Effects of the menopause transition and hormone use on cognitive performance in midlife women

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ABSTRACT

Background: There is almost no longitudinal information about measured cognitive performance during the menopause transition (MT).

Methods: We studied 2,362 participants from the Study of Women's Health Across the Nation for 4 years. Major exposures were time spent in MT stages, hormone use prior to the final menstrual period, and postmenopausal current hormone use. Outcomes were longitudinal performance in three domains: processing speed (Symbol Digit Modalities Test [SDMT]), verbal memory (East Boston Memory Test [EBMT]), and working memory (Digit Span Backward).

Results: Premenopausal, early perimenopausal, and postmenopausal women scored higher with repeated SDMT administration ($p \leq 0.0008$), but scores of late perimenopausal women did not improve over time ($p = 0.2$). EBMT delayed recall scores climbed during premenopause and postmenopause ($p \leq 0.01$), but did not increase during early or late perimenopause ($p \geq 0.14$). Initial SDMT, EBMT-immediate, and EBMT-delayed tests were 4%–6% higher among prior hormone users ($p \leq 0.001$). On the SDMT and EBMT, compared to the premenopausal referent, postmenopausal current hormone users demonstrated poorer cognitive performance ($p \leq 0.05$) but performance of postmenopausal nonhormone users was indistinguishable from that of premenopausal women.

Conclusions: Consistent with transitioning women's perceived memory difficulties, perimenopause was associated with a decrement in cognitive performance, characterized by women not being able to learn as well as they had during premenopause. Improvement rebounded to premenopausal levels in postmenopause, suggesting that menopause transition–related cognitive difficulties may be time-limited. Hormone initiation prior to the final menstrual period had a beneficial effect whereas initiation after the final menstrual period had a detrimental effect on cognitive performance. ***Neurology*® 2009;72:1850–1857**

GLOSSARY

CVD = cardiovascular disease; **DSB** = Digit Span Backward; **EBMT** = East Boston Memory Test; **FMP** = final menstrual period; **MT** = menopause transition; **SDMT** = Symbol Digit Modalities Test; **SWAN** = Study of Women's Health Across the Nation.

Although 60% of women report memory problems during the menopause transition (MT), information about measured cognitive performance during MT is scant.[1-3] The relation between MT and measured cognitive performance has been the subject of only two published longitudinal studies.[4,5] One reported a deficit in verbal memory during perimenopause,[4] whereas the other witnessed no cognitive effect of MT.[5] These studies were constrained by small sample sizes and short durations.

Supplemental data at www.neurology.org

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In addition to responding to the cognitive concerns of midlife women, scientific interest in the relation between menopause and cognition stems from a well-developed literature that attests to estrogen's salutary neurophysiologic effects.[6,7] The human hippocampus and prefrontal cortex, which serve episodic and working memory, are rich in estrogen receptors.[6] In animal and in vitro models, estrogens elevate levels of neurotransmitters, promote neuronal growth and formation of synapses, are antioxidants, and regulate calcium homeostasis and second messenger systems.[6,7] Thus, it has been postulated that a drop in estrogen (as in postmenopause) or substantial fluctuations in estrogen (as in perimenopause) could be detrimental to brain function.

The Study of Women's Health Across the Nation (SWAN) measured cognitive performance during the MT. This 4-year, longitudinal analysis addresses the following questions: 1) Does advancement though MT stages affect the trajectory of measured cognitive performance? 2) Is prior hormone use related to the trajectory of cognitive performance? 3) In postmenopause, does current hormone use affect the trajectory of cognitive performance?

METHODS SWAN is a community-based, multisite, longitudinal study of the MT.[8] Cohort entry requirements were as follows: age 42 to 52 years; intact uterus and at least one ovary; no current use of estrogens or other medications known to affect ovarian function; at least one menstrual period in the 3 months prior to screening; and self-identification as Caucasian, African American, Hispanic, Chinese, or Japanese. Institutional Review Board approval and written informed consent were obtained. SWAN sites and administration are described in the appendix at the end of the text.

