5 years of BSO there is lower hippocampal activation during associative encoding,¹⁸ it is unknown whether BSO affects hippocampal function during encoding, retrieval, or both processes and whether these changes relate to associative memory task performance.

Anatomy and function vary along the hippocampal anteroposterior axis.¹⁹ While some studies emphasize the importance of the posterior hippocampus for associative *retrieval*, others highlight the importance of the anterior hippocampus for novelty processing and associative *encoding*.²⁰ In mixed-sex studies, volume decreases in the anterior hippocampus and, to a lesser extent, posterior hippocampus, are observed in AD.²¹ Posterior hippocampal volume decline is seen predominantly in healthy aging, suggesting potentially diverging effects of AD and aging on specific hippocampal regions. The effects of ET may also vary. After SM, ET ameliorates both anterior²² and posterior²³ hippocampal volume loss. Thus, to understand the effects of early 17 β -estradiol loss on AD risk, it is critical to examine both anterior and posterior hippocampal function.

Given widespread effects of 17 β -estradiol on synaptic function and organization,²⁴⁻²⁶ 17 β -estradiol may play an important role in associative encoding and/or retrieval processes. SM is associated with lower verbal episodic memory, associative memory, and hippocampal activation.^{26,27} Further, ET after SM is related to increased

hippocampal volume and function.^{23,28,29} We found that participants with BSO had lower hippocampal activation during associative encoding and lower volume in hippocampal dentate gyrus and cornu ammonis 2/3 (DG-CA2/3).^{18,30} Thus, ovarian hormone loss can negatively affect hippocampal-dependent memory, but changes may occur earlier and more dramatically in those with BSO.

It is still unclear whether BSO specifically affects function of the anterior and/or posterior hippocampus. Thus, objectives of the current study were to characterize functional responses along the hippocampal anteroposterior axis, and to corroborate previous outcomes from our research group using a larger cohort but additionally tease apart whether the functional effects of BSO on encoding extend to retrieval. Given the influence of 17 β -estradiol on structure and function of the hippocampus, as well as the abundance of 17 β -estradiol receptors in this brain region, we investigated whether changes in hippocampal function related to associative memory task performance.³¹

We carried out a cross-sectional functional magnetic resonance imaging (fMRI) study comparing midlife participants with BSO (with and without ET) to age-matched controls (AMCs) with intact ovaries during a face-name associative memory task. We asked if early midlife BSO lowers and ET ameliorates:

1. Associative memory task performance (*performance*),
2. Hippocampal function during associative encoding and retrieval (*function*), and
3. Hippocampal activation correlated with successful associative memory (*performance-function relationships*).

2 | MATERIALS AND METHODS

2.1 | A note about ET terminology

Literature focused on hormone therapy is frequently inconsistent with terminology regarding 17 β -estradiol; the terms 17 β -estradiol (E2), 17 β -estradiol replacement therapy (ERT), and ET have all been used to describe this therapy with or without other ovarian hormones such as progestogens after menopause. In the case of BSO prior to SM, it has been suggested that “ERT” be used to acknowledge the attempt to *replace* 17 β -estradiol to premenopausal levels after surgery.³² However, levels of bioavailable 17 β -estradiol from exogenous therapy may not be equivalent to those of endogenous 17 β -estradiol given influences from various factors, such as dose, route of administration, treatment regimen, and genetics.³³ Thus, even if serum 17 β -estradiol levels are within the typical premenopausal range, ET postmenopause does not actually *replace* or restore the pre-BSO hormonal milieu. With this in mind, we believe it is important not to use the term “replacement,” particularly after BSO performed prior to SM. However, it is important to differentiate ET given to women in SM—which tends to be administered at lower doses—from ET given to younger women with BSO prior to SM.³⁴ Thus, when needed, we use subscripting throughout this manuscript (i.e., ET_{BSO}, ET_{SM}) to ensure clarity regarding who was taking the ET.

RESEARCH IN CONTEXT

1. **Systematic review:** We reviewed the literature extensively using traditional sources (e.g., PubMed). Most work regarding neural effects of ovarian hormones focuses on non-human animals. A small body of human research documents hippocampal changes across the spontaneous/natural menopause transition, but neural effects of oophorectomy are underexplored, which may have implications for dementia risk.
2. **Interpretation:** We provide evidence that task-based posterior hippocampal activation is lower in midlife participants with oophorectomy. Results shed light on how early midlife events affect women's brain health and, potentially, dementia risk.
3. **Future directions:** Future research should replicate our results in larger cohorts, with a focus on longitudinal analyses of neurocognitive changes in those with oophorectomy to better understand women's trajectory toward dementia or healthy brain aging. To best address hippocampal heterogeneity, high-resolution functional magnetic resonance imaging should be used.

2.2 | Recruitment

This study was carried out in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committees of the University of Toronto, McGill University, and Linköping University. All participants provided informed consent.

Participants with BSO were recruited from familial breast and ovarian cancer clinics in Toronto and Montreal, Canada, and Linköping, Sweden. The AMCs were recruited from the general community in the same cities. Exclusion criteria for all participant groups included: being younger than 35 or older than 55 years, contraindications for MRI safety, perimenopause, BSO after SM, pregnancy, breastfeeding, chemo/radiation/adjunct therapies within 6 months of testing, unmanaged health/psychiatric conditions, and endocrine disorders. There were two additional exclusion criteria for women in the AMC group: irregular menstruation and taking hormonal contraceptives within 6 months prior to entering the study. We ensured that each participant in the BSO groups had a corresponding participant in the AMC group whose age fell within a similar 5-year range. Participant demographic and behavioral characteristics are summarized in Table 1.

2.3 | Procedure

Data included in this study are a subset of a larger longitudinal dataset comparing neuropsychological performance, brain structure, and brain function of women with BSO to AMC.^{17,18,30} Therefore, instead of data from only the first timepoint of testing, data from the second timepoint

TABLE 1 Demographic and behavioral characteristics.

