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Original Contribution

Menopause-associated Symptoms and Cognitive Performance: Results From the Study of Women's Health Across the Nation

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A long-standing, but unproven hypothesis is that menopause symptoms cause cognitive difficulties during the menopause transition. This 6-year longitudinal cohort study of 1,903 midlife US women (2000–2006) asked whether symptoms negatively affect cognitive performance during the menopause transition and whether they are responsible for the negative effect of perimenopause on cognitive processing speed. Major exposures were depressive, anxiety, sleep disturbance, and vasomotor symptoms and menopause transition stages. Outcomes were longitudinal performance in 3 domains: processing speed (Symbol Digit Modalities Test (SDMT)), verbal memory (East Boston Memory Test), and working memory (Digit Span Backward). Adjustment for demographics showed that women with concurrent depressive symptoms scored 1 point lower on the SDMT ($P < 0.05$). On the East Boston Memory Test, the rate of learning among women with anxiety symptoms tested previously was 0.09 smaller per occasion ($P = 0.03$), 53% of the mean learning rate. The SDMT learning rate was 1.00 point smaller during late perimenopause than during premenopause ($P = 0.04$); further adjustment for symptoms did not attenuate this negative effect. Depressive and anxiety symptoms had a small, negative effect on processing speed. The authors found that depressive, anxiety, sleep disturbance, and vasomotor symptoms did not account for the transient decrement in SDMT learning observed during late perimenopause.

cohort studies; longitudinal studies; memory; menopause

Abbreviations: CES-D, Center for Epidemiologic Studies Depression; DSB, Digit Span Backward; EBMT, East Boston Memory Test; SDMT, Symbol Digit Modalities Test; SWAN, Study of Women's Health Across the Nation.

During the menopause transition, a majority of women report memory problems (1). Studies of measured cognitive performance during the menopause transition are few, but 2 of 3 published longitudinal studies corroborate women's perceptions (2–4). The Kinmen Women-Health Investigation (KIWI) reported a perimenopause-related deficit in verbal memory (2). In a 2-year substudy performed at the Chicago, Illinois, site of the Study of Women's Health Across the Nation (SWAN), processing speed and working memory were unaffected by the menopause transition (3). Finally, a 4-year longitudinal study of cognitive performance conducted at all 7 SWAN sites found that perimenopause was associated with a transient decrement in processing speed and verbal memory that resolved in postmenopause (4). The perimenopause effect was manifested by lack of improvement with repeated administrations of the cognitive tests over time; improvement with repetition is expected during midlife (5).

Two pathways may underlie perimenopause-associated alteration in cognitive function. First, estrogen may directly benefit neural tissue: estrogen augments hippocampal and prefrontal cortical function, potentially enhancing verbal memory and executive function (6–9). Fluctuations in gonadal steroid levels during perimenopause could therefore negatively impact cognitive performance. Second, symptoms associated with the menopause transition may explain poorer cognitive performance. Recently postmenopausal women (many of whom have vasomotor symptoms) and

surgically menopausal women (who experience more severe vasomotor symptoms than naturally menopausal women) derive greater cognitive benefit from hormone therapy than do older, naturally postmenopausal women (8, 10). One interpretation of these differential cognitive effects of hormone therapy among menopause subsets is that vasomotor symptoms are detrimental to cognition and their amelioration benefits it.

Our analysis addresses the hypothesis that menopause transition–associated symptoms may account, at least in part, for the cognitive performance decrement observed during the perimenopause in SWAN (4). Besides vasomotor symptoms, our model incorporates depressive, anxiety, and sleep disturbance symptoms, which are related to the menopause transition in SWAN (11–15) and other longitudinal menopause transition studies (16–20). Depressive, anxiety, and sleep disturbance symptoms are also implicated in suboptimal attention and memory (21–29). The analysis asks 2 questions: 1) Do depressive, anxiety, sleep disturbance, or vasomotor symptoms lead to poorer cognitive performance over time in midlife women? 2) Do the perimenopause-related cognitive decrements observed in SWAN occur independently of these symptoms?

MATERIALS AND METHODS

SWAN is a community-based, multisite, longitudinal study of the menopause transition (30). Entry requirements were age 42–52 years; intact uterus and at least 1 ovary; no current use of estrogens or other medications that affect ovarian function; at least 1 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.

Cognition was first tested at the fourth annual follow-up, attended by 2,658 participants (80.5% of 3,302 in the inception cohort); 2,416 (91.0%) of the fourth-visit attendees completed cognitive testing. To be part of this analysis, spanning the fourth–eighth follow-up visits, participants were required to have 1) cognition tests performed according to protocol at 1 or more visits, 2) no self-reported history of stroke, 3) determinable menopause transition stage, and 4) no use of hormone therapy between SWAN baseline and the first cognitive test visit. A total of 1,903 women (72% of the fourth-visit attendees) were eligible. Participants were subsequently censored if they started hormone therapy or reported a new stroke.

Outcomes

Processing speed was assessed with the Symbol Digit Modalities Test (SDMT) (31). Verbal episodic memory (immediate and delayed recall) was evaluated by using the East Boston Memory Test (EBMT) (32, 33). Digit Span Backward (DSB) tested working memory (34, 35). Tests were professionally forward and back translated. Bilingual participants always took tests in the same language.