Cognitive testing was first administered to the entire SWAN cohort at the fourth follow-up, attended by 2,658 participants (80.5% of 3,302 women in the inception cohort); 2,416 (91.0%) of the fourth visit attendees completed cognitive testing. To be eligible for the current analysis, spanning the fourth to the eighth follow-up visits, the following were required: 1) cognitive data collected according to protocol at ≥1 cognitive testing visits; 2) no self-reported history of stroke; and 3) determinable MT stage and calculable amount of time spent in each stage (description below). Thus, 1,985 women (75% of the fourth visit attendees) were eligible. Women entered the analytic data set subsequently (by initiating cognitive tests or by discontinuing hormones). Patterns of participation of the 2,362 SWAN participants who were included are summarized in appendix e-1 on the *Neurology*® Web site at www.neurology.org.

Cognitive outcomes. Processing speed was assessed with the Symbol Digit Modalities Test (SDMT).[9] Verbal episodic memory was evaluated using the East Boston Memory Test (EBMT), similar to the Logical Memory subtest of the Wechsler Memory Scales.[10,11] Working memory was assessed by Digit Span Backward (DSB).[12,13] Tests were professionally forward and back translated; an adjudication panel resolved discrepancies. Bilingual participants took the tests in the same language each time.

Primary predictors. We hypothesized that the rate of change in cognitive performance would depend on MT stage, i.e., cognition score at any follow-up visit would vary according to time spent in each MT stage between the initial test (cognitive baseline) and follow-up tests. We considered five MT stages: premenopausal, early perimenopausal, late perimenopausal, postmenopausal, and postmenopausal with current hormone use. Premenopause was defined as having had no change in predictability of menses. Experiencing decreased predictability of menses, but having no gaps of ≥3 months, was the criterion for early perimenopause. Having no menses for 3–11 months characterized late perimenopause. Women with natural or surgical menopause were considered as a single postmenopausal category. Absent menses for 12 or more months defined natural postmenopause. Surgical postmenopause was the occurrence of bilateral oophorectomy with or without hysterectomy. Those who underwent a hysterectomy without bilateral oophorectomy prior to the final menstrual period (FMP) were permanently censored at the time of hysterectomy. Postmenopausal participants who initiated hormones after their FMP were categorized as postmenopausal current hormone users. Participants who had not achieved their FMP when they began using hormones were not included in the analysis during the time they used hormones, because natural bleeding patterns were unobservable. However, between cognitive study initiation and follow-up visit eight, 446 such participants subsequently discontinued hormones, allowing entry or re-entry into the sample. We also created an indicator to capture prior hormone use (oral contraceptives or menopausal hormones) that occurred between cohort baseline and cognitive study initiation; 475 women reported hormone use during this interval; 98.3% began use prior to their FMP. To account for the possibility that the rate of change in cognitive functioning may be different in those with prior hormone exposure, a time off hormones variable was created, which accounted for time since cohort baseline. The mean number of years off hormones was as follows: 2.0 (SD = 0.7) at follow-up four, 2.6 (SD = 1.2) at follow-up six, 2.7 (SD = 1.6) at follow-up seven, and 3.2 (SD = 1.7) at follow-up eight. Appendix e-2 details the calculation of time-in-MT-stage, participant re-entry after hormone discontinuation, and calculation of time off hormones.

Covariates. Covariates were age (years), educational level (less than high school, high school, some college, college or post baccalaureate degree), difficulty paying for basics (food and housing; classified as not hard, somewhat hard, very hard), race/ethnicity (self-designated Caucasian, African American, Hispanic, Japanese, or Chinese), testing language (English or non-English), and site.[14] To minimize bias from differential attrition, we included a count score for number of cognitive test visits completed.[15]

Statistical analyses. Analyses were performed using SAS version 9.1.3. Using a mixed effects model, we fit a two-parameter growth curve, with an intercept (score at cognitive baseline) and a linear aging effect (decline or improvement at constant slope) including a random intercept. For participants whose MT stage became unclassifiable for some time after the cognitive study baseline (due to hormone use prior to the FMP) but became

Table 1 Demographic and menopause transition stage characteristics of SWAN participants included compared to those not included in the current analysis