Characteristic	AMC		BSO+ET		BSO	
	n = 40		n = 35		n = 28	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	44.0	3.2	44.5	5.0	45.6	4.9
Education (years)	17.2	2.8	16.4	3.0	16.1	3.5
BMI (kg/m ²)	24.6	4.5	26.1	5.4	26.0	3.4
CES-D score	9.1	6.9	12.3	10.4	9.5	9.3
PSS score	14.8	5.7	15.3	7.1	13.4	7.0
BDI score	6.3	6.8	8.7	8.5	10.4	8.0
Age at BSO (years)	NA	NA	40.4	3.8	41.0	4.3
Time since BSO (years)	NA	NA	4.1	3.4	4.7	3.3
Urinary E1G (ng/ml)	38.1	23.0	39.1	41.2	18.1 ^a	8.8
Urinary PdG (μ/ml)	4.5	5.3	8.0	21.2	0.9 ^a	0.8
Face-name task accuracy (%)	76.1	0.1	79.5	0.1	78.1	0.1
	n	%	n	%	n	%
History of cancer treatment	0	0	3	8.6	14 ^b	50.0
BRCA1 mutation	NA	NA	20	57.1	17	60.7
BRCA2 mutation	NA	NA	12	34.3	9	32.1

Abbreviations: AMC, age-matched control; BDI, Beck Depression Inventory (administered only to the Swedish participants); BMI, body mass index; BRCA, breast cancer gene; BSO, bilateral salpingo-oophorectomy; BSO+ET, bilateral salpingo-oophorectomy with current use of 17β-estradiol therapy (with or without progestogens); CES-D, Center for Epidemiological Studies–Depression Scale (administered only to the Toronto and Montreal participants); E1G, estrone-3-glucuronide; History of cancer treatment, personal history of breast cancer treatment including chemotherapy, radiation therapy, and/or adjuvant tamoxifen use; NA, not applicable; PdG, pregnanediol glucuronide; PSS, perceived stress scale; SD, standard deviation.

^aSignificant post hoc Dunn test; E1G: BSO < AMC, PdG: BSO < AMC

^bSignificant Fisher exact test; History of cancer treatment: BSO > AMC.

of the study were included if there were technical issues during scanning at the first timepoint or if participants had their BSO between the first and second timepoints (AMC, $n = 4$; BSO+ET, $n = 12$; BSO, $n = 5$). The scanning sessions at both timepoints used identical stimuli and were conducted with an ≈ 1 -year interval between sessions. We included scan timepoint as a covariate in all analyses because significantly more women in the BSO+ET group had their included scan session at the second timepoint compared to AMCs and there was a trend toward a significant effect of timepoint on face-name associative memory task performance ($t[101] = -1.74$, $p = 0.09$, $d = -0.43$).

Participants also provided urine samples for ovarian hormone level assessment. Levels of estrone-3-glucuronide (E1G) and pregnanediol glucuronide (PdG) were analyzed in urine using enzyme-linked immunoassays at the Women's Health and Exercise Laboratory at Pennsylvania State University.

2.4 | Face-name associative memory task

2.4.1 | Task description

This task was modeled after the face-name associative memory task introduced by Sperling et al. in 2001, which revealed diminished hippocampal activation during face-name pair encoding in individuals

with AD.³⁵ Our task consisted of two functional runs, which contained five alternating encoding and retrieval “blocks” (Figure 1A). Each of the two runs consisted of five encoding blocks alternating with five retrieval blocks. The encoding blocks consisted of participants encoding 23 face-name pairs (including 15 novel face-name pairs and eight repeat face-name pairs distributed throughout). Each block comprised 3 to 6 face-name encoding and retrieval trials. During encoding blocks, each novel face-name pair was presented once for 4 seconds. The repeat face-name pairs were presented for 4 seconds each, with the face-name pairs being categorized as repeat if they were presented more than once (either during encoding, retrieval, or both phases).

During the encoding phase, faces were presented on a black background with a name printed beside each face followed by a white fixation cross on a black background. As each face-name pair appeared on the screen, participants indicated whether they thought the presented name was a “good” or “bad” name for the face by pressing buttons on a response pad. By incorporating a judgment about how appropriate the assigned name was for each face, this encouraged participants to engage in a deeper level of processing of each face-name pair than if they were simply passively studied.

During the retrieval phase, participants were presented with a face on a black background with three letters printed beside each face and instructed to retrieve the previously paired name. They indicated their answer by pressing one of three buttons on a response pad to indicate

