

Sex differences in episodic memory in early midlife: impact of reproductive aging

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Abstract

Objective: Few have characterized cognitive changes with age as a function of menopausal stage relative to men, or sex differences in components of memory in early midlife. The study aim was to investigate variation in memory function in early midlife as a function of sex, sex steroid hormones, and reproductive status.

Methods: A total of 212 men and women aged 45 to 55 were selected for this cross-sectional study from a prenatal cohort of pregnancies whose mothers were originally recruited in 1959 to 1966. They underwent clinical and cognitive testing and hormonal assessments of menopause status. Multivariate general linear models for multiple memory outcomes were used to test hypotheses controlling for potential confounders. Episodic memory, executive function, semantic processing, and estimated verbal intelligence were assessed. Associative memory and episodic verbal memory were assessed using Face-Name Associative Memory Exam (FNAME) and Selective Reminding Test (SRT), given increased sensitivity to detecting early cognitive decline. Impacts of sex and reproductive stage on performance were tested.

Results: Women outperformed men on all memory measures including FNAME ($\beta = -0.30$, $P < 0.0001$) and SRT ($\beta = -0.29$, $P < 0.0001$). Furthermore, premenopausal and perimenopausal women outperformed postmenopausal women on FNAME (initial learning, $\beta = 0.32$, $P = 0.01$) and SRT (recall, $\beta = 2.39$, $P = 0.02$). Across all women, higher estradiol was associated with better SRT performance (recall, $\beta = 1.96$, $P = 0.01$) and marginally associated with FNAME (initial learning, $\beta = 0.19$, $P = 0.06$).

Conclusions: This study demonstrated that, in early midlife, women outperformed age-matched men across all memory measures, but sex differences were attenuated for postmenopausal women. Initial learning and memory retrieval were particularly vulnerable, whereas memory consolidation and storage were preserved. Findings underscore the significance of the decline in ovarian estradiol production in midlife and its role in shaping memory function.

Key Words: Aging – Gonadal hormones – Memory – Menopause – Reproductive aging – Sex differences.

Epidemiological estimates suggest that approximately 75% of older adults report memory-related problems¹ in the face of a rapidly increasing population of adults aged 65 and older.² Women report increased forgetfulness and “brain fog” during the menopausal transition.³ Given that women are disproportionately at risk for memory impairment and dementia in contrast to men,^{4,5} improving our understanding of sex differences in cognitive aging is paramount. In

this cross-sectional study, we characterized the sex-dependent variation in episodic memory that occurs with aging, as women transition through menopause relative to age-matched men.

Age-related cognitive decline has been reported for verbal encoding,⁶ verbal memory,^{7,8} verbal learning,^{7,9} and associative memory.^{10,11} In fact, verbal stimuli may be more vulnerable to age-related decline relative to nonverbal

Received May 20, 2016; revised and accepted August 30, 2016.

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J.M.G. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses and interpretations.

Funding/support: The work of this study was supported by the National Institute of Mental Health (R01 MH090291, J.M.G., PI). Additional support for Dr Jacobs’s time was provided by ORWH-NICHD BIRCWH K12

HD051959. The Harvard Clinical and Translational Science Center (NIH UL1 RR025758) provided support for serologic acquisition and evaluations.

Financial disclosure/conflicts of interest: D.M.R. has served as a paid consultant for Eli Lilly, Janssen Pharmaceuticals and Biogen Idec. She also serves on the Neurotrack Scientific Advisory Board as a paid member. These associations are not related to this paper. All other authors have no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal’s Website (www.menopause.org).

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stimuli,⁶ and at midlife, verbal memory performance may be an especially sensitive indicator of cognitive decline in old age. A recent study demonstrated that deficits in initial learning of verbal episodic memory before age 50 often foreshadowed additional cognitive impairments in adults over age 65.¹²

To date, only a few studies directly tested for sex differences in age-related cognitive decline, and all found that women had better memory performance.^{7,9,13} In fact, sex differences in memory performance, particularly verbal material, begin in childhood, grow larger in effect size just postpuberty,¹⁴ and are retained into adulthood.^{7,13} Although women's performance attenuates with menopause,¹⁵ a small female advantage is maintained in the healthy aging brain through midlife and old age.^{7,13} Some of these earlier studies, however, include a large age range, and no studies of sex differences have examined the impact of menopause and sex steroid hormone concentrations on particular domains of memory.

