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Cognition in perimenopause: The effect of transition stage

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Abstract

Objective—The aims of this cross-sectional study were to determine if cognitive function differs across stages of reproductive aging and to evaluate whether hormones or menopausal symptoms predict cognition in the perimenopause. We hypothesized that women in late menopausal transition and early postmenopause would perform more poorly than those in the late reproductive stage on attention and verbal memory tasks, and that estradiol, depressive symptoms, anxiety symptoms, hot-flashes, and sleep disturbance would predict cognitive performance on those tasks.

Methods—One hundred and seventeen middle-aged women enrolled in the Rochester Investigation of Cognition Across Menopause (RICAM) were categorized into late reproductive (n = 34), early menopausal transition (n = 28), late menopausal transition (n=41), or early postmenopause (n=14) stage according to criteria from the STRAW+10 workshop. We administered a neuropsychological battery assessing six domains of cognition, assessed menopausal symptoms, and measured serum levels of estradiol and follicle stimulating hormone. Multivariate regressions were conducted to determine the impact of menopausal stage and symptoms on cognition.

Results—Women in the first year of postmenopause performed significantly worse than women in the late reproductive and late menopausal transition stages on measures of verbal learning, verbal memory and motor function. They also performed significantly worse than women in the late menopausal transition stage on attention/working memory tasks.

Conclusions—Cognitive function does not change linearly across perimenopause. Decreases in attention/working memory, verbal learning, verbal memory, and fine motor speed may be most evident in the first year after the final menstrual period.

Keywords

Memory; perimenopause; cognition; estrogen; menopausal transition

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Introduction

Our understanding of the impact of reproductive aging stage on cognitive performance has been significantly advanced in recent years due to findings from large-scale studies of the menopausal transition. In the Kinmen Women's Health Investigation (KIWI), 573 Chinese women completed five cognitive tests at baseline and 18-month follow-up. Compared with participants who remained premenopausal, those who entered perimenopause had significantly less improvement in verbal fluency[1]. The Chicago site of the Study of Women's Health Across the Nation (SWAN) found no effect of menopausal stage on working memory or perceptual speed in a sample of 803 women who completed two or more successive annual evaluations[2]. A subsequent four-year longitudinal study of 2,362 SWAN participants found an effect of menopausal stage on verbal episodic memory and processing speed[3], with evidence of decreased verbal episodic memory in the early and late perimenopausal stage and deficits in processing speed in the late perimenopausal stage. Consistent with the earlier SWAN study[2], no effect of stage was observed on a test of working memory[3]. Findings from cross-sectional studies with smaller numbers of perimenopausal women, including a study from the Melbourne Women's Midlife Health Project that included 50 perimenopausal women, show no impact of perimenopausal stage on cognitive function[4]. In general, however, findings from large studies suggest that there are small but measurable objective declines in cognitive function during the perimenopause that warrant further investigation.

These apparent discrepant findings may be due, in part, to differing criteria for staging the menopausal transition. In the KIWI, perimenopause was defined as irregular menstrual cycles or last menstrual cycle between 3 and 12 months prior to study baseline. The SWAN defines early perimenopause as decreased predictability of menses but no gap of ≥3 months and late perimenopause as 3-11 months amenorrhea. The Melbourne study defines early menopausal transition as changes in menstrual cycles with menstruation in the prior 3 months and late menopausal transition as 3-12 months amenorrhea. In the SWAN, postmenopause was defined as beginning at the final menstrual period, that is, at the beginning of the first 12-month period of amenorrhea. In the KIWI and Melbourne studies, postmenopause was defined as beginning after 12 months of amenorrhea. Recently, an expert group convened to revise the criteria for the onset of late reproductive life and early menopausal transition[5]. Key revisions to this common staging system include refinement of the criteria for entry into late reproductive life, early menopausal transition and the early postmenopausal stage. These revisions have resulted in finer differentiation between reproductive aging stages, and allow us to investigate women experiencing the earliest changes in menstrual cycles as well as evaluate finer differences in the early postmenopausal period.