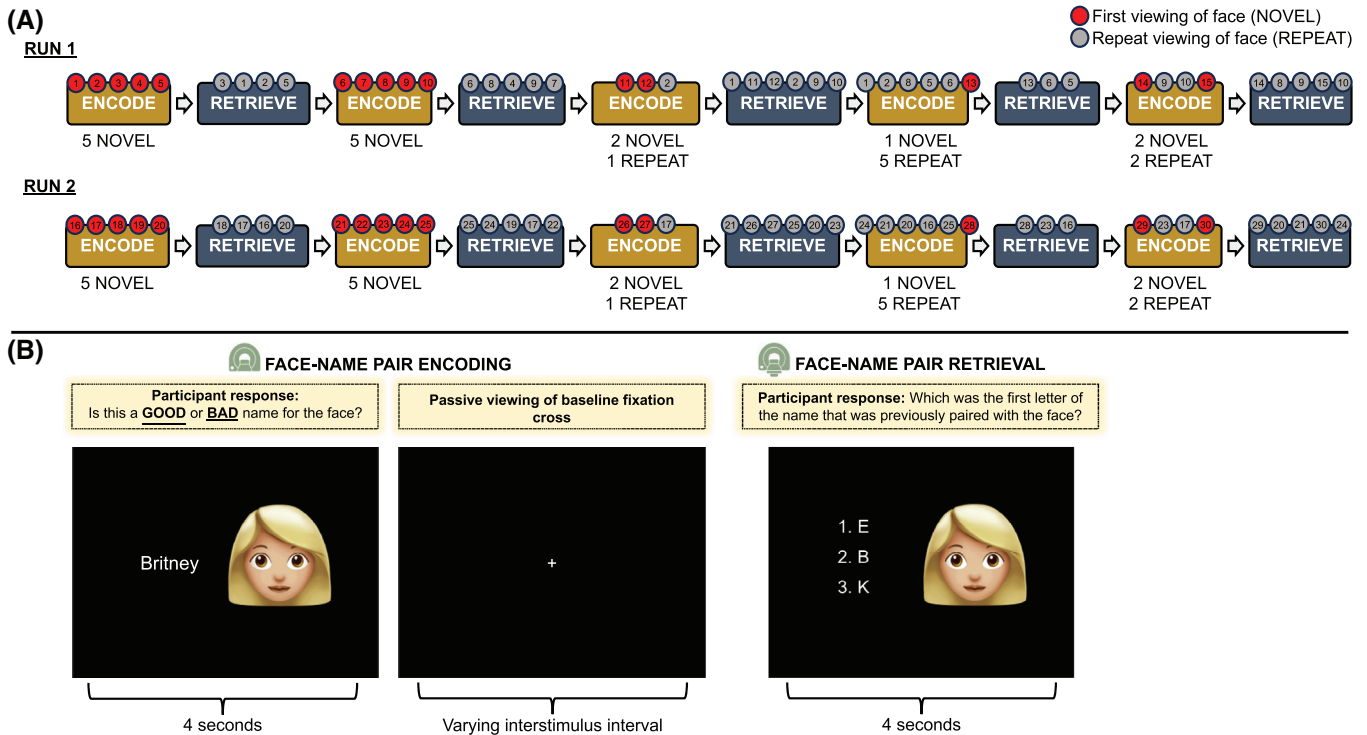


FIGURE 1 Face-name task design. A, Task includes 23 retrieval, 15 novel encoding, and 8 repeat encoding trials per run. Each circled number represents a different face-name pair trial. B, Outline of task timing and conditions.

which letter they thought was the first letter of the name paired with the face during the encoding phase. Each trial was followed by a white fixation cross on a black background. All retrieval blocks consisted of retrieving/remembering the name for 23 faces. For each retrieval trial, participants had 4 seconds to select their answer (Figure 1B). In Toronto and Montreal, face-name task stimuli were presented using E-Prime.³⁶ In Linköping, face-name task stimuli were presented using the SuperLab Stimulus Presentation System (Cedrus).

2.4.2 | Task design

The task used for this study had a mixed block-event related design. Stimulus order (repeat vs. novel face-name pairs) and interstimulus intervals were optimized using Tor Wager's Genetic Algorithm.³⁷ The Genetic Algorithm created ≈ 1000 stimulus orderings and interstimulus intervals to arrive at the final two optimized experimental runs. Each set of stimulus orderings/interstimulus intervals was manually inspected to ensure event types were evenly distributed, and there were the same number of events in each block.

An equal number of feminine- and masculine-presenting faces were selected from the FACES database.³⁸ For the Swedish and English versions of the task, names were selected from the most common names from Swedish and Canadian government lists of baby names during the past 20 years, respectively. Each face was then randomly assigned to a conventionally gender-appropriate name. Each face-name pair was pseudorandomly assigned to either be a repeat or novel stimulus such

that masculine/feminine and younger/older faces were equally represented in the repeat and novel event types. The design files for the two experimental runs were checked using SPM12 (Statistical Parametric Mapping; Wellcome Trust Centre for Neuroimaging) to ensure maximal orthogonality between experiment regressors. The task was piloted in four healthy adults to ensure single-subject activation maps had sufficient statistical power at the event level. Participants were shown the same face-name pair stimuli for all sessions and timepoints.

2.5 | Image acquisition

Across the three sites, scans were collected using a 3T MAGNETOM Prisma scanner (Toronto Neuroimaging Institute at the University of Toronto), a Siemens 3T MAGNETOM Prisma-Fit scanner (Douglas Hospital Research Institute Brain Imaging Center), and a Philips 3T scanner (Linköping University).

In Toronto and Montreal, T1-weighted structural scans were acquired using a 3D gradient echo magnetization-prepared rapid gradient echo sequence (repetition time [TR] = 2000 ms, echo time [TE] = 2.67 ms, flip angle = 9°, 160 sagittal slices, 1mm³ isometric voxels; field of view [FOV] = 256mm²). In Linköping, T1-weighted structural scans were acquired using a 3D gradient echo turbo field echo sequence (TR = 7.0 ms, TE = 3.2 ms, flip angle = 9°, 170 sagittal slices, 1mm³ isometric voxels; FOV = 256 × 240 mm²).

In Toronto and Montreal, functional images were acquired with a T2*-weighted blood-oxygen-level-dependent (BOLD) gradient

echo-planar imaging sequence with 28 coronal, interleaved slices perpendicular to the anterior/posterior commissure line, with voxel dimensions = $3.4 \times 3.4 \times 4\text{mm}^3$ with 0.5 mm interslice gap, FOV = 220mm^2 , flip angle = 77° , TE = 30 ms, TR = 1500 ms, and image dimensions = $64 \times 64 \times 28$ mm. In Linköping, functional images were acquired with a T2*-weighted BOLD gradient echo-planar imaging sequence with 39 coronal, transverse slices with voxel dimensions = 3.5mm^3 with 0.5 mm interslice gap, FOV = 224mm^2 , flip angle = 70° , TE = 27 ms, TR = 2000 ms, and image dimensions = $64 \times 64 \times 39$ mm.

In Toronto and Montreal, each run had a total duration of 7.5 minutes for 300 TRs and participants were administered the task and instructions in English. In Linköping, each run had a total duration of 7.5 minutes for 225 TRs and participants were administered the task and instructions in Swedish. All participants were fluent in the task language.