Substantial preclinical and clinical evidence suggests that neuroactive sex steroid hormones, including 17 β -estradiol, play a role in learning and memory in women and may underlie sex differences in performance.^{16,17} Estradiol impacts the structure and function of brain regions throughout memory circuitry.¹⁶⁻³⁰ Endogenous fluctuations in estradiol during the menstrual cycle have been associated with verbal working memory performance.^{27,31} Performance on verbal fluency, verbal learning, and immediate and delayed verbal recall decreases during the menopausal transition, independent of age.^{15,32,33} In early postmenopause, greater endogenous estradiol has been associated with better cognitive performance in semantic memory.³⁴ Furthermore, longer reproductive periods (indicating greater exposure to endogenous estrogens) are associated with better immediate and delayed verbal memory in mid- to late-life postmenopausal women.^{35,36} A review of neuropsychological studies in women aged at least 60 years found that higher estradiol levels were associated with better memory performance across multiple domains, including episodic and semantic memory.³⁷ Moreover, we recently demonstrated substantial reproductive age-related changes in regional brain activity and network-level connectivity in memory circuitry in early midlife.³⁸ Decline in estradiol during menopausal transition was directly related to brain activity changes in hippocampus, further implicating sex steroids in regulating memory circuitry.^{38,39}

Despite these findings, less is known about memory changes in women during the menopausal transition compared with age-matched men, or sex differences in specific memory domains early in the aging process. The purpose of this study was to investigate changes in memory function that occur in early midlife as a function of sex, sex steroid hormones, and reproductive status. Furthermore, to identify memory domains related to perceived memory complaints in postmenopausal women, we selected particularly challenging memory tests that are sensitive to executive and temporolimbic dysfunction in clinically normal adults.⁴⁰ Finally, we investigated whether memory function in early midlife was

associated with low versus high risk for dementia/Alzheimer's disease (AD) (based on family history) and if this differed by sex or reproductive status.

METHODS

Participants

Adult participants were selected from 17,741 pregnancies in the New England Family Study (NEFS; subsidiary of the National Collaborative Perinatal Project), a representative sample of those receiving prenatal care in Boston-Providence from 1959 to 1966.^{41,42} In a series of studies over 20 years, we followed subsets of NEFS offspring to investigate the fetal programming of adult psychiatric and general medical disorders and sex differences therein.⁴³⁻⁴⁵

We recently completed a study of the fetal stress-immune programming of sex differences in memory circuitry in early midlife (NIMH R01 MH090291, Goldstein, PI). To insure variability in prenatal exposure, discordant same-sex siblings from NEFS were recruited, one of whom was exposed to preeclampsia or fetal growth restriction and the other was not. When siblings were not available for an exposed offspring, an unexposed offspring was individually matched based on maternal age, ethnicity, and socioeconomic status, and offspring sex and gestational age.

Two hundred twelve offspring (equally divided by sex) were recruited at 45 to 55 years of age and completed clinical, cognitive, and neuropsychological assessments, of whom 200 completed functional and structural magnetic resonance imaging. The community-based sample was found to be 88.6% white, 8.5% African American, 2.8% Other (primarily Hispanic). Exclusionary criteria included any history of neurologic disease, central nervous system damage, head injury with loss of consciousness, endocrine disorders, heart disease, alcohol-related diseases, current or history of psychosis, other medical illnesses that may significantly alter central nervous system function, or any magnetic resonance imaging contraindication. Demographic information, including body mass index (BMI), marital status, race/ethnicity, and alcohol abuse/dependence, were collected as part of the clinical interview via self-report.

The set of analyses reported here focused on neuropsychological evaluations. One participant (female) was not able to complete the neuropsychological battery, resulting in a final sample of 211. Two males had incomplete data on two tasks (family history information and Face-Name Test performance). The Partners Human Research Committee and Brown University's Institutional Review Board granted Human Studies participants' approval. All volunteers gave written informed consent and were paid for their participation.

Study design and procedures

Participants were seen at Brigham and Women's Hospital Outpatient Clinical Research Center. Women who were still menstruating were scheduled within the early follicular menstrual cycle phase (days 3-5). Participants fasted for at least 8 hours before morning baseline blood draw. They were

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offered a light standardized breakfast (excluding caffeine). Structured clinical interviews, including alcohol or substance disorders, neuropsychological testing, family medical history, and reproductive history, administered by an experienced clinical interviewer/clinician, were conducted after magnetic resonance scanning.