Factors contributing to cognitive declines in the menopausal transition have not yet been clearly identified. It is postulated that fluctuations in endogenous estrogen levels and symptoms associated with the menopausal transition, such as depression, sleep disturbance and hot flashes, may independently or additively underlie these changes[6]. Estrogen influences hippocampal and prefrontal cortex function and the cognitive functions subserved by these brain regions, including verbal memory and executive function[7-10]. Studies of midlife women, however, have failed to find a linear relationship between serum hormone levels and cognition[11-13]. A number of observational studies have failed to find a relationship between self-reported hot flashes and cognitive function, including the SWAN[6,14,15]. Furthermore, estrogen effects on menopausal symptoms have been shown to be decoupled from cognitive effects[16,17]. New data from 2,362 SWAN participants demonstrate that differences in cognition across menopausal stages are not due to differences in menopause symptoms across stages[6].

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The present study builds upon these new findings in several ways to understand cognitive function in the perimenopause. First, we used a comprehensive test battery assessing six cognitive domains. The battery included a measure of verbal memory that has a high ceiling and allows for the assessment of three stages of memory: encoding, storage and retrieval. The use of a verbal memory measure with a high ceiling is important since many participants in the SWAN study started with maximum verbal memory scores[3]. Second, we examined cognitive performance as a function of four rather than two or three reproductive aging stages, and included women at earlier stages of transition. Third, we examined cognitive change in the context of endogenous sex steroid levels and other menopausal symptoms.

The primary aims of the present study were two-fold. First, we sought to determine if cognition in midlife women differed across stages of reproductive aging. We hypothesized that women in late menopausal transition and early postmenopause would perform worse than those in the late reproductive stage on cognitive tasks supported by the hippocampus and prefrontal cortex. Second, we aimed to determine how menopause related factors, including hormone levels, mood, vasomotor symptoms, and sleep quality impact cognition in perimenopause. We hypothesized that lower levels of estradiol, increased depressive symptoms, increased anxiety, increased hot-flashes, and poor sleep quality would all be associated with worse cognitive performance.

Methods

Data for this study were collected in three waves in a manner that was fully consistent across each wave. Wave I was an unfunded pilot study conducted from January 2005 to December 2006. Wave II was a federally funded study conducted from April 2007 to December 2009. Wave III is an ongoing, federally funded longitudinal study begun in September 2010. Women were recruited to participate in a study of memory in perimenopause. Participants were asked to complete a baseline evaluation, 6-month follow-up and 1-year follow-up in Waves I and II, and bi-annual evaluations for 5 years in Wave III. Twenty-four women participated in Wave I, and their baseline data has been reported previously[16]. Fourteen of the 24 women continued their participation, and an additional 51 women were recruited in Wave II. Thirty seven of these women continued their participation and an additional 42 were recruited in Wave III, yielding a total sample of 117 women. The baseline data for the entire sample is presented here (24 at Wave I, 51 at Wave II, and 42 at Wave III).

Subjects

Participants were recruited through advertisements placed in local newspapers, recruitment posters displayed at local obstetrics/gynecology and primary care clinics affiliated with the University of Rochester Medical Center, and recruitment posters placed throughout the Medical Center itself. The advertisements and posters described a study of memory in perimenopause, but did not specifically target women with memory complaints. Inclusionary criteria were: (a) ages 40 to 60; (b) reports of changes in menstrual cycles; (c) reports of at least one menstrual period in the prior 12 months; and (d) intact uterus. Exclusion criteria were: (a) history of neurological disease; (b) history of psychiatric illness; (c) surgical menopause; and (d) use of exogenous hormone preparations affecting ovarian or pituitary function in the prior three months. All participants gave written informed consent. Our study was approved by the University of Rochester Research Subjects Review Board. Participants in Wave II received $20 for time and travel and free parking, and were eligible for a total of $75 if they participated in all follow-up evaluations. Participants in Wave III received $25 for time and travel and free parking, and were eligible for a total of $250 if they participated in all follow-up evaluations.