Participant characteristics	Participants in analysis* (n = 2,362)	Participants not in analysis† (n = 940)
Categorical variables (statistical significance level‡)		
Menopause transition stage§		
Premenopause	55.03	49.78
Early perimenopause	44.97	50.22
Race‖		
Black	28.03	29.04
Caucasian	46.15	48.94
Chinese	9.27	3.30
Hispanic	5.93	15.53
Japanese	10.63	3.19
Educational level‖		
Less than high school	5.98	10.55
High school	16.57	20.78
Some college	31.77	33.05
College	21.31	17.44
More than college	24.38	18.19
Difficulty paying for basics‖		
Very hard	7.88	12.98
Somewhat hard	29.26	34.23
Not hard at all	62.86	52.79
Language used in reading/speaking‖		
Other than English	8.66	13.89
Bilingual	7.55	6.89
English only	83.79	79.22
Continuous variable, mean (SD)		
Age, y	45.86 (2.67)	45.82 (2.73)

Eligibility criteria for inclusion in analysis sample were 1) cognitive data collected according to protocol standards at one or more visits (follow-ups four, six, seven, or eight); 2) no self-reported stroke through the eighth follow-up visit; 3) menopause transition stages and amount of time spent in menopause transition stages determinable (see Methods and appendix e-2). Values in table 1 are based on data from SWAN cohort baseline data, rather than visit four, because 377 women in the analytic sample did not attend visit four and because some characteristics were measured only at cohort baseline. For categorical variables, values shown are percents.

*Of the 2,362 women in the analytic sample, 1,984 began the study at the fourth follow-up visit and 377 entered the study at a later visit (visit six, seven, or eight).

†There were 3,302 women in SWAN at cohort baseline. Data in this column are from the 940 SWAN cohort participants who are not represented in this analysis.

‡Statistical significance of chi-square test or t test for differences between eligible and ineligible SWAN participants: §$p < 0.01$; ‖$p < 0.001$.

SWAN = Study of Women's Health Across the Nation.

classifiable at a later visit (after hormone discontinuation), we fit two growth curves, one for the first set and one for the later set of visits (with a new baseline and new random intercept). The intercept (baseline score) was allowed to vary by MT stage at the baseline cognition visit, prior hormone use, demographic characteristics (age, educational level, difficulty paying for basics, race/ethnicity), language of testing, study site, and number of cognitive visits completed. The slope (score rate of change over time) was also allowed to vary by time-invariant demographic characteristics, testing language, study site, and number of cognition assessments. To capture the effect of time-varying characteristics (MT stage and hormone use) on slope, we modeled follow-up cognition scores as varying linearly with time spent in each MT stage between the cognitive baseline and the follow-up visit and with time off hormones. Because the distributions of EBMT scores were skewed, we used robust, empirical estimates of standard errors for all analyses.[16,17] Difficulty paying for basics was missing for 14 women; the modal value (not very hard) was used. Interviews were conducted in more than one language for 25 women; data were used from interviews corresponding to language used most often. Adjustment was not made for multiple comparisons. We conducted statistical sensitivity analyses, summarized in appendix e-2.

RESULTS

Participants. Characteristics of women in this analysis, compared to the remainder of women in SWAN, are summarized in table 1. Compared to those included, those not included had less education, more economic hardship, and higher prevalence of non-English language use. Distributions of race/ethnicity also differed, with lower representation of Hispanic and higher representation of Chinese women in the analytic sample. The mean age of in-analysis participants was 45 years, not different from those not included. At follow-up four, the mean age of the 2,362 women in-analysis was 50 years (range 45 to 57). At cognitive study baseline, 181 (8%) women in the sample were premenopausal, 1,165 (49%) were early perimenopausal, 278 (12%) were late perimenopausal, 643 (27%) were postmenopausal not taking hormones, and 95 (4%) were postmenopausal currently using hormones. The range of years spent in each MT stage was as follows: premenopause, 0 to 4.33; early perimenopause, 0 to 4.63; late perimenopause, 0 to 4.11; postmenopause, 0 to 5.07; and postmenopause currently using hormones, 0 to 4.43.

