Women's Brain Health: Effects of Aging and Menopausal Status on Episodic Memory and Brain Function

Arielle Crestol

McGill ID: 260691913

Supervised by Dr. M. Natasha Rajah

Presented in Partial Fulfillment for the Requirements for the Degree of Master of Science

Integrated Program in Neuroscience

Faculty of Medicine

McGill University

November 1, 2021

Table of Contents

Abstract

Chronological aging is associated with a decline in episodic memory – our ability to encode, store, and retrieve past items and events in rich contextual detail. Episodic memory decline for context (source memory) begins as early as midlife, at which point memory for content (item memory) is still intact. Midlife is the period when women experience menopause, a major neuroendocrine transition that is associated with substantial hormonal fluctuations. Reproductive aging research has recorded episodic memory decline in a subset of middle-aged post-menopausal women. While chronological and reproductive aging co-occur, most studies have examined one without considering the other. The objective of this study was therefore to assess the interactive effects of chronological and reproductive aging on source and item memory, and associated brain function in young and middle-aged women (18–65). We compared fMRI task-related brain activity patterns in 54 pre-menopausal women and 23 post-menopausal women as they encoded and retrieved face-location associations. Robust regressions were conducted to evaluate item and source memory based on age and menopausal status. A between-group behaviour partial least squares (BPLS) analysis was then performed to assess brain-behaviour correlations between age and performance-related patterns of activity in pre- and post-menopausal women. Our behavioural results reveal that source memory is impacted by chronological aging, and this effect is compounded by reproductive aging. From our fMRI analysis, we saw that age-related brain activations map onto behaviour differently in pre- and post-menopausal women in regions of the medial temporal lobes, fronto-parietal network, and default mode network. These results highlight that while few cognitive aging studies take reproductive aging into consideration, menopause is impacting both episodic memory and brain function, which may be creating an unbalanced perception of brain aging in women.

Le vieillissement chronologique est associé à un déclin de la mémoire épisodique, c'est-à-dire de notre capacité à enregistrer et récupérer des éléments et des événements passés dans un contexte riche en détails. Le déclin de la mémoire épisodique pour le contexte (mémoire de source) peut commencer dès les quarantaines, alors que la mémoire du contenu (mémoire des éléments) est encore intacte. Les quarantaines-cinquantaines sont la période où les femmes connaissent la ménopause, une transition neuroendocrinienne majeure qui est associée à d'importantes fluctuations hormonales. La recherche sur le vieillissement reproductif a relevé un déclin de la mémoire épisodique dans un sous-ensemble de femmes ménopausées d'âge moyen. Bien que le vieillissement chronologique et le vieillissement reproductif se produisent simultanément, la plupart des études ont examiné l'un sans tenir compte de l'autre. L'objectif de cette étude était donc d'évaluer les effets interactifs du vieillissement chronologique et reproductif sur la mémoire des sources et des éléments, et sur les fonctions cérébrales associées chez des femmes jeunes et d'âge moyen (18–65 ans). Nous avons comparé les schémas d'activité cérébrale liés aux tâches par IRMf chez 54 femmes pré-ménopausées et 23 femmes post-ménopausées alors qu'elles enregistraient et récupéraient des associations de visages et d’emplacements. Des régressions robustes ont été effectuées pour évaluer la mémoire des éléments et des sources en fonction de l'âge et du statut ménopausique. Une analyse des moindres carrés partiels du comportement entre les groupes a ensuite été réalisée pour évaluer les corrélations de cerveau-comportement entre l'âge et les schémas d'activité liés à la performance chez les femmes pré et post-ménopausées. Nos résultats comportementaux révèlent que la mémoire des sources est affectée par l'âge chronologique, et que cet effet est aggravé par l'âge reproductif. Notre analyse IRMf nous a permis de constater que les activations cérébrales liées à l'âge correspondent au comportement de manière différente chez les femmes pré et post-ménopausées, dans les régions des lobes temporaux médians, du réseau fronto-

pariétal et du réseau du mode par défaut. Dans l'ensemble, ces résultats soulignent que, bien que peu d'études sur le vieillissement cognitif prennent en compte le vieillissement reproductif, la ménopause a un impact sur la mémoire épisodique et les fonctions cérébrales, ce qui peut créer une perception déséquilibrée du vieillissement cérébral chez les femmes.

Acknowledgments

First and foremost, I would like to thank my supervisor Dr. M. Natasha Rajah for her continued mentorship and guidance. I would also like to thank all the members of the Rajah Lab for their support, and in particular, the members who provided instrumental contributions to this study. Drs. Sylvia Villeneuve and Signy Sheldon contributed valuable feedback to this project. This research was supported by CIHR Grant # PJT201610 – 153321, CIHR Grant # GS9 – 171369, and NSERC Discovery Grant # RGPIN-2018-05761 that were awarded to Dr. Rajah and the HBHL Master's Fellowship.

Contribution of Authors

Dr. Rajah supervised the project, provided guidance and feedback on study design and analyses, and developed the spatial source memory task. The primary author of the thesis, Arielle Crestol, contributed to each stage of the project (study design, recruitment, data collection, fMRI preprocessing and quality control, data analysis, and thesis writing). Additional assistance was provided by lab members involved in the larger project assessing Brain Health at Midlife and Menopause (BHAMM): Sricharana Rajagopal (fMRI preprocessing, quality control, analysis support), Alicia Duval (analysis support, data collection), Stamatoula Pasvanis (recruitment, data collection), Lina Khayyat (recruitment, data collection, fMRI quality control), Rosalie Young (recruitment, data collection), Jamie Snytte (fMRI quality control), Sophia LoParco (fMRI preprocessing, data collection), Abdelhalim Elshiekh (analysis support).

Women's Brain Health: Effects of Aging and Menopausal Status on Episodic Memory and Brain Function

Life expectancy has steadily increased globally over the last century, and the proportion of older adults, aged 65 and above, continues to grow alongside it (World Health Organization, 2020). Chronological aging is accompanied by a decline in episodic memory – our ability to encode, store, and retrieve past items and events in rich contextual detail (Tulving, 1972). Episodic memory is comprised of item memory (where the individual's attention was focused) and source memory (the external features associated with the item). Age-related declines in episodic memory negatively impact older adults' quality of life and can be an early marker of age-related dementias (i.e., Alzheimer's disease; Bäckman et al., 2005). Therefore, a concentrated effort has emerged from the scientific community to understand the neural basis of episodic memory decline in healthy aging, with the goal of identifying neurocognitive targets for interventions/treatments aimed at maintaining episodic memory function in older adults, and potentially preventing or delaying the onset of age-related dementias.

There is growing behavioral evidence that the first signs of episodic memory decline may occur earlier in the aging trajectory, at midlife. Past studies have found that declines in item memory appear in older adulthood. However, deficits in source memory and distinctions in the associated brain function have been reported during earlier stages of life (Cansino et al., 2015; Kwon et al., 2016). Previous studies from our lab and others have also reported sex differences in the effect of age on brain function associated with episodic memory (Gur & Gur, 2002; Subramaniapillai et al., 2019). Taken together, these studies highlight the importance of identifying the factors that contribute to episodic memory decline and differences in neural activity within sexes and at midlife.

At midlife, women experience menopause, a major neuroendocrine transition that results in the cessation of menstruation. Many women who experience menopause have reported cognitive issues such as forgetfulness and difficulty concentrating (Greendale et al., 2011). Yet, inconsistent results have been published on whether these complaints translate to tangible declines in episodic memory, and a limited number of studies have evaluated memory-related brain activity as a function of menopausal status (Epperson et al., 2013; Jacobs et al., 2016; Maki & Henderson, 2016; Rentz et al., 2017; Taylor et al., 2019). While chronological and reproductive aging co-occur, most studies have focused on one while not considering the other. This may be producing these inconsistent reports and obscuring our understanding of brain aging in women. The objective of the current study was therefore to assess the interactive effects of chronological and reproductive aging on episodic memory and associated brain-behaviour correlations in a cohort of healthy young and middle-aged (MA) women.

Episodic Memory and Associated Brain Function

In 1972, Endel Tulving coined the term episodic memory, which is defined as our ability to consciously recollect past events in vivid temporal and spatial detail (Tulving, 1972). Overall, episodic memory involves successful encoding and retrieval of the content (item memory), the context surrounding the item (source memory), and the binding of item and source (Chalfonte & Johnson, 1996). For example, item memory would constitute remembering seeing an individual's face. Source memory in a lab setting would comprise of remembering seeing the individual's face on the right side of the screen. In day-to-day life, they would perhaps remember sitting next to that person at a specific restaurant for a friend's birthday. However, recollecting personal past events, referred to as autobiographical memory, encompasses both episodic and semantic memory (Levine et al., 2002).

Episodic encoding and retrieval are associated with brain activity in distinct regions. According to the hemispheric encoding/retrieval asymmetry (HERA) model, episodic encoding is lateralized to the left prefrontal cortex (PFC) and episodic retrieval is lateralized to the right PFC (Habib et al., 2003; Nyberg et al., 1996). This model was challenged by Spaniol and colleagues (2009), whose meta-analysis on episodic memory demonstrated that both encoding and retrieval activations are observed primarily in the left PFC. In young adults, episodic encoding is further supported by activity in regions of the medial temporal lobes (MTL; e.g., hippocampus and parahippocampal cortex), as well as activity in superior parietal and occipito-temporal areas (e.g., fusiform gyri), and the cerebellum (Cabeza & Nyberg, 2000; Spaniol et al., 2009). Episodic retrieval is further supported by activity in lateral and inferior parietal regions, medial parieto-occipital regions (e.g., cuneus), anterior cingulate cortex, regions of the MTL (e.g., parahippocampal cortex), and the cerebellum (Cabeza & Nyberg, 2000; Spaniol et al., 2009). Altogether, episodic encoding and retrieval involve a distributed pattern of activity primarily in the PFC, MTL, and parietal regions.

When assessing item vs. source memory, further distinctions are observed in memory-related functional connectivity. Davachi, Mitchell, and Wagner (2003) assessed episodic memory-related encoding activations and determined that source and item memory are supported by different regions within the MTL. Specifically, item memory is supported by the perirhinal cortex, whereas source memory is supported by the parahippocampal cortex and hippocampus. However, alternative theories of MTL processes have stipulated that the hippocampus is further sub-divided into sections that are associated with either item or source memory (Ranganath & Ritchey, 2012; Ritchey et al., 2015). The hippocampus is also believed to be activated during feature binding of item and source (Mitchell & Johnson, 2009). Activation differences between successful item and

source memory are additionally observed in the PFC, lateral occipital cortex, as well as medial and lateral regions of the posterior parietal cortex (Cansino et al., 2002; Spaniol et al., 2009). Involvement of the PFC is essential for source memory because of its role in strategizing and executive function, as well as its role in cognitive control alongside the parietal cortex (Fletcher & Henson, 2001; Kuhl et al., 2013; Ranganath et al., 2003).

There are various ways of measuring episodic memory. For example, item memory is often measured using free recall, cued recall, and item recognition tasks. Associations are commonly assessed when examining episodic memory using item-item association tasks (e.g., picture pairs) and source-item association tasks, which are of particular interest for this project (Old & Naveh-Benjamin, 2008). Source-item association tasks typically entail remembering both an item as well as the source. At the encoding phase, participants are exposed to a series of items (e.g., pictures, words) with a distinct associative feature. This feature can vary in source modality (e.g., spatial, temporal). At retrieval, participants are shown both new and old items, and are tasked with remembering whether the item was previously seen, and if it was, additionally remembering the source information of interest. Item and source memory can be parcellated in these studies by categorizing successful responses into source hits (remembering the source along with the item) or item recognition hits (items that were remembered without the source).

Chronological Aging Effects on Episodic Memory and Associated Brain Function

Studying episodic memory using source-item paradigms is advantageous when evaluating aging effects in MA adults as source memory declines are detected at midlife, at which point item memory is still intact (Kwon et al., 2016). Likewise, distinctions in episodic memory-related brain activity are observed in MA compared to young adults (Cansino et al., 2015; Kwon et al., 2016; Park et al., 2013). Kwon and colleagues (2016) assessed the neural correlates of spatial and

temporal source memory in young and MA adults. They observed declines in spatial source memory in MA adults when compared to younger adults at higher encoding loads. Similar declines were seen in the temporal source memory of MA adults regardless of encoding load, highlighting the importance of distinguishing modality type in episodic memory assessment. No group differences were recorded in brain activity at encoding, with similar activations observed in the right parahippocampal cortex, bilateral ventrolateral PFC (VLPFC), left dorsolateral PFC (DLPFC), as well as ventral occipital and temporal regions during spatial and temporal source memory. There was a group by difficulty interaction at retrieval such that activity in the right DLPFC, left anterior PFC (APFC), left middle occipital cortex, and right fusiform cortex was increased in MA adults during the easy compared to the hard versions of both source memory tasks. In contrast, activity in these regions did not differ based on task difficulty in young adults. Kwon and colleagues (2016) then further evaluated whether memory accuracy could be predicted from task-related functional connectivity in the MTL, PFC, and occipito-temporal regions. Group differences were detected in brain-behaviour associations at both encoding and retrieval. During encoding, activity in the left VLPFC predicted retrieval accuracy for spatial and temporal source memory in young adults. In MA adults, activity in the left anterior temporal cortex predicted retrieval accuracy for temporal and spatial source memory, which was negatively correlated with temporal source memory accuracy in young adults. During retrieval, activity in the left middle occipital cortex predicted temporal source retrieval accuracy in young adults, while activity in the APFC predicted source and temporal retrieval accuracy in MA adults. Overall, MA adults performed more poorly on source memory tasks than young adults. Moreover, they displayed distinct activation patterns at retrieval during successful source memory and at encoding and retrieval when predicting retrieval accuracy.

Source memory performance continues to decline in older adulthood, at which point deficits in item recognition also emerge. Older adulthood is accompanied by distinctions in activity in the bilateral DLPFC, medial superior frontal gyrus, bilateral fusiform gyrus, left hippocampus, and bilateral parahippocampal gyrus during encoding of successful source memory, as well as in the left APFC, right lateral PFC, and perirhinal cortex during retrieval (Dennis et al., 2008; Dulas & Duarte, 2012; McDonough et al., 2013; Rajah et al., 2010). These results maintain that while many studies in neuroscience assess cognitive declines exclusively in individuals above the age of 65, discrepancies begin prior to older adulthood, underscoring the importance of studying episodic memory and neural activity at midlife.

Reproductive Aging Effects on Episodic Memory and Associated Brain Function in Women

Sex differences are frequently observed when assessing brain function, cognition, and behaviour (McCarthy, Arnold, Ball, Blaustein, & De Vries, 2012). For example, a female advantage is seen for tasks involving verbal memory, while a male advantage is observed in spatial memory tasks such as navigation (Andreano & Cahill, 2009). Unfortunately, while many differences between the sexes in cognition and brain function have been identified, few cognitive neuroscience studies have taken the reproductive health and status of women into account (Taylor, Pritschet, Yu, & Jacobs, 2019). This is problematic, as hormonal fluctuations have a robust impact on cognition in women (Heys et al., 2011; McEwen et al., 2012; Ryan, Carrière, Scali, Ritchie, & Ancelinab, 2009; Taylor et al., 2019). Estrogen plays a number of regulatory and protective roles in brain regions that are relevant to episodic memory such as the hippocampus and PFC (McEwen et al., 2012). Hormonal effects on cognition are further established by the fact that differences in estrogen exposure throughout the lifespan have been shown to impact learning and memory (Heys et al., 2011; Ryan et al., 2009). For example, a longer reproductive stage, fewer pregnancies, and

a reduced breast-feeding period are all associated with improved cognitive functioning in older women (Heys et al., 2011). In contrast, younger age of menarche and younger age of first pregnancy are associated with poorer cognitive functioning (Ryan et al., 2009).

Of particular interest to this study is natural menopause. Menopause is a neuroendocrine transition that involves the cessation of menstruation, and can be subdivided into four categories according to age, and whether the menopausal transition occurred spontaneously or was induced (Edwards, Duchesne, Au, & Einstein, 2019). Natural menopause is the most prominent form and occurs spontaneously around the age of 51 (Weismiller, 2009). With natural menopause, the transitional period known as peri-menopause occurs over several years and is characterized by a reduction in E2 levels, an elevation in follicular stimulating hormone (FSH) and luteinizing hormone (LH), as well as inconsistent menstrual cycle lengths (Soules et al., 2001; Weismiller, 2009). Post-menopause is characterized by the depletion of E2 levels, a further increase in FSH and LH, and amenorrhea for at least 12 consecutive months (Weismiller, 2009). Natural menopause can also include additional features such as disruptions to sleep, symptoms of depression, and problems with cognitive function (Read & Grundy, 2017; Rentz et al., 2017).