Neuropsychological assessments and family history

Participants completed a neuropsychological battery to assess episodic memory, executive function, semantic processing, and estimated verbal intelligence (IQ). Measures of episodic memory included the 12-item Face-Name Associative Memory Exam (FNAME)^{40,46} and the 6-trial Selective Reminding Test (SRT).^{47,48} These tests were chosen because they are particularly challenging and sensitive to working memory and learning deficits associated with early aging. The FNAME is a paired-associate face-name task that is sensitive to temporolimbic integrity. Use of associative learning paradigms, in contrast to list learning procedures, has the benefit of controlling attention within the learning process by pairing items together, thus requiring the participant to make associations between them. Memory impairments on associative learning paradigms are often consistent with temporolimbic amnesic dysfunction.^{49,50}

As reported by Papp et al,⁴⁶ the 12-item FNAME asks the participant to study 12 unfamiliar face-name-occupation groupings. The test consists of two learning exposures, followed by the presentation of the face and the request to recall the name and occupation associated with that face (ILN/ILO). After a 10-minute delay, participants are shown the face and asked to recall the name and occupation (CRN/CRO). A multiple-choice format was presented that asked the participants to choose the name and occupation from three choices of names and three choices of occupations (MCN/MCO).

Although forming face-name associations is particularly difficult, pairing the face with an occupation is an inherently easier task because of its association with previously stored semantic knowledge.⁴⁰ Although reported in only two studies, the associative memory test, FNAME was found to decline with age.^{40,51} Furthermore, FNAME is thought to isolate medial temporal lobe memory storage capacities apart from frontal executive mechanisms involved in memory processing, thus a good choice to elucidate memory vulnerabilities associated with menopausal transition.

The SRT, on the contrary, is a selective reminding procedure that relies on feedback tailored to the individual, that is, individuals are only reminded of words they failed to recall in the previous trial. This procedure taps into executive processing because it requires the individual to hold information online, within working memory, as only a portion of the list that was not immediately recalled is presented for learning. More specifically, once the individual is exposed to all the words in trial 1, they are reminded only of the words that were not immediately recalled in the previous trial. Although more challenging than a traditional list learning test, the SRT was chosen because it taps into executive

compromise,⁵² an important component to learning and memory and potentially relevant to menopausal vulnerabilities. Thus, our rationale for utilizing these two specific episodic memory tests was to determine whether menopausal memory changes are related to frontal executive retrieval deficits common in aging (ie, as detected on the SRT) or hippocampal dysfunction consistent with early neurodegeneration or pre-clinical AD (ie, as detected on the FNAME).

Z-score composites were created for FNAME including (1) initial learning of names and occupations (trial 1: ILN, ILO); (2) cued recall of names and occupations (CRN and CRO), and (3) FNAME summary score (ILN, ILO, CRN, and CRO). Finally, we explored SRT performance that included list learning over six trials (total recall; TR), delayed recall at 30 minutes (DR30),⁴⁷ and an SRT summary score. Executive function was assessed as performance on measures of verbal fluency and working memory. Verbal fluency was assessed using Controlled Oral Word Fluency Test (ie, sum of words generated in a minute for letters F-A-S [FAS])⁵³ and working memory using Digit Span Backwards (DSB).⁵⁴ Semantic processing included word fluency to three categories of animals, fruits, and vegetables (CAT).⁵⁵ The American National Adult Reading Test (AMNART)⁵⁶ was used to assess estimated verbal IQ. Participants also completed the Spielberger State-Trait Anxiety Index (STAI), Profile of Moods Questionnaire (POMS), and two sleep measures (Pittsburgh Sleep Quality Index and Insomnia Severity Index). Family history of dementia was assessed by a self-reported medical questionnaire given by the clinical interviewer. Participants were determined to have a family history for AD or other dementias if they reported first degree or other family members with these diagnoses.

Endocrine assessments

Trained nurses inserted a saline-lock IV line in the non-dominant forearm and acquired a fasting morning blood at approximately 08:00 hours to evaluate hypothalamic-pituitary-gonadal axis hormone concentrations, including sex steroids (estradiol, progesterone, and testosterone) and gonadotropins (leutinizing hormone and follicle-stimulating hormone [FSH]). Approximately 10 mL of blood were collected at Brigham and Women's Hospital Center for Clinical Investigation. Samples were allowed to clot for 30 to 45 minutes, after which blood was centrifuged (1,500 × g for 10 min) and sera aliquoted into 2 mL microtubes. Serum aliquots were stored at -20°C for later evaluations. 17β-estradiol, progesterone, and testosterone concentrations were determined via liquid chromatography-mass spectrometry at the Brigham and Women's Hospital Research Assay Core. Assay sensitivities, dynamic range, and intra-assay coefficients of variation were as follows (respectively): estradiol (1 pg/mL, 1-500 pg/mL, <5% reproducibility standard deviation [RSD]), progesterone (0.05 ng/mL, 0.05-10 ng/mL, 5.75% RSD), and testosterone (1.0 ng/dL, 1-2,000 ng/dL, <2% RSD). FSH levels were determined via chemoluminescent assay (Beckman Coulter), with assay sensitivity of 0.2 mIU/mL,

dynamic range 0.2 to 200 mIU/mL, and intra-assay coefficient of variation 3.1% to 4.3%.