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Menopausal Transition Stage

Menopausal transition stage was based on self-reported bleeding patterns according to STRAW +10[5]. Specifically, participants were classified into one of four stages of reproductive aging: 1) *late reproductive* (-3a): subtle changes in menstrual flow and/or cycle length; 2) *early menopausal transition* (-2): persistent cycle irregularity, defined as ≥7 day difference in length of consecutive cycles at least twice over the prior 10 cycles; 3) *late menopausal transition* (-1): interval of amenorrhea of ≥ 60 days and 4) *early postmenopause* (1a): the first 12 months following the final menstrual period (FMP). The staging categories were mutually exclusive, thus once a participant met criteria for a later stage, they we not eligible for the earlier stage. At baseline, we obtained participants' retrospective self-report of bleeding patterns prior to study entry. As part of a standard interview, participants were asked the date of their last menstrual period and the average length of their current and past (prior to perimenopause) menstrual cycles. Given the anchor of the prior 12 months, they were asked to indicate whether they had skipped any periods or undergone a period of amenorrhea, and to provide their shortest and longest cycle lengths. They were also asked to provide information about the lengths of their current and past periods. After the baseline visit, participants tracked their menstrual cycles using monthly calendars on which they recorded all bleeding activity. Thus, we were able to calculate cycle lengths and variability and determine timing of FMP in order to determine group status at later visits. One-hundred of our 117 participants had prospective data following the baseline visit, and for those participants, we utilized the self-reported bleeding patterns and the 6-month diary data to determine baseline group status. For eight of those cases, there were discrepancies between baseline self-report and the first 6 month calendar data; thus, staging was based on consensus between the study investigators using bleeding criteria and hormone levels (FSH and estradiol) as recommended by STRAW +10. For the 17 cases in which there was no prospective data, staging was based on baseline self-report of bleeding patterns only. We had 6-month data on 31 of the 41 participants in the late menopausal transition group, and thus were able to confirm that they had not experienced their FMP. Of the remaining 10 participants, none had experienced a cycle length of > 90 days in the prior 12 months.

Measures

Each participant completed a cognitive battery and self-report questionnaires assessing depression, anxiety, general health, quality of life and memory function.

Cognitive Battery

Attention—We assessed basic attention using the Digit Span (DS) subtest of the Wechsler Memory Scales – III (WMS-III)[18]. Participants were asked to repeat increasingly longer strings of digits, first in the order in which the digits were presented (e.g., Forward) and then in reverse order (i.e., Backward). The dependent measure was the total number of correct trials. We assessed vigilance/complex attention using the D2 Test of Attention[19]. Participants were asked to search for targets (a lower case *d* with two dots above or below it) in an array of foils (a lower case *d* with more than 2 or fewer than 2 dots, or a lower case *p* with any number of dots above or below it) over repeated timed trials. The dependent measure was the total number of items completed minus errors (D2TN-E).

Working Memory—We assessed working memory using the Letter-Number Sequencing (LNS) subtest of the WMS-III[18]. Participants were presented with increasingly longer series of digits and letters, which they had to sequence in a specified order (i.e., alphabetical or chronological). Total score was based on the total number of series correctly sequenced.

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Verbal Fluency—We assessed verbal fluency using the Controlled Oral Word Association Test[20]. Participants were asked to name as many words as possible beginning with a specified letter (phonemic), and fitting a specified category (semantic) in one minute. In this study, the letters *FAS* and the category *animals* were used. The dependent measure was the total number of words generated for each task.

Motor—We assessed fine motor skills and dexterity using the Grooved Pegboard Test[21]. Participants were asked to place grooved pegs in a pegboard as quickly as possible. The task was completed once using the dominant hand (GPDH) and once using the non-dominant hand (GPNDH). The dependent measure was the time taken to correctly place all of the pegs.

Visuospatial—We assessed visuospatial skill using the Hooper Visual Organization Test (HVOT)[22]. Participants were asked to identify an object that had been cut into pieces and rearranged. The dependent measure was the total number of correctly identified objects.

Memory—We assessed verbal encoding and retention using the Rey Auditory Verbal Learning Test (RAVLT)[23]. Participants were presented a list of 15 words on each of 5 trials. They were then presented a second list of 15 words (interference). Recall of the first (repeated) list was assessed following a short delay (i.e., immediately after the interference trial) and again after a 30-minute delay. A forced choice recognition test followed. The dependent measures were total correct recall from Trial 1, total words recalled across the five trials, Trial 6 (short-delay), Trial 7 (long-delay), and Recognition (hits).

Self-report questionnaires

Depression—On the Beck Depression Inventory-II (BDI-II)[24], participants rated the intensity of their experience of 21 symptoms of depression over the past 2 weeks using a four-point scale for each item. Each of the 21 items is summed to give a total score. A total score of 0-13 is considered minimal, 14-19 is considered mild depression, 20-28 is considered moderate, and 29-63 is considered severe. Higher total scores indicate more severe depression.