Both premature and early menopause also transpire spontaneously, although early menopause emerges in women between the ages of 40–45 and occurs in approximately five percent of women, while premature menopause appears in women younger than 40 and affects approximately one percent of women (Edwards et al., 2019; Santoro, 2003). Early menopause tends to progress in a similar fashion to natural menopause, although premature menopause involves additional criteria and some distinct hormonal changes (Edwards et al., 2019). Both early and premature menopause have been associated with a number of health risks such as cognitive declines and osteoporosis (Shuster et al., 2010). Induced menopause is triggered by removal of the

ovaries as a result of surgery, chemotherapy, or radiation, which is performed to treat or prevent diseases such as breast cancer (Shuster et al., 2010). Induced menopause immediately results in a steep decline of E2 and progesterone and a boost in FSH and LH levels (Edwards et al., 2019). Women who undergo induced menopause are at increased risk of several adverse health outcomes such as cardiovascular disease, neurological disorders, and cognitive decline (Shuster et al., 2010).

To our knowledge, no studies have assessed menopausal effects on source memory. Studies that have evaluated the impact of natural menopause on other measures of episodic memory have reported inconsistent results (Epperson et al., 2013; Henderson & Sherwin, 2007; Herlitz et al., 2007; Rentz et al., 2017). This is a contested area, because not all women experience neurocognitive effects with natural menopause. Existing studies have primarily focused on verbal memory, due to age-related declines and the reported female advantage. One such analysis was conducted by Rentz and colleagues (2017), who demonstrated that natural menopause and associated E2 decline have a negative impact on verbal episodic memory. They examined differences in memory performance between sexes in early midlife and further grouped the women by menopausal status. Estradiol levels in women correlated positively with successful initial learning and retrieval. A female advantage was observed in performance, although this advantage diminished in post-menopausal women. However, consolidation and storage of information remained intact in the post-menopausal group. Notably, a subset of post-menopausal women did not differ in performance relative to pre-menopausal women. This inconsistency suggests that certain post-menopausal women may show increased susceptibility to memory-related decline compared to others.

When assessing functional connectivity associated with verbal episodic memory at encoding, Jacobs and colleagues (2016) reported that neural activity varied based on biological

sex, menopausal status (natural menopause), and E2 levels. When dividing their sample by sex, men showed greater activity in the left posterior parietal cortex, and greater connectivity both within the VLPFC and between the VLPFC and posterior parietal cortex. Conversely, women displayed increased bilateral hippocampal connectivity. However, when exclusively assessing the group of women, the authors revealed that this effect was only seen in post-menopausal women, driving the observed sex difference. Similarly, E2 levels were negatively correlated with increased bilateral hippocampal connectivity. Reduced activity in the left hippocampus was also seen in post-menopausal women compared to pre- and peri-menopausal women. Finally, task-related brain activity in post-menopausal women with higher performance scores more closely resembled the activity in pre-menopausal women than the lower performing post-menopausal women. The disparity observed within the post-menopausal group gives further credence to the possibility that certain post-menopausal women demonstrate more resilience to the neuroendocrine effects of menopause, suggesting that other factors may be playing a moderating role.

Rationale, Objectives, and Hypotheses

Rationale

We chose to study the combined effects of chronological and reproductive aging on memory and associated brain function. Few studies consider both processes together in either neuroimaging or cognition-related research, despite the fact that their effects may impact the same brain systems. This may be creating an unbalanced perception of brain aging in women. The present study therefore aims to provide fundamental insight into healthy cognitive aging, allowing for a deeper understanding of how these factors interactively affect episodic memory systems in women at midlife. Additionally, menopause is often perceived exclusively as a hormonal transition that results in the end of menstruation. However, behavioural and cognitive features are equally as

important, with women reporting brain fog and other memory-related issues at menopause. Finally, both menopause and aging have been linked to various disorders that differentially affect men and women such as Alzheimer's disease, which is associated with a decline in episodic memory. It is imperative that we have a strong foundational basis for healthy brain aging in women, so that pathological brain aging can be properly differentiated and understood.

Objectives

The objective of the current task fMRI study was to assess the interactive effects of reproductive and chronological aging on episodic memory performance and brain function in cognitively healthy young and MA women. Due to the diverse nature of the onset and features associated with different menopause types, the current study focused exclusively on natural menopause, the menopause type that most commonly occurs in women. We evaluated episodic memory using a spatial source memory task to compare item and source memory performance. To date, no studies have assessed the effects of menopause on source memory. We therefore evaluated source vs. item memory in young and MA women to discern whether episodic memory-related patterns of brain aging differed as a function of menopausal status.

The specific aims of this project include:

1. Evaluate how chronological and reproductive aging, measured as menopausal status, affect episodic memory performance for source and item recognition
2. Determine how chronological aging and performance for source and item recognition memory relate to brain activity during memory encoding and retrieval in pre- and post-menopausal women

Hypotheses

The specific hypotheses for this project include:

1. We predicted that with advanced chronological age, there would be a reduction in source memory and a stabilizing of item recognition memory. We predicted that this effect would be magnified by reproductive aging such that source memory would decline with both age and menopause, and older post-menopausal women would present with the most severe source memory failures (Kwon et al., 2016; Rentz et al., 2017)
2. We predicted that chronological aging would affect MTL and fronto-parietal systems, and that these changes would be more pronounced in post-menopausal women (Kwon et al., 2016; Jacobs et al., 2016)

It is important to note that in this study, chronological aging may be referred to as age, and reproductive aging is identified by menopausal status. Additionally, source memory is not generalized, but refers specifically to spatial source memory, as is evaluated by the episodic memory task.

Methods

Participants

Participants included young (18–39) and MA women (40–65). Subjects were divided into groups based on the Stages of Reproductive Aging Workshop (STRAW) categorization via self-report questionnaires into pre, peri, and post-menopausal women (Soules et al., 2001). Grouping was confirmed as a secondary step by assessing hormone levels when STRAW categorization was unclear. The participants were then further split by age group. In total, there were four groups of women: young pre-menopausal women, MA pre-menopausal women, MA peri-menopausal women, and MA post-menopausal women. We chose to split participants by menopausal group rather than assessing hormone levels as continuous variables. While hormone levels were sufficient for grouping participants according to menopausal status, they were not precise enough for assessment. As per an a priori power calculations using G*power and an average effect size from literature in the field, a sample size of 37 participants was required to observe significant behavioural effects (f = .29; α=.05; power=.80; Faul, Erdfelder, Buchner, & Lang, 2009; Spencer & Raz, 1996). To observe significant task-related fMRI effects, a sample size of 24 participants per group was required as determined by simulation experiments (α=.05 corrected; power=.80; Desmond & Glover, 2002). Finally, a sample of 80 participants was required to observe significant effects for task fMRI brain-behaviour correlations (Grady et al., 2021).

Participants were recruited via advertisements posted on websites and around the Montreal community. Each participant provided informed consent and was compensated $40 for session one and $60 for session two. This study was approved by the Douglas Mental Health University Institute Research Ethics Board. Participants were initially included in the study if they had previously obtained a high school diploma, were willing to provide a blood sample, and were in

good health. Participants were excluded if they reported any of the following in their medical history: bilateral oophorectomy, cataract, glaucoma, untreated age-related maculopathy, risk factors for cardiovascular disease such as uncontrolled hypertension or untreated high cholesterol, diabetes, history of estrogen-related cancers, neurological diseases or insult, psychiatric disorders, claustrophobia, prior serious head injury, history of alcoholism, currently drinking >14 units of alcohol/week, or currently smoking >40 cigarettes per day. Participants were also excluded from the study if they did not meet the requirements for magnetic resonance imaging (MRI) safety (e.g., implanted pacemaker), or if they performed below chance during a practice version of the spatial source memory task. Additional exclusion criteria based on neuropsychological testing are outlined below under background measures.

Procedure

Online Inclusion Questionnaire

Participants first consented to filling out an online questionnaire. They responded to questions related to demographics, medical history, reproductive history, and education to screen out individuals who were not cognitively, physically, or psychologically healthy. In total, the questionnaire took approximately 20 minutes to complete.

Session 1: Behavioural Testing

After initial screening, eligible participants were invited to the Brain Imaging Center (BIC) at the Douglas Mental Health University Institute for further testing. Participants first consented to the study with two separate forms: one constituting general information regarding the two sessions of the study, and the other specific to blood testing and genotyping. After obtaining consent, participants filled out the MRI safety questionnaire. Next, they completed a battery of standardized assessments. Blood samples were then collected by a certified research nurse. Finally,

participants performed a practice version of the spatial source memory task in a mock MRI scanner to familiarize them with the task and ensure they felt comfortable enough to partake in the real MRI scan. This session took approximately 2.5 hours. After completion, participants were compensated with $40.

Session 2: fMRI Scan

After further screening, eligible participants were invited to return to the BIC at the Douglas Institute. Participants first took a pregnancy test to confirm that they were not pregnant prior to entering the MRI. Blood pressure was measured, and blood samples were collected by a research nurse. Participants were then brought to the scanning room. They were instructed to lie down in a supine position in the scanner where their head was constrained to minimize movement. They were asked to remain still while in the scanner and instructed to use fibre optic response button boxes that were provided to make responses during the spatial source memory task. Participants were in the scanner for a total of 1.5 hours, after which they filled out a debriefing and mind-wandering questionnaire and were compensated with $60. This session took approximately 2.5 hours.

Behavioural Methods

Background Measures

A battery of preliminary tests was administered to participants for exclusionary purposes. Tests relevant to this project are listed:

The Mini-International Neuropsychiatric Interview (M.I.N.I; Sheehan et al., 1998) is used to identify psychiatric disorders. One point is obtained when all the diagnostic criteria are met for a single disorder. Participants were excluded from the study dependent on positive modules.

The Edinburgh Inventory (Oldfield, 1971) is a measure of handedness. Participants indicate whether they use their left, right, or both hands to perform various tasks. Participants who exclusively use their right hand for all tasks received a score of 100%. While participants were not excluded if they were left-handed, scores were noted for each individual and reported within groups.

The Beck Depression Inventory II (BDI-II; Beck, Steer, & Brown; 1996) is a 21-item self-report questionnaire for depressive symptoms from the previous two weeks. Out of a total score of 63, a score above 13 suggests mild depression, a score above 20 suggests moderate depression, and a score above 29 suggests severe depression. Participants with a score above 20 were excluded from this study.

The Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988) is a 21-item self-report questionnaire for anxiety symptoms during the last month. Out of a total score of 63, a score above 21 suggests moderate anxiety and a score above 36 suggests potential cause for concern. Participants with a score above 21 were excluded from this study.

The Mini-Mental State Exam (MMSE; Cockrell & Folstein, 1988) is a measure of general cognitive functioning. This tool is used to evaluate mental status and cognitive impairment in the elderly population. The assessment consists of 11 sections assessing diverse cognitive abilities. Out of a total score of 30, participants with a score below 27 were excluded from the study.

The California Verbal Learning Test II (CVLT-II; Delis et al., 2000) is a measure of verbal episodic memory. This test includes measures for short-term and long-term recall for both cued and free recall. The CVLT was used as a measure for exclusion. The cut-off scores for the CVLT are varied dependent on age and education level (Norman, Evans, Miller, & Heaton, 2000).

The National Adult Reading Test (NART; Strauss et al., 2006)/French NART (fNART; (Mackinnon & Mulligan, 2005) is used as an estimate of premorbid intelligence. Predicted full-scale IQ is derived from equations and calibrated against the Wechsler Adult Intelligence Scale full-scale IQ (WAIS-IV FSIQ; English version) or WAIS-R verbal (French version; Nelson, 1982; Mackinnon and Mulligan, 2005; Wechsler, 2008). Subjects with scores exceeding 2.5 standard deviations from the mean after adjusting for age and education were excluded.

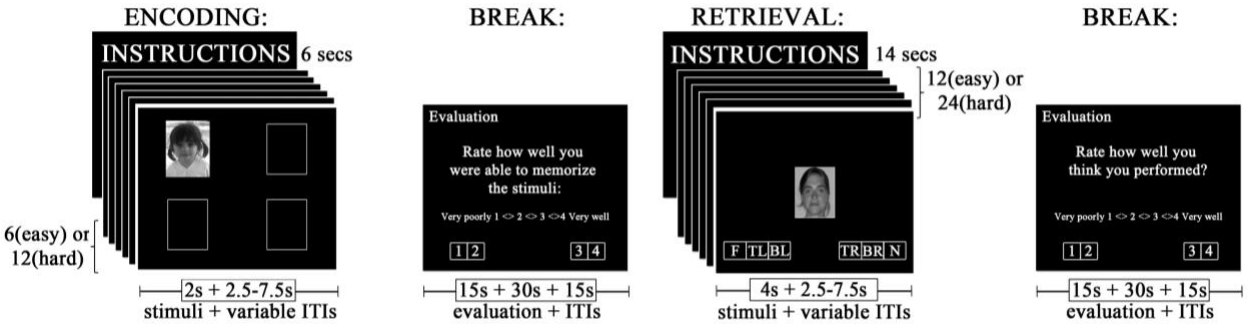
Task fMRI: Spatial Source Memory Task

A mixed rapid event-related design was used for this experiment. Participants were scanned during encoding and retrieval of four easy and four hard runs that were counterbalanced. Task difficulty was manipulated by increasing encoding load. Two tasks were performed within each easy run (9 minutes and 42 seconds per run) and one task was performed within each hard run (7 minutes and 14 seconds per run), resulting in 287 volume acquisitions per easy run, and 213 volume acquisitions per hard run. In total, participants were exposed to 96 faces at encoding (48 easy, 48 hard) and 192 faces at retrieval (96 old, 96 new) across all eight runs. The task was presented through E-Prime software (Psychology Software Tools, PA), projected into the scanner bore, and made visible to participants via a mirror mounted within the head coil. Participants were given two fibre optic response boxes to respond throughout the task. During each run, response options and the corresponding buttons for each task were displayed at the bottom of the screen for clarity (see Figure 1 for a visual summary of the task).

Encoding Phase. Participants were presented with instructions for the first nine seconds of the run. Subjects were informed that they would see a series of either six (easy) or 12 (hard) faces, dependent on task difficulty. Participants were instructed to (1) memorize the face, (2) memorize the location of the face, and (3) rate the face as either pleasant or neutral by pressing the

Figure 1

Visual Summary of the Spatial Source Memory Task



corresponding button on the provided response box. The pleasantness rating was added as emotional and social stimuli can impact brain activity and contribute to successful memory encoding (Harvey, Fossati & Lepage, 2007). However, pleasantness was not considered in the framework of this experiment. Participants were then presented with black-and-white images of faces varying in age and ethnicity in one of four quadrants sequentially for two seconds at a time. The inter-trial interval (ITI) was varied (2.2–8.8 seconds) since adding jitter to the experiment increases sampling points and eliminates any overlap between task-related blood oxygen level dependent (BOLD) responses (Dale & Buckner, 1997). Subsequent to the encoding phase, participants rated their performance on a four-point scale from not well (1) to very good (4) during a 60 second break.

Retrieval Phase. Participants were presented with instructions for nine seconds. They were informed that they would be shown a series of faces and would have to press the corresponding button for one of the following options: (1) new; this face was not displayed during the encoding phase, (2) familiar; the face is familiar but the participant cannot recall the quadrant in which it was presented (they are instructed not to guess), (3) top left; the face was displayed in the top left quadrant, (4) bottom left; the face was displayed in the bottom left quadrant, (5) top right; the face

was displayed in the top right quadrant, (6) bottom right; the face was displayed in the bottom right quadrant (see Tables 1, 2). These six options were provided to distinguish face recognition (item memory) from remembering the quadrant the face was seen in (source memory). The participants were then presented with either 12 (easy) or 24 (hard) faces per run, dependent on task difficulty. Each face was presented for six seconds at a time at the center of the screen with a variable ITI. Finally, participants were given 60 seconds to rate how well they thought they performed on a four-point scale from not well (1) to very good (4). Responses from the spatial source memory task were classified according to six categories (see Tables 1, 2).

Table 1

Response Categories for the Spatial Source Memory Task

	Participant responses			
Correct responses	New	Familiar	Top left	Top right
New	Correct rejection	False alarm	False alarm	False alarm
Top left	Miss	Correct item recognition	Correct source	Source misattribution
Top right	Miss	Correct item recognition	Source misattribution	Correct source

Note. Categories are shown for new, top left, and top right responses. Bottom left and bottom right were additional response options that were not included in this table for simplicity.