2.6 | Image preprocessing

After image acquisition and prior to statistical analysis, fMRI data from each participant were converted to NIfTI format and preprocessed using a standard pipeline implemented through Optimization of Preprocessing Pipelines for NeuroImaging (OPPN), a software package that uses functions developed by researchers at the Rotman Research Institute;³⁹ Analysis of Functional NeuroImages (AFNI⁴⁰); and FMRIB Software Library (FSL⁴¹), to control for sources of noise and artifact. For the current study, the same preprocessing steps were applied to all groups and conditions.

Functional images were aligned to the anterior/posterior commissure plane. They were corrected for head motion using AFNI's 3dvolreg with MOTCOR, which aligned each volume to a reference volume, estimated as the volume being the least affected by head motion. Removal of estimated physiological noise components was accomplished using PHYPLUS, an Octave script that uses the data-driven PHYCAA+ algorithm to identify and remove noise with a strong vascular component.

Each participant had a non-neuronal tissue mask created to discard confounding signal coming from non-brain tissue (ventricles, vasculature, and sinuses). Temporal detrending was then applied using DETREND, which used a quadratic polynomial function (maximum polynomial order 2) fitted to regress out low-frequency noise. Further motion correction for residual artifacts was also completed. Task design (condition onset timing) was inputted in the model and mapped onto the hemodynamic response function to ensure the noise regressed out in previous stages was not strongly related to task activation, preventing the inadvertent removal of task-related signal.

Steps not belonging to the OPPNI pipeline were also conducted: spatial normalization both in the participant's native space and in standard space, as each participant's functional images were co-registered to their T1 structural image and normalized and registered to 4mm^3 standard space using FSL's anatomical 2mm^3 MNI152 brain template. Using AFNI's 3dmerge with SMOOTH, images were then spatially smoothed by 6 mm, convolving BOLD signal with a 3D isotropic full

width at half-maximum Gaussian kernel to reduce signal noise and ameliorate differences in intersubject localization. Noise from white matter, cerebrospinal fluid, and vessels that could potentially interfere with the BOLD signal of interest from gray matter was also removed.

2.7 | Region-of-interest analysis: Do BSO and ET affect hippocampal activation?

2.7.1 | First-level analysis

Using SPM12, mean activity for each voxel was modeled independently for both novel > repeat encoding and retrieval > encoding task contrasts. BOLD response was analyzed using a mixed-effects general linear model fit for every participant. The fMRI generalized linear model first-level analysis consisted of four conditions used as explanatory variables (i.e., regressors of interest): (1) encoding of novel face-name pairs (novel encoding condition), (2) encoding of repeated face-name pairs (repeat encoding condition), (3) first-time retrieval of face-name pairs (first retrieval condition), and 4) repeated retrieval of face-name pairs (repeat retrieval condition). Each regressor was convolved with a hemodynamic response function and temporally filtered with a high-pass cut-off of 260 seconds to remove low-frequency signal drifts.¹ The primary first-level contrasts of interest were novel > repeat encoding (novel encoding > repeat encoding) and retrieval > encoding ([first retrieval+repeat retrieval] > [novel encoding+repeat encoding]). These contrasts were selected to: (1) leverage the novelty response in the hippocampus¹ and (2) examine potential differences in hippocampal activation between encoding and retrieval processes.

To assess the reliability of fMRI activation estimates between the two functional runs, whole-brain Pearson correlation coefficients were calculated between beta images from the two independent runs for each participant. This analysis was conducted separately for the novel and repeat encoding conditions as well as the retrieval and encoding conditions. Correlations were calculated across all voxels in the brain after excluding voxels with "Not a Number" values.

2.7.2 | Regions of interest for second-level analysis

Given heterogeneity of hippocampal function along its anteroposterior axis,¹⁹ we analyzed anterior (head) and posterior (body and tail) hippocampal regions of interest (ROIs) separately. Steps involved in creation of the hippocampal ROIs are specified in detail elsewhere (Figure 2).⁴² Briefly, left and right hippocampi were automatically segmented for a separate group of 20 young adult men and women.⁴³ Whole-brain T1-weighted scans were run through FreeSurfer's (v. 5.3) "recon-all" program, and left and right hippocampi were extracted from the subcortical segmentation labels provided by FreeSurfer.⁴⁴ Each ROI was visually inspected and then warped to Montreal Neurological Institute (MNI) space. An average mask was then created and thresholded to include voxels with the ROI present in at least half of the participants. Left and right ROIs were then subdivided into anterior (hippocampal head) and posterior (hippocampal body and tail) based on

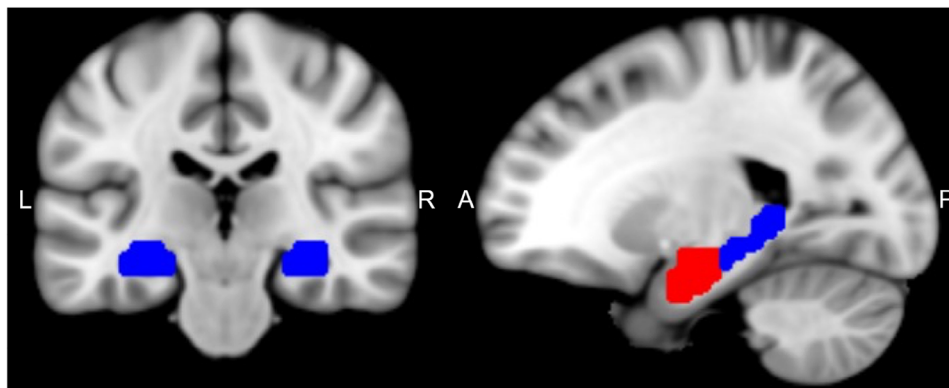


FIGURE 2 Locations of anatomical hippocampal ROIs. ROIs are shown in Montreal Neurological Institute space presented from coronal and sagittal views. A, anterior; Blue, posterior; L, left; P, posterior; Red, anterior; ROIs, regions of interest.

the location of the uncus apex. ROIs were binarized and downsampled to the same resolution as the functional data.