Primary predictors, aim 1

To address whether symptoms negatively affect cognitive performance, we examined the relation between high-level (defined in the context of this cohort; refer to the information below) depressive, anxiety, sleep disturbance, and vasomotor symptoms and each cognitive test. Depressive symptoms were measured by the Center for Epidemiologic Studies Depression (CES-D) Scale, which assesses the frequency of 20 symptoms during the past week, scored 0 (rarely) to 3 (most or all the time) (36). CES-D score (range, 0–60) is the sum of scores for each endorsed symptom. We categorized depressive symptoms as high level when the CES-D score was in the top quartile ($\geq$13). Participants reported the frequency of 4 anxiety symptoms (irritability/grouchiness, tense/nervous, pounding/racing heart, or feeling fearful for no reason) during the past 2 weeks, scored 1 (not at all) to 5 (daily); the anxiety score is the sum of the 4 symptom ratings (11). We modeled anxiety symptoms as high level when the score was in the top quartile ($\geq$7).

Using an abbreviated Pittsburgh Sleep Quality Index, we assessed sleep during the prior 2 weeks (15, 37). Sleep disturbance symptoms were coded high level if any of the following were reported for 3 or more nights per week: difficulty falling asleep, waking up several times nightly, or waking up earlier than planned with an inability to fall asleep again (38). The frequency of 3 types of vasomotor symptoms—hot flashes, cold sweats, or night sweats—during the previous 2 weeks was recorded as not at all, 1–5 days, 6 –8 days, 9 –13 days, or daily. Vasomotor symptoms were considered high level if any of the vasomotor symptoms categories occurred 6 or more days per week (11). We counted the number of high-level symptoms at each visit (range, 0–4).

Primary predictors, aim 2

To address whether inclusion of symptoms in the model would attenuate the previously reported negative effect of perimenopause on cognition, we considered menopause transition stages primary predictors of cognitive performance: premenopause, early perimenopause, late perimenopause, and postmenopause (4). Premenopause was defined as having had no change in predictability of menses. Experiencing decreased predictability of menses, but having no gaps of 3 or more months, was the criterion for early perimenopause. No menses for 3–11 months characterized late perimenopause. Natural and surgical menopause constituted 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. Data for those who underwent a hysterectomy without bilateral oophorectomy prior to the final menstrual period were censored, because menopause transition stage became unknowable.

Covariates

Covariates for both aims were age (years) at the time of the first cognitive test, educational level (less than high

school, high school, some college, college, more than college), difficulty paying for basics (food and housing; classified as not difficult at all, somewhat difficult, very difficult), race/ethnicity (Caucasian, African American, Hispanic, Japanese, Chinese), testing language (English vs. non-English), and study site (39). Covariates were time invariant, assessed at the first cognitive visit.

Statistical analyses

Analyses were performed by using SAS (v9.1.3) software (SAS Institute, Inc., Cary, North Carolina). Crude cognition scores increased over the 4 testing occasions. We conducted longitudinal analyses to determine whether the increases over time represented improvement with aging and/or practice gains with repeat testing (reflecting both learning and increased self-assurance) (40). In mixed-effects models, no association was observed between improvement in cognition scores from one testing occasion to the next and length of time elapsed between testing (range, 0.3–3.1; median, 1.1; interquartile range, 0.9–1.9); P values ranged from 0.24 for EBMT delayed to 0.83 for SDMT. Thus, on average, no age-related decline or improvement in cognition scores occurred; rather, longitudinal gains reflected mainly learning effects.

To capture these learning effects, we modeled cognition scores as increasing linearly with number of previous exposures to the test. To allow for a decrement in the magnitude of learning after repeated testing (i.e., repeated learning opportunities), we fit 2 candidate mixed-effects null models, with only intercept, number of previous testing occasions (n), and a spline with knot fixed at either $n = 1$ or $n = 2$ (allowing learning to fall after the first testing or second testing, respectively). There was no decrement in EBMT learning after either 1 occasion ($P > 0.5$) or 2 occasions ($P > 0.6$). For SDMT and DSB, there was a decrement in learning after the second testing ($P = 0.008$ and $P = 0.0004$, respectively).

Therefore, we modeled each cognition score as a function of current value (at each annual visit) of the primary predictor (menopause transition symptoms or menopause transition stages for aims 1 and 2, respectively), covariates, number of previous exposures to the cognitive test (n), and (for SDMT and DSB models only) a spline with knot fixed at $n = 2$ (to allow learning to fall after the second testing). We used mixed-effects modeling with random intercept and random effects for both n and the spline at $n = 2$ to account for within-woman correlation between repeated measurements. We modeled the initial learning effect as varying by the value of the primary predictor (and covariates) at the time of the previous tests as a fixed effect. To capture the effect of each symptom on learning, we included a term for the number of previous testing visits during which the participant reported a high level of the symptom; to quantify the effect of menopause transition stage on learning, we included terms for the number of previous cognitive tests in each of the menopause transition stages. Because the distributions of EBMT scores were skewed, we used robust, empirical estimates of standard errors for all analyses (41, 42). Information on difficulty paying for basics was missing for 14 women; the modal value (not very difficult) was used. Tests were conducted in 2 languages for 25 women, and we used data from only the language used most often. We did not adjust for multiple comparisons.

RESULTS

Table 1 summarizes the characteristics, at cohort baseline, of women analyzed compared with the remainder. Women who were excluded had less education and more non-English-language use. Distributions of race/ethnicity also differed, with a lower representation of Caucasian and Hispanic women and a higher representation of Chinese and Japanese women in the analytic sample.