Cognitive scores. At visit four, crude mean SDMT and DSB scores approximated the midpoint of the range and distributions were symmetric. Crude means for the EBMT-immediate and delayed were approximately 10, with 28% and 24% of women achieving the maximum (appendix e-3).

MT stage and hormone effects. For each cognitive test, results for the primary predictors based on the full model are detailed in table 2. For each MT stage, the growth curve slope and the mean initial score (intercept) are shown. A positive slope that is significantly different from zero indicates improvement. To assess whether there was an MT-related change in cognitive performance, table 2 also compares initial scores and slopes in each later MT stage to the premenopausal referent. Finally, the effect of prior hormone use on the initial score and slope is summarized. Prior hormone users took HT or oral contraceptives prior to their FMP, stopped using

Table 2 Menopause transition stage and hormone therapy associations with initial cognitive test scores and slopes of scores over time

	Cognitive tests (possible range)							
	Symbol Digit Modalities (0–110)		East Boston Memory Immediate Recall (0–12)		East Boston Memory Delayed Recall (0–12)		Digit Span Backward (0–12)	
Menopause transition stage*	Initial score	Annual slope (SE)	Initial score	Annual slope (SE)	Initial score	Annual slope (SE)	Initial score	Annual slope (SE)
Premenopausal	55.7	+0.94 (0.28)†	10.2	+0.08 (0.06)	9.9	+0.14 (0.06)†	6.7	+0.01 (0.07)
Early perimenopausal	55.2	+0.54 (0.11)†	10.1	+0.06 (0.02)	9.9	+0.04 (0.02)‡	6.6	+0.05 (0.03)
Late perimenopausal	55.0	+0.26 (0.22)‡	10.2	+0.03 (0.0)	10.0	+0.01 (0.04)‡	6.6	+0.11 (0.05)
Postmenopausal	54.7	+0.63 (0.13)†	10.0	+0.11 (0.03)§	9.8	+0.13 (0.03)†§	6.5	+0.06 (0.03)
Postmenopausal with current hormone use	55.6	−0.02 (0.31)‖	10.4	−0.06 (0.07)	10.1	−0.09 (0.07)‖	6.3§	+0.14 (0.09)
Effect of prior hormone use on initial test scores and slopes#	+3.5¶	−0.38 (0.17)‡¶	+0.6¶	−0.16 (0.04)‡¶	+0.5¶	−0.15 (0.04)‡¶	+0.2	−0.01 (0.05)

*Initial scores and slopes for menopause transition stage are based on data from women who did not have prior hormone exposure between Study of Women's Health Across the Nation (SWAN) cohort baseline and their initial cognitive visit. We modeled the effect of time spent in each menopause transition stage on the change in cognitive performance over time (slope). Details are contained in the Statistical methods section of the text. Values in the table are adjusted for age at cognitive baseline, difficulty paying for basics, educational level, race/ethnicity, language of testing, number of cognitive test visits attended, and SWAN clinical site (see Methods). For slopes, 95% confidence intervals may be calculated by multiplying standard error by ±1.96.

†Slope estimates significantly different from zero at the 0.05 level; exact *p* values for tests of non-zero slopes are provided in text.

‡$0.05 < p < 0.1$ for test of difference from value in premenopause.

§$p < 0.05$ for test of difference in trajectory parameter values in postmenopausal women vspostmenopausal current hormone users.

‖$p < 0.05$ for test of difference from value in premenopause.

¶$p < 0.05$ for test of effect of prior hormone use on initial score or slope.

#The effect of prior hormone use on the initial score and slope is reported as the mean parameter in prior hormone users minus the corresponding mean in those without prior hormone use who are in the same menopause transition stage, after adjusting for the covariates listed above. For slopes, 95% confidence intervals may be calculated by multiplying standard error by ±1.96.

hormones, and were then MT stage classifiable; referents are those in equivalent MT stages who were not prior hormone users. The initial score for prior hormone users is the increment in baseline score relative to the same MT-staged comparator; the slope is the increment in slope relative to the same comparator. Key findings from table 2 are highlighted below.