Table 2

Response Category Descriptions for the Spatial Source Memory Task

Response type	Description
Correct source	The participant correctly responded that the face was previously seen in the correct location
Correct item recognition	The participant correctly responded that the face was previously seen but did not recall the location
Correct rejection	The participant correctly responded that the face was new
Source misattribution	The participant correctly responded that the face was previously seen but responded with the incorrect location
Miss	The participant incorrectly responded that the face was new when it was previously seen
False alarm	The participant incorrectly responded that the face was previously seen (with or without a source) when it was new

Specific Aim 1: Behavioural Analyses

We predicted that there would be a decline in source memory with older age that would be further compounded in post-menopausal women, but did not expect to see any differences in item recognition memory. While chronological and reproductive aging are oftentimes considered independent processes, they are highly intertwined. We created analyses that we felt captured the complex nature of the relation between these two variables. To address the first hypothesis, we applied three regression models, across which we conducted robust regressions for multiple dependent variables:

1. DV ~ Age + error (Aged 18–65; pre-, peri-, and post-menopausal women)
2. DV ~ Age + menopausal status + error (Aged 18–65; pre- and post-menopausal women)
3. DV ~ Menopausal status + error (Aged 40–65; pre- and post-menopausal women)

For the first set of analyses, we included all female participants aged 18–65 and conducted robust regressions with the predictor of age. For the second set of analyses, we removed the peri-menopausal women from the sample and conducted robust regressions with the same outcome variables, although this time with age and menopausal status as predictors (pre- and post-menopausal women). Young and MA pre-menopausal women were combined into one group to assess menopausal status for this analysis. Finally, we removed both peri-menopausal women and all young women from the third set of analyses, exclusively assessing women aged 40–65 to conduct regressions with menopausal status as the predictor (pre- and post-menopausal MA women).

Dependent variables for the primary hypothesis testing included correct source rate and correct item recognition rate during both the easy and hard versions of the task. Rates were

calculated for these four variables by dividing the number of each by the total number of easy or hard old events. Old events encompass correct source hits, correct item recognition hits, source misattributions, and misses (see Table 1). Four additional dependent variables were calculated and analyzed, with the intent of exploring the effects of age and menopause on response bias. These variables were probability scores, including probability of source (pSource) which adjusts for bias of guessing the source by taking source misattributions into consideration, and probability of recognition (pRecog), which adjusts for bias of guessing old by accounting for false alarms.

Probability scores for source and item recognition retrieval accuracy were calculated with the following formulas (Snodgrass & Corwin, 1988):

$$\text{pSource} = Z_{(\text{correct source rate})} - Z_{(\text{source misattribution rate})} \quad (1)$$

$$\text{pRecog} = Z_{(\text{correct item recognition rate})} - Z_{(\text{false alarm rate})} \quad (2)$$

Robust regressions were conducted in R (R Core Team, 2016) with the Mass package, using the robust linear modeling function (rlm; Venables & Ripley, 2002). This function uses iteratively reweighted least squares to find a huber m-estimator, or maximum likelihood estimation. Robust regressions were chosen as they control for highly influential data points and because many of the dependent variables from this project are not normally distributed. This is due to the design of the experiment, as abnormal distributions are common when responses are interdependent. We used a Bonferroni correction to adjust for multiple comparisons. With four dependent variables from the primary hypothesis testing, we used a *p*-value of .01 for significance.

We also calculated whether participants were performing above chance level for correct source accuracy and total hits. These scores were computed based on button probability (the chance that you hit the right button) and stimulus probability (the chance that the stimulus was seen at the encoding phase). For correct source, the button probability was $\frac{1}{6}$ since there are a total

of 6 button options, and the stimulus probability was $\frac{1}{8}$ as half the images presented at retrieval were old, and there were four possible quadrants to choose from. The chance probability for correct source, summed for all four quadrants was 8.33%. For total hits, the button probability was $\frac{5}{6}$ and the stimulus probability was $\frac{1}{2}$. Therefore, the chance probability for hits was 42%.

fMRI Methods

fMRI Data Acquisition

Participants were scanned with a 3T Siemens Prisma-Fit scanner while wearing a standard 32-channel head coil. High-resolution T1-weighted anatomical images were collected using a 3D Magnetization-Prepared Rapid Gradient-Echo (MP-RAGE) sequence (repetition time [TR] = 14 ms, echo time [TE] = 4.92 ms, flip angle = 25°, 176 1 mm thick transverse slices, 1 mm x 1 mm x 1mm voxels, field-of-view [FOV] = 256 mm, acquisition time = 5 min). While performing the spatial source memory task, functional BOLD images were acquired using single shot T2*-weighted gradient echo-planar imaging (EPI) pulse sequence (TR = 2000 ms, TE = 30 ms, FOV = 256 mm, matrix size = 64 X 64, in-plane resolution = 4 X 4 mm). High resolution T2-weighted scans, resting state fMRI scans, and diffusion tensor imaging scans were also acquired, although only T1 and T2*-weighted scans are relevant for the purposes of this study.

Image Preprocessing

RThe DICOM files were first converted to BIDS format. Volumes collected during the first 10 seconds of scanning were removed to ensure that magnetization had stabilized. Preprocessing was conducted using fMRIprep version 20.2.0 (Esteban et al., 2019). FMRIprep is a robust preprocessing workflow in Python version 3.0 that implements tools from various software packages including Advanced Normalization Tools version 2.3.3 (ANTs), FMRIB Software Library version 5.0.9 (FSL), and FreeSurfer 6.0.1. The T1-weighted images were first

corrected for intensity nonuniformity and skull stripped via Nipype (ANTs; Tustison et al., 2010). The anatomical images were then tissue segmented (cerebrospinal fluid, grey matter, and white matter; FSL; Zhang, Brady, and Smith 2001). Brain surface reconstruction was conducted with recon-all (FreeSurfer; Dale et al., 1999) and brain mask refinement was customized to accommodate the segments of cortical gray-matter from both ANTs and FreeSurfer (Klein et al., 2017). Finally, the images were normalized to the MNI template (ICBM 152 Nonlinear Asymmetrical template version 2009c; MNI152NLin2009cAsym; ANTs). For the BOLD images, a reference volume and its skull-stripped version were generated and co-registered with six degrees of freedom to the T1-weighted reference using bbregister (FreeSurfer; Greve & Fischl, 2009). Head-motion parameters were estimated using mcflirt (FSL 5.0.9, Jenkinson et al., 2002). Spatial distortions were corrected with a fieldmap and unwarping. The BOLD time-series was resampled onto their original, native space by applying transforms to correct for head-motion and then resampled into standard space, generating a preprocessed BOLD run in MNI152NLin2009cAsym space. Confounding time-series were calculated based on the preprocessed BOLD (i.e., framewise displacement; Power et al., 2012, and three region-wise global signal; Jenkinson et al., 2002).

Quality Control

Scans from each run were visually analyzed across different stages of preprocessing in FSL or Statistical Parametric Mapping software version 12 (SPM12). Volumes of raw scans from each run were first analyzed for abnormalities or dropout. Subsequently, volumes were examined at the co-registration step to evaluate alignment with the T1-weighted images. Images were then inspected at the normalization step to ensure they were properly aligned with the MNI template. Finally, the raw scans were analyzed for movement based on framewise displacement (Power et al., 2012) with a cut-off of 1mm. When less than 25% of scans within a run were above the 1mm

cut-off, these scans were scrubbed. If the number of scans over 1mm exceeded 25%, these scans were censored.

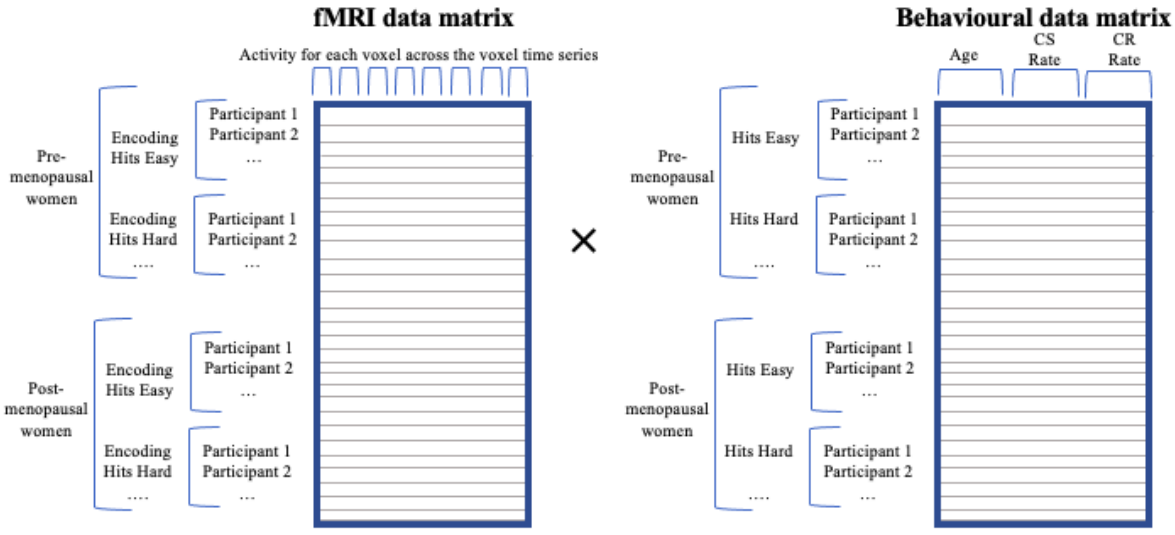
Specific Aim 2: fMRI Analysis

To address the second hypothesis assessing brain-behaviour correlations in pre- and post-menopausal women, a between-group behaviour partial least squares (BPLS) analysis was conducted via open source PLSGUI software (https:// www.rotman-baycrest.on.ca/index.php?section=345) in MATLAB (R2012a; Mathworks, Inc., Natick, MA). Partial least squares was chosen because it is a powerful statistical analysis that can be used to objectively assess spatiotemporal functional patterns in neuroimaging datasets. Moreover, PLS analyses directly assess the correlation between these patterns with different behavioural or experimental measures (McIntosh, Chau, & Protzner, 2004). Partial least squares analyses do not make any assumptions about the hemodynamic response function, and reliably yield generalizable and stable results through the use of permutation and bootstrapping methods (McIntosh et al., 2004).

For a BPLS analysis, the data is stored in two matrices: one consisting of fMRI data, and the other consisting of behavioural data (see Figure 2 for the data matrices that were constructed for this analysis). The fMRI data was averaged for each participant and stored in the first matrix, consisting of activity for each voxel across the voxel time series during encoded and retrieved events of successful hits. A successful hit required the participant to have either correctly recognized the face, or both the face as well as the location. Successful hits therefore included correct source, correct item recognition, and source misattribution responses. Brain activity was further split by task difficulty into easy and hard events. In total, four different event types were assessed: (1) encoding hits easy, (2) encoding hits hard, (3) retrieval hits easy, and (4) retrieval

Figure 2

Data Matrices for Behaviour Partial Least Squares Analysis



Note. CS = correct source, CR = Correct item recognition.

hits hard. The rows of the fMRI data matrix accounted for each participant and were nested by event type, while the columns represented activity within each voxel for each of the time points associated with encoding and retrieval. The data was stacked by group according to menopausal status into pre- and post-menopausal women.

The behavioural data was stored in a separate matrix. The behavioral measures of interest included: (1) age, (2) correct source rate, and (3) correct item recognition rate. The rows of the behaviour matrix followed the same order of participants as the fMRI data matrix, although each column of the behaviour matrix represented one of the three behavioural measures. The behaviour matrix was also stacked according to group into pre- and post-menopausal women. The behaviour matrix was transposed and cross-correlated with the fMRI data matrix, producing a combined correlation matrix which was then decomposed using singular value decomposition. Orthogonal paired latent variables (LV) were created by projecting the original matrices onto their saliences.

Each LV included a singular value, a singular image, and a correlation profile. The singular value portrayed the proportion of covariance accounted for by the LV. The singular image included positive and/or negative saliences which establish the weighted contributions of each voxel at a given time point, producing a spatiotemporal pattern of whole-brain activity. Finally, the correlation profile portrayed the association between the pattern of brain activity from the singular image with the behavioural measures.

Permutation testing was conducted on the LVs to establish significance ($p < 0.05$; McIntosh et al., 2004; Krishnan et al., 2011). One thousand permutation tests were conducted using sampling without replacement, reassigning the order of event types within each subject and across conditions. Stability and 95% confidence intervals were evaluated by estimating the standard error for each LV from 500 bootstrap tests. Sampling with replacement and fixed event types was conducted for all participants. A bootstrap ratio for each voxel was computed by dividing the voxel salience by its estimated standard error. Voxels with a bootstrapping ratio of ± 3.28 ($p < 0.01$) within a cluster of at least 10 significant voxels were retained.

Temporal brain scores were calculated to obtain time lags with the strongest correlation profile for significant LVs. Time lags are the number of TRs after the stimulus of interest is presented. Temporal brain scores reveal the strength of the pattern of brain activity for each subject at each time lag. We retained only peak coordinates from time lags with maximal differences and converted them to Talairach space using the icbm2tal transform (Lancaster et al., 2007), implemented in GingerAle 2.3 (Eickhoff et al., 2009). Peak coordinates from the cerebellum and brainstem were not included as the fMRI acquisition in these regions was incomplete. Relevant Brodmann areas were established using the Talairach and Tournoux atlas (Talairach & Tournoux, 1988) and confirmed in FSL.

Endocrine Assessments

Thirty-nine ml of blood was collected by a certified research nurse at the Douglas Institute. Blood samples were analyzed for various measures, although for the purposes of this study E2, FSH, and LH levels were assessed to corroborate menopausal staging when STRAW categorization was unclear. Blood samples were sent to the Proteomics Platform of the McGill University Health Centre for endocrine assessments. Chemiluminescent immunoassay was used to establish E2, FSH, and LH levels.

Results

Behavioural Results

Participants

A total of 192 women were initially enrolled in this study. Seventy-six subjects either withdrew or were excluded based on the tests listed above. Seven participants were additionally excluded as a result of technical issues in the scanner, performing below chance on the spatial source memory task, or due to undetermined menopausal status. This left 109 participants (see Table 3 for participant characteristics). Remaining participants included 41 young pre-menopausal women (18–39; M = 28.71, SD = 6.13), 26 MA pre-menopausal women (40–65; M = 45.16, SD = 3.06), 18 MA peri-menopausal women (40–65; M = 50.04, SD = 4.03), and 24 MA post-menopausal women (40–65; M = 57.94, SD = 3.83; see Table 4 for responses from the spatial source memory task by group). From the 109 participants, 70.6% were Caucasian, 4.6% Latin American, 2.8% Black, 1.8% South Asian, 1.8% Chinese, .9% aboriginal, .9% Caucasian-Southeast Asian, and .9% Caucasian-Black. Ethnic data was missing for the remaining 11.9% of women. Kruskal-Wallis H-tests were conducted in IBM SPSS Statistics for Macintosh, Version 27.0 (IBM Corp.) to assess demographic measures by age × menopausal group for the dependent measures of age, education, BMI, BAI, and BDI. Age was significantly different across groups ($p < .05$) as each group was statistically different from the others, with age increasing from young pre-menopausal to MA pre-menopausal, then from MA pre-menopausal to MA peri-menopausal, with the oldest women in the MA post-menopausal group. Otherwise, there were no statistical differences between groups for education level, BMI, or our measures of depression (BDI) and anxiety (BAI; $p > .05$).

Table 3

Participant Characteristics by Age × Menopausal Group

	Total	Young Pre	MA Pre	MA Peri	MA Post
Sample size	109	41	26	18	24
*Age (years)	42.60 (12.55)	28.72 (6.03)	45.16 (3.06)	50.04 (4.03)	57.94 (3.83)
EDU (years)	15.76 (2.20)	16.07 (1.93)	16.56 (1.99)	15.67 (1.94)	14.88 (2.74)
BMI (kg/m^2)	24.70 (4.50)	23.95 (4.26)	25.10 (5.41)	25.20 (4.37)	25.17 (4.00)
BAI	4.16 (3.86)	4.49 (4.17)	3.23 (3.57)	4.44 (3.20)	4.38 (4.12)
BDI-II	3.92 (3.76)	3.54 (3.44)	3.31 (3.38)	4.22 (3.69)	5.00 (4.62)
Hand (% right)	79.08 (43.17)	69.02 (52.81)	93.85 (12.03)	72.22 (48.94)	85.42 (38.33)
Hysterectomy (%)	3.67	.00	.00	5.56	12.5
Antidepressant (%)	9.17	11.54	5.56	8.33	9.17
OC (%)	18.35	39.02	11.54	5.55	.00
HRT (%)	4.59	.00	3.85	5.56	12.50
ENG (%)	33.90	34.15	34.62	44.44	25.00
FR (%)	45.00	41.46	50.00	27.78	58.33
Other (%)	21.10	24.40	15.38	27.78	16.67

Note. Mean (standard deviation). Pre = pre-menopausal; Peri = peri-menopausal; Post = post-menopausal. EDU = education; BMI = body mass index; BDI-II = Beck Depression Inventory-II; BAI = Beck Anxiety Inventory; Hand = Handedness (% who are right-handed); OC = Oral contraceptive; HRT = Hormone replacement therapy (% on each medication); ENG = English; FR = French; Other = Language other than English or French (% whose mother tongue was English, French, or a different language). '*' denotes statistical significance ($p < .05$).