At visit 4, the first time that cognition was measured, the mean age of women being analyzed was 49.74 years (range, 45–57). At the same visit, 169 (9%) were premenopausal, 1,042 (57%) were early perimenopausal, 231 (13%) were late perimenopausal, and 382 (21%) were postmenopausal. By visit 8, the mean numbers of prior SDMT testing visits (representing learning opportunities; range, 0–3) that occurred during each menopause transition stage were 0.23 in premenopause, 1.62 in early perimenopause, 0.44 in late perimenopause, and 0.36 in postmenopause. Numbers of visits that took place during each menopause transition stage were similar for the other cognitive tests. At visit 8, the last one included, 21 (3%) of the women were premenopausal, 279 (35%) were early perimenopausal, 151 (19%) were late perimenopausal, and 349 (43%) were postmenopausal.

Crude mean SDMT and DSB scores at visit 4 approximated the midpoint of the test ranges, and distributions were symmetric (Table 2). Means for the EBMT-immediate and EBMT-delayed were approximately 10, with 28% and 24% of women achieving the maximum values, respectively. Means for all tests increased slightly over time.

The prevalence of high-level depressive, anxiety, sleep disorder, and vasomotor symptoms ranged between 20% and 45% (Table 2). The mean number of high-level symptoms at each visit was approximately 1. At visit 4, 39% of participants had no high-level symptoms; that fraction diminished to 33% at the final visit.

By visit 8, the mean numbers of prior SDMT cognitive testing visits during which women reported high levels of the symptoms were 0.55 for depressive symptoms, 0.77 for anxiety symptoms, 1.04 for sleep disturbance symptoms, and 0.50 for vasomotor symptoms. Numbers of prior visits accompanied by high levels of each of the symptoms were similar for the remainder of the cognitive tests. By visit 8, the average numbers of prior SDMT testing visits during which none to 4 of the high-level symptoms were reported was 1.43 for none, 0.70 for 1, 0.45 for 2, 0.28 for 3, and 0.09 for 4 symptoms. Numbers of visits with none to 4 of the high-level symptoms were similar for the remainder of the cognitive tests.

Unadjusted, concurrent high-level depressive symptoms were associated with slower processing speed (Table 3). On average, those women with high-level depressive symptoms scored 2 points lower on the SDMT compared with those with lower CES-D scores ($P < 0.001$). Similarly,

Table 1. Demographic and Menopause Transition Stage Characteristics of SWAN Participants Included Versus not Included in the Current Analysis, United States, 2000–2006[a,b]

Characteristic[c]	Participants Included[d] (n = 1,903)	Participants Not Included (n = 1,399)
Menopause transition stage***		
Premenopause	40.61	54.45
Early perimenopause	59.39	45.55
Race***		
African American	28.22	28.45
Caucasian	44.51	50.25
Chinese	9.93	4.36
Hispanic	6.88	11.08
Japanese	10.46	5.86
Educational level**		
Less than high school	6.79	7.93
High school	16.77	19.11
Some college	30.79	33.96
College	21.87	17.95
More than college	23.78	21.05
Difficulty paying for basics		
Very difficult	8.42	10.57
Somewhat difficult	30.17	31.34
Not difficult at all	61.41	58.09
Language used in reading/speaking*		
Other than English	9.54	10.97
Bilingual	8.32	6.06
English only	82.14	82.97
Age, years (mean, standard deviation)***	45.64 (2.61)	46.14 (2.77)

Abbreviation: SWAN, Study of Women's Health Across the Nation.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$: statistical significance of chi-squared test or t test for differences between eligible ($n = 1,903$) and ineligible ($n = 1,399$) SWAN participants.

[a] Eligibility criteria for inclusion in the analysis sample: 1) cognitive data collected according to protocol standards at one or more visits (follow-ups 4, 6, 7, or 8); 2) no self-reported stroke through the fourth follow-up visit; and 3) no self-reported hormone use from the SWAN baseline visit through the fourth follow-up visit.

[b] All values are from SWAN cohort baseline, rather than visit 4, because 153 women in the analytic sample did not attend visit 4 and because some characteristics were measured at cohort baseline only.

[c] All values, except those for age, are expressed as percentages.

[d] Of the 1,903 women in the analytic sample, 1,759 began the study at the fourth follow-up visit and 153 entered the study at a later visit (visit 6, 7, or 8).

unadjusted, concurrent verbal memory scores were approximately one-quarter point lower among women with high-level depressive symptoms compared with the remainder ($P < 0.001$, EBMT-immediate and EBMT-delayed). Unadjusted, learning from prior administrations of the SDMT and EBMT (immediate and delayed) was also smaller among those with high-level depressive symptoms. Adjusted for covariates, only the negative association between concurrent high-level depressive symptoms and SDMT persisted ($P < 0.05$); those women with concurrent high-level depressive symptoms scored 1 point lower (or 0.08 standard deviation) on the SDMT than those who were not so classified, about 2% lower than the mean SDMT performance in the sample (54.1 points).

Only processing speed was negatively related to concurrent high-level anxiety symptoms; in unadjusted analyses, women with high-level anxiety symptoms scored about 0.9 points lower than women with lesser anxiety (Table 3) ($P < 0.01$). In crude analyses, learning on 3 of the 4 tests was diminished by high-level anxiety symptoms (SDMT, $P < 0.05$; EBMT immediate, $P < 0.01$; EBMT delayed, $P < 0.05$). After adjustment, there remained a negative association between high-level anxiety symptoms and learning from prior EMBT-immediate administrations ($P < 0.05$): the rate of learning among women with high-level anxiety symptoms on previous testing occasions was 0.09 smaller per occasion than the rate of learning among women without this level of anxiety ($P = 0.03$). The difference was 53% of the mean rate in the cohort (0.17 per testing occasion).