Anxiety—On the Beck Anxiety Inventory (BAI)[25], participants rated their experience of 21 subjective, somatic, or panic-related symptoms of anxiety on a four-point scale with the following points: “Not at all” (0); “Mildly; it did not bother me much” (1); “Moderately; it was very unpleasant, but I could stand it” (2); and “Severely; I could barely stand it” (3). The items are summed to obtain a total score. Total score of 0-7 is considered minimal anxiety, 8-15 is considered mild, 16-25 is considered moderate, and 26-63 is considered severe. Higher total scores indicate more anxiety.

Overall Health—On the Women’s Health Questionnaire[26], participants rated their experience of 36 problems across nine domains of physical and emotional health over the past few days. Each item is scored on a two-point scale, with responses of, “Yes, definitely” or “Yes, sometimes” earning 1 point, and “No, not much” or “No, not at all” earning 0 points. The dependent measures were scores on the following subscales: a) somatic symptoms; b) vasomotor symptoms; c) sexual behavior; d) sleep problems; e) menstrual symptoms; and f) attractiveness. The score for each subscale is the total score divided by the total number of items completed, with a maximum score of one. We utilized the vasomotor symptoms and sleep problems subscales for this analysis. The vasomotor symptoms subscale includes two items. We assigned the possible scores of 0, 0.5, or 1 as none, mild to moderate, or severe symptoms, respectively. The sleep problems subscale consists of three

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items. We assigned the possible scores of 0, 0.33, 0.67, or 1 as none, mild, moderate, or severe symptoms, respectively.

Hormone Levels

Serum estradiol (E_2) and follicle stimulating hormone (FSH) levels were collected on the day of the cognitive testing. Women who were experiencing monthly periods were examined in the early or mid-follicular phase of their cycles (cycle days 4-7). Assays were performed by the Clinical Laboratory at the University of Rochester Medical Center. Total E_2 and FSH were assessed by competitive immunoassay using direct chemiluminescent technology (Advia-Centaur System, Bayer Diagnostics, Tarrytown, NY, USA). The Estradiol-6 serum assay has a sensitivity and assay range of 10-1000pg/mL (36.7-3670 pmol/L), and a coefficient of variation of 8.1-13.6%. The FSH serum assay has a sensitivity and assay range of 0.3 – 200 mIU/mL (IU/L), and a coefficient of variation of 2.9-3.9%.

Statistical analyses

Composite Cognitive Domain Scores—To reduce the number of statistical comparisons, we created composite z-scores for each domain of cognitive functioning. Attention/Working Memory consisted of DS, LNS, and D2TN-E, Executive consisted of letter and category verbal fluency, Visuospatial consisted of the HVOT, Motor consisted GPDH and GPNDH, Verbal Learning consisted of the RAVLT Trail 1 and Total number of words recalled across 5 trials, and Verbal Memory consisted of RAVLT Short-Delay, Long-Delay and Recognition measures. For each of these, we first computed z-scores for individual tests from the raw scores and then averaged these z-scores for each domain.

Statistical Analysis—Before conducting the primary analyses, we first examined the distribution of each cognitive outcome to ensure normality and check for statistical outliers (i.e., values more than 3 standard deviations above or below the mean). We found two low outliers on the visuospatial domain and one low outlier on the motor domain. There were no significant differences in the results of analyses performed including and excluding the outliers; thus, results including the outliers are reported here.

To determine if cognition in midlife women differed across stages of reproductive aging and whether menopausal related factors impacted cognition, we conducted a series of multivariable linear regression analyses. In these models, we included age, years of education, stage of reproductive aging, vasomotor symptoms, sleep symptoms, depression, anxiety, estradiol, and FSH. Based on our hypotheses, our primary focus was comparing each reproductive stage to the late reproductive stage. Exploratory analyses were also conducted to examine each stage relative to the previous stage (late reproductive vs. early transition; late transition vs. early postmenopause). All p values are two-sided, and the statistical significance level was set at $p<0.05$. All analyses were performed using SAS (version 9.2, SAS Institute Inc, Cary, NC).