Table 4

Proportion Per Response Type from the Spatial Source Memory Task by Age × Menopausal Group

	Total	Young Pre	MA Pre	MA Peri	MA Post
Hits easy	.90 (.08)	.91 (.07)	.93 (.08)	.89 (.10)	.88 (.10)
Hits hard	.84 (.12)	.83 (.11)	.87 (.13)	.84 (.11)	.83 (.12)
Correct source easy	.57 (.22)	.60 (.22)	.66 (.21)	.57 (.19)	.41 (.18)
Correct source hard	.38 (.19)	.43 (.19)	.45 (.20)	.35 (.17)	.26 (.13)
Correct item recog easy	.17 (.14)	.15 (.11)	.12 (.10)	.17 (.16)	.24 (.17)
Correct item recog hard	.28 (.16)	.24 (.15)	.25 (.14)	.32 (.16)	.34 (.18)
Correct rejection easy	.85 (.16)	.88 (.16)	.86 (.16)	.89 (.08)	.77 (.18)
Correct rejection hard	.81 (.16)	.85 (.15)	.81 (.19)	.81 (.10)	.75 (.17)
False alarm easy	.14 (.15)	.10 (.13)	.14 (.15)	.10 (.08)	.23 (.18)
False alarm hard	.17 (.15)	.13 (.13)	.18 (.17)	.17 (.10)	.24 (.17)
Source misattribution easy	.15 (.11)	.12 (.09)	.14 (.13)	.13 (.08)	.21 (.11)
Source misattribution hard	.18 (.13)	.15 (.13)	.17 (.13)	.17 (.08)	.23 (.16)
Miss easy	.10 (.08)	.09 (.07)	.08 (.08)	.11 (.10)	.12 (.10)
Miss hard	.14 (.10)	.14 (.08)	.12 (.13)	.14 (.10)	.17 (.12)
pSource easy	.01 (1.72)	.41 (1.64)	.47 (1.91)	.16 (1.33)	−1.27 (1.27)
pSource hard	.01 (1.57)	.46 (1.63)	.38 (1.60)	−.12 (1.19)	−1.07 (1.14)
pRecog easy	−.03 (1.40)	.11 (1.06)	−.35 (1.20)	.23 (1.17)	−.14 (2.10)
pRecog hard	−.02 (1.54)	.05 (1.33)	−.28(1.61)	.27(1.19)	−.09(2.04)

Note. Mean (standard deviation). Pre = pre-menopausal; Peri = peri-menopausal; Post = post-menopausal. Rates were calculated as the number of events/total new or old events, easy or hard. pSource = $z_{(\text{correct source rate})} - z_{(\text{source misattribution rate})}$. pRecog = $z_{(\text{correct item recognition rate})} - z_{(\text{false alarm rate})}$.

Behavioural Results

We predicted that with age, we would see a decline in correct source rate and a stabilization of correct item recognition rate, and that this effect would be amplified in post-menopausal women. To address this primary hypothesis, we performed regressions across three models which evaluated the effects of age and menopausal status separately (models 1, 3) and together (model 2). The dependent variables of interest were correct source rate and correct item recognition rate, easy and hard. Additional regressions were conducted across these models to explore the effects of age and menopausal status on response bias. The dependent variables for these analyses were pSource and pRecog, easy and hard. The assumption of homoscedasticity was met, and Cook's distance was not exceeded for any of the reported regression analyses. Additionally, a Bonferroni correction was used to correct for multiple comparisons, with a *p*-value of .01 for significance.

The first model of robust regressions was conducted with age as the independent variable (continuous; aged 18–65; n=109; see Tables 5–8 and Appendix A). Age was a significant predictor of correct source rate for the easy ($\beta = -.07$, $SE = .02$, $t = -3.30$, $p < .001$) and hard ($\beta = -.06$, $SE = .02$, $t = -3.36$, $p < .001$) versions of the task. Source accuracy decline was associated with older age at both encoding loads. When assessing correct item recognition rate, age was a significant predictor for the hard version of the task ($\beta = .05$, $SE = .02$, $t = 3.07$, $p < .01$) such that correct item recognition rate increased with older age. This effect was no longer significant for the easy version after correcting for multiple comparisons ($\beta = .03$, $SE = .01$, $t = 2.30$, $p = .02$). Age was also a significant predictor for pSource easy ($\beta = -.57$, $SE = .17$, $t = -3.32$, $p < .001$) and hard ($\beta = -.53$, $SE = .14$, $t = -3.71$, $p < .001$). At both encoding loads, pSource declined with older age. Age was not a significant predictor for pRecog easy or hard. To sum, age was a significant predictor of correct source rate (easy/hard), correct item recognition rate (hard), and pSource (easy/hard).

Table 5

Effect Sizes (β), Standard Errors (SE), and T-Values for Robust Regressions Models 1–3, Examining the Effects of (1) Age, (2) Age and Menopausal status, and (3) Menopausal Status on Correct Source Rate.

		Correct Source Easy			Correct Source Hard		
Model	Fixed effects	*β*	*SE*	*t-value*	*β*	*SE*	*t-value*
1	Age	−.07	.02	−3.30***	−.06	.02	−3.36***
2	Age	−.01	.04	−.34	−.01	.03	−.40
	Meno	−.10	.04	−2.53**	−.08	.04	−2.24*
3	Meno	−.13	.03	−4.32***	−.10	.02	−4.39***

Note. Age was measured as a continuous variable. Meno = menopausal status represented as two effect-coded variables: −1 = pre-menopausal women, 1 = post-menopausal women. '∗' denotes *p* or *Pr* (>|*z*|) .05; '∗∗' denotes *p* or *Pr* (>|*z*|) .01; '∗∗∗' denotes *p* or *Pr* (>|*z*|) .001.

Table 6

Effect Sizes (β), Standard Errors (SE), and T-Values for Robust Regressions Models 1–3, Examining the Effects of (1) Age, (2) Age and Menopausal status, and (3) Menopausal Status on Correct Item Recognition Rate.

		Correct Item Recog Easy			Correct Item Recog Hard		
Model	Fixed effects	*β*	*SE*	*t-value*	*β*	*SE*	*t-value*
1	Age	.03	.01	2.30*	.05	.02	3.07**
2	Age	.01	.02	.39	.04	.03	1.26
	Meno	.04	.02	1.5	.02	.03	.76
3	Meno	.05	.02	2.66**	.06	.03	2.10*

Note. Age was measured as a continuous variable. Meno = menopausal status represented as two effect-coded variables: −1 = pre-menopausal women, 1 = post-menopausal women. '∗' denotes *p* or *Pr* (>|*z*|) .05; '∗∗' denotes *p* or *Pr* (>|*z*|) .01; '∗∗∗' denotes *p* or *Pr* (>|*z*|) .001.

Table 7

Effect Sizes (β), Standard Errors (SE), and T-Values for Robust Regressions Models 1–3, Examining the Effects of (1) Age, (2) Age and Menopausal status, and (3) Menopausal Status on pSource.

		pSource Easy			pSource Hard		
Model	Fixed effects	*β*	*SE*	*t-value*	*β*	*SE*	*t-value*
1	Age	−.57	.17	-3.32***	−.53	.14	−3.7***
2	Age	−.07	.26	−.26	−.16	.23	−.69
	Meno	−0.82	0.30	−2.79**	−.61	.26	−2.33*
3	Meno	−.87	.21	−4.23***	−.69	.18	−3.86***

Note. Age was measured as a continuous variable. Meno = menopausal status represented as two effect-coded variables: −1 = pre-menopausal women, 1 = post-menopausal women. pSource = $z_{(\text{correct source rate})} - z_{(\text{source misattribution rate})}$. '∗' denotes *p* or *Pr* (>|*z*|) .05; '∗∗' denotes *p* or *Pr* (>|*z*|) .01; '∗∗∗' denotes *p* or *Pr* (>|*z*|) .001.

Table 8

Effect Sizes (β), Standard Errors (SE), and T-Values for Robust Regressions Models 1–3, Examining the Effects of (1) Age, (2) Age and Menopausal status, and (3) Menopausal Status on pRecog.

		pRecog Easy			pRecog Hard		
Model	Fixed effects	*β*	*SE*	*t-value*	*β*	*SE*	*t-value*
1	Age	.008	.10	.07	.05	.14	.36
2	Age	−.07	.18	−.37	.04	.26	.14
	Meno	.13	.21	.61	.04	.29	.14
3	Meno	.17	.16	1.07	.17	.24	.72

Note. Age was measured as a continuous variable. Meno = menopausal status represented as two effect-coded variables: −1 = pre-menopausal women, 1 = post-menopausal women. pRecog = $z_{(\text{correct item recognition rate})} - z_{(\text{false alarm rate})}$. '∗' denotes *p* or *Pr* (>|*z*|) .05; '∗∗' denotes *p* or *Pr* (>|*z*|) .01; '∗∗∗' denotes *p* or *Pr* (>|*z*|) .001.

For the second model, the peri-menopausal women were removed from the sample, and robust regressions were conducted with the predictors of age (continuous; aged 18–65), and menopausal status (categorical; pre- vs. post-menopausal women; n = 91; see Tables 5–8 and Appendix B). Menopausal status was a significant predictor of correct source rate for the easy version of the task ($\beta = -.10$, $SE = .04$, $t = -2.53$, $p = .01$), with higher scores observed in pre- compared to post-menopausal women. However, menopausal status was not a significant predictor for the hard version of the task after correcting for multiple comparisons ($\beta = -.08$, $SE = .04$, $t = 2.24$, $p = .03$). Age was not a significant predictor for easy or hard correct source rate. Correct item recognition rate was not significantly predicted by either age or menopausal status for the easy or hard versions of the task. Menopausal status was a significant predictor for pSource easy ($\beta = -0.82$, $SE = 0.30$, $t = -2.79$, $p < .01$), as higher scores were observed for pSource in pre-menopausal compared to post-menopausal women, but this effect did not extend to pSource hard. Age was not a significant predictor for pSource easy or hard. Finally, neither age nor menopausal status were significant predictors for pRecog, regardless of task difficulty. From this model, menopausal status was a significant predictor of correct source rate (easy) and pSource (easy), and there were no main or interactive effects with the predictor of age for any of the dependent variables.

The third model was conducted exclusively in a sample of MA women (aged 40–65) with the predictor of menopausal status (categorical; pre- vs. post-menopausal women; n = 50; see Tables 5–8 and Appendix C). From this model, menopausal status was a significant predictor for easy ($\beta = -.13$, $SE = .03$, $t = -4.32$, $p < .001$) and hard ($\beta = -.10$, $SE = .02$, $t = -4.39$, $p < .001$) correct source rate, with higher correct source rates for pre-menopausal compared to post-menopausal women at both encoding loads. Menopausal status was a significant predictor for correct item recognition rate during the easy version of the task ($\beta = .05$, $SE = .02$, $t = 2.66$, $p <$

.01), increasing in the post-menopausal group compared to the pre-menopausal group. However, menopause was not a significant predictor for the hard version of the task after correcting for multiple comparisons (β = .06, SE = .03, t = 2.10, p = .04). Menopausal status was a significant predictor for easy (β = −.13, SE = .03, t = −4.32, p < .001) and hard (β = −.10, SE = .02, t = −4.39, p < .001) pSource, declining in post-menopausal women compared to pre-menopausal women. Finally, neither pRecog easy nor hard were significantly predicted by menopausal status. This model demonstrated an effect of menopause on correct source rate (easy/hard), correct item recognition rate (easy), and pSource (easy/hard).

fMRI Results

Participants

Of the 109 participants that were included behaviourally, 77 subjects were retained for the fMRI analyses (see Table 9 for participant characteristics). From the excluded participants, 18 were omitted because they were peri-menopausal. Fourteen participants were excluded as a result of the following: quality control, old fMRI parameters that were used, and lost images. Participants included in the fMRI analysis were 54 pre-menopausal women (18–65; 31 young pre-menopausal women and 23 MA pre-menopausal women; M = 34.90, SD = 9.73) and 23 MA post-menopausal women (40–65; M = 58.10, SD = 3.84; see Table 10 for responses from the spatial source memory task by group). From this total, 72.7% were Caucasian, 3.9% Chinese, 2.6% Latin American, 2.6% South Asian, 1.3% Black, 1.3% Caucasian and Black, and 1.3% Caucasian and Latin American. Ethnic data was missing for 14.3% of women. Young women were included in the pre-menopausal sample due to sample size limitations. The higher number of participants included in a PLS analysis, the more stable the results will be. When the current sample is further enriched with additional MA participants, a separate analysis will be conducted on MA women exclusively to parallel the behavioural analyses comparing pre- and post-menopausal MA women.

Mann-Whitney U-Tests were conducted in IBM SPSS Statistics for Macintosh, Version 27.0 (IBM Corp.) to assess demographic measures by group (pre- vs. post-menopausal women) for measures of age, education, BMI, BAI, and BDI. Age was significantly different between pre- and post-menopausal women ($p < .05$), as post-menopausal women were significantly older than pre-menopausal women. Post-menopausal women had significantly lower levels of education ($p <. 05$). Otherwise, there were no statistically significant differences between groups for BMI, BAI, or BDI ($p >. 05$). Since education was significantly different between pre- and post-menopausal

Table 9

Participant Characteristics by Menopausal Group

	Total	Pre	Post
Sample size	77	54	23
*Age (years)	41.83 (13.58)	34.90 (9.73)	58.10 (3.84)
*EDU (years)	15.93 (2.33)	16.40 (1.95)	14.83 (2.79)
BMI (kg/m^2)	24.57 (4.57)	24.29 (4.77)	25.21 (4.08)
BAI	4.16 (4.03)	4.09 (4.00)	4.30 (4.19)
BDI-II	3.75 (3.76)	3.30 (3.27)	4.83 (4.64)
Hand (% right)	82.21 (40.19)	80.74 (40.88)	85.65 (39.18)
Hysterectomy (%)	3.90	.00	13
Antidepressant (%)	10.39	11.11	8.70
OC (%)	20.78	29.63	.00
HRT (%)	5.19	1.85	13.04
English (%)	32.5	35.18	26.09
French (%)	51.9	48.15	60.87
Other (%)	15.6	16.67	13.04

Note. Mean (standard deviation). Pre = pre-menopausal; Peri = peri-menopausal; Post = post-menopausal. EDU = education; BMI = body mass index; BDI-II = Beck Depression Inventory-II; BAI = Beck Anxiety Inventory; Hand = Handedness (% who are right-handed); OC = Oral contraceptive; HRT = Hormone replacement therapy (% on each medication); ENG = English; FR = French; Other = Language other than English or French (% whose mother tongue was English, French, or a different language). '*' denotes statistical significance ($p < .05$).

Table 10

Proportion Per Response Type from the Spatial Source Memory Task by Menopausal Group

	Total	Pre	Post
Hits easy	.91 (.08)	.92 (.07)	.88 (.10)
Hits hard	.85 (.11)	.86 (.10)	.82 (.12)
Correct source easy	.57 (.23)	.64 (.20)	.41 (.18)
Correct source hard	.39 (.20)	.45 (.19)	.25 (.13)
Correct item recog easy	.17 (.14)	.14 (.11)	.24 (.17)
Correct item recog hard	.28 (.17)	.25 (.16)	.35 (.18)
Correct rejection easy	.84 (.17)	.88 (.15)	.76 (.18)
Correct rejection hard	.81 (.17)	.83 (.17)	.75 (.18)
False alarm easy	.15 (.16)	.11 (.14)	.23 (.19)
False alarm hard	.18 (.16)	.16 (.15)	.24 (.17)
Source misattribution easy	.15 (.11)	.13 (.10)	.21 (.11)
Source misattribution hard	.18 (.15)	.16 (.14)	.23 (.16)
Miss easy	.09 (.08)	.08 (.07)	.12 (.10)
Miss hard	.13 (.10)	.12 (.09)	.17 (.12)
pSource easy	−.01 (1.79)	.54 (1.70)	−1.28 (1.30)
pSource hard	.02 (1.69)	.49 (1.67)	−1.09 (1.16)
pRecog easy	−.10 (1.48)	−.09 (1.12)	−.11 (2.14)
pRecog hard	−.07 (1.70)	−.06 (1.53)	−.08 (2.08)

Note. Mean (standard deviation). Pre = pre-menopausal; Post = post-menopausal. Rates were calculated as the number of events/total new or old events, easy or hard. pSource = $z_{(\text{correct source rate})} - z_{(\text{source misattribution rate})}$. pRecog = $z_{(\text{correct item recognition rate})} - z_{(\text{false alarm rate})}$.

women, and education level is a strong measure of cognitive reserve, we re-ran the robust regression analyses with the sample of participants included in the BPLS (n=77) and added education as an additional independent variable to each of the models. However, there were no main or interaction effects for education, and our results were consistent with what was previously shown.

fMRI Results

A B-PLS was conducted to test our second hypothesis, which stipulated that age and performance-related brain-behavioural correlations would differ according to menopausal status in MTL and fronto-parietal regions. From the BPLS, there was one significant latent variable, LV1 ($p < .001$). The second LV (LV2; $p = .059$) was nearing significance and will also be discussed. Local maxima (see Tables 11, 12 for LV1 and LV2 respectively) vary according to the brain-behaviour correlations for the corresponding LV (see Figures 3, 4). Thus, they are not specifically associated with either encoding or retrieval. Positive correlations show an association between behavior and positive-weighted regions, which are represented by warmer colours in the singular image, and are negatively associated with cooler coloured regions. The opposite is true for negative correlations.