Those with high-level vasomotor symptoms had smaller improvements in SDMT scores with repeated testing compared with those without them (Table 3) ($P < 0.05$), but negative effects on learning were not upheld in adjusted analyses. We found no associations with high-level sleep symptoms in either crude or adjusted analyses (Table 3).

Unadjusted, concurrent processing speed and verbal memory were negatively related to the number of high-level symptoms (data not shown). For each additional symptom, SDMT score was 0.49 points lower ($P < 0.001$) and EBMT immediate recall score was 0.06 points lower ($P < 0.01$). In crude analysis, only learning on the SDMT was negatively affected by number of high-level symptoms, and this finding was confined to those with 4 symptoms (1.26 points lower, $P = 0.02$). None of the associations persisted after adjustment.

To assess whether accounting for high-level symptoms affected the menopause transition–associated decrements in learning, we first quantified the learning trajectories within each menopause transition stage (Table 4) and compared the trajectory observed in premenopause (referent) with that of each later menopause transition stage (Table 5). (Estimations of menopause transition effects were required because our published analysis quantified the menopause transition exposure differently; the Discussion section of this paper contains additional commentary) (4).) Adjusted for covariates, learning was not statistically different from zero on the SDMT and the EBMT-immediate recall during late perimenopause, but learning trajectories were positive and different from zero in premenopause, early perimenopause, and postmenopause. For the EBMT-delayed recall, learning trajectories did not differ from zero in early and late perimenopause, whereas learning rates were positive and nonzero during premenopause and postmenopause. Finally, during premenopause and late perimenopause, learning trajectories did not differ from zero on the DSB, but learning was present in early perimenopause and postmenopause (Table 4).

Table 2. Mean Values for Measured Cognitive Test Performance and Frequencies of High-level Symptom Reporting at Each Study Visit, the SWAN Study, United States, 2000–2006[a]

	SWAN Follow-up Visit			
	4	6	7	8
Cognitive test (score range)[b]				
Symbol Digit Modalities (0–110)				
Mean (SD)	54.26 (12.37)	56.37 (11.49)	57.80 (11.00)	58.85 (11.50)
No.	1,742	1,321	1,289	830
East Boston Memory Test				
Immediate (0–12)				
Mean (SD)	9.98 (1.85)	10.13 (1.82)	10.36 (1.65)	10.51 (1.53)
No.	1,747	1,326	1,296	830
Delayed (0–12)				
Mean (SD)	9.81 (1.90)	9.97 (1.91)	10.23 (1.71)	10.35 (1.64)
No.	1,745	1,326	1,296	829
Digit Span Backward (0–12)				
Mean (SD)	6.51 (2.34)	6.75 (2.39)	6.92 (2.30)	7.00 (2.35)
No.	1,729	1,307	1,262	812
Prevalence of high-level symptoms[c]				
Depressive symptoms[d]				
%	25	21	21	22
No.	1,750	1,323	1,273	809
Anxiety symptoms[d]				
%	30	31	31	29
No.	1,703	1,277	1,288	822
Sleep disturbance symptoms[e]				
%	38	42	43	45
No.	1,703	1,274	1,270	813
Vasomotor symptoms[f]				
%	20	24	24	27
No.	1,703	1,277	1,290	824
Mean no. of high-level symptoms, %				
0	39	35	36	33
1	28	30	27	31
2	17	20	22	19
3	10	11	11	12
4	5	4	4	5
Mean no. of symptoms at each visit	1.13	1.19	1.22	1.24

Abbreviations: SD, standard deviation; SWAN, Study of Women's Health Across the Nation.

[a] The first cognitive test assessment was conducted during SWAN annual follow-up visit 4.

[b] The number of cognitive tests taken at visit 4 is less than the number of participants analyzed ($n = 1,903$) because some women did not contribute cognitive data at visit 4 but did so at subsequent visits.

[c] Percentage reporting a high level of each of the symptoms using the cutpoints described in the next 3 footnotes.

[d] Top quartiles (indicating higher numbers of symptoms).

[e] Those reporting any of the following symptoms 3 or more times per week: 1) trouble falling asleep, 2) waking up several times a night, or 3) waking up earlier than planned and unable to fall asleep again.

[f] Women reporting any of the following symptoms on 6 or more days per week during the past 2 weeks: hot flashes, cold sweats, or night sweats.

Table 3. Crude and Adjusted Associations Between Concurrent Menopause-associated Symptoms and Cognitive Test Scores and Associations Between Number of Previous Visits With Symptoms Present and Learning From Repeated Test Administration, the SWAN Study, United States, 2000–2006[a]

	Cognitive Test							
	Symbol Digit Modalities		East Boston Memory: Immediate Recall		East Boston Memory: Delayed Recall		Digit Span Backward	
	Concurrent Score (Mean, 54.12)	Learning[b] (Mean, 1.27)	Concurrent Score (Mean, 9.96)	Learning (Mean, 0.17)	Concurrent Score (Mean, 9.80)	Learning (Mean, 0.18)	Concurrent Score (Mean, 6.50)	Learning[b] (Mean, 0.19)
Depressive[c]								
Crude	−1.97***	−0.74**	−0.21***	−0.13**	−0.25***	−0.14**	−0.13	−0.09
Adjusted	−1.01**	−0.29	−0.02	−0.07	−0.06	−0.08	0.06	−0.01
Anxiety[c]								
Crude	−0.89**	−0.44	−0.10	−0.12**	−0.10	−0.09*	−0.06	0.05
Adjusted	−0.32	−0.06	−0.01	−0.09*	−0.00	−0.06	0.01	0.07
Sleep disturbance[d]								
Crude	−0.08	−0.29	−0.02	0.03	0.03	−0.02	−0.02	0.05
Adjusted	0.04	−0.09	−0.02	0.03	0.03	−0.01	−0.01	0.06
Vasomotor[e]								
Crude	−0.41	−0.54*	−0.09	−0.03	−0.02	−0.05	−0.11	−0.08
Adjusted	0.11	0.06	−0.01	0.02	0.06	0.02	−0.01	0.01

Abbreviation: SWAN, Study of Women's Health Across the Nation.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

[a] Each symptom was tested separately as the primary predictor, before (crude) and after adjustment for age, race/ethnicity, educational level, difficulty paying for basics, testing language, and study site.