Voxels were added and removed as needed to fill in any small gaps and refine the mask shape. AFNI's "3dmaskave" was used to calculate average contrast estimates for each ROI and condition contrast. Each contrast estimate reflected the strength/magnitude of the fMRI signal averaged across every voxel within each specified ROI.

2.8 | Statistical analyses

2.8.1 | Univariate analyses

Univariate statistical analyses were conducted using R 4.2.0 (R Core Team, 2019). Statistical assumptions were tested, including sphericity, normality, and homogeneity of variance. When violated, we either Winsorized data to the value of the 90th or 10th percentile of the distribution or used non-parametric tests. Analysis of variance (ANOVA), Kruskal–Wallis, or Fisher exact tests were conducted to compare groups on demographic characteristics. False discovery rate (FDR) was used to correct for multiple comparisons for all follow-up independent samples *t* tests and Fisher exact tests. Effect size estimates (η^2 or Cohen *d*) were calculated for all parametric performance and ROI analyses.

Data from the second timepoint of the study were included if there were technical issues during scanning at the first timepoint or if participants had their BSO between the first and second timepoints (AMC, $n = 4$; BSO+ET, $n = 12$; BSO, $n = 5$). Because significantly more women in the BSO+ET group had their included scan session at the second timepoint compared to the AMC group, we included scan timepoint (first, second) as a covariate in all performance and ROI analyses. Scanner site (Toronto, Montreal, Sweden) was also included as a covariate in these analyses.⁴⁵ G*Power version 3.1 was used to calculate post hoc power for detecting a significant ROI x group interaction. Exploratory analyses were conducted to rule out BRCA mutation status and cancer treatment history as sources of influence on group differences in the outcome measures (supporting information).

ANCOVA: Do BSO and ET affect associative memory task performance?

Face-name associative memory task accuracy (percent correct = [number of correctly retrieved trials/total number of retrieval trials]*100) was entered into an analysis of covariance (ANCOVA) model to test for the main effect of group (BSO, BSO+ET, AMC) while controlling for scan timepoint and scanner site. Group, scan timepoint, and scanner site were treated as between-participant factors.

ANCOVA: Do BSO and ET affect hippocampal activation?

Average contrast estimates for each hippocampal ROI (anterior, posterior) were entered into two repeated-measures ANCOVA models (one per contrast: novel > repeat encoding and retrieval > encoding) to test for main effects of group, group x ROI, and group x ROI x hemisphere interactions while controlling for scan timepoint and scanner site; significant interactions were followed up with independent samples *t* tests. ROI and hemisphere (left, right) were treated as within-participant factors, and group, scan timepoint, and scanner site as between-participant factors.

As an exploratory question, we also asked whether novel and repeat encoding activation in the frontal cortex differed by group (supporting information). The average contrast estimates for a frontal cortical ROI for the novel > repeat encoding contrast were entered into an ANCOVA model to test for the main effect of group while controlling for scan timepoint and scanner site.

2.8.2 | Correlation analyses: Do BSO and ET affect how brain activation relates to associative memory task success?

Few participants had associative memory task accuracy < 70% (BSO $n = 8$, BSO+ET $n = 8$, AMC $n = 16$). As a result, for most participants there were too few incorrect trials to conduct a meaningful comparison of brain function between correct and incorrect face-name pair encoding trials. Given this limited number of memory errors, we focused on analyzing overall associative memory task accuracy and

its correlation with hippocampal activation for all trials. To investigate the relationship between hippocampal BOLD responses and task performance, we used Pearson correlations between bilateral posterior hippocampal activation and face-name task accuracy. To determine whether group differences in novel and repeat encoding whole-brain activation correlated with face-name task accuracy, we also conducted exploratory multivariate behavioral partial least squares (PLS)⁴⁶ analysis (supporting information).

3 | RESULTS

3.1 | Demographic characteristics

As expected, BSO, BSO+ET, and AMC groups did not differ significantly in age. BSO and BSO+ET also did not differ significantly in the age of BSO or proportion of participants with *BRCA1* or *BRCA2* mutations. BSO and BSO+ET did differ significantly with respect to cancer treatment history (chemotherapy, radiation therapy, and/or adjuvant therapy; $P < 0.0001$), with more women in the BSO group having a history of cancer treatment compared to BSO+ET ($p = 0.001$) and AMC ($P < 0.0001$). A total of 17 participants reported a cancer treatment history (BSO $n = 14$, BSO+ET $n = 3$). The average duration between the final cancer treatment session and study date was ≈ 6 years (standard deviation = 4.57; between 7 months and 5 years for nine participants and between 6 and 15 years for eight participants).

There was a significant effect of group on scan timepoint ($p = 0.03$), with more participants in BSO+ET having their included scan session at the second testing timepoint compared to AMC ($p = 0.04$). There were not significant differences in scan timepoint between BSO and AMC ($p = 0.47$) and between BSO and BSO+ET ($p = 0.25$).

Data regarding urinary ovarian hormone levels were not available for a subset of participants (E1G: BSO $n = 8$, BSO+ET $n = 15$, AMC $n = 8$; PdG: BSO $n = 8$, BSO+ET $n = 16$, AMC $n = 8$). For participants for whom these data were available, there was a significant effect of group on urinary E1G levels ($\chi^2 = 11.16$, $p = 0.004$): BSO had significantly lower E1G levels than AMC ($Z = 3.33$, $p = 0.003$). E1G levels did not significantly differ between BSO and BSO+ET ($Z = -2.05$, $p = 0.06$) or between BSO+ET and AMC ($Z = 1.06$, $p = 0.29$). There was also a significant effect of group on urinary PdG levels ($\chi^2 = 10.27$, $p = 0.01$): BSO had significantly lower PdG levels than AMC ($Z = 3.03$, $p = 0.01$). PdG levels did not significantly differ between BSO and BSO+ET ($Z = -0.78$, $p = 0.44$) or between BSO+ET and AMC ($Z = 2.12$, $p = 0.051$). There were no significant group differences for any other demographic measure (Table 1).