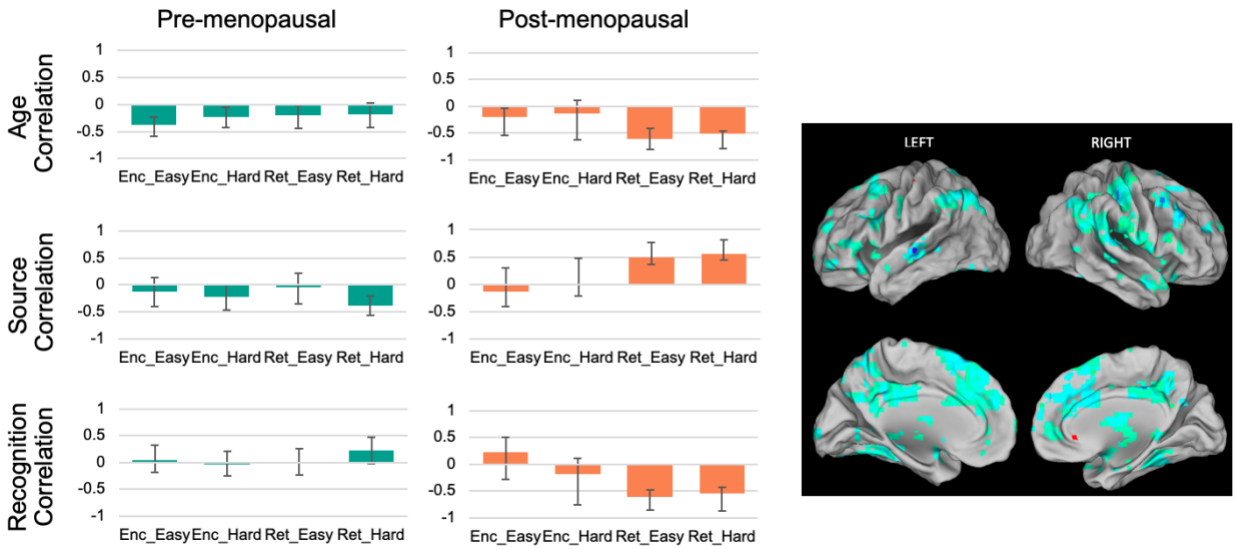
Latent variable 1 accounted for 22.78% of cross-block covariance (See Figure 3; Table 11). Negative salience regions correlated with age in both groups at encoding and retrieval. However, this LV was primarily driven by post-menopausal women at retrieval. More specifically, a pattern of age-related differences in activation in negative salience regions supported item recognition and was negatively correlated with performance for correct source in post-menopausal women. In contrast, these same negative salience regions that were tracking with age and were activated during item recognition memory in post-menopausal women supported source memory in pre-

menopausal women at higher encoding loads. Thus, the regions that supported source memory at a higher level of difficulty in pre-menopausal women shifted to supporting item recognition memory in older post-menopausal women regardless of task difficulty. Negative salience regions primarily include areas of medial and lateral fronto-parietal networks (i.e., default mode and cognitive control networks; Uddin et al., 2019).

Latent variable 2 accounted for 15% of cross-block covariance and was trending towards significance (p = .059; see Figure 4; Table 12). From this LV we saw an effect that was exclusive to post-menopausal women, primarily at encoding. Age-related differences in performance, which changed in proportion from source to item recognition, were correlated with different patterns of activation. Specifically, positive salience brain regions, including posterior regions of the MTL, bilateral DLPFC and medial parietal areas were associated with younger age and better source memory. Negative salience regions were associated with older age and item recognition memory and included the right fusiform gyrus and putamen.

Figure 3

Behaviour Partial Least Squares Analysis LV1



Note. Brain-behavior correlation profile (left) and singular image (right) for LV1, which displays an interaction effect between menopausal status and memory type accuracy at retrieval. Error bars represent 95% CI. Positive correlations show an association between behavior and positive-weighted regions, which are represented by warmer colours in the singular image and are negatively associated with cooler coloured regions. The opposite is true for negative correlations. Peak activity from the BPLS temporal brain correlation plots was observed at lags 3–5. The singular image presented are based on these lags. Singular images were created with Caret software (http://brainvis.wustl.edu/wiki/index.php/Caret:Download).

Table 11

Local Maxima LV1

			Talairach Coordinates				
Temporal lag	*BSR*	*Cluster size*	*x*	*y*	*z*	*Gyral location*	*BA*
Negative saliences							
Left hemisphere							
3, 4	−7.99	119	−48	22	−2	Inferior frontal gyrus	47
2, 3, 4	−7.67	620	−9	7	63	Superior frontal gyrus	6
4	−7.54	22	−1	−95	−1	Cuneus	17
3	−7.31	70	−57	−20	−2	Middle temporal gyrus	21
3, 4, 5	−6.57	36	−42	51	1	Middle frontal gyrus	10
4	−6.28	150	−39	−79	29	Superior occipital gyrus	19
3, 5	−6.20	284	−2	−35	−37	Cingulate gyrus	31
2, 3	−6.04	186	−39	−49	31	Supramarginal gyrus	40
4	−5.78	24	−61	−55	9	Superior temporal gyrus	22
5	−5.42	11	−1	−95	−5	Lingual gyrus	18
4, 5	−4.88	85	−2	−51	43	Precuneus	7
2	−4.45	13	−23	−42	−11	Parahippocampal gyrus	36
3	−4.36	15	−5	25	43	Medial frontal gyrus	8
3	−4.24	36	−5	−52	21	Posterior cingulate	31
3, 4	−4.06	30	−50	−15	31	Precentral gyrus	6

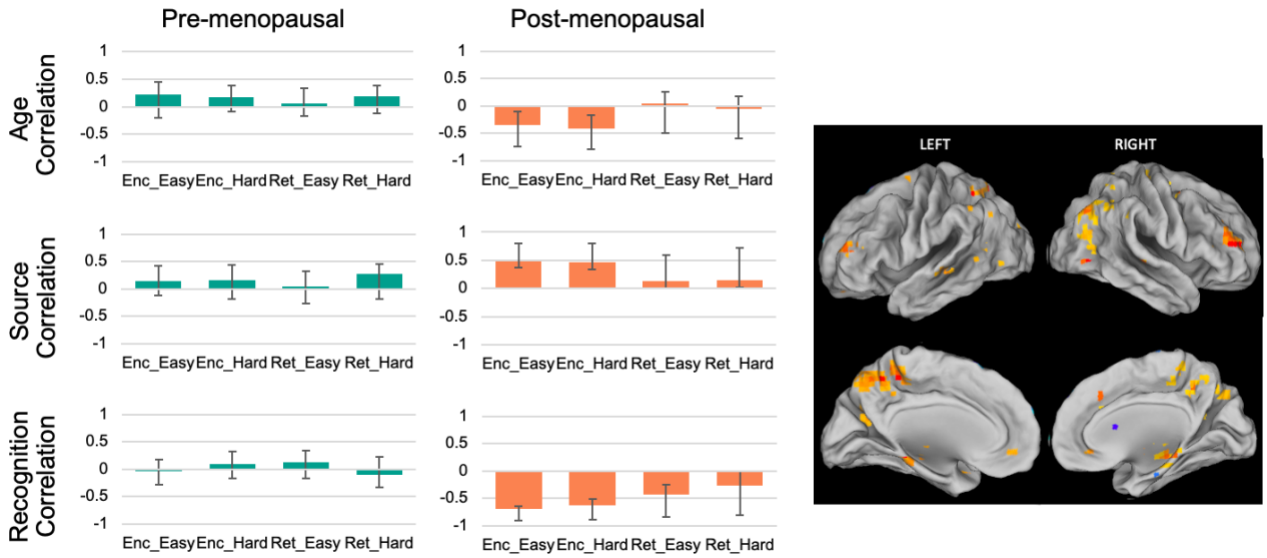
Table 11 (continued)

			Talairach Coordinates				
Temporal lag	*BSR*	*Cluster size*	*x*	*y*	*z*	*Gyral location*	*BA*
Right hemisphere							
3, 4	−8.86	130	35	−29	45	Post-central gyrus	3
3, 4	−8.21	380	39	−22	17	Insula	13
3, 5	−7.84	584	51	17	0	Inferior frontal gyrus	47
4, 5	−6.09	129	2	8	63	Superior frontal gyrus	6
4	−5.99	40	14	−11	18	Thalamus	−
3, 4	−5.78	31	35	5	49	Middle frontal gyrus	6
4	−5.44	22	51	14	−1	Superior temporal gyrus	22
2	−5.32	29	29	−37	−17	Fusiform gyrus	20
3	−5.24	14	10	−39	1	Parahippocampal gyrus	30
3	−4.80	28	6	34	26	Anterior cingulate	32
3	−4.70	10	47	−58	3	Middle temporal gyrus	37
2, 4, 5	−4.51	12	24	−51	43	Precuneus	7
2	−4.16	11	27	−60	57	Superior parietal lobule	7
4	−3.87	12	18	−13	0	Globus pallidus	−
2	−3.80	10	21	10	−2	Putamen	−

Note. Temporal lags reflect the time (s) after event onset, when a cluster of voxels exhibited an effect of interest. BSR = bootstrap ratio, set to ± 3.28 ($p < .001$). Cluster size = number of voxels (threshold = 10). BA = Brodmann area. Stereotaxic coordinates, gyral location, and Brodmann area were established using the Talairach and Tournoux atlas (1998).

Figure 4

Behaviour Partial Least Squares Analysis LV2



Note. Brain-behavior correlation profile (left) and singular image (right) for LV2, which displays a main effect of correct source vs. item recognition at encoding in post-menopausal women. Error bars represent 95% CI. Positive correlations show an association between behavior and positive-weighted regions, which are represented by warmer colours in the singular image and are negatively associated with cooler coloured regions. The opposite is true for negative correlations. Peak activity from the BPLS temporal brain correlation plots was observed at lags 3–5. The singular image presented are based on these lags. Singular images were created with Caret software (http://brainvis.wustl.edu/wiki/index.php/Caret:Download).

Table 12

Local Maxima LV2

			Talairach coordinates				
Temporal lag	*BSR*	*Cluster size*	*x*	*y*	*z*	*Gyral location*	*BA*
Positive saliences							
Left hemisphere							
4	6.08	41	−42	34	29	Middle frontal gyrus	9
5	5.70	31	−13	−44	47	Precuneus	7
5	4.63	42	−20	−59	16	Posterior cingulate	31
5	4.62	10	−53	−24	1	Superior temporal gyrus	21
5	4.27	21	−27	−66	5	Lingual gyrus	19
Right hemisphere							
3	4.85	10	40	−65	−8	Middle occipital gyrus	19
4, 5	5.10	37	36	41	27	Middle frontal gyrus	10
4	4.56	10	58	−24	3	Superior temporal gyrus	22
5	8.03	303	32	−73	34	Precuneus	19
5	5.43	40	9	−41	55	Paracentral Lobule	5
5	4.06	15	25	−19	−8	Parahippocampal Gyrus	28
Negative saliences							
Left hemisphere							
2	−4.73	24	−31	−6	7	Putamen	−

Table 12 (continued)

			Talairach coordinates				
Temporal lag	*BSR*	*Cluster size*	*x*	*y*	*z*	*Gyral location*	*BA*
Right hemisphere							
2	−5.52	32	54	3	27	Inferior frontal gyrus	9

Note. Temporal lags reflect the time (s) after event onset, when a cluster of voxels exhibited an effect of interest. BSR = bootstrap ratio, set to ± 3.28 ($p < .001$). Cluster size = number of voxels (threshold = 10). BA = Brodmann area. Stereotaxic coordinates, gyral location, and Brodmann area were established using the Talairach and Tournoux atlas (1998).

Discussion

Behavioural Discussion

The purpose of this study was to assess the effects of chronological and reproductive aging on episodic memory performance and associated brain function. We predicted that we would see a decline in source accuracy rate with increased age, which would be more pronounced in post-menopausal women. Further, we hypothesized that correct item recognition rate would be stable regardless of age or menopausal status. Our results support this hypothesis. Both age and menopausal status were significant predictors of source memory decline for the easy and hard versions of the task when evaluated separately. When evaluating the impact of age and menopausal status in the same model, the significant effect was lost for the hard version of the task, since the variance was shared by both age and menopause. However, the source memory decline during the easy version of the task was retained with the predictor of menopause, highlighting the compounding impact of menopause on the age effect.

These findings are mirrored by the item recognition results. Correct item recognition rate increased for the easy version of the task in post-menopausal women, yet increased during the hard version of the task with age. The way the spatial source memory task was designed, participants could either choose to respond that they remembered seeing the face, but not the location (i.e., the participant correctly responded with familiar), or they could choose to respond that they remembered the face as well as its location (i.e., the participant correctly responded either top left, top right, bottom left, or bottom right). Thus, item recognition hits encapsulate remembering only the face, while source hits encapsulate remembering both the face and the source. When correct source rate declined with both age and menopausal status, there was a reduction in the number of locations these participants remembered. However, the number of faces remained the same. Thus,

while correct item recognition rate increased, this uptick represents a stabilization of item recognition memory that accompanied the decline in source memory. These results were observed from the easy version of the task in post-menopausal women, and from the hard version of the task with increased age.

The behavioural findings align with previous research on chronological aging at midlife, which has demonstrated negative aging effects on spatial source memory performance at higher encoding loads (Kwon et al., 2016). Kwon and colleagues (2016) reported a decline in spatial source memory in MA adults compared to young adults at higher encoding loads but not lower encoding loads. In contrast, declines were reported in the MA sample for both lower and higher levels of encoding load for temporal source memory, suggesting that source memory decline with age is sensitive to modality type. Consequently, these results cannot be generalized to all measures of source memory, but specifically to spatial source memory.

To our knowledge, menopausal effects on source vs. item memory have not previously been studied. However, inconsistent results have been reported from studies evaluating menopausal effects on other measures of episodic memory (Epperson et al., 2013; Henderson et al., 2003; Herlitz et al., 2007; Luetters et al., 2007; Maki & Henderson, 2016). For example, in a study assessing verbal episodic memory, Herlitz and colleagues (2003) saw no difference in performance between pre, peri, and post-menopausal women. Conversely, Epperson and colleagues (2013) conducted a longitudinal study and reported a decline in verbal episodic memory performance from when the participants were pre-menopausal compared to when they were post-menopausal. Some of these studies, including the one conducted by Herlitz and colleagues (2007) covaried out the age effects. This may have split the variance and could account for the lack of observed menopausal effects, similar to what was demonstrated in our study. In the present study,

significance for various dependent variables was lost in the regression model that included age and menopausal status as predictors compared to the model with menopausal status alone (Herlitz et al., 2007; Henderson et al., 2003). It is also plausible that these inconsistencies represent the fact that some women do not experience cognitive declines as a result of menopause. Rentz and colleagues (2017) demonstrated that while generally, post-menopausal women had lower scores on their verbal episodic memory task, a subset of post-menopausal women displayed memory performance that was comparable to pre-menopausal women, suggesting that additional factors may be interacting with hormonal fluctuations at menopause (Rentz et al., 2017; Scheyer et al., 2018).

In addition to the primary hypothesis assessing correct source and correct item recognition, pSource and pRecog were evaluated to explore the effects of aging and menopausal status on response bias. We found that pSource was impacted by both age and menopausal status during the easy and hard versions of the task. These results indicate that both older and post-menopausal participants had a higher number of source misattributions in addition to a lower number of source hits. In the Source Monitoring Framework presented by Mitchell and Johnson (2009), the researchers suggested that source misattributions are accounted for by the same mechanisms as true source memories. Schacter and colleagues (1997) suggested that source misattributions in older adults result from frontal lobe dysfunction causing a reduction in the ability sufficiently strategize, which is required to remember the source features associated with an item. Since pSource performance in our study parallels source memory performance, our results are consistent with these theories.

We saw no group differences in pRecog, indicating that response bias for old responses, which takes false alarms into consideration, was consistent across groups. This is in line with

previous research, which indicates that false alarms only begin appearing in older adulthood (Schacter, Koutstaal & Norman, 1997). False alarms have been associated with a deficit in episodic memory performance, which mediates inhibition processes (Lövdén, 2003). The results for false alarms match item recognition performance in our study, as both processes were retained regardless of age or menopausal status. Our results support Lövden's theory and suggest that both item recognition memory and inhibition processes remain intact in women at midlife. To sum, we saw source memory decline in women at midlife due to chronological aging, which was further compounded by reproductive aging. This decline was accompanied by an increase in source misattributions. However, item recognition memory and associated inhibition processing were preserved.

fMRI Discussion

This is one of the few studies to evaluate memory-related brain function from both a chronological and reproductive aging perspective in women (Mosconi et al., 2018; Taylor et al., 2019). We hypothesized that chronological aging would affect MTL and fronto-parietal activity during memory performance at encoding and retrieval, and that these changes would be more pronounced in post-menopausal women. Our results from the BPLS analysis align with this hypothesis. From LV1, we saw activation differences in these systems with increased age and menopause. An interaction between menopausal status and source memory accuracy was observed primarily in the medial fronto-parietal (i.e., default mode) network, which is associated with recollection, and the lateral fronto-parietal network, which is primarily linked to cognitive control processes (Rugg & Vilberg, 2013; Uddin, Yeo, & Spreng, 2019).