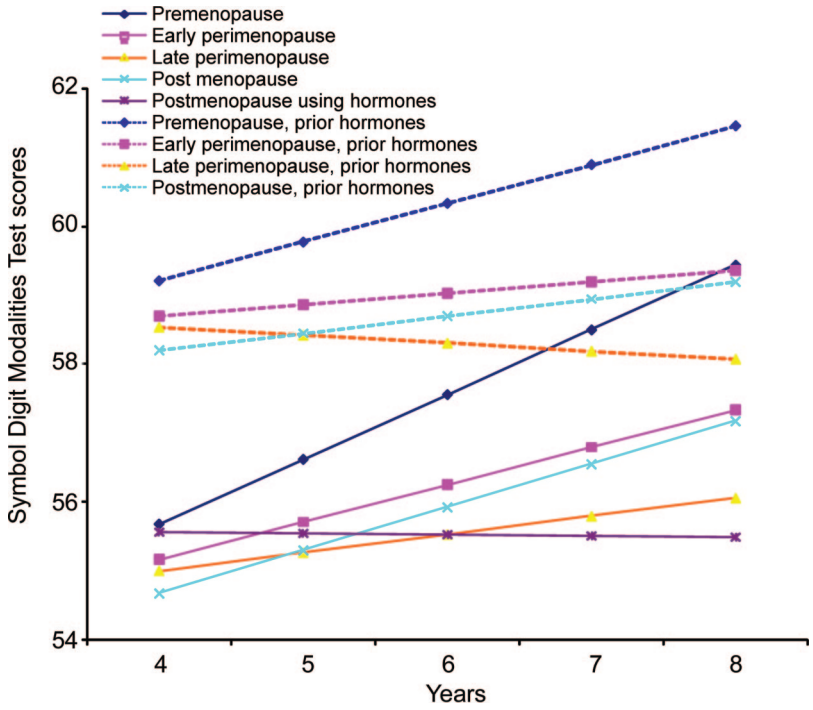
Processing speed (SDMT). Premenopause (slope 0.94, $p = 0.0008$) and early perimenopause (slope 0.54, $p < 0.0001$) were characterized by improvement in cognitive processing speed with repeated testing; premenopausal and early perimenopausal slopes were not different from each other ($p = 0.2$). Processing speed did not improve during late perimenopause (slope 0.26, $p = 0.2$) and this slope was marginally different from the premenopausal slope ($p = 0.06$). Performance improved in postmenopause (slope 0.63, $p < 0.0001$) and the postmenopausal slope differed from that in premenopause ($p = 0.3$).

Improvement was not manifest by postmenopausal hormone users (slope −0.02, $p = 0.96$). Moreover, the SDMT slope among postmenopausal hormone users was different from the premenopausal slope ($p = 0.03$). Prior hormone users scored 3.53 higher on their first SDMT examination ($p < 0.0001$), but had smaller slopes over time compared to women in the same MT stages ($p = 0.03$). Although their advantage waned over time, average SDMT scores of postmenopausal hormone users remained higher than those of nonusers. Figure 1 graphs the model-predicted trajectories of the SDMT.

Verbal memory (EBMT-immediate). Immediate recall did not change during any MT stage or during postmenopausal current hormone use. Prior hormone use conferred a baseline advantage; initial EBMT-immediate scores were 0.61 higher than scores of women in the same MT stage who were not former hormone users ($p < 0.0001$). Verbal memory benefits of prior hormone exposure completely dissipated with time ($p < 0.0001$). Figure 2 shows the model-predicted trajectories of EBMT-immediate scores.

Verbal memory (EBMT-delayed). Premenopausal women improved on the EBMT-delayed test (slope 0.14, $p = 0.01$) but early perimenopausal ($p = 0.13$) and late perimenopausal women ($p = 0.8$) did not.

Figure 1 Multiply adjusted model-predicted trajectories of Symbol Digit Modalities Test scores



Slopes are calculated assuming women remained in the same menopause transition stage throughout 4 years and, for prior hormone users, that they stopped using hormones just prior to cognitive baseline.