Menopausal staging

Timing of menopause between the first clinical appearance of decreased ovarian function (ie, shorter intermenstrual time periods) to menstrual irregularity and final amenorrhea is highly variable and can occur over several years. Women in this sample were between the ages of 45 to 55 years and in various states of ovarian decline. Some women were already in menopause with permanent amenorrhea, low estradiol levels, and elevated gonadotropins; some exhibited signs of follicular failure (elevated FSH and oligoamenorrhea); and some showed normal cycling. Reproductive histories and hormonal evaluations were used to determine reproductive stage after the Stages of Reproductive Aging Workshop-10 guidelines.⁵⁷ Women were categorized into late reproductive (“premenopause”), menopausal transition (“perimenopause”), and early postmenopausal (“postmenopause”). An additional eight women reported current use of hormone therapy and were excluded from reproductive analyses.

Statistical analyses

Simple descriptive comparisons of continuous data, including neuropsychological test performance, between men and women, and by reproductive status, were evaluated using nonparametric methods, primarily Wilcoxon rank-sum test. Kolmogorov-Smirnov test was used when the populations differed in spread. Comparisons of categorical data were assessed using χ^2 tests. Significant differences in comparisons (not including the outcomes of interest) were selected as potential confounders to adjust for in multivariate regression analyses.

Using multivariate multiple regression analysis, we estimated a single regression model with two memory domain outcomes (FNAME and SRT summary scores) with sex and reproductive status as independent predictors, adjusted for age, BMI, marital status, race/ethnicity, and alcohol abuse and/or dependence. Multivariate regression was conducted using SAS (v.9.3) PROC GLM to provide an overall F test (Wilk's λ), “protected” for multiple comparisons. This allowed for further analyses of the individual components of the summary measures that may be driving the results. General linear models (GLMs) based on generalized estimating equations for the individual components were adjusted for age, ethnicity, BMI, lifetime alcohol abuse and/or dependence, and intrafamilial correlation between siblings.⁵⁸ Of those associations that were significant, parallel analyses were then performed to determine whether family history of clinical dementia/AD altered the association between sex/reproductive status and memory performance. Any family history of clinical dementia/AD was used because there were too few first-degree family history positive participants to warrant analysis. A $P \leq 0.05$ was designated as statistical significance. For the purpose of graphically representing our findings, age-adjusted memory scores for each participant

were calculated as the observed score plus the difference between the mean and actual age multiplied by the unstandardized beta obtained by regressing the memory score on age.

RESULTS

The sample included 211 participants (106 men/105 women). Among women, 36 (34%) were premenopausal, 29 (28%) were perimenopausal, and 32 (30%) were postmenopausal. Eight women reported current use of hormone therapy and were excluded from analyses based on menopause status. Table 1 shows demographic characteristics of the sample by sex and menopausal stage in women compared with men. Groups were comparable on educational attainment, substance abuse or dependence, family history of AD or clinical dementia, and estimated verbal IQ. There were significant, but clinically minimal, group differences in age, BMI, ethnicity, marital status, and alcohol abuse or dependence (see Table 1). Men had larger BMIs, were more often single, particularly compared with premenopausal women, and had more alcohol abuse or dependence than women. There were more African American women than men, particularly among postmenopausal women. Premenopausal women were slightly younger than postmenopausal women, although there was only a 7-year age difference between the youngest and oldest woman.