From LV1, we saw that the systems that older *pre*-menopausal women were using to support source memory during hard tasks (i.e., the negative salience regions) were the same

systems that were activated during item recognition memory in older *post*-menopausal women (see Figure 3, Table 11). Thus, the systems that were initially involved in remembering both the face and the quadrant at a higher encoding load in pre-menopausal women with older age, shifted to supporting only facial recognizing in older post-menopausal women at both encoding loads. The older post-menopausal women were activating these memory systems for a less distinct, more generalized process. Recruitment of these systems were compensatory in nature for pre-menopausal women with advanced age, but in post-menopausal women, they maintained a simpler process.

These results are consistent with different cognitive aging theories, such as the compensation-related utilization of neural circuits, or CRUNCH model of aging (Reuter-Lorenz & Cappell, 2008). The CRUNCH model stipulates that higher levels of brain activity are observed as a compensatory measure when performing difficult cognitive tasks. As task load increases, the maximum compensatory mechanism is met for older individuals, and activation levels may fall below the level of activity for younger individuals, whose neural activity continues to increase to meet the heightened task demands (Reuter-Lorenz & Cappell, 2008). In this study, these age effects are observed, although they map onto performance differently in pre- compared to post-menopausal women. Compensation can be seen in the pre-menopausal group, as older pre-menopausal women recruited these systems at higher encoding loads. In older post-menopausal women, the maximum compensatory mechanism was surpassed, and activity in these regions was no longer detected for source memory performance.

The second LV was nearing significance (p=.059) and accounted for a meaningful portion of the cross-block covariance from the BPLS analysis. From LV2, we saw age-related increases at menopause that specifically affected encoding-related processes in a broad set of regions including

the MTL. More specifically, older age was differentially correlated to encoding success and supporting successful subsequent source memory at the cost of item recognition memory. Both menopause and MTL dysfunctions are known to occur in later midlife. Estradiol, whose concentration level drops at menopause, has a significant impact on MTL function (Koebele & Bimonte-Nelson, 2017). Additionally, MTL function is crucial for episodic memory encoding (Squire & Zola-Morgan, 1991). Taken together, it can be interpreted that the estradiol decline at menopause may be driving some of the MTL dysfunction observed in women at encoding in later midlife.

It is important to note that source memory performance was positively correlated with activity specifically in the posterior MTL (see positive salience regions in the right hemisphere from LV2; Table 12, Figure 4). The posterior medial/anterior temporal (PMAT) model of the MTL suggests that the MTL are divided into two systems of cognitive functioning (Ranganath & Ritchey, 2012; Ritchey, Libby, & Ranganath, 2015). According to this model, regions of the MTL are essential components of two larger cortical systems of memory and cognition. The perirhinal cortex is a fundamental structure of the anterior temporal system, which sends information to subsections of the hippocampus (i.e., distal/temporal CA1 and proximal/temporal subiculum) via the lateral entorhinal cortex. The perirhinal cortex is involved in the processing and storage of item memory. The parahippocampal cortex is a central structure of the posterior medial system, which sends information to distinct subsections of the hippocampus (i.e., proximal/septal CA1 and distal/septal subiculum) via the medial entorhinal cortex. The parahippocampal cortex is involved in processing and storing source features associated with items. Our results are consistent with this model, as we observed that activity in posterior regions of the MTL accompanied source memory

performance. To sum, our BPLS results maintain that age and performance-related brain activity at encoding and retrieval differ in pre- and post-menopausal women.

Limitations

This study included some limitations. First, only 24 post-menopausal women were included in this study. Results from a PLS analysis are more variable with smaller sample sizes, and as previously noted, a sample of 80 participants is necessary for reliable brain-behaviour correlations. This study is therefore currently underpowered. A very high number of women were excluded from the study after session one primarily because they failed our cognitive tests, had high levels of anxiety and depression, or a combination of the two. This suggests that the MA women tested in our study were experiencing additional cognitive deficits and symptoms of mood disorders, further demonstrating that midlife is a critical time to study cognition in women. We hope to include these women in future analyses to understand how additional factors such as clinical symptoms interact with memory in women at this life stage. Brain activity in the PLS analysis was also assessed during total hits. Ideally, activity would have been independently assessed during correct source hits and correct item recognitions, but too much data was lost this way. Partial least squares requires a minimum number of events per condition. When splitting the fMRI data into item and source memory, there was not enough events for correct item recognition for high performers or correct source events for low performers. Moreover, this study was conducted using cross-sectional data rather than longitudinal data. Our results may in part be the product of generational and societal differences between cohorts rather than aging effects. Finally, this study was conducted during the COVID-19 pandemic. Aside from the reduced sample size, an additional consideration is how the pandemic, and COVID-19 itself, may have affected

cognition in our participants. Additionally, certain individuals may have been more willing to come for testing in person than others during a pandemic which may potentially bias the results.

Future Directions

This project is part of the larger Brain Health at Midlife and Menopause (BHAMM) study that is being conducted in the Rajah Lab. In the future, we hope to run the BPLS analysis on MA women only, so that the menopausal analysis that was run behaviourally can be paralleled with fMRI analyses. We would also like to analyze the interaction between chronological aging, reproductive aging, and genetic risk factors for Alzheimer's disease (i.e., Apoliprotein E [APOE] status). It is plausible that cognitive effects are seen in only some post-menopausal women because of additional variables that are interacting with the hormonal fluctuations at menopause. Furthermore, a gender component will be added to this study to evaluate how sociocultural aspects of women's experiences interact with measures of aging, as we hope to distinguish aging effects from generational and societal differences. Finally, we would like to include a group of men in the larger study, to assess how sex differences in episodic memory performance at midlife relate to both chronological and reproductive aging.

Conclusions

To conclude, results from the behavioural and fMRI analyses aligned with our outlined hypotheses. Behaviourally, source memory decline was associated with increased age, and this effect was magnified by reproductive aging. Item recognition memory remained intact regardless of age and menopausal status. From the fMRI analyses, we saw interactions between episodic memory-related brain activity with age and performance in regions of the medial temporal lobes, as well as fronto-parietal and default mode networks that varied according to menopausal status. Overall, our results underscore the need for chronological and reproductive aging to be considered

together in future cognitive aging studies in women, as they impact the same brain systems. This study is therefore contributing to a more accurate representation of female brain aging and memory at midlife.

References

Andreano, J. M., & Cahill, L. (2009). Sex influences on the neurobiology of learning and memory. *Learning & Memory, 16*, 248–266. https://doi.org/10.1101/lm.918309

Bäckman, L., Jones, S., Berger, A.-K., Laukka, E. J., & Small, B. J. (2005). Cognitive impairment in preclinical Alzheimer's disease: A meta-analysis. *Neuropsychology*, *19*, 520–531. https://doi.org/10.1037/0894-4105.19.4.520

Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology*, *56*(6), 893–897. https://doi.org/10.1037/0022-006X.56.6.893

Beck, A. T., Steer, R. A., & Brown, G. (1996). Beck Depression Inventory–II. https://doi.org/10.1037/t00742-000

Cabeza, R., & Nyberg, L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience*, *12*, 1–47. https://doi.org/10.1162/08989290051137585

Cansino, S. (2009). Episodic memory decay along the adult lifespan: A review of behavioral and neurophysiological evidence. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology*, *71*, 64–69. https://doi.org/10.1016/j.ijpsycho.2008.07.005

Cansino, S., Estrada-Manilla, C., Trejo-Morales, P., Pasaye-Alcaraz, E. H., Aguilar-Castañeda, E., Salgado-Lujambio, P., & Sosa-Ortiz, A. L. (2015). FMRI subsequent source memory effects in young, middle-aged and old adults. *Behavioural Brain Research*, *280*, 24–35. https://doi.org/10.1016/j.bbr.2014.11.042

Cansino, S., Maquet, P., Dolan, R. J., & Rugg, M. D. (2002). Brain activity underlying encoding and retrieval of source memory. *Cerebral Cortex, 12*(10), 1048–1056. https://doi.org/10.1093/cercor/12.10.1048

Chalfonte, B. l., & Johnson, M. K. (1996). Feature memory and binding in young and older adults. *Memory & Cognition*, *24*, 403–416. https://doi.org/10.3758/BF03200930

Cockrell, J.R., Folstein, M.F. Mini-Mental State Examination (MMSE). (1988). *Psychopharmacol Bull*, *24*, 689–92.

Dale, A. M., & Buckner, R. L. (1997). Selective averaging of rapidly presented individual trials using fMRI. *Human Brain Mapping*, *5*, 329–340. https://doi.org/10.1002/(SICI)1097-0193(1997)5:5<329::AID-HBM1>3.0.CO;2-5

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis: I. Segmentation and surface reconstruction. *NeuroImage*, *9*, 179–194. https://doi.org/10.1006/nimg.1998.0395

Davachi, L., Mitchell, J. P., & Wagner, A. D. (2003). Multiple routes to memory: Distinct medial temporal lobe processes build item and source memories. *Proceedings of the National Academy of Sciences*, *100*(4), 2157–2162. https://doi.org/10.1073/pnas.0337195100

Delis, D.C., Kramer, J.H., Kaplan, E., Ober. B.A. (2000). California Verbal Learning Test – second edition. Adult version. *Psychological Corporation (San Antonio, TX.)*

Dennis, N. A., Hayes, S. M., Prince, S. E., Madden, D. J., Huettel, S. A., & Cabeza, R. (2008). Effects of aging on the neural correlates of successful item and source memory encoding. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *34*, 791–808. https://doi.org/10.1037/0278-7393.34.4.791

Desmond, J. E., & Glover, G. H. (2002). Estimating sample size in functional MRI (fMRI) neuroimaging studies: Statistical power analyses. *Journal of Neuroscience Methods*, *118*(2), 115–128. https://doi.org/10.1016/S0165-0270(02)00121-8

Division of data, analytics and delivery for impact, WHO Geneva. (2020, December). *WHO methods and data sources for life tables 1990-2019*. https://www.who.int/data/maternal-newborn-child-adolescent-ageing/advisory-groups/gama/gama-advisory-group-members

Dulas, M. R., & Duarte, A. (2012). The effects of aging on material-independent and material-dependent neural correlates of source memory retrieval. *Cerebral Cortex*, *22*, 37–50. https://doi.org/10.1093/cercor/bhr056

Edwards, H., Duchesne, A., Au, A. S., & Einstein, G. (2019). The many menopauses: Searching the cognitive research literature for menopause types. *Menopause (New York, N.y.)*, *26*(1), 45–65. https://doi.org/10.1097/GME.0000000000001171

Eickhoff, S. B., Laird, A. R., Grefkes, C., Wang, L. E., Zilles, K., & Fox, P. T. (2009). Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: A random-effects approach based on empirical estimates of spatial uncertainty. *Human Brain Mapping*, *30*(9), 2907–2926. https://doi.org/10.1002/hbm.20718

Epperson, C. N., Sammel, M. D., & Freeman, E. W. (2013). Menopause effects on verbal memory: Findings from a longitudinal community cohort. *The Journal of Clinical Endocrinology & Metabolism*, *98*(9), 3829–3838. https://doi.org/10.1210/jc.2013-1808

Esteban, O., Markiewicz, C. J., Blair, R. W., Moodie, C. A., Isik, A. I., Erramuzpe, A., Kent, J. D., Goncalves, M., DuPre, E., Snyder, M., Oya, H., Ghosh, S. S., Wright, J., Durnez, J., Poldrack, R. A., & Gorgolewski, K. J. (2019). fMRIPrep: A robust preprocessing pipeline

for functional MRI. *Nature Methods*, *16*, 111–116. https://doi.org/10.1038/s41592-018-0235-4

Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods, 41*, 1149–1160. doi: 10.3758/BRM.41.4.1149

Fletcher, P. C., & Henson, R. N. A. (2001). Frontal lobes and human memory: Insights from functional neuroimaging. *Brain*, *124*(5), 849–881. https://doi.org/10.1093/brain/124.5.849

Grady, C. L., Rieck, J. R., Nichol, D., Rodrigue, K. M., & Kennedy, K. M. (2021). Influence of sample size and analytic approach on stability and interpretation of brain-behavior correlations in task-related fMRI data. *Human Brain Mapping*, *42*, 204–219. https://doi.org/10.1002/hbm.25217

Greendale, G. A., Derby, C. A., & Maki, P. M. (2011). Perimenopause and cognition. *Obstetrics and Gynecology Clinics*, *38*, 519–535. https://doi.org/10.1016/j.ogc.2011.05.007

Greve, D. N., & Fischl, B. (2009). Accurate and robust brain image alignment using boundary-based registration. *NeuroImage*, *48*, 63–72. https://doi.org/10.1016/j.neuroimage.2009.06.060

Gur, R. E., & Gur, R. C. (2002). Gender differences in aging: Cognition, emotions, and neuroimaging studies. *Dialogues in Clinical Neuroscience*, *4*, 197–210.

Habib, R., Nyberg, L., & Tulving, E. (2003). Hemispheric asymmetries of memory: The HERA model revisited. *Trends in Cognitive Sciences*, *7*, 241–245. https://doi.org/10.1016/S1364-6613(03)00110-4

Harvey, P.-O., Fossati, P., & Lepage, M. (2007). Modulation of memory formation by stimulus content: Specific role of the medial prefrontal cortex in the successful encoding of social pictures. *Journal of Cognitive Neuroscience*, *19*, 351–362. https://doi.org/10.1162/jocn.2007.19.2.351

Henderson, V. W., Guthrie, J. R., Dudley, E. C., Burger, H. G., & Dennerstein, L. (2003). Estrogen exposures and memory at midlife: A population-based study of women. *Neurology*, *60*(8), 1369–1371. https://doi.org/10.1212/01.WNL.0000059413.75888.BE

Henderson, V. W., & Sherwin, B. B. (2007). Surgical versus natural menopause: Cognitive issues. *Menopause*, *14*, 572–579. https://doi.org/10.1097/gme.0b013e31803df49c

Herlitz, A., Thilers, P., & Habib, R. (2007). Endogenous estrogen is not associated with cognitive performance before, during, or after menopause. *Menopause*, *14*, 425–431. https://doi.org/10.1097/01.gme.0000247019.86748.e3

Heys, M., Jiang, C., Cheng, K. K., Zhang, W., Yeung, S. L. A., Lam, T. H., Leung, G. M., & Schooling, C. M. (2011). Life long endogenous estrogen exposure and later adulthood cognitive function in a population of naturally postmenopausal women from Southern China: The Guangzhou Biobank Cohort Study. *Psychoneuroendocrinology*, *36*, 864–873. https://doi.org/10.1016/j.psyneuen.2010.11.009

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. *Journal of Neuroscience*, *36*(39), 10163–10173. https://doi.org/10.1523/JNEUROSCI.0951-16.2016

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *NeuroImage*, *17*(2), 825–841. https://doi.org/10.1006/nimg.2002.1132

Klein, A., Ghosh, S. S., Bao, F. S., Giard, J., Häme, Y., Stavsky, E., Lee, N., Rossa, B., Reuter, M., Neto, E. C., & Keshavan, A. (2017). Mindboggling morphometry of human brains. *PLOS Computational Biology*, *13*(2), e1005350. https://doi.org/10.1371/journal.pcbi.1005350

Koebele, S. V., & Bimonte-Nelson, H. A. (2017). The endocrine-brain-aging triad where many paths meet: Female reproductive hormone changes at midlife and their influence on circuits important for learning and memory. *Experimental Gerontology*, *94*, 14–23. https://doi.org/10.1016/j.exger.2016.12.011

Krishnan, A., Williams, L. J., McIntosh, A. R., & Abdi, H. (2011). Partial Least Squares (PLS) methods for neuroimaging: A tutorial and review. *NeuroImage*, *56*, 455–475. https://doi.org/10.1016/j.neuroimage.2010.07.034

Kuhl, B. A., Johnson, M. K., & Chun, M. M. (2013). Dissociable neural mechanisms for goal-directed versus incidental memory reactivation. *Journal of Neuroscience*, *33*(41), 16099–16109. https://doi.org/10.1523/JNEUROSCI.0207-13.2013

Kwon, D., Maillet, D., Pasvanis, S., Ankudowich, E., Grady, C. L., & Rajah, M. N. (2016). Context memory decline in middle aged adults is related to changes in prefrontal cortex function. *Cerebral Cortex*, *26*(6), 2440–2460. https://doi.org/10.1093/cercor/bhv068