[b] For the Symbol Digit Modalities and Digit Span Backward tests, learning refers to initial learning from each of the first and second testing occasions (for these 2 tests, there was a dropoff in learning at the third testing occasion). For the East Boston Memory tests, learning refers to learning at all 3 testing occasions (there was no dropoff in learning).

[c] Top quartiles (indicating higher numbers of symptoms) of depressive and anxiety symptoms.

[d] Those reporting any of the following symptoms 3 or more times per week: 1) trouble falling asleep, 2) waking up several times a night, or 3) waking up earlier than planned and unable to fall asleep again.

[e] Women reporting any of the following symptoms on 6 or more days each week during the past 2 weeks: hot flashes, cold sweats, or night sweats.

Table 5 summarizes results of formal comparisons between learning rates in premenopause (referent) to later menopause transition stages and subsequent adjustment for symptoms. Adjusted for covariates, the SDMT learning rate was 1.00 point smaller during late perimenopause than during premenopause ($P = 0.04$; Table 5, column 2). Further adjustment for all 4 of the high-level symptoms (Table 5, column 3) did not attenuate the negative effect of late perimenopause on SDMT learning. Similarly, adjustment for high-level symptom count did not alter the detrimental effect of late perimenopause on SDMT learning, which remained 1.00 point lower than the premenopausal value ($P = 0.04$, data not shown).

DISCUSSION

This study had 2 aims. The first was to investigate whether 4 menopause-associated symptoms were related to cognitive function. Having higher levels of depressive and anxiety symptoms (being in the top quartile of the SWAN sample) was disadvantageous to cognitive performance. Women with high-level depressive symptoms concurrent with cognitive assessment scored an average of 1 point lower on the test of processing speed (SDMT)—a statistically significant, albeit small decrement. High-level depressive symptoms during prior SDMT tests did not have an effect on the trajectory of learning over time. In contrast, concurrent verbal memory performance (EBMT immediate) was unaffected by high-level anxiety symptoms, but there was a negative association between prior high-level anxiety symptoms and learning. Those women with high-level anxiety symptoms during previous EBMT-immediate testing manifested a significantly lower learning rate than the remainder of the cohort, approximately 53% less than the mean rate. Sleep disturbance or vasomotor symptoms was unrelated to current cognitive performance and learning.

The association between depressive symptoms and slower cognitive processing is consistent with evidence that depressive disorders are characterized by attention and concentration deficits (23). A meta-analysis of the cognitive consequences of depression in adults found the largest cognitive decrements in processing speed (24). We ascertained depressive symptoms with the CES-D Scale but did not use the cutpoint of 16 in this analysis because we were not

Table 4. Cognitive Test Scores and Learning From Previous Cognitive Test Administrations by Menopause Transition Stage, Adjusted for Demographic Characteristics,[a] The SWAN Study, United States, 2000–2006

Cognitive Test[b]	Menopause Transition Stage	Current Score	Learning From Each Previous Test[b]
Symbol Digit Modalities Test	Premenopause	54.78	1.32**
Range: 1–110	Early perimenopause	54.04	0.78**
Mean score: 54.12	Late perimenopause	53.82	0.32
Mean learning[b]: 1.27	Postmenopause	53.90	0.67*
East Boston Memory: immediate recall	Premenopause	10.03	0.17*
Range: 1–12	Early perimenopause	9.92	0.10*
Mean score: 9.96	Late perimenopause	10.11	0.10
Mean learning: 0.17	Postmenopause	9.93	0.15*
East Boston Memory: delayed recall	Premenopause	9.89	0.16*
Range: 1–12	Early perimenopause	9.77	0.07
Mean score: 9.80	Late perimenopause	9.86	0.08
Mean learning: 0.18	Postmenopause	9.74	0.13*
Digit Span Backward	Premenopause	6.54	0.17
Range: 1–12	Early perimenopause	6.41	0.16***
Mean score: 6.50	Late perimenopause	6.53	0.15*
Mean learning[b]: 0.19	Postmenopause	6.53	0.13*

Abbreviation: SWAN, Study of Women's Health Across the Nation.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$: P values for comparison of learning effect to zero (no learning).

[a] Demographics: age, race/ethnicity, educational level, difficulty paying for basics, testing language, and study site.

[b] For the Symbol Digit Modalities and Digit Span Backward tests, learning refers to initial learning from each of the first and second testing occasions; for the East Boston Memory tests, learning refers to learning at all 3 testing occasions.

screening for clinical depression (36, 43, 44). That 25% of SWAN women scored 13 or higher is compatible with community-based validations of the CES-D Scale, in which approximately 21% of the general populations surveyed scored 16 or higher (36). Others have reported significant cognitive consequences of modest levels of depressive symptoms in community samples (45, 46). Using a 10-item CES-D Scale and a 4-item global cognition battery administered over 5 years to women and men aged 65 years or older, Wilson et al. (45) found that, for each depressive symptom endorsed, the rate of cognitive decline increased by 5%. Another cross-sectional study of men aged 40 years or older reported a negative association between continuous scores on the Beck Depression Inventory and each of 3 cognitive domains, including processing speed (46). The mean Beck Depression Inventory score in that sample was 7, and only 22% of the cohort scored higher than 11 (mild depression).