Adult memory performance

Multivariate GLM predicting the two summary memory measures as a set demonstrated a significant impact of sex and reproductive status (Wilk's $\lambda = 0.853$, $F = 5.07$, $P < 0.0001$), controlled for age, BMI, ethnicity, marital status, alcohol abuse or dependence, and sibships. In subsequent GLMs examining the impact of sex and reproductive status on the specific memory components, women outperformed men on all memory measures (Table 2), including for Men_{mean} versus Women_{mean}, respectively: FNAME initial learning (-0.2 vs 0.2 ; $\beta = -0.28$, $P < 0.0001$), FNAME cued recall (-0.3 vs 0.3 ; $\beta = -0.32$, $P < 0.0001$), and FNAME summary (-0.3 vs 0.3 ; $\beta = 0.30$, $P < 0.0001$); and SRT TR (43.7 vs 47.8; $\beta = -2.22$, $P = 0.0001$), SRT DR30 (6.1 vs 7.8; $\beta = -0.91$, $P < 0.0001$), and SRT summary (-0.3 vs 0.3 ; $\beta = -0.29$, $P < 0.0001$). Women also outperformed men on measures of word fluency to semantic categories (Men_{mean} = 44.5 vs Women_{mean} = 48.0; $P < 0.05$), but not executive tasks of letter fluency or Digit Span (see Supplementary Table 1, Supplemental Digital Content 1, <http://links.lww.com/MENO/A195>). Sex differences were present in the face of virtually identical verbal IQ for men and women (including across reproductive status), which was high for a population sample (mean of 116.6 ± 10.2 ; see Table 1). Furthermore, men and women did not differ on clinical state with regard to mood or anxiety (data not shown).

Examining performance related to reproductive status, pre- and perimenopausal women, who did not significantly differ among themselves, outperformed men on all memory tasks

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TABLE 1. Study sample demographics, $n = 211$

Categorical variables	Total	Men	Women ^a	Premenopausal	Perimenopausal	Postmenopausal
	n = 211 %	n = 106 %	n = 105 %	women n = 36 %	women n = 29 %	women n = 32 %
Sex		100%	100%	100%	100%	100%
Men	50.2					
Women	49.9					
Education level						
Less than high school	1.4	1.9	1.0	2.8	0.0	0.0
High school or GED	21.3	22.6	20.0	13.9	24.1	25.0
Some college/technical/certificate/associate	40.8	42.5	39.0	47.2	31.0	34.4
4-y college	27.0	25.5	28.6	27.8	34.5	28.1
Graduate school	8.1	6.6	9.5	8.3	10.3	6.3
Missing	1.4	0.9	1.9	0.0	0.0	6.3
Ethnicity						
White	88.6	89.6	87.6	91.7	86.2	81.3
African American	8.5	5.7 ^b	11.4	8.3	10.3	18.8 ^b
Other	2.8	4.7	1.0	0.0	3.4	0.0
Marital status						
Married or living with someone as if married	59.7	62.3	57.1	63.9	48.3	53.1
Widowed	2.4	0.0	4.8	5.6	3.4	3.1
Divorced or annulled	17.1	15.1	19.0	25.0	17.2	15.6
Separated	2.8	2.8	2.9	0.0	6.9	3.1
Single	17.5	18.9 ^b	16.2	5.6 ^b	24.1	25.0
Missing	0.5	0.9	0.0	0.0	0.0	0.0
Alcohol abuse or dependence						
Yes	43.6	54.7 ^b	32.4 ^b	27.8 ^b	24.1 ^b	40.6
No	56.4	45.3	67.6	72.2	75.9	59.4
Substance abuse or dependence						
Yes	39.8	44.3	35.2	30.6	31.0	43.8
No	60.2	55.7	64.8	69.4	69.0	56.3
Family history of Alzheimer's and/or dementia ^c						
Yes	46.9	47.2	46.7	50.0	41.4	46.9
No	52.6	51.9	53.3	50.0	58.6	53.1
Missing	0.5	0.9	0.0	0.0	0.0	0.0

Continuous variables	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age at adult interview	50.0	2.1	50.1	2.3	49.8	2.0	49.3 ^b	1.7	49.8	2.0	50.6 ^b	2.2
Body mass index	28.6	5.7	29.4 ^b	5.5	27.9 ^b	5.8	28.0	6.0	28.7	6.0	27.6	5.8
Verbal IQ (AMNART)	116.6	10.2	116.7	10.8	116.5	9.5	118.6	7.9	115.0	10.7	115.2	11.0

AMNART, American National Adult Reading Test; BMI, body mass index; GED, General Educational Development; Pre, premenopausal; Peri, perimenopausal; Post, postmenopausal.

^aThere are 105 women in the sample, 8 (7.6%) of whose menopause status was not determined.

^bIn general, there were no sociodemographic differences between groups except for the following measures: ethnicity—African American (Post>Men, $\chi^2 = 6.5$, $P = 0.04$); marital status—single (Men>Pre, $\chi^2 = 11.4$, $P = 0.02$); alcohol abuse or dependence (Men>Women, $\chi^2 = 10.7$, $P = 0.001$), (Men>Pre, $\chi^2 = 7.8$, $P = 0.005$), (Men>Peri, $\chi^2 = 8.5$, $P = 0.004$); age at adult interview (Pre>Peri, $z = -2.4$, $P = 0.02$); BMI (Men>Women, $z = 2.3$, $P = 0.02$).