Lancaster, J. L., Tordesillas-Gutiérrez, D., Martinez, M., Salinas, F., Evans, A., Zilles, K., Mazziotta, J. C., & Fox, P. T. (2007). Bias between MNI and Talairach coordinates

analyzed using the ICBM-152 brain template. *Human Brain Mapping*, *28*(11), 1194–1205. https://doi.org/10.1002/hbm.20345

Levine, B., Svoboda, E., Hay, J. F., Winocur, G., & Moscovitch, M. (20021204). Aging and autobiographical memory: Dissociating episodic from semantic retrieval. *Psychology and Aging*, *17*, 677. https://doi.org/10.1037/0882-7974.17.4.677

Lövdén, M. (2003). The episodic memory and inhibition accounts of age-related increases in false memories: A consistency check. *Journal of Memory and Language*, *49*, 268–283. https://doi.org/10.1016/S0749-596X(03)00069-X

Luetters, C., Huang, M.-H., Seeman, T., Buckwalter, G., Meyer, P. M., Avis, N. E., Sternfeld, B., Johnston, J. M., & Greendale, G. A. (2007). Menopause transition stage and endogenous estradiol and follicle-stimulating hormone levels are not related to cognitive performance: Cross-sectional results from the Study of Women's Health across the Nation (SWAN). *Journal of Women's Health*, *16*, 331–344. https://doi.org/10.1089/jwh.2006.0057

Mackinnon, A., & Mulligan, R. (2005). Estimation de l'intelligence prémorbide chez les francophones. *L'Encéphale*, *31*, 31–43. https://doi.org/10.1016/S0013-7006(05)82370-X

Maki, P. M., & Henderson, V. W. (2016). Cognition and the menopause transition. *Menopause*, *23*(7), 803–805. https://doi.org/10.1097/GME.0000000000000681

McCarthy, M. M., Arnold, A. P., Ball, G. F., Blaustein, J. D., & Vries, G. J. D. (2012). Sex differences in the brain: The not so inconvenient truth. *Journal of Neuroscience*, *32*(7), 2241–2247. https://doi.org/10.1523/JNEUROSCI.5372-11.2012

McDonough, I. M., Wong, J. T., & Gallo, D. A. (2013). Age-related differences in prefrontal cortex activity during retrieval monitoring: Testing the compensation and dysfunction accounts. *Cerebral Cortex*, *23*(5), 1049–1060. https://doi.org/10.1093/cercor/bhs064

McEwen, B. S., Akama, K. T., Spencer-Segal, J. L., Milner, T. A., & Waters, E. M. (2012). Estrogen effects on the brain: Actions beyond the hypothalamus via novel mechanisms. *Behavioral Neuroscience*, *126*, 4–16. https://doi.org/10.1037/a0026708

McEwen, B. S., Nasca, C., & Gray, J. D. (2016). Stress effects on neuronal structure: hippocampus, amygdala, and prefrontal cortex. *Neuropsychopharmacology*, *41*, 3–23. https://doi.org/10.1038/npp.2015.171

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. https://doi.org/10.1016/j.neuroimage.2004.05.018

Mitchell, K. J., & Johnson, M. K. (2009). Source monitoring 15 years later: What have we learned from fMRI about the neural mechanisms of source memory? *Psychological Bulletin*, *135*, 638–677. https://doi.org/10.1037/a0015849

Mosconi, L., Rahman, A., Diaz, I., Wu, X., Scheyer, O., Hristov, H. W., Vallabhajosula, S., Isaacson, R. S., Leon, M. J. de, & Brinton, R. D. (2018). Increased Alzheimer's risk during the menopause transition: A 3-year longitudinal brain imaging study. *PLOS ONE*, *13*, 1–13. https://doi.org/10.1371/journal.pone.0207885

Nelson, H.E. (1982). *The National Adult Reading Test (NART): Test Manual*. Windsor, Berks, U.K.: NFER-Nelson.

Norman, M. A., Evans, J. D., Miller, W. S., & Heaton, R. K. (2000). Demographically corrected norms for the California Verbal Learning Test. *Journal of Clinical and Experimental Neuropsychology, 22*, 80–94. https://doi.org/10.1076/1380-3395(200002)22:1;1-8;FT080

Nyberg, L., Cabeza, R., & Tulving, E. (1996). PET studies of encoding and retrieval: The HERA model. *Psychonomic Bulletin & Review*, *3*(2), 135–148. https://doi.org/10.3758/BF03212412

Old, S. R., & Naveh-Benjamin, M. (2008). Differential effects of age on item and associative measures of memory: A meta-analysis. *Psychology and Aging*, *23*, 104–118. https://doi.org/10.1037/0882-7974.23.1.104

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, *9*, 97–113. https://doi.org/10.1016/0028-3932(71)90067-4

Park, H., Kennedy, K. M., Rodrigue, K. M., Hebrank, A., & Park, D. C. (2013). An fMRI study of episodic encoding across the lifespan: Changes in subsequent memory effects are evident by middle-age. *Neuropsychologia*, *51*, 448–456. https://doi.org/10.1016/j.neuropsychologia.2012.11.025

Power, J. D., Mitra, A., Laumann, T. O., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. *NeuroImage*, *84*, 320–341. https://doi.org/10.1016/j.neuroimage.2013.08.048

Rajah, M. N., Languay, R., & Valiquette, L. (2010). Age-related changes in prefrontal cortex activity are associated with behavioural deficits in both temporal and spatial context memory retrieval in older adults. *Cortex, 46*, 535–549. https://doi.org/10.1016/j.cortex.2009.07.006

Ranganath, C., Johnson, M. K., & D'Esposito, M. (2003). Prefrontal activity associated with working memory and episodic long-term memory. *Neuropsychologia*, *41*, 378–389. https://doi.org/10.1016/S0028-3932(02)00169-0

Ranganath, C., & Ritchey, M. (2012). Two cortical systems for memory-guided behaviour. *Nature Reviews Neuroscience*, *13*, 713–726. https://doi.org/10.1038/nrn3338

Read, S. L., & Grundy, E. M. D. (2017). Fertility history and cognition in later life. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *72*(6), 1021–1031. https://doi.org/10.1093/geronb/gbw013

Rentz, D. M., Weiss, B. K., Jacobs, E. G., Cherkerzian, S., Klibanski, A., Remington, A., Aizley, H., & Goldstein, J. M. (2017). Sex differences in episodic memory in early midlife: Impact of reproductive aging. *Menopause (New York, N.Y.)*, *24*, 400–408. https://doi.org/10.1097/GME.0000000000000771

Reuter-Lorenz, P. A., & Cappell, K. A. (2008). Neurocognitive aging and the compensation hypothesis. *Current Directions in Psychological Science*, *17*, 177–182. https://doi.org/10.1111/j.1467-8721.2008.00570.x

Ritchey, M., Libby, L. A., & Ranganath, C. (2015). Cortico-hippocampal systems involved in memory and cognition. *Progress in Brain Research*, *219*, 45–64. https://doi.org/10.1016/bs.pbr.2015.04.001

Rugg, M. D., & Vilberg, K. L. (2013). Brain networks underlying episodic memory retrieval. *Current Opinion in Neurobiology*, *23*, 255–260. https://doi.org/10.1016/j.conb.2012.11.005

Ryan, J., Carrière, I., Scali, J., Ritchie, K., & Ancelin, M.-L. (2009). Life-time estrogen exposure and cognitive functioning in later life. *Psychoneuroendocrinology*, *34*, 287–298. https://doi.org/10.1016/j.psyneuen.2008.09.008

Santoro, N. (2003). Mechanisms of premature ovarian failure. *Annales d'endocrinologie*, *64*, 87–92.

Schacter, D. L., Koutstaal, W., & Norman, K. A. (1997). False memories and aging. *Trends in Cognitive Sciences*, *1*, 229–236. https://doi.org/10.1016/S1364-6613(97)01068-1

Scheyer, O., Rahman, A., Hristov, H., Berkowitz, C., Isaacson, R. S., Diaz Brinton, R., & Mosconi, L. (2018). Female sex and Alzheimer's risk: The menopause connection. *The Journal of Prevention of Alzheimer's Disease*, *5*, 225–230. https://doi.org/10.14283/jpad.2018.34

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of Clinical Psychiatry*, *59*, 22–33.

Shuster, L. T., Rhodes, D. J., Gostout, B. S., Grossardt, B. R., & Rocca, W. A. (2010). Premature menopause or early menopause: Long-term health consequences. *Maturitas*, *65*, 161–166. https://doi.org/10.1016/j.maturitas.2009.08.003

Snodgrass, J. G., & Corwin, J. (19881101). Pragmatics of measuring recognition memory: Applications to dementia and amnesia. *Journal of Experimental Psychology: General*, *117*(1), 34. https://doi.org/10.1037/0096-3445.117.1.34

Soules, M. R., Sherman, S., Parrott, E., Rebar, R., Santoro, N., Utian, W., & Woods, N. (2001). Executive summary: Stages of Reproductive Aging Workshop (STRAW). *Climacteric*, *4*(4), 267–272. https://doi.org/10.1080/cmt.4.4.267.272

Spaniol, J., Davidson, P. S. R., Kim, A. S. N., Han, H., Moscovitch, M., & Grady, C. L. (2009). Event-related fMRI studies of episodic encoding and retrieval: Meta-analyses using activation likelihood estimation. *Neuropsychologia*, *47*(8), 1765–1779. https://doi.org/10.1016/j.neuropsychologia.2009.02.028

Spencer, W., & Raz, N. (1996). Differential effects of aging on memory for content and context: A meta-analysis. *Psychology and Aging*, *10*, 527–539. https://doi.org/10.1037/0882-7974.10.4.527

Squire, L. R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science*, *253*(5026), 1380–1386. https://doi.org/10.1126/science.1896849

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary, 3rd ed* (pp. xvii, 1216). Oxford University Press.

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. *Journal of Cognitive Neuroscience*, *31*(12), 1895–1916. https://doi.org/10.1162/jocn_a_01455

Takahashi, T. A., & Johnson, K. M. (2015). Menopause. *Medical Clinics*, *99*, 521–534. https://doi.org/10.1016/j.mcna.2015.01.006

Talairach, J., & Tournoux, P. (1988). Co-planar stereotaxic atlas of the human brain. *New York: Thieme Medical Publishers, Inc.* https://ci.nii.ac.jp/naid/10008533708/

Taylor, C. M., Pritschet, L., Yu, S., & Jacobs, E. G. (2019). Applying a women's health lens to the study of the aging brain. *Frontiers in Human Neuroscience*, *13*. https://doi.org/10.3389/fnhum.2019.00224

Tulving, E. (1972). Organization of memory. *Episodic and Semantic Memory*. https://ci.nii.ac.jp/naid/10017350531/

Tustison, N. J., Avants, B. B., Cook, P. A., Zheng, Y., Egan, A., Yushkevich, P. A., & Gee, J. C. (2010). N4ITK: Improved N3 Bias Correction. *IEEE Transactions on Medical Imaging*, *29*(6), 1310–1320. https://doi.org/10.1109/TMI.2010.2046908

Uddin, L. Q., Yeo, B. T. T., & Spreng, R. N. (2019). Towards a universal taxonomy of macro-scale functional human brain networks. *Brain Topography*, *32*(6), 926–942. https://doi.org/10.1007/s10548-019-00744-6

Venables, W. N., & Ripley, B. D. (2002) *Modern applied statistics with S.* Fourth Edition. Springer, New York. ISBN 0-387-95457-0, https://www.stats.ox.ac.uk/pub/MASS4/.

Weismiller, D. (2009). Menopause. *Primary Care*, *36*, 199–226, x. https://doi.org/10.1016/j.pop.2008.10.007

Wechsler, D. (2008). *Wechsler adult intelligence scale–Fourth Edition (WAIS–IV).* Pearson (San Antonio, TX.)

Wechsler, D. (2008). *WAIS-IV administration and scoring manual*. San Antonio, TX: Pearson.

Zhang, Y., Brady, M., & Smith, S. (2001). Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Transactions on Medical Imaging*, *20*(1), 45–57. https://doi.org/10.1109/42.906424

Appendix A: Figures from model 1 with the predictor of age

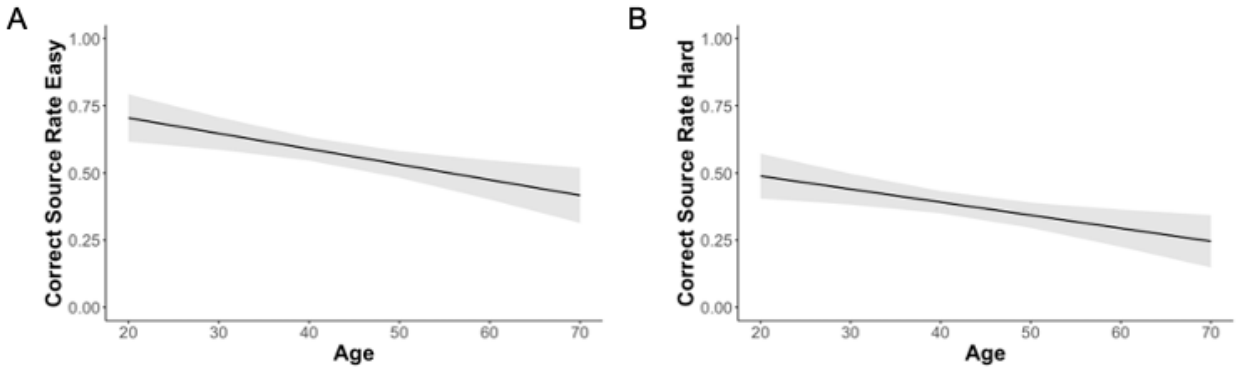


Figure 5. (A) Performance as a function of age for correct source easy rate. (B) Performance as a function of age for correct source hard rate. Age was a significant predictor for easy and hard correct source rate, with a decline in source rate as age increased. Shaded error bands represent the 95% confidence intervals.

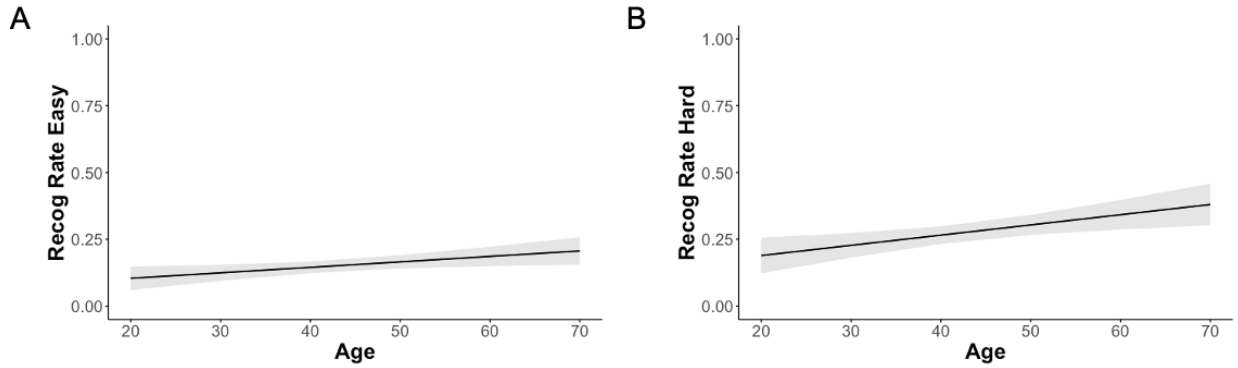


Figure 6. (A) Performance as a function of age for correct item recognition easy rate. (B) Performance as a function of age for correct item recognition hard rate. Age was a significant predictor for the hard version of the task, with an increase in correct item recognition as age increased. Age was not a significant predictor for the easy version of the task. Shaded error bands represent the 95% confidence intervals.

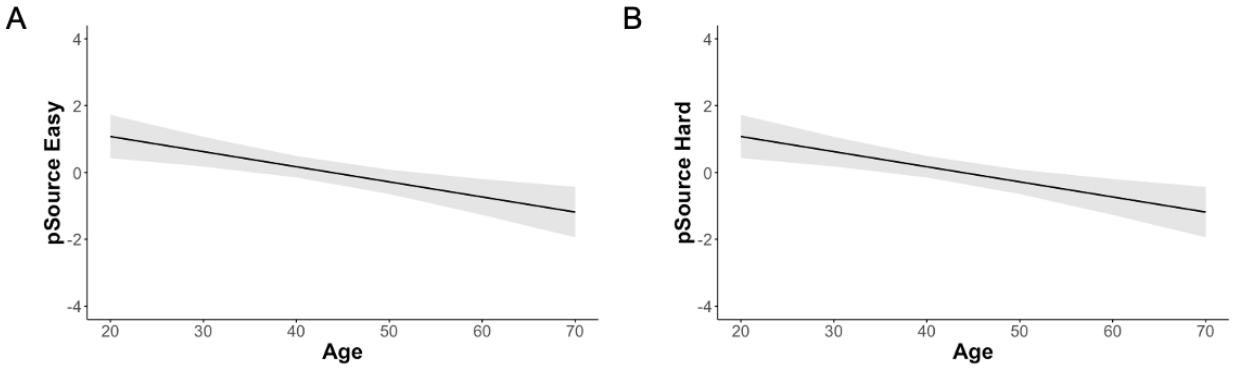


Figure 7. (A) Performance as a function of age for pSource easy rate. (B) Performance as a function of age for pSource hard rate. pSource = $z_{(\text{correct source rate})} - z_{(\text{source misattribution rate})}$. Age was a significant predictor for easy and hard pSource, with a decline in pSource with older age. Shaded error bands represent the 95% confidence intervals.