Concordant with prior reports that cognition, especially episodic memory, is reduced in middle-aged adults with anxiety disorders, learning was approximately 50% lower among women who scored in the top quartile of anxiety compared with those who did not (25). This comparison must be tempered by the acknowledgment that we did not use a formal anxiety scale. Anxiety may impair cognitive performance by depleting cognitive resources, sapping the attention required to concentrate during testing and constraining auditory working memory (26, 27, 47).

We hypothesized that poor sleep would predict inferior cognitive performance, because sleep deprivation diminishes attention, worsens perceptual memory, and reduces memory consolidation (28, 29). No detrimental effects of sleep disturbance were witnessed, perhaps because SWAN did not ask whether women were functionally impaired by sleep problems (48, 49).

We found no relation between vasomotor symptoms and cognitive performance, contrary to the ''cascade theory''—that vasomotor symptoms lead to disturbed sleep, fatigue, depressive symptoms, and memory problems (21, 22). Other small, cross-sectional studies also failed to find an association between self-reported vasomotor symptoms and cognitive performance, but one pilot study reported that objectively measured hot flashes were related to worse verbal memory (22, 50, 51).

Table 5. Comparisons of Concurrent Cognitive Test Scores and Learning From Past Test Administrations by Menopause Transition Stage,[a] the SWAN Study, United States, 2000–2006

	Unadjusted		Adjusted for Demographics[b]		Adjusted for Demographics and High Levels of All 4 Symptoms[c,d,e]	
	Current Score	Learning From Each Previous Testing	Current Score	Learning From Each Previous Testing	Current Score	Learning From Each Previous Testing
Symbol Digital Modalities Test (Range: 1–110)—Mean Score: 54.12, Mean Learning[f]: 1.27						
Effect of menopause transition stage[g]						
Early perimenopause	−1.91***	−0.87*	−0.74	−0.54	−0.64	−0.48
Late perimenopause	−2.83***	−1.55**	−0.96	−1.00*	−1.05	−1.08*
Postmenopause	−2.92***	−1.16**	−0.87	−0.64	−0.85	−0.54
East Boston Memory Test: Immediate Recall (Range: 1–12)—Mean Score: 9.96, Mean Learning: 0.17						
Effect of menopause transition stage[g]						
Early perimenopause	−0.29**	−0.10	−0.10	−0.07	−0.13	−0.06
Late perimenopause	−0.18	−0.10	−0.08	−0.07	0.05	−0.07
Postmenopause	−0.40***	−0.04	−0.10	−0.02	−0.13	−0.01
East Boston Memory Test: Delayed Recall (Range: 0–12)—Mean Score: 9.80, Mean Learning: 0.18						
Effect of menopause transition stage[g]						
Early perimenopause	−0.30**	−0.13†	−0.12	−0.09	−0.12	−0.07
Late perimenopause	−0.30*	−0.13	−0.03	−0.08	−0.06	−0.07
Postmenopause	−0.47***	−0.10	−0.16	−0.03	−0.17	−0.01
Digit Span Backward Test (Range: 0–12)—Mean Score: 6.50, Mean Learning[e]: 0.19						
Effect of menopause transition stage[g]						
Early perimenopause	−0.34*	−0.04	−0.13	−0.01	−0.16	−0.03
Late perimenopause	−0.31†	−0.08	0.01	−0.03	0.01	−0.03
Postmenopause	−0.36*	−0.13	0.00	−0.04	−0.04	−0.06

Abbreviation: SWAN, Study of Women's Health Across the Nation.

† $0.05 < P < 0.1$; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$: P values for comparison of mean score or learning rate during each later menopause transition state to the mean score or learning rate during premenopause.

[a] Crude, adjusted for demographic characteristics, and further adjusted for the presence of high levels of depressive, anxiety, sleep disturbance, and vasomotor symptoms.

[b] Demographics: age, race/ethnicity, educational level, difficulty paying for basics, testing language, and study site.

[c] Top quartiles (indicating higher numbers of symptoms) of depression and anxiety symptoms; refer to the Materials and Methods section of the text for details.

[d] Those reporting any of the following symptoms 3 or more times per week: 1) trouble falling asleep, 2) waking up several times a night, or 3) waking up earlier than planned and unable to fall asleep again; refer to the Materials and Methods section of the text for details.

[e] Women reporting any of the following symptoms on 6 or more days each week during the past 2 weeks: hot flashes, cold sweats, or night sweats; refer to the Materials and Methods section of the text for details.

[f] For the Symbol Digit Modalities and Digit Span Backward tests, learning refers to initial learning from each of the first and second testing occasions; for the East Boston Memory tests, learning refers to learning at all 3 testing occasions.

[g] Premenopause is the referent category.

SWAN reported that, during late perimenopause, learning was absent on the SDMT and the EBMT (4). In that analysis, the learning rates of late perimenopausal women did not differ from zero, whereas learning rates were positive and different from zero among both premenopausal and postmenopausal women. However, when formally compared, the postmenopausal SDMT and EBMT learning trajectories differed from the premenopausal referent trajectories, with borderline significance ($P = 0.06$ for each test). In the current analysis, learning was modeled as a function of number of prior test exposures that occurred during each menopause transition stage, whereas, in our prior work (4), it was modeled as

a function of time spent in each menopause transition stage; the current modeling approach improved precision. When the present modeling strategy was used, learning in late perimenopausal women was again absent (not different from zero) on the SDMT and EBMT-delayed recall, as it was in our published work (4). Moreover, we were now able to show absence of learning in late perimenopause on the EBMT-immediate recall and DSB. Moreover, in the current formal between-stages comparison, we demonstrated that the SDMT learning rate was statistically significantly smaller during late perimenopause than during premenopause ($P = 0.03$).