EBMT slopes during early ($p = 0.08$) and late perimenopause ($p = 0.06$) were marginally different from the premenopausal referent. A positive slope was seen during postmenopause (slope 0.13, $p < 0.0001$) but not among postmenopausal hormone users (slope −0.09, $p = 0.2$).

EBMT-delayed score slopes of postmenopausal hormone users were lower than those of premenopausal women ($p = 0.01$). Previous hormone users had initial EBMT-delayed scores that were 0.53 higher ($p = 0.004$) than baseline scores of comparably staged women; this advantage completely dissipated over time ($p = 0.004$). Figure 3 illustrates the model-predicted trajectories of EBMT-delayed scores.

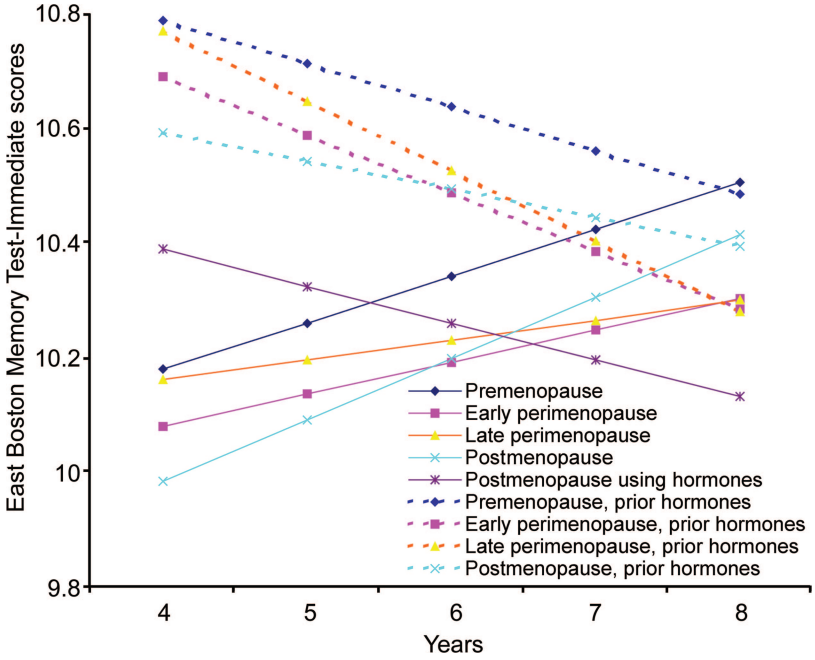
Working memory (DSB). Slopes during each MT stage did not differ from zero and slopes during later MT stages were not distinguishable from the premenopausal slope. Working memory was unaffected by current or prior hormone use.

Covariate and adherence effects. More education and absence of financial hardship predicted higher baseline scores on all tests but did not affect performance over time. For the SDMT, older participants had lower initial scores (−0.37 per year, $p < 0.0001$). Age did not affect longitudinal performance on any test. Japanese, Chinese, Hispanic, and African American subjects posted lower initial EBMT and DSB scores compared to Caucasian subjects. On the SDMT, compared to Caucasian subjects, Hispanic and African American subjects scored worse, Japanese subjects scored better, and Chinese subjects did not differ. English test-takers performed better on SDMT (1.91 higher, $p = 0.02$) and worse on the DSB (−0.58 lower, $p = 0.001$) than did non-English test-takers. Women who attended a greater number of cognitive visits displayed greater improvements over time on all but the DSB (each $p \leq 0.03$).

DISCUSSION The menopause transition, prior hormone use, and current postmenopausal hormone use were each related to measured cognitive performance, but the patterns of these relations varied by cognitive domain. An MT-related cognitive disadvantage was most apparent in the domain of processing speed: while premenopausal, early perimenopausal, and postmenopausal women manifested significant gains in SDMT scores with repeated testing, late perimenopausal women did not. Perimenopause was also disadvantageous to verbal episodic memory: although scores for premenopausal and postmenopausal participants improved with repetition of the EBMT-delayed test, scores for early and late perimenopausal women did not. Former hormone use, taken prior to the FMP, was associated with better processing speed and verbal memory: initial SDMT scores were approximately 6% higher and initial EBMT-immediate and delayed scores were roughly 4%–5% greater among prior hormone users. In contrast, current hormone use among postmenopausal women predicted worse processing speed and verbal episodic memory performance over time compared to premenopausal performance.