^cFamily history of Alzheimer's or dementia among first- or nonfirst-degree relatives self-reported by participant.

(see Table 3; Fig. 1). Postmenopausal women, who differed from pre- and perimenopausal women, were, however, not statistically different from men, except on SRT DR30 (respectively, 7.5 vs 6.1, $\beta = 0.80$, $P = 0.004$) and SRT summary (0.07 vs -0.3, $\beta = -0.19$, $P = 0.04$). This suggests that postmenopausal women had difficulty with initial learning and retrieval of information, but not consolidation and storage of that information.

We also examined, across all women, whether estradiol and progesterone levels were associated with memory performance. Adjusted for age, sibships, and progesterone, estradiol was significantly and positively associated with better performance on SRT TR ($\beta = 1.96$, $P = 0.01$), and marginally significant for FNAME initial learning and SRT summary (see Table 4), suggesting estradiol impacts initial learning and

retrieval of information. Finally, family history of dementia/AD did not alter associations between sex/reproductive status for any cognitive outcome (all $P \geq 0.1$). Furthermore, analyses controlling for mood or anxiety state also did not change the results, and thus clinical state was not a confounder.

DISCUSSION

In this population-based study, we identified specific changes in memory function that occur during early midlife (ages approximately 45-55) as a function of sex and menopause status in women. Women performed significantly better than age-matched men across all memory measures. This held true until postmenopause, when the memory performance advantage among women attenuated, in particular for the

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TABLE 2. Mean adult memory performance by sex

Measures of adult memory	Total n = 211 ^a		Men n = 106 ^b		Women n = 105 ^c		Men vs women (ref.): multivariate analysis ^d	
	Mean	SD	Mean	SD	Mean	SD	β	P
Initial learning: names and occupations ^e	0.00	1.0	-0.24	0.9	0.24	1.0	-0.28 ^h	<0.001
Cued recall: names and occupations ^e	0.00	1.0	-0.29	0.9	0.29	1.1	-0.32 ^h	<0.001
Associative memory ^{e,f}	0.00	0.9	-0.27	0.8	0.26	1.0	-0.30 ^h	<0.001
SRT: 30-min delayed recall	6.95	2.8	6.08	2.8	7.84	2.5	-0.91 ^h	<0.001
SRT: total recall	45.72	8.9	43.71	8.8	47.75	8.5	-2.22 ^h	<0.001
SRT: summary score ^{e,g}	0.00	0.9	-0.27	0.9	0.27	0.8	-0.29 ^h	<0.001

^an = 211 for all measures except for Selective Reminding Test (SRT): 30-minute delayed recall (n = 210), initial learning: names and occupations (n = 209), cued recall: names and occupations (n = 209), and associative memory (n = 209).

^bn = 106 for all measures except for initial learning: names and occupations (n = 104), cued recall: names and occupations (n = 104), and associative memory (n = 104).

^cn = 105 for all measures except for SRT: 30-minute delayed recall (n = 104).

^dMultivariate linear regression analyses applied generalized estimating equations models to control for intrafamilial correlation. Models were adjusted for intrafamilial correlation, age, body mass index, ethnicity, marital status, and alcohol abuse or dependence. The reference category (ref.) in these analyses is women. β is interpreted as the number of units memory performance will differ between men and women, on average.

^eIndividual test scores z-scored before combining into summary score.

^fSummary score: initial learning (names and occupations) and cued recall (names and occupations).

^gSummary score: SRT (total recall and delayed recall, 30 min).

^hP < 0.05.

retrieval of previously recalled information (SRT30 and SRT summary score). Consolidation and storage were, however, preserved on the FNAME cued recall for both names and occupations, suggesting that the memory deficit in postmenopausal women predominantly affected frontal network retrieval processes and not consistent with temporolimbic dysfunction. We also found that endogenous estradiol levels were associated with better initial learning. Sex differences in memory measures were present in the context of similar verbal IQ, clinical mood and anxiety states, and family history of clinical dementia.

Our finding that women outperformed men on verbal memory tasks is consistent with other studies exploring

midlife memory changes.^{5,7,9,13} In our study, sex differences, however, varied depending on reproductive status, with attenuation for postmenopausal women compared with men. Family history of clinical dementia/AD did not alter these associations. The measurement of family history, however, came from only one informant and included both first- and nonfirst-degree relatives, thus limiting the interpretation of these findings with respect to the impact of genetic vulnerability.