The next step was to examine whether the lower learning rate during late perimenopause was independent of symptoms of interest. When all 4 symptoms were added (as main effects) to the models of menopause transition stage and cognition, the negative effect of late perimenopause on SDMT learning was unaltered, suggesting that the presence of symptoms does not account for the learning decrement. However, this model allowed for only additive contributions; having more than one symptom could be synergistic. Adding a count of the symptoms to the SDMT model left the negative effect of late perimenopause unaltered.

Sensitivity to participant burden constrained ascertainment of outcome and exposure variable. We were limited to a small cognitive test battery. There was a ceiling effect on the verbal memory test, minimizing the ability to detect learning over time. Similarly, symptom measures were limited in scope and did not consider whether symptoms were bothersome; it may be that only bothersome symptoms affect cognition (52). Because visits were annual and questionnaires inquired about the past 2 weeks, we could not identify persistent symptoms, which could be more disruptive.

In conclusion, depressive and anxiety symptoms had a small, negative effect on cognitive processing speed in this sample of midlife women. However, the menopause-associated symptoms we examined—depressive, anxiety, sleep disturbance, and vasomotor—did not account for the transient absence of SDMT learning observed during the late perimenopause in SWAN.

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REFERENCES

1. Sullivan Mitchell E, Fugate Woods N. Midlife women's attributions about perceived memory changes: observations from the Seattle Midlife Women's Health Study. *J Womens Health Gend Based Med.* 2001;10(4):351–362.
2. Fuh JL, Wang SJ, Lee SJ, et al. A longitudinal study of cognition change during early menopausal transition in a rural community. *Maturitas*. 2006;53(4):447–453.
3. Meyer PM, Powell LH, Wilson RS, et al. A population-based longitudinal study of cognitive functioning in the menopausal transition. *Neurology.* 2003;61(6):801–806.
4. Greendale GA, Huang MH, Wight RG, et al. Effects of the menopause transition and hormone use on cognitive performance in midlife women. *Neurology.* 2009;72(21):1850–1857.
5. Lamar M, Resnick SM, Zonderman AB. Longitudinal changes in verbal memory in older adults: distinguishing the effects of age from repeat testing. *Neurology.* 2003;60(1):82–86.