3.2 | ANCOVA: Do BSO and ET affect associative memory task performance?

There was no significant main effect of group on associative memory task accuracy (percent correct for the retrieval of face-name pairs) ($F[2,97] = 0.46$, $p = 0.63$, partial $\eta^2 = 0.01$). Thus, BSO and ET did

not seem to significantly influence face-name associative memory task performance (Table 1).

3.3 | ANCOVA: Do BSO and ET affect hippocampal activation?

3.3.1 | Reliability of activation between functional runs

Across participants, the mean correlation (r) for the novel encoding condition was 0.56 (standard deviation = 0.28), while the mean correlation (r) for the repeat encoding condition was 0.53 (standard deviation = 0.32). The mean correlation (r) for the encoding condition was 0.53 (standard deviation = 0.30), while the mean correlation (r) for the retrieval condition was 0.55 (standard deviation = 0.28). These results indicate moderate reliability of activation patterns between runs for all conditions. Moderate reliability values are often reported in neuroimaging studies, which is important given that measures with low reliability may not be helpful for predicting clinical health outcomes.⁴⁷ One promising method to improve the reliability of fMRI is to collect more data for each participant. Critically, another investigation from our group used a similar functional associative memory paradigm (with different face-name stimuli) and yielded comparable hippocampal activation results from a subset of participants included in the current study.¹⁸ Consistency of our findings with this prior work further highlights the robustness of our approach.

3.3.2 | Effects of BSO and ET on hippocampal activation during novel > repeat encoding contrast

We next asked if novel and repeat encoding activation in anterior and posterior hippocampal ROIs differed by group and hemisphere. Average contrast estimates for each hippocampal ROI (anterior, posterior) for the novel > repeat encoding contrast were entered into a single repeated-measures ANCOVA model to test for main effects of group, group \times ROI, and group \times ROI \times hemisphere interactions while controlling for scan timepoint and scanner site; significant interactions were followed up with independent samples t tests.

There were significant main effects for group ($F[2,97] = 5.15$, $p = 0.01$, partial $\eta^2 = 0.10$) and for the ROI \times group interaction ($F[2,97] = 3.12$, $p = 0.049$, partial $\eta^2 = 0.06$). The main effect of ROI was not significant ($F[1,97] = 2.51$, $p = 0.12$, partial $\eta^2 = 0.0004$). The group \times ROI \times hemisphere interaction effect was also not significant ($F[2, 97] = 0.03$, $p = 0.97$, partial $\eta^2 = 0.00001$); therefore, reported analyses were run on left and right hemispheres averaged.

Using G*Power version 3.1, we calculated the post hoc power we had to detect a significant ROI \times group interaction for novel and repeat encoding activation in the anterior and posterior hippocampus. With a medium effect size of Cohen $f = 0.25$, three groups, two measurements (anterior and posterior hippocampal contrast estimates), a significance level of 0.05, a correlation (Pearson r) among repeated measures of 0.58, and 103 participants, we determined that we had 99% power

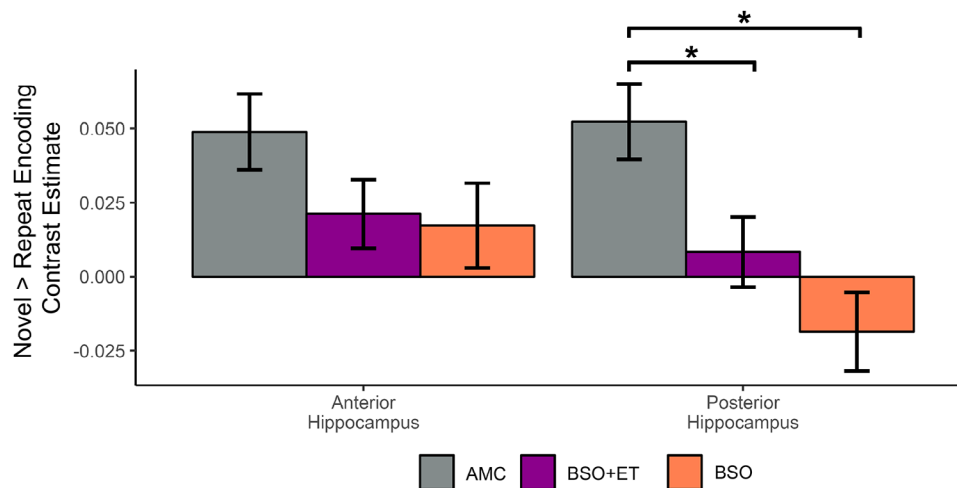


FIGURE 3 Effect of group on region-of-interest mean novel > repeat encoding contrast estimates for anterior and posterior hippocampus. Values are Winsorized; error bars represent standard error of the mean; * = $P < 0.05$ (FDR-corrected). AMC, age-matched control; BSO, bilateral salpingo-oophorectomy; BSO+ET, bilateral salpingo-oophorectomy with current use of 17β -estradiol therapy (with or without progestogens).

TABLE 2 Novel > repeat encoding independent samples t test group contrast results.