In the past, self-perceived memory complaints of “brain fog” or forgetfulness during midlife were often associated with job stress and multiple life roles rather than menopausal transition.^{5,9} Several recent reports indicated changes in verbal

TABLE 3. Mean adult memory performance among women by reproductive status

Measures of adult memory	Premenopausal n = 36 ^a							Perimenopausal n = 29					Postmenopausal n = 32					
	Mean	SD	Pre vs peri (ref.) ^b		Pre vs post (ref.) ^b		Men vs pre (ref.) ^b		Mean	SD	Peri vs post (ref.) ^b		Men vs peri (ref.) ^b		Mean	SD	Men vs post (ref.) ^b	
			β	P	β	P	β	P			β	P	β	P			β	P
Initial learning: names and occupations ^c	0.47	1.1	0.01	0.94	0.32 ^f	0.01	-0.36 ^f	<0.001	0.39	1.1	0.28 ^f	0.03	-0.36 ^f	<0.001	-0.11	0.9	-0.04	0.64
Cued recall: names and occupations ^c	0.36	1.1	-0.19	0.11	0.14	0.29	-0.27 ^f	0.01	0.58	1.0	0.31 ^f	0.01	-0.47 ^f	<0.001	-0.15	1.0	-0.13	0.17
Associative memory ^{c,d}	0.42	1.0	-0.09	0.44	0.228 ^f	0.05	-0.31 ^f	0.001	0.49	1.0	0.29 ^f	0.01	-0.42 ^f	<0.001	-0.13	0.8	-0.09	0.31
SRT: 30-min delayed recall	7.97	2.6	-0.06	0.83	0.01	0.97	-0.85 ^f	0.003	8.10	2.4	0.21	0.51	-1.11 ^f	<0.001	7.47	2.6	-0.80 ^f	0.004
SRT: total recall	48.86	8.8	-0.33	0.66	2.39 ^f	0.02	-2.40 ^f	<0.001	49.45	8.4	1.65	0.13	-3.15 ^f	<0.001	45.34	8.2	-0.84	0.34
SRT: summary score ^{c,e}	0.36	0.9	-0.03	0.71	0.14	0.20	-0.29 ^f	<0.001	0.42	0.9	0.13	0.23	-0.38 ^f	<0.001	0.07	0.8	-0.19 ^f	0.04

^an = 36 for all measures except Selective Reminding Test (SRT): 30-minute delayed recall (n = 35).

^bMultivariate linear regression analyses applied generalized estimating equations models to control for intrafamilial correlation. Models were adjusted for intrafamilial correlation, age, body mass index, ethnicity, marital status, and alcohol abuse or dependence. The reference category for each comparison is denoted by (ref.). β is interpreted as the number of units memory performance will differ between the two groups of comparison, on average.

^cIndividual test scores z-scored before combining into summary score.

^dSummary score: initial learning (names and occupations) and cued recall (names and occupations).

^eSummary score: SRT (total recall and delayed recall, 30 min).

^fP < 0.05.

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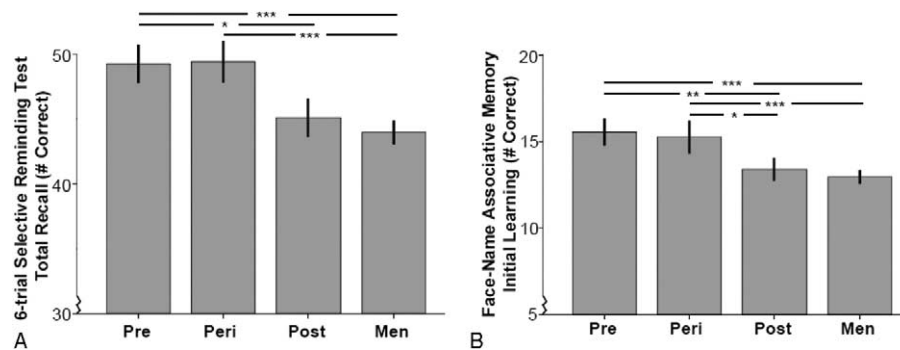