Results

Cohort Characteristics

Table 1 provides demographic information, hormone levels, cognitive performance, memory complaints, menopausal symptoms, health symptoms, quality of life ratings, and mood symptoms for the sample. Participants ranged in age from 40 to 60 years (mean age = 48.7) and all completed at least 12 years of education. Ninety-one percent were white, 6% African American, and 2% Asian. Two percent of the sample described their ethnicity as Hispanic. One-way analyses of variance (ANOVA) revealed that the groups significantly differed in age ($F=8.675$, $p<.001$), but not education ($F=.651$, $p=.584$). Pearson product moment

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correlations revealed that age was significantly positively correlated with verbal learning (r=.19, p=.044), and education was significantly correlated with several domain scores including, Attention/Working memory (r=.29, p=.002) Executive function (r=.244, p=.008), Verbal Learning (r=.274, p=.003), and Motor (r=.246, p=.008).

Predictors of cognitive performance

Table 2 provides the unadjusted composite cognitive domain scores as a function of stage of reproductive aging. Women in the early postmenopause performed worse than women in the late reproductive stage on the verbal learning (B=-0.95, SE=0.42, p=0.02), verbal memory (B=-0.97, SE=0.40, p=0.02), and fine motor skills (B=-0.88, SE=0.40, p=0.03) composite scores. There was a trend for women in the early postmenopause to perform worse than women in the late reproductive stage on the attention/working memory composite score, but this did not reach statistical significance (B=-0.60, SE=0.34, p=0.08). Additionally, women in the early postmenopause performed worse than women in the late menopausal transition stage on the verbal learning (B=-0.93, SE=0.33, p<0.01), verbal memory (B=-0.80, SE=0.32, p=0.01), fine motor skills (B=-0.70, SE=0.32, p=0.03), and attention/working memory (B=-0.55, SE=0.28, p=0.04) composite scores. (See Figure 1). Women in the early menopausal transition stage did not differ from late reproductive stage or late menopausal transition stage on any of the cognitive composite scores.

Higher estradiol levels were associated with better performance on the fine motor skills composite (B=0.002, SE=0.0008, p=0.02). Estradiol was not a significant predictor of any other cognitive composite measure. Higher FSH levels (B=0.008, SE=0.004, p=0.07) was marginally associated with better performance on the fine motor skills composite. Vasomotor, sleep and anxiety symptoms were not significant predictors of any cognitive composite measure.

Discussion

The aims of this study were to determine if cognitive function differs across stages of reproductive aging and to evaluate whether hormone levels and/or menopausal symptoms (e.g., E_2, FSH, depression, anxiety, hot flashes, and sleep disturbance) predicted cognitive function in the transition. We predicted that women in the late menopausal transition and early postmenopausal stages would perform worse on cognitive tasks supported by the hippocampus and prefrontal cortex than women in the late reproductive and early menopausal transition stages, and that lower levels of estradiol, increased depressive symptoms, increased anxiety symptoms, increased hot-flashes, and poor sleep quality would all be associated with poorer cognitive performance. The primary finding from our study was that women in early postmenopause performed worse than those in the late reproductive and late menopausal transition stages on verbal learning, verbal memory and motor tasks and worse than those in the late menopausal transition on measures of attention/working memory. These differences were not explained by menopausal symptoms, mood, or hormone levels. All of the women in the early postmenopausal stage had been in that stage for less than 12 months.

In comparison to our findings, SWAN showed a decrement in verbal memory and processing speed in late perimenopause that improved in the postmenopausal period and that could not be explained by symptoms[3,6]. Two factors may be important in explaining differences in outcomes between the SWAN and the current study: criteria for staging menopause and time spent in the postmenopausal stage. In the current study we used updated criteria to define stages of reproductive aging[5], and those criteria differ from the SWAN criteria. SWAN defined early perimenopause as decreased predictability of menses and fewer than 3 months of amenorrhea. In comparison, we defined early transition as