Contrast	$t(97)$	Uncorrected P value	Corrected P value _{FDR}	Cohen d
Anterior hippocampus				
AMC > BSO	1.83	0.07	0.14	0.46
AMC > BSO+ET	1.62	0.11	0.16	0.39
BSO > BSO+ET	-0.25	0.80	0.80	-0.07
Posterior hippocampus				
AMC > BSO	3.93	0.0002	0.001	0.98
AMC > BSO+ET	2.76	0.01	0.02	0.66
BSO > BSO+ET	-1.22	0.23	0.27	-0.32

Abbreviation: AMC, age-matched control; BSO, bilateral salpingo-oophorectomy; BSO+ET, bilateral salpingo-oophorectomy with current use of 17β -estradiol therapy (with or without progestogens); FDR, false discovery rate

to detect a significant group \times ROI interaction. Although the cohort size in our study may be modest, it represents the largest investigation focused on brain function in participants post-ovarian removal. Moreover, this is only the second fMRI study to examine this population, with the first being another investigation from our group using a similar functional paradigm and yielding comparable results.¹⁸ Even in the absence of large cohorts, smaller fMRI studies have revealed valuable insights into brain function, such as identifying sex differences in brain activity during long-term memory retrieval, with some studies including as few as 10 participants per group.⁴⁸ These studies lay the groundwork for larger investigations. Studies of smaller cohorts are important for research involving rare or understudied populations, such as ours, especially when individuals face increased risk for neurological disorders. In such cases, smaller cohort sizes are more common but still provide sufficient power to detect significant and meaningful group differences.

To interrogate the significant ROI \times group interaction, we performed follow-up independent samples t tests. Follow-up t tests

showed that for the novel > repeat contrast there were not significant group differences in anterior hippocampus activation (Figure 3; Table 2). Importantly, compared to AMC, contrast estimates from the posterior hippocampus were significantly lower for BSO ($t[97] = 3.93$, $P_{FDR} = 0.001$, $d = 0.98$) and BSO+ET ($t[97] = 2.76$, $P_{FDR} = 0.02$, $d = 0.66$). Posterior hippocampus activation did not differ significantly between BSO and BSO+ET. Thus, the significant ROI \times group interaction was driven by *greater* reductions in posterior compared to anterior hippocampal activity for both BSO groups.

3.3.3 | Effects of BSO and ET on hippocampal activation during retrieval > encoding contrast

We also asked if retrieval and encoding activation in anterior and posterior hippocampal ROIs differed by group and hemisphere. Average contrast estimates for each hippocampal ROI (anterior, posterior) for the retrieval > encoding contrast were entered into a single

repeated-measures ANCOVA model to test for main effects of group, group \times ROI, and group \times ROI \times hemisphere interactions while controlling for scan timepoint and scanner site.

The main effect for ROI was significant ($F[1,97] = 15.30, p = 0.0002$, partial $\eta^2 = 0.03$). The main effects for group ($F[2,97] = 0.67, p = 0.51$, partial $\eta^2 = 0.01$), as well as the group \times ROI ($F[2,97] = 1.19, p = 0.31$, partial $\eta^2 = 0.01$) and group \times ROI \times hemisphere ($F[2,97] = 0.26, p = 0.77$, partial $\eta^2 = 0.0004$) interactions were not significant. Given that there were not significant group \times ROI or group \times ROI \times hemisphere interactions, we did not run independent samples *t* tests for the retrieval $>$ encoding contrast and did not pursue this contrast further in the analyses below.

3.4 | Do BSO and ET affect how brain activation contributes to associative memory task success?

3.4.1 | Correlation: relationship between novel $>$ repeat encoding hippocampal activation and associative memory task success

We used Pearson correlation to assess the relationship between face-name task accuracy and the novel $>$ repeat encoding posterior hippocampal ROI activation that showed a significant group difference in the univariate comparison above; there were no significant relationships between posterior hippocampal activation during associative encoding and task accuracy.

4 | DISCUSSION

4.1 | Summary of findings

In the first investigation of brain activity during associative memory task-based encoding and retrieval in midlife women with BSO, we showed BSO was linked to lower posterior hippocampal activation during encoding. We also found that hippocampal activation during encoding was not significantly correlated with associative memory task performance.

4.2 | Effect of BSO on posterior hippocampal activation during associative encoding

Women with BSO had lower posterior hippocampus activation during encoding (but not retrieval) compared to AMC. This novel work supports findings from our previous study, which used a different face-name task and smaller cohort.¹⁸ Mixed-sex research suggests encoding failure originates in hippocampal dysfunction and is associated with AD risk, while retrieval failure originates in frontal lobe dysfunction, and may not be as strongly related to AD risk.^{49,50} Thus, women with BSO may demonstrate a pattern of brain activity similar to those at heightened risk for AD. However, other mixed-sex work demonstrated that healthy older adults had lower task-related hippocampal function compared to younger adults.¹ These studies suggest that ovarian removal

may lead to accelerated aging, consistent with research showing BSO is linked to accelerated aging of multiple bodily systems and patterns of hippocampal change similar to those of older women.^{18,51} Our result is notable as it pertains to a younger and highly educated cohort.

Significant differences between BSO and BSO+ET were not found. This lack of difference could be related to variation in formulation, dose, route of administration, duration, and whether ET was administered with a progestogen. When testing 17β -estradiol levels for someone with BSO taking transdermal ET, who may be at increased risk for breast cancer, clinicians aim for serum levels aligned with the early follicular menstrual phase range, when 17β -estradiol levels are lowest.^{52,53} Thus, it is possible that ET dose was not high enough in the current study to exert significant functional hippocampal changes in women with BSO.

Lower hippocampal activation among women with BSO may be due to hippocampal atrophy. For example, older women with BSO (≈ 65 years) had thinner parahippocampal-entorhinal cortices and lower entorhinal white matter fractional anisotropy.⁵⁴ Further, high-resolution MRI revealed that ≈ 5 years post-BSO hippocampal DG-CA2/3 volume was lower compared to AMC.³⁰

At first glance, our results—lower posterior hippocampal activation in a group of women at increased risk for AD—may seem contrary to previous research showing that the anterior hippocampus bears the brunt of volume changes in persons with amnesic MCI and AD.⁵⁵ However, previous studies usually control for sex rather than disaggregate data by sex; thus, we know little of what the case might be for either men or women. Young adult women may have greater posterior hippocampal volume than men, setting the stage for sex-specific hippocampal changes in AD.⁵⁶ Indeed, in a study including mostly women, it was posterior hippocampal atrophy that characterized MCI.⁵⁷ Further, in a triple transgenic mouse model of AD, dorsal (congruent to human posterior) DG neurogenesis decreased in both males and females, but in females this decrease happened earlier and was more pronounced.⁵⁸ Thus, research focused on females supports results from the current study.