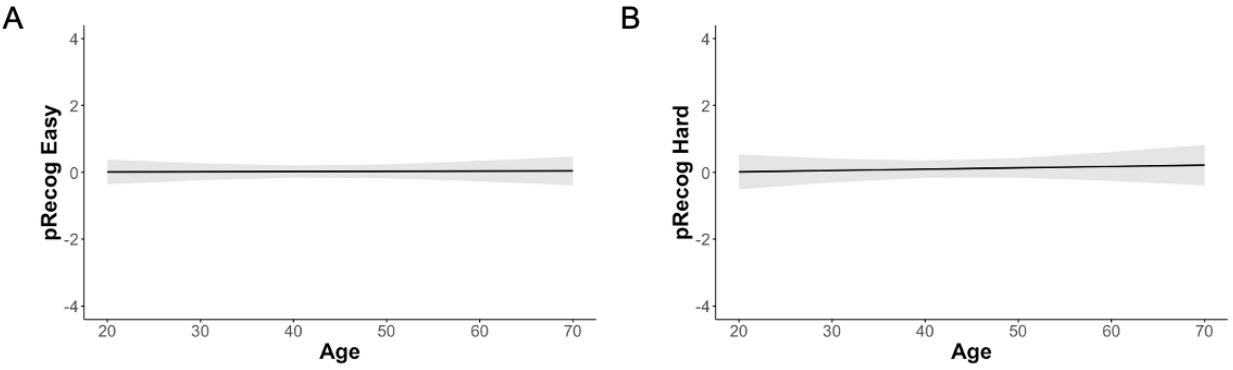


Figure 8. (A) Performance as a function of age for pRecog easy rate. (B) Performance as a function of age for pRecog hard rate. pRecog = $z_{(\text{correct item recognition rate})} - z_{(\text{false alarm rate})}$. Age was not a significant predictor for the easy or hard version of the task. Shaded error bands represent the 95% confidence intervals.

Appendix B: Figures from model 2 with the predictors of age and menopausal status

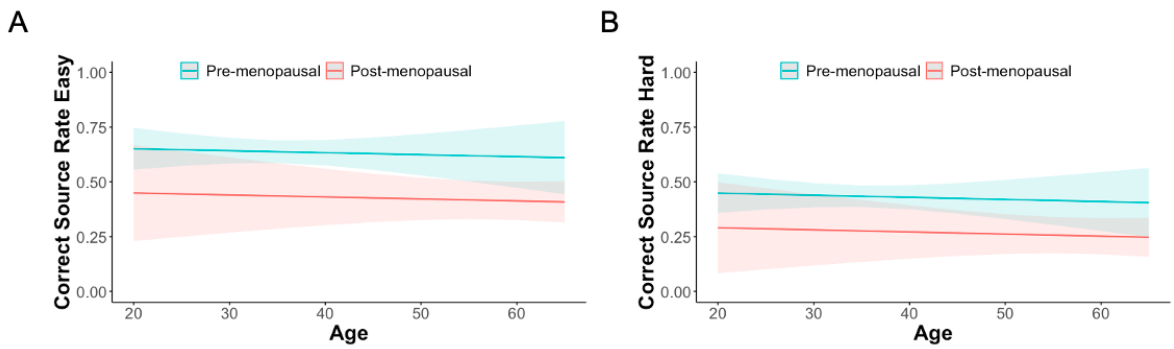


Figure 9. (A) Performance as a function of age and menopausal status for correct source easy rate. (B) Performance as a function of age and menopausal status for correct source hard rate. Menopause was a significant predictor for correct source easy rate, with higher scores observed in pre- compared to post-menopausal women. However, menopause was not a significant predictor for the hard version of the task. Age was not a significant predictor for easy or hard correct source rate. Shaded error bands represent the 95% confidence intervals.

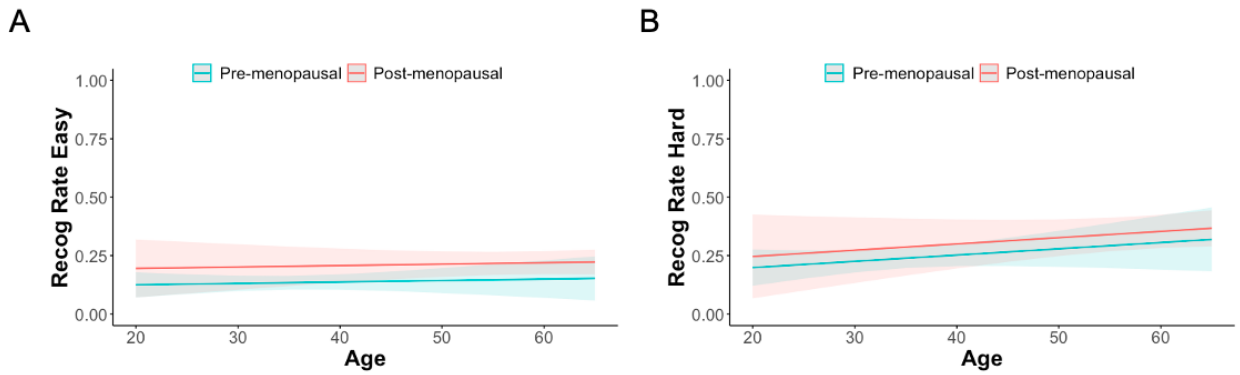


Figure 10. (A) Performance as a function of age and menopausal status for item recognition easy rate. (B) Performance as a function of age and menopausal status for item recognition hard rate. Menopause and age were not a significant predictor for item recognition rate regardless of encoding load. Shaded error bands represent the 95% confidence intervals.

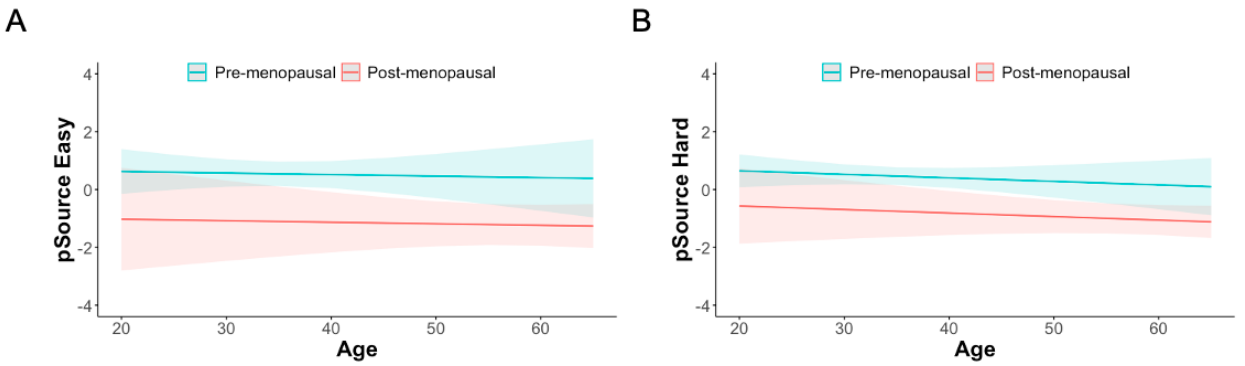


Figure 11. (A) Performance as a function of age and menopausal status for pSource easy rate. (B) Performance as a function of age and menopausal status for pSource hard rate. pSource = $z_{(\text{correct source rate})} - z_{(\text{source misattribution rate})}$. Menopause was a significant predictor for pSource easy, with higher scores observed in pre-menopausal women. Menopause was not a significant predictor for pSource hard. Age was not a significant predictor for pSource rate easy or hard. Shaded error bands represent the 95% confidence intervals.

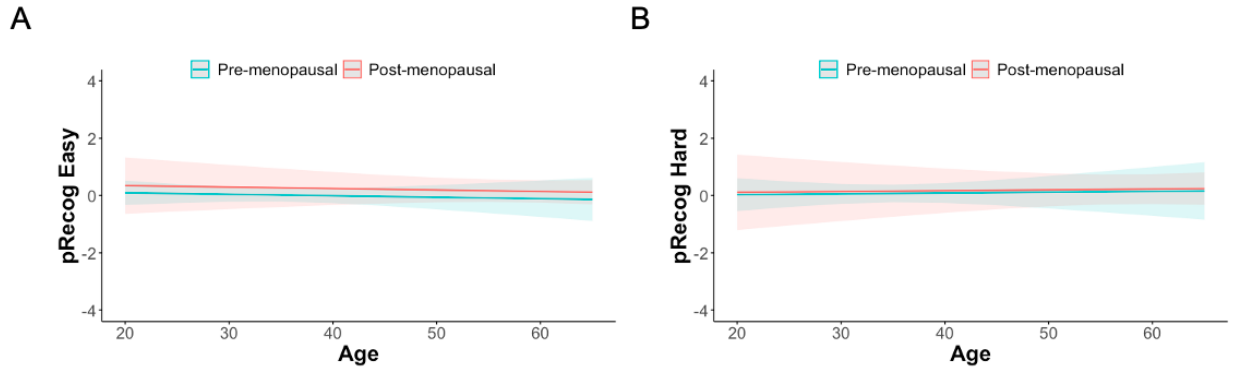


Figure 12. (A) Performance as a function of age and menopausal status for pRecog easy rate. (B) Performance as a function of age and menopausal status for pRecog hard rate. pRecog = $z_{(\text{correct item recognition rate})} - z_{(\text{false alarm rate})}$. Age and menopause were not a significant predictor for pRecog easy or hard. Shaded error bands represent the 95% confidence intervals.

Appendix C: Figures from model 3 with the predictor of menopausal status

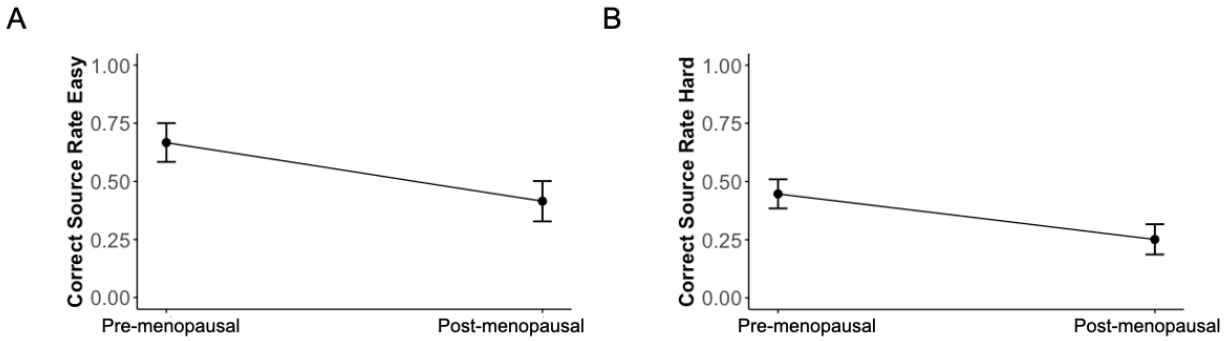


Figure 13. (A) Performance as a function of menopausal status for correct source easy rate. (B) Performance as a function of menopausal status for correct source hard rate. Menopause was a significant predictor for easy and hard correct source rate, with a decline in correct source rate in post-menopausal women. Error bars represent the 95% confidence intervals.

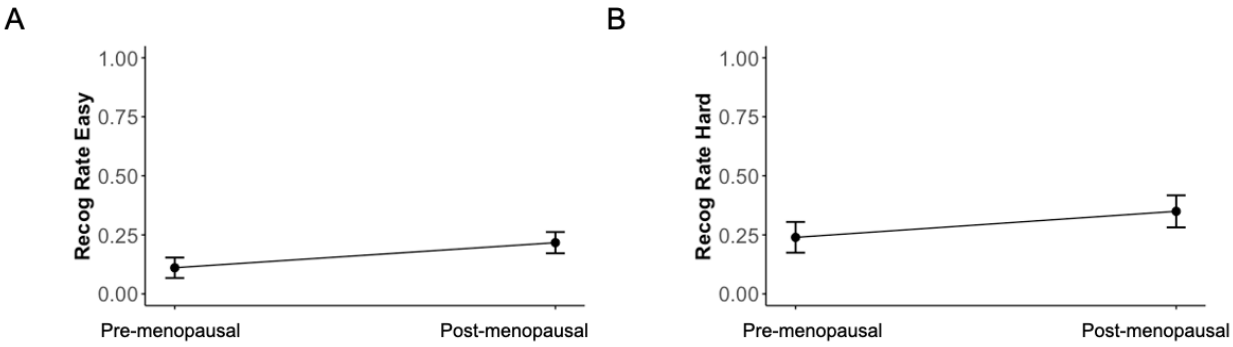


Figure 14. (A) Performance as a function of menopausal status for correct item recognition easy rate. (B) Performance as a function of menopausal status for correct item recognition hard rate. Menopause was a significant predictor for easy correct source rate, increasing in post-menopausal women, but not hard. Error bars represent the 95% confidence intervals.

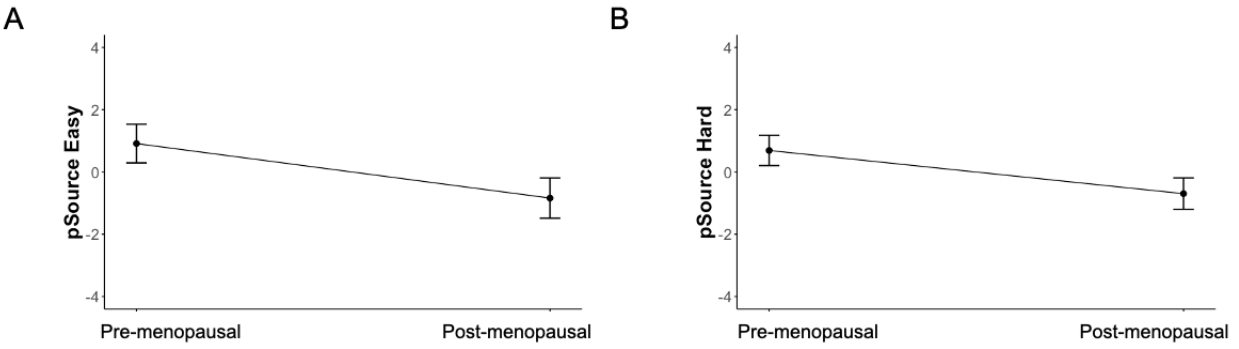


Figure 15. (A) Performance as a function of menopausal status for pSource easy rate. (B) Performance as a function of menopausal status for pSource hard rate. pSource = $z_{(\text{correct source rate})}$ - $z_{(\text{source misattribution rate})}$. Menopause was a significant predictor for easy and hard correct source rate, with pSource declining in post-menopausal women. Error bars represent the 95% confidence intervals.

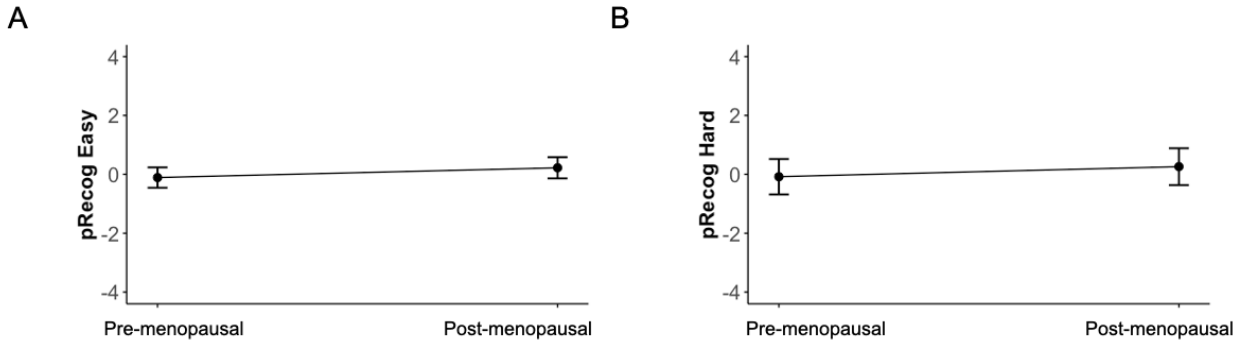


Figure 16. (A) Performance as a function of menopausal status for pRecog – easy rate. (B) Performance as a function of menopausal status for pRecog – hard rate. pRecog = $z_{(\text{correct item recognition rate})} - z_{(\text{false alarm rate})}$. Menopause was not a significant predictor for pRecog easy or hard. Error bars represent the 95% confidence intervals.