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persistent cycle irregularity, defined as ≥7 day difference in length of consecutive cycles on at least two occasions in the prior 10 cycles. SWAN defined late perimenopause as 3-11 months of amenorrhea, and we defined late transition as an interval of amenorrhea of ≥ 60 days. Both studies defined postmenopause as beginning at the final menstrual period. A second characteristic of our postmenopausal group that differs from SWAN is that the women in our postmenopausal group were in the first year following the FMP, corresponding to the first of year of the 6-year STRAW+10 Early Postmenopause Stage (+1a). In comparison, the SWAN participants were in the postmenopausal stage from 0 to 5 years[3]. It is therefore likely our postmenopausal group was at an earlier stage of postmenopause than the postmenopausal SWAN group. Longitudinal data from the SWAN demonstrates that estradiol levels decline and FSH levels rise from two years prior to the FMP up to two years after the FMP and then plateau[27]. In this way, our postmenopausal group, being in the first year of the FMP, might be more similar to the SWAN "late perimenopause" stage than the SWAN "postmenopausal" stage.

It is notable that the one of the specific cognitive domains affected by reproductive aging stage was verbal memory. This finding is consistent with the KIWI and SWAN studies, two longitudinal studies that found an effect of perimenopausal stage on delayed verbal memory[1,3]. In both studies, the differences in verbal memory were found as a failure to improve over repeated administrations of the same task, rather than a decline from prior performance. This failure to demonstrate a practice effect is a common focus of in longitudinal cognitive studies and recognizes the considerable improvements on tests that emerge with practice. Practice effects result from increased familiarity with a test, or "learning" the test. Ongoing testing of our cohort will provide the longitudinal assessments needed to compare more directly with SWAN and KIWI.

We also found that attention/working memory and verbal learning was affected by reproductive aging stage. This finding supports our prediction that the specific cognitive domains affected in the menopausal transition are those supported by the hippocampus and the PFC, brain regions that are a putative target for the effects of estrogen[9],[10]. The hippocampus plays a critical role in verbal episodic memory, including memory encoding and storage. The PFC also plays a critical role in early memory processing and is consistently activated on tasks of memory encoding[28] and working memory[29]. In a study of perimenopausal women, we previously reported an association between reports of memory difficulties and performance on tasks supported by the PFC, such as attention, verbal encoding and working memory[16,30]. Taken together, these findings suggest that women's concerns about their memory function during the menopausal transition are warranted, and that they might experience particular vulnerabilities in the year following the final menstrual period.

Contrary to our prediction, but consistent with some of the literature finding no effect of menopausal symptoms on cognition in the menopausal transition, we found that depression, anxiety, sleep disturbance and vasomotor symptoms did not predict cognitive performance. This suggests that cognitive declines through the transition period are an independent process rather than a consequence of, or a correlate of, sleep disruption or depression. It is presumed that cognitive declines in the menopausal transition are hormonally-mediated. Peripheral hormone levels are an imperfect though acceptable marker of CNS levels; CSF steroid levels are typically lower than circulating levels and brain steroid hormone levels generally exceed circulating levels because of accumulation and/or synthesis[31]. We found that neither FSH nor estradiol related to cognitive function. The exception was that estradiol predicted motor function in the present study, corroborating previous evidence that women perform better during phases of the menstrual cycle that correspond to high estrogen levels compared to phases characterized by low levels[32]. There is some suggestion that

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menopausal-related mood symptoms are related to hormonal fluctuations[33], rather than to absolute hormone levels. It is possible that the relationship to cognition is similar. As this study did not measure fluctuations, it is possible that we missed an association between changes in hormones and performance on verbally mediated tasks. The fact that the worst cognitive performance was observed in the first 12 months following the FMP might be viewed as consistent with an influence of fluctuating hormone levels.

There are several limitations to the present study. We had a relatively small sample of high functioning, highly educated, predominantly white women. It remains to be seen if these same findings generalize to a larger, more representative sample. Second, we did not have comparisons with women in the peak reproductive or late postmenopausal stages. Finally, the staging of 17 women was based on recall of bleeding patterns, as we did not have prospective calendars or diaries. It is possible that some of those women were misclassified based on recollection errors.

Conclusions

We found that cognitive function varies across the menopausal transition, with early postmenopause being a critical time period during which subtle declines in attention/working memory, verbal learning, verbal memory and fine motor speed and dexterity may be seen. We found that menopausal symptoms were not associated with cognitive performance, suggesting that cognitive declines are independent of these factors. A larger, longitudinal evaluation of the RICAM cohort through the entire transition is underway to better clarify patterns of cognitive change and suggest possible mechanisms for such changes.