FIG. 1. Episodic memory performance by reproductive stage and sex. Age-adjusted scores are reported by group for 6-trial Selective Reminding Test (SRT) total recall (Pre, premenopausal, $n = 32$; Peri, perimenopausal, $n = 28$; Post, postmenopausal, $n = 31$; Men, $n = 94$) and Face-Name initial learning: names and occupations (Pre, premenopausal, $n = 31$; Peri, perimenopausal, $n = 29$; Post, postmenopausal, $n = 32$; Men, $n = 93$). The SRT total recall score represents the average total number correct across six trials, with a range of 0 to 72. Face-Name initial learning represents the average total number correct for names and occupations, with a range of 0 to 24. Error bars represent ± 1 SEM. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

memory, complex attention/working memory, and verbal fluency during postmenopause.^{15,33,34} Our findings, in part, extend these reports proposing difficulties in initial learning and retrieval of information during *early* postmenopause caused by attention and working memory deficits. These findings implicate frontal executive processes, with no difficulty in consolidation and storage of that information over time, a more worrisome symptom often associated with temporolimbic dysfunction seen in early AD. The ability to identify these more fine-grained memory changes early in midlife was, in part, due to our choice of more challenging memory tasks and analyses by reproductive status. In fact, the association between endogenous estradiol levels and initial learning paradigms suggested that depletion of estradiol may, in part, be associated with these initial learning and retrieval changes seen in early midlife postmenopause. Unlike Fuh et al,⁶⁰ who found verbal fluency changes as women transitioned from pre- to perimenopause, we did not find any significant differences in verbal fluency across menopausal transitions. Our findings were, however, cross-sectional and not longitudinal. Nevertheless, changes in verbal fluency, as

described by Fuh et al, suggest they found similar decrements in frontal executive functions that affected activation retrieval, which is consistent with our findings using challenging tests of memory. In essence, these cognitive changes observed by women during the menopausal transition are most likely related to hormonal processes affecting frontal executive neural networks and not temporolimbic dysfunction.

Not all postmenopausal women experience memory or cognitive changes, and it remains unclear why some women experience these changes more acutely than others. Variation in memory function during the postmenopausal period may be associated with variation in the production of alternative sources of estrogenicity in the brain other than 17β -estradiol, a result of psychosocial pressures, or changes representative of a transient condition that may resolve. Conversely, there is increasing evidence that subjective memory complaints and decrements in semantic processing along with memory deficits noted on challenging tests of memory may be evidence of preclinical AD.^{40,61-64} Women are disproportionately affected by AD, but the mechanisms of this observed sex difference remain unclear. Future studies using *in vivo* biomarkers,

TABLE 4. Association between measures of adult memory performance and hormones among women (pre-, peri-, and postmenopausal)^a

Measures of adult memory	Estradiol $n = 91^b$		Progesterone $n = 91^b$		Estradiol (adjusted for progesterone)		Progesterone (adjusted for estradiol)	
	β	P	β	P	β	P	β	P
Initial learning: names and occupations ^c	0.13	0.10	-0.01	0.89	0.19	0.06	-0.08	0.24
Cued recall: names and occupations ^c	0.03	0.68	-0.01	0.84	0.06	0.55	-0.03	0.63
Associative memory ^{c,d}	0.08	0.25	-0.01	0.85	0.13	0.16	-0.05	0.38
SRT: 30-min delayed recall	0.11	0.62	-0.04	0.81	0.19	0.47	-0.10	0.57
SRT: total recall	1.36 ^f	0.03	-0.10	0.83	1.96 ^f	0.01	-0.81	0.14
SRT: summary score ^{c,e}	0.10	0.14	-0.01	0.81	0.15	0.06	-0.06	0.27

^aMultivariate linear regression analyses applied generalized estimating equations models to control for intrafamilial correlation. Models were adjusted for intrafamilial correlation and age. Estradiol and progesterone data were natural log transformed (ln) before analysis to normalize their distributions.

^b $n = 91$ for all measures excluding Selective Reminding Test (SRT): 30-minute delayed recall, where $n = 90$.

^cIndividual test scores z-scored before combining into summary score.

^dSummary score: initial learning (names and occupations) and cued recall (names and occupations).

^eSummary score: SRT (total recall and delayed recall, 30 min).

^f $P < 0.05$.

particularly in postmenopausal women at genetic dementia risk, will help to elucidate whether early cognitive changes associated with menopause are early indicators of preclinical AD or whether they are unrelated to neurodegenerative illness.

CONCLUSIONS

In summary, consistent with previous reports, we found that women tend to outperform men in memory function in early midlife. We extended these findings by using a controlled age range (45-55 y) and challenging memory tests, demonstrating that reproductive status rather than chronologic age drives these findings. Furthermore, we showed that loss of ovarian estradiol during menopause plays a significant role in shaping memory function. In the future, we hope to understand which memory changes experienced by women in early midlife are associated with healthy aging and which memory deficits may be initial indicators of preclinical AD and eventual memory decline later in life.

Acknowledgments: We thank Dr Stephen Buka and his Brown University team who conducted the location and recruitment efforts in tandem with our team to engage our New England Family Studies cohort, and Shalendar Bhasin, MD, for overseeing mass spectrometry.

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