The relation between MT stage and cognitive performance has been the subject of only two longitudinal studies.[4,5] The first was a cohort of 573 Chinese women with average age of 46 years and average education of 6.5 years. On the Rey Auditory Verbal Learning Test, those who transitioned to perimenopause had significantly less improvement than those who remained premenopausal, similar to the EBMT results of perimenopausal SWAN participants. The second was a SWAN site-specific cognitive substudy that began at SWAN cohort baseline. With 2 years of follow-up in ~800 women aged 42–52 years, adjusting for social and demographic variables, small time-related improvements were observed but no MT effects were identified.[5] Our observation that perimenopause negatively impacted cognitive performance likely differs from the substudy's findings because the current sample size is three times larger, follow-up is twice as long, and the substudy did not account for

Figure 2 **Multiply adjusted model-predicted trajectories of East Boston Memory Test–Immediate Recall scores**



Slopes are calculated assuming women remained in the same menopause transition stage throughout 4 years and, for prior hormone users, that they stopped using hormones just prior to cognitive baseline.

the effects of prior and current hormones. Unlike prior reports, the current study modeled time in MT stage as its primary exposure.

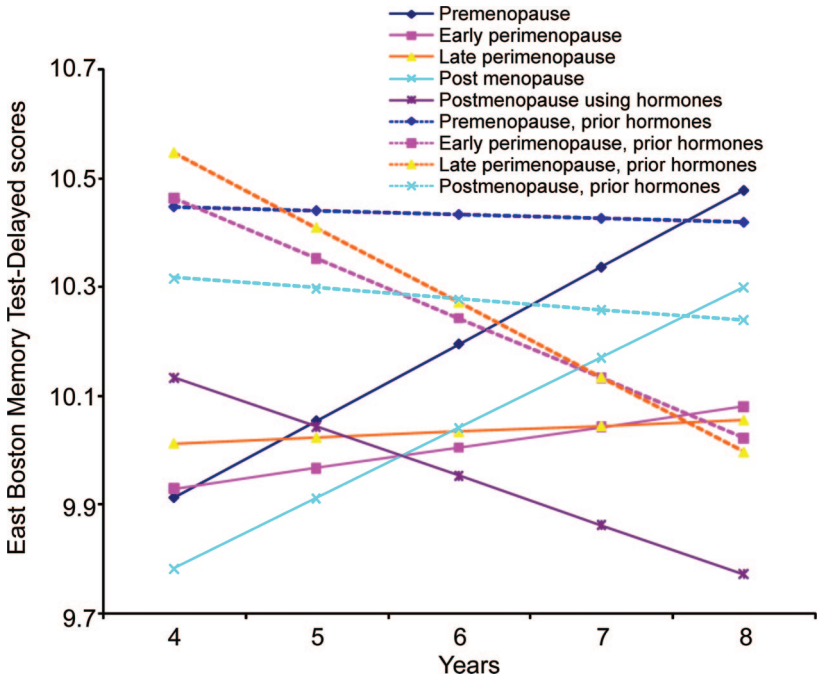
The disturbance in cognitive performance during perimenopause was subtle, manifested by lack of improvement over time rather than an overt decline. Although there are limited longitudinal data in this age range, improvement with repeated testing is believed to be the norm. In the Baltimore Longitudinal Study of Aging, among men and women aged 55–90 years, annual gains on the California Verbal Learning test were observed until subjects reached their mid 60s; the authors postulated that in young persons, the absence of improvement with serial testing may be an indicator of abnormal cognitive function.[18] Our participants ranged in age from 49 to 61 years, thus would be expected to improve with repeated tests. Further support that the absence of improvement observed during perimenopause was related to MT stage and not to chronological aging comes from the finding that improvement resumed in postmenopause.