Notably, different types of menopause may lead to distinctive cognitive trajectories.⁵⁹ For example, early oophorectomy was associated with increased risk of non-amnesic MCI,⁶⁰ a subtype characterized by cognitive decline in non-memory domains that have been previously linked to 17β -estradiol loss and subjective cognitive decline.⁶¹ Tasks outside verbal episodic memory may be more sensitive to post-oophorectomy cognitive decline, especially considering that women show a verbal memory advantage compared to men in MCI despite similar levels of hippocampal atrophy.⁶² Given that amnesic MCI is more typically defined as a precursor to AD, it is critical for future research to investigate whether women with early midlife BSO experience a unique dementia trajectory compared to women in SM.

4.3 | Relationships between brain activation and associative memory task performance

Hippocampal activation was not correlated significantly with associative memory task performance. This result is consistent with recent

work demonstrating that the sizes of many previously reported brain-behavior correlations are likely smaller and more difficult to detect than previously acknowledged.⁶³ Our work also aligns with research showing that for both men and women prefrontal cortical gray matter volume predicts associative memory task performance better than hippocampal gray matter volume,⁶⁴ underscoring that future research should examine brain-behavior relationships in regions beyond the hippocampus.

Women with BSO (with and without ET) had lower posterior hippocampal activation, and it is important to consider the whole-brain effects of this functional difference. The posterior hippocampus is functionally connected to a wide range of associative memory-related brain regions, including the polysynaptic intrahippocampal pathway connecting the hippocampus with frontal and parietal cortices via the fornix.^{65,66} Avenues for future research include considering how ET_{BSO} and ET_{SM} may support functional connectivity by diminishing white matter hyperintensity load and maintaining/strengthening polysynaptic connections to support associative memory.

Exploratory whole-brain PLS analysis showed that compared to BSO and AMC, women with BSO taking ET had a stronger relationship between associative memory task performance and activation in a variety of regions, including superior and inferior frontal gyri, suggesting ET_{BSO} may aid in recruitment of these regions to support associative memory (supporting information). There were no significant group differences in frontal cortical activation, suggesting ET_{BSO} was not associated with greater task-based frontal recruitment, but rather an *enhanced link* between frontal recruitment and successful memory (supporting information). However, with 33% cross-validation accuracy, these exploratory PLS results should be interpreted cautiously, as they may not generalize beyond individuals with this cohort's specific hormonal milieu. While PLS has significant advantages, it also has some limitations. At times, PLS may prioritize variance explained by noise rather than genuine signal. This occurs because PLS aims to maximize covariance between the independent and dependent variables, which can inadvertently amplify random patterns or noise in the data.⁶⁷ Future research should explore machine learning techniques to develop predictive models that better generalize across populations.

4.4 | Strengths and limitations

To date, this is the second study to investigate effects of early ovarian removal on task-related brain function in a healthy, young group of women. However, the relatively small cohort size necessitates replication of these findings in larger cohorts. Additionally, while all women with BSO taking ET were taking some form of 17 β -estradiol, hormone therapy regimen varied between participants. We did not include participants who were taking other estrogen forms (e.g., conjugated equine estrogens) and did not analyze data based on ET formulation (e.g., oral vs. transdermal) or concomitant use of progestogens. Given that brain structure and function may depend on menstrual phase,^{25,68} future research should also investigate how this endogenous ovarian hormone level fluctuation relates to performance and brain function.

Additionally, *BRCA* mutation status and cancer treatment history did not significantly correlate with associative memory or hippocampal function in participants with BSO (supporting information). Future studies should aim to examine the distinct neurocognitive effects of *BRCA* mutation status and BSO, as well as cancer therapies, considering treatment combinations, dosages, and durations.

Although we were able to assess functional activity along the hippocampal anteroposterior axis, we did not have high enough image resolution to determine differences between hippocampal subfields.^{69,70} Rodent studies show significant effects of 17 β -estradiol on dendritic spine density in hippocampal CA1 and studies of women with BSO show volume loss in hippocampal DG-CA2/3.³⁰ DG-CA2/3 regions tend to be more active during encoding than retrieval of face-name pairs;⁷⁰ therefore, future research should use high-resolution fMRI to map where exactly in the hippocampus 17 β -estradiol loss leads to functional activity changes. To effectively investigate successful encoding mechanisms, it may also be necessary to select tasks that are more challenging and sensitive to relevant ROIs, such as those involving detailed spatial representations that engage posterior hippocampus-dependent processes.²⁰ These tasks are critical for not only advancing understanding of the neural mechanisms underlying successful encoding but also for identifying precise biomarkers of cognitive decline.

5 | CONCLUSIONS

This study reveals crucial insights into brain function and its connection to associative memory in women with ovarian removal. During associative encoding, women with BSO (with and without ET) exhibited lower posterior hippocampal activation compared to age-matched controls. We support and extend findings from our previous work by involving a larger and more diverse group of participants and by thoroughly examining both encoding and retrieval processes, emphasizing that dynamic memory circuitry changes related to BSO are evident in early midlife and may precede changes in behavioral performance.

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CONFLICT OF INTEREST STATEMENT

The authors have no financial or non-financial interests to disclose. Author disclosures are available in the [supporting information](#).

ETHICS APPROVAL

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the ethics committees of the University of Toronto, McGill University, and Linköping University.

CONSENT STATEMENT

All participants provided informed consent.

IN MEMORIAM

In memory of our most valued colleague, Jan Ernerudh, an outstanding scientist who gave generously of his time and expertise and who will be sorely missed.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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