6. McEwen B. Estrogen actions throughout the brain. *Recent Prog Horm Res.* 2002;57:357–384.
7. Morrison JH, Brinton RD, Schmidt PJ, et al. Estrogen, menopause, and the aging brain: how basic neuroscience can inform hormone therapy in women. *J Neurosci*. 2006;26(41): 10332–10348.
8. Maki PM, Sundermann E. Hormone therapy and cognitive function. *Hum Reprod Update*. 2009;15(6):667–681.
9. Barrett-Connor E, Laughlin GA. Endogenous and exogenous estrogen, cognitive function, and dementia in postmenopausal women: evidence from epidemiologic studies and clinical trials. *Semin Reprod Med*. 2009;27(3):275–282.
10. Yaffe K, Sawaya G, Lieberburg I, et al. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. *JAMA*. 1998;279(9):688–695.
11. Gold EB, Colvin A, Avis N, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: Study of Women's Health Across the Nation. *Am J Public Health*. 2006;96(7): 1226–1235.
12. Bromberger JT, Meyer PM, Kravitz HM, et al. Psychologic distress and natural menopause: a multiethnic community study. *Am J Public Health*. 2001;91(9):1435–1442.
13. Bromberger JT, Assmann SF, Avis NE, et al. Persistent mood symptoms in a multiethnic community cohort of pre- and perimenopausal women. *Am J Epidemiol.* 2003;158(4): 347–356.
14. Bromberger JT, Matthews KA, Schott LL, et al. Depressive symptoms during the menopausal transition: the Study of Women's Health Across the Nation (SWAN). *J Affect Disord.* 2007;103(1–3):267–272.
15. Kravitz HM, Zhao X, Bromberger JT, et al. Sleep disturbance during the menopausal transition in a multi-ethnic community sample of women. *Sleep*. 2008;31(7):979–990.
16. Woods NF, Mitchell ES. Symptoms during the perimenopause: prevalence, severity, trajectory, and significance in women's lives. *Am J Med*. 2005;118(suppl 12B):14–24.
17. Freeman EW, Sammel MD, Lin H, et al. Symptoms associated with menopausal transition and reproductive hormones in midlife women. *Obstet Gynecol.* 2007;110(2 pt 1): 230–240.
18. Cohen LS, Soares CN, Vitonis AF, et al. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. *Arch Gen Psychiatry.* 2006;63(4): 385–390.
19. Freeman EW, Sammel MD, Lin H. Temporal associations of hot flashes and depression in the transition to menopause. *Menopause*. 2009;16(4):728–734.
20. Young T, Rabago D, Zgierska A, et al. Objective and subjective sleep quality in premenopausal, perimenopausal, and postmenopausal women in the Wisconsin Sleep Cohort Study. *Sleep*. 2003;26(6):667–672.
21. Kronenberg F. Hot flashes: epidemiology and physiology. *Ann N Y Acad Sci.* 1990;592:52–86.
22. Maki PM, Drogos LL, Rubin LH, et al. Objective hot flashes are negatively related to verbal memory performance in midlife women. *Menopause*. 2008;15(5):848–856.
23. Zakzanis KK, Leach L, Kaplan E. On the nature and pattern of neurocognitive function in major depressive disorder. *Neuropsychiatry Neuropsychol Behav Neurol*. 1998;11(3):111–119.
24. Herrmann LL, Goodwin GM, Ebmeier KP. The cognitive neuropsychology of depression in the elderly. *Psychol Med*. 2007;37(12):1693–1702.
25. Airaksinen E, Larsson M, Forsell Y. Neuropsychological functions in anxiety disorders in population-based samples: evidence of episodic memory dysfunction. *J Psychiatr Res.* 2005;39(2):207–214.
26. Wetherell JL, Reynolds CA, Gatz M, et al. Anxiety, cognitive performance, and cognitive decline in normal aging. *J Gerontol B Psychol Sci Soc Sci.* 2002;57(3):246–255.
27. Beaudreau SA, O'Hara R. Late-life anxiety and cognitive impairment: a review. *Am J Geriatr Psychiatry.* 2008;16(10): 790–803.
28. Walker MP. The role of sleep in cognition and emotion. *Ann N Y Acad Sci.* 2009;1156:168–197.
29. Diekelmann S, Wilhelm I, Born J. The whats and whens of sleep-dependent memory consolidation. *Sleep Med Rev.* 2009;13(5):309–321.
30. Sowers MF, Crawford SL, Sternfeld B, et al. SWAN: a multicenter, multiethnic, community-based cohort study of women and the menopausal transition. In: Lobo RA, Kelsey J, Marcus R, eds. *Menopause Biology and Pathobiology.* San Diego, CA: Academic Press; 2000:175–188.
31. Smith A. *Symbol Digit Modalities Test*. Los Angeles, CA: Western Psychological Service; 1982.
32. Albert M, Smith LA, Scherr PA, et al. Use of brief cognitive tests to identify individuals in the community with clinically diagnosed Alzheimer's disease. *Int J Neurosci.* 1991;57(3-4):167–178.
33. Wechsler D. A standardized memory scale for clinical use. *J Psychol*. 1945;19:87–95.
34. Jonides J, Smith EE, Marshuetz C, et al. Inhibition in verbal working memory revealed by brain activation. *Proc Natl Acad Sci U S A*. 1998;95(14):8410–8413.
35. Psychological Corporation. *WAIS-III and WMS-III: Technical Manual*. San Antonio, TX: Harcourt Brace; 1997.
36. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;385–401.
37. Buysse DJ, Reynolds CF III, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989;28(2):193–213.
38. Becker PM. Insomnia: prevalence, impact, pathogenesis, differential diagnosis, and evaluation. *Psychiatr Clin North Am.* 2006;29(4):855–870; abstract vii.
39. Matthews KA, Kiefe CI, Lewis CE, et al. Socioeconomic trajectories and incident hypertension in a biracial cohort of young adults. *Hypertension*. 2002;39(3):772–776.
40. Rabbitt P, Diggle P, Smith D, et al. Identifying and separating the effects of practice and of cognitive ageing during a large longitudinal study of elderly community residents. *Neuropsychologia*. 2001;39(5):532–543.
41. StataCorp. Obtaining robust variance estimates. In: *Stata Statistical Software User's Guide: Release 7.0*. College Station, TX: Stata Corporation; 2001:254–258.
42. White HA. Heteroskedasticity-consistent covariance matrix estimator and direct test for heteroskedasticity. *Econometrica*. 1980;38:817–838.
43. Myers JK, Weissman MM. Use of a self-report symptom scale to detect depression in a community sample. *Am J Psychiatry.* 1980;137(9):1081–1084.
44. Roberts RE, Vernon SW. The Center for Epidemiologic Studies Depression Scale: its use in a community sample. *Am J Psychiatry.* 1983;140(1):41–46.
45. Wilson RS, Mendes De Leon CF, Bennett DA, et al. Depressive symptoms and cognitive decline in a community population of older persons. *J Neurol Neurosurg Psychiatry.* 2004;75(1):126–129.
46. Lee DM, Tajar A, Ulubaev A, et al. The association between different cognitive domains and age in a multi-centre study of

middle-aged and older European men. *Int J Geriatr Psychiatry.* 2009;24(11):1257–1266.
47. Eysenck MW, Derakshan N, Santos R, et al. Anxiety and cognitive performance: attentional control theory. *Emotion*. 2007;7(2):336–353.
48. Lichstein KL, Durrence HH, Taylor DJ, et al. Quantitative criteria for insomnia. *Behav Res Ther.* 2003;41(4):427–445.
49. Edinger JD, Bonnet MH, Bootzin RR, et al. Derivation of research diagnostic criteria for insomnia: report of an American Academy of Sleep Medicine Work Group. *Sleep*. 2004;27(8):1567–1596.
50. Polo-Kantola P, Portin R, Koskinen T, et al. Climacteric symptoms do not impair cognitive performances in postmenopause. *Maturitas*. 1997;27(1):13–23.
51. LeBlanc ES, Neiss MB, Carello PE, et al. Hot flashes and estrogen therapy do not influence cognition in early menopausal women. *Menopause*. 2007;14(2):191–202.
52. Chodosh J, Kado DM, Seeman TE, et al. Depressive symptoms as a predictor of cognitive decline: MacArthur Studies of Successful Aging. *Am J Geriatr Psychiatry.* 2007;15(5):406–415.