Prior hormone users (prior to the FMP) had better baseline processing speed and verbal memory relative to women in equivalent MT stages who had not used hormones. Conversely, current hormone use during postmenopause was detrimental to performance in these domains. These discordant effects may be reconciled by the critical timing hypothesis, which predicts that early hormone initiation would benefit cognition (higher initial scores) but late initiation would be detrimental to it (less improvement in postmenopausal hormone users).[19-21] Critical timing for cardiovascular disease (CVD) was reported in the Women's Health Initiative: women <10 years postmenopause at hormone initiation did not have increased risk of CVD and those aged 50–59 years at hormone startup had regression of vascular calcifications.[22,23] The SWAN results suggest that critical timing applies to cognitive performance, but that the critical period may be substantially earlier than that for CVD. Mechanisms underlying critical timing have been reviewed.[19-21,24,25] Poorer cognitive performance among postmenopausal hormone users could also result from confounding. Symptomatic women are more likely to use hormones; if MT symptoms lead to poorer cognition, it could appear that hormones cause poorer performance. However, this thesis does not fit with the observed benefit of hormones prior to the FMP because these women were probably using hormones for MT symptoms.[26]

The effects of perimenopause and prior and current hormone use were apparent for processing speed (SDMT) and verbal episodic memory (EBMT). These findings are consistent with theories about cognitive aging and cognitive function during the MT. Slowed processing speed is considered one of the earliest indicators of cognitive aging.[9,27] We also expect MT and hormone effects on verbal memory because the hippocampus and prefrontal cortex, brain areas that serve these functions, are rich in estrogen receptors.[6,7] We posit that MT effects were picked up by the delayed, but not the immediate, EBMT because the delayed assessment was slightly more difficult. Contrary to expectation, we witnessed no MT effects on working memory (DSB), a cognitive domain also served by estrogen receptor–rich brain regions.[9,27] Also unexplained is the lack of improvement in this domain. DSB scores decline very little with age in cross-sectional studies[28] and other longitudinal data show that men and women substantially older than our cohort learn with repeated DSB administration.[29]

Limitations of this study include the small cognitive battery and that many participants started with maximum verbal memory scores, precluding improvement over time. Whether menopause symptoms (e.g., hot flashes) mediate the cognitive difficulties observed during perimenopause and whether endogenous sex steroids are related to cognition during the MT remain important questions that

Figure 3 **Multiply adjusted model-predicted trajectories of East Boston Memory Test-Delayed Recall scores**



Slopes are calculated assuming women remained in the same menopause transition stage throughout 4 years and, for prior hormone users, that they stopped using hormones just prior to cognitive baseline.

are beyond the scope of this analysis, but will be the subjects of future work.

AUTHOR CONTRIBUTIONS

R.G.W., M.-H.H., and A.S.K. performed statistical analyses.

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APPENDIX

SWAN Clinical Centers: University of Michigan, Ann Arbor—MaryFran Sowers, PI; Massachusetts General Hospital, Boston—Robert Neer, PI 1994–1999; Joel Finkelstein, PI 1999–present; Rush University, Rush University Medical Center, Chicago, IL—Lynda Powell, PI; University of California, Davis/Kaiser—Ellen Gold, PI; University of California, Los Angeles—Gail Greendale, PI; University of Medicine and Dentistry–New Jersey Medical School, Newark—Gerson Weiss, PI 1994–2004; Nanette Santoro, PI 2004–present; and the University of Pittsburgh, PA—Karen Matthews, PI. *NIH Program Office:* National Institute on Aging, Bethesda, MD—Marcia Ory 1994–2001; Sherry Sherman 1994–present; National Institute of Nursing Research, Bethesda, MD–Program Officers. *Central Laboratory:* University of Michigan, Ann Arbor—Daniel McConnell (Central Ligand Assay Satellite Services). *Coordinating Center:* New England Research Institutes, Watertown, MA—Sonja McKinlay, PI 1995–2001; University of Pittsburgh, PA—Kim Sutton-Tyrrell, PI 2001–present. *Steering Committee:* Chris Gallagher, Chair; Susan Johnson, Chair.

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