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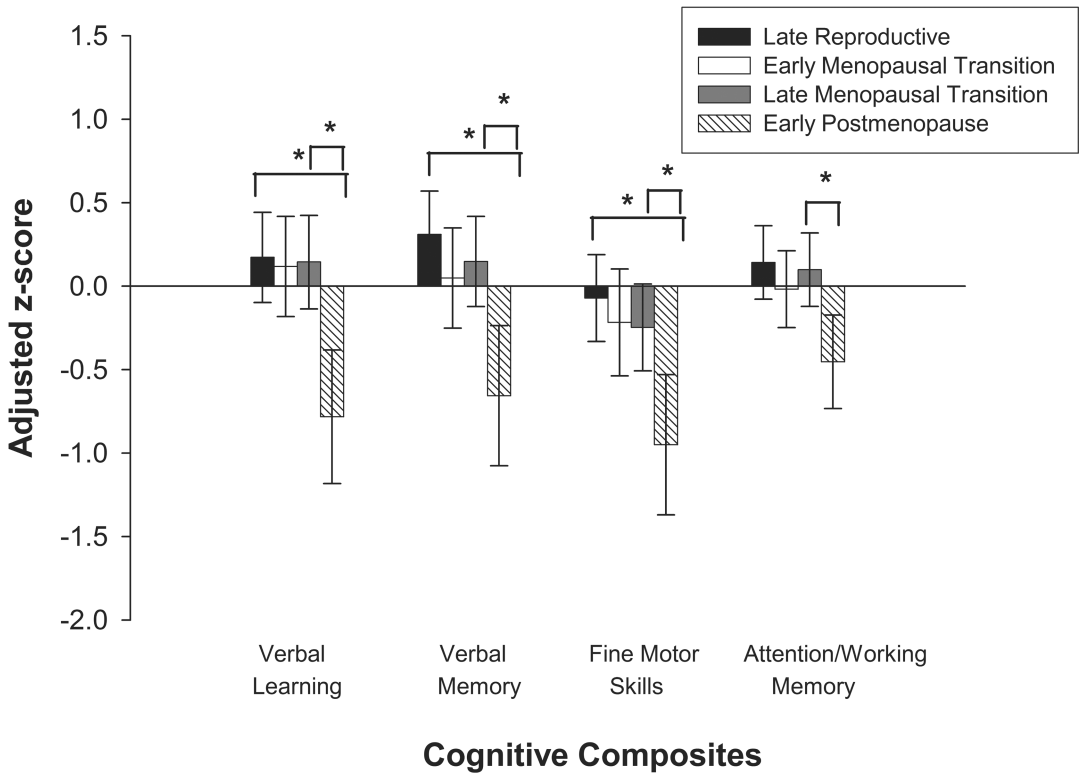

Figure 1.

Adjusted z-scores and standard errors as a function of menopausal transition stage for verbal learning, verbal memory, fine motor skills, and attention/working memory cognitive composites. * $p<0.05$.Analyses adjusted for age, education, vasomotor symptoms, sleep symptoms, depression, anxiety, estradiol, and FSH. Consequently, adjusted z-scores will not add to 0.

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Table 1

Characteristics and outcomes of sample

	Late Reproductive (n=34)		Early Transition (n=28)		Late Transition (n=41)		Early Postmenopause (n=14)	
Variable	**Mean ± SD**	**Range**	**Mean ± SD**	**Range**	**Mean ± SD**	**Range**	**Mean ± SD**	**Range**
Demographics								
Age, y	46.5 ± 3.6	41-53	48.3 ± 3.5	40-55	49.8 ± 3.6	42-56	51.8 ± 4.7	44-60
Education, y	15.8 ± 2.1	12-20	16.0 ± 2.2	12-20	15.8 ± 2.4	12-20	16.7 ± 2.4	13-20
Hormone levels								
Estradiol, pmol/L	67.3 ± 55.3	6-285	91.1 ± 96.4	9-412	85.8 ± 145.9	4-754	18.9 ± 18.6	8-73
FSH, mIU/mL	10.2 ± 7.7	3.7-46.6	13.1 ± 12.5	2.8-61.7	35.2 ± 22.6	3-94.8	84.8 ± 34.2	34.3-152.9
Cognitive outcomes								
Rey Auditory Verbal Learning								
Trial 1 (Encoding)	6.6 ± 1.6	4-11	6.6 ± 1.8	4-11	7.0 ± 1.8	3-11	6.6 ± 1.4	4-9
Total learning across trials 1-5	51.2 ± 6.7	31-65	49.6 ± 6.5	39-61	52.5 ± 8.7	32-71	48.6 ± 7.8	33-62
Trial 6 (Short Delay)	10.7 ± 1.8	7-14	10.2 ± 2.1	6-14	10.4 ± 3.1	3-15	9.0 ± 3.0	4-14
Trial 7 (Retention)	11.1 ± 1.8	8-15	10.1 ± 2.0	5-13	10.8 ± 3.1	4-15	8.8 ± 2.8	4-14
Long-delay Recognition	13.9 ± 1.2	11-15	13.4 ± 1.8	8-15	13.8 ± 1.5	9-15	13.3 ± 1.9	8-15
WAIS-III								
Digit Span	19.7 ± 4.4	14-29	17.9 ± 3.1	13-25	18.9 ± 4.4	9-29	18.4 ± 4.6	12-27
Letter-Number Sequencing	11.7 ± 2.5	7-18	11.2 ± 2.1	7-15	11.7 ± 2.3	7-17	11.3 ± 3.1	8-18
D2 Test of Attention (TN-E)	427.0 ± 79.0	276-594	433.4 ± 76.5	276-537	456.5 ± 67.6	329-599	436.0 ± 89.4	288-549
Controlled Oral Word Association	41.5 ± 10.4	22-70	45.0 ± 9.4	33-68	40.5 ± 11.8	14-61	39.1 ± 9.3	25-57
Animal Naming	22.9 ± 4.5	14-31	23.3 ± 5.4	13-33	22.8 ± 4.1	14-31	23.3 ± 4.0	17-31
Grooved Pegboard								
Dominant hand	63.1 ± 10.0	49-94	65.4 ± 9.0	52-91	65.7 ± 14.3	31-120	70.5 ± 8.5	55-87
Non-dominant hand	70.9 ± 11.9	52-102	71.1 ± 11.4	50-106	70.7 ± 11.1	52-95	76.1 ± 9.9	59-96
Hooper Visual Organization	26.6 ± 2.0	21-30	26.2 ± 2.7	19-30	26.5 ± 2.1	21-30	25.3 ± 2.7	19-29
Questionnaires								
Beck Depression Inventory	10.7 ± 7.7	0-38	9.2 ± 5.6	0-21	9.0 ± 7.9*a*	0-29	11.1 ± 10.0	1-34
Beck Anxiety Inventory	9.9 ± 8.7	0-43	4.5 ± 3.8	0-12	6.8 ± 6.7*a*	0-24	9.8 ± 5.6	2-21

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	Late Reproductive (n=34)		Early Transition (n=28)		Late Transition (n=41)		Early Postmenopause (n=14)	
Variable	**Mean ± SD**	**Range**	**Mean ± SD**	**Range**	**Mean ± SD**	**Range**	**Mean ± SD**	**Range**
Women's Health Questionnaire								
Vasomotor	.34 ± .36	0-1	.39±.42	0-1	.49 ± .45*a*	0-1	.68 ± .46	0-1
Sleep problems	.53 ± .38	0-1	.44±.29	0-1	.43 ± .39*a*	0-1	.43 ± .40	0-1

[a] based on 40 subjects

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Table 2
Unadjusted composite cognitive domain scores by group

	Late Reproductive (n=34)	Early Transition (n=28)	Late Transition (n=41)	Early Postmenopause (n=14)
Variable	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Cognitive Domain (*z*-scores)				
Attention/Working Memory	.037 ± .801	−.152 ± .681	.104 ± .690	−.091 ± .878
Executive Function	−.022 ± .765	.186 ± .918	−.078 ± .841	−.092 ± .728
Visuospatial Function	.142 ± .851	−.049 ± .1.17	.068 ± .908	−.446 ± 1.19
Verbal Learning	−.025 ± .828	−.127 ± .876	.173 ± .1.04	−.191 ± .802
Verbal Memory	.188 ± .598	−.124 ± .754	.090 ± 1.01	−.473 ± .994
Motor	.124 ± .864	.010 ± .816	.038 ± 1.02	−.433 ± .727