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Objective hot flashes are negatively related to verbal memory performance in midlife women

Pauline M. Maki, PhD^{1,2}, Lauren L. Drogos, BS², Leah H. Rubin, MA^{1,2}, Suzanne Banuvar, MHSA⁴, Lee P. Shulman, MD⁴, and Stacie E. Geller, PhD³

¹Department of Psychiatry, University of Illinois, Chicago, IL

²Department of Psychology, University of Illinois, Chicago, IL

³Department of Obstetrics and Gynecology, University of Illinois, Chicago, IL

⁴Department of Obstetrics and Gynecology, Feinberg School of Medicine, Northwestern University, Chicago, IL.

Abstract

Objective—To test the hypothesis that hot flashes specifically relate to verbal memory performance by examining the relationship between objective hot flashes and cognitive test performance in women with moderate to severe vasomotor symptoms.

Design—In an observational study, 29 midlife women (mean age, 53 y) with moderate to severe hot flashes provided measures of objective hot flashes with an ambulatory hot flash monitor, subjective hot flashes with a diary and questionnaire, and objective measures of verbal memory and other cognitive functions with standardized neuropsychological tests.

Results—The mean number of objective hot flashes was 19.5 per day (range, 6 to 35), including 15.3 (range, 6 to 35) during waking hours and 4.2 (range, 0 to 9) during sleep. The mean sensitivity (ie, subjective detection of objectively measured hot flashes) was 60%. Regression analyses revealed that total number of objective hot flashes, sleep duration, and verbal knowledge were significant predictors of delayed verbal memory. Verbal fluency correlated positively with objective daytime hot flashes. Hot flashes did not predict performance on any of the other secondary cognitive measures (ie, attention, working memory, visual memory), although poor sleep predicted worse performance on several outcome measures.

Conclusions—Highly symptomatic women underreport the number of objective hot flashes that they experience by 43%. Verbal memory performance relates significantly to the objective number of hot flashes women experience but not to the number of hot flashes that they report. These findings suggest that physiological factors related to hot flashes, rather than psychological factors, predict poorer verbal memory function.

Keywords

Cognition; Memory; Menopause; Hot flashes; Hormones; Vasomotor; Monitoring; Ambulatory

Hot flashes are the most frequently reported and recognizable symptom of menopause. As many as 75% of women experience hot flashes during menopause, and 15% of these symptomatic women report bothersome hot flashes.¹ The rapid change in vasodilatation and sweating on the skin during a hot flash can be objectively studied by monitoring skin conductance.² This objective technique to measure hot flashes has been validated in several studies, including a study measuring sternal skin conductance changes in relation to changes in core body temperature (via radiotelemetry pills) during a hot flash.³ Studies have compared objective measures of hot flashes and subjective hot flashes quantified through event markers on a skin conductance monitor. In laboratory settings, healthy postmenopausal women have detected a high proportion of objectively measured hot flashes, with sensitivities close to 100%.⁴ Healthy midlife women in ambulatory settings detect as many as 95% of hot flashes,⁴ although variability in detection can be high, with some women failing to report any objective hot flashes and other women reporting all objective hot flashes.⁵ As with healthy women, breast cancer patients have under-reported the number of objective hot flashes on average by 60%, with as many as 64% of objective hot flashes unreported while awake and as many as 78% unreported when asleep.⁶ Although subjective hot flashes are the endpoint on which the US Food and Drug Administration evaluates the clinical efficacy of treatments for vasomotor symptoms,⁷ objective hot flashes are useful in exploring the physiology of hot flashes and potential relationships with other menopausal symptoms and clinical outcomes.

Studies using objective hot flash measures have challenged some commonly held assumptions about the relationships among menopausal symptoms. For example, it has been suggested that vasomotor symptoms may be linked to other menopausal symptoms through a cascade of events in which hot flashes disturb sleep, and sleep disturbance in turn leads to fatigue, irritability, depression, and memory dysfunction.¹ However, a recent investigation using objective measures of both hot flashes and sleep found that women are as likely to wake before an objectively measured hot flash as after one.⁸ To date, the relationship between objectively measured hot flashes and memory complaints has not been explored.

Memory complaints are common at midlife. In the Study of Women's Health Across the Nation (SWAN), more than 40% of perimenopausal and postmenopausal women endorsed forgetfulness on a symptom inventory compared with 31% of premenopausal women.⁹ In the Seattle Midlife Women's Health Study, approximately 62% of midlife women reported an undesirable change in memory.¹⁰ Meta-analyses suggest that hormone therapy confers stronger cognitive benefits in young compared with older postmenopausal women, leading to speculation that this effect could be due, at least in part, to hot flash relief among symptomatic younger women.¹¹ The relationship between menopausal symptoms and cognition has been examined in correlational studies, but these studies have generally failed to find a significant association between subjective reports of hot flashes and cognition.¹²⁻¹⁴ Our understanding of the relationship between hot flashes and cognition may be limited by the use of self-report measures of hot flashes.

The aim of this study was to investigate the relationship between objective measures of hot flashes and one particular domain, verbal episodic memory, in a sample of midlife women. As used in this study, verbal episodic memory (hereafter called verbal memory) refers to the recollection of verbal material, including words, names, word pairs, paragraphs, and stories that were encountered at a particular place and time (eg, the woman at the party was named Gloria, orange was one of the words encountered in the memory test). In light of findings that lapses in verbal memory are a common menopausal complaint and improve with hormone therapy in surgical menopause and in women undergoing pharmacological ovarian hormone suppression,^{15,16} we hypothesized that objective hot flashes would be negatively related to verbal memory performance, but not other cognitive abilities. In secondary analyses, we explored the relationship between menopausal symptoms and other secondary cognitive

outcomes, including attention, verbal fluency, visual memory, and visuospatial ability. We predicted that we would find no relationship between hot flashes and other cognitive abilities.

METHODS

Participants

Participants were recruited from a pool of women screened for entry into a randomized clinical trial comparing black cohosh, red clover, conjugated equine estrogens plus medroxyprogesterone acetate (Prempro), and placebo on menopausal symptoms. Women were recruited into the main clinical trial by advertisements on the Internet and bulletin boards and by targeted mailings to women residing in the Chicago area. Inclusion criteria for the clinical trial included (1) last menstrual period between 6 months and 10 years before recruitment, (2) reports of a minimum of 35 hot flashes per week as indicated by diaries (ie, minimum of 2 weeks, most 1 month or more), and (3) intact uterus and ovaries. Exclusion criteria included (1) use of menopausal therapies, including oral hormone therapy within 2 months of study entry, transdermal estradiol within 1 month of study entry, and herbal botanicals within 1 month of study entry; (2) smoking; (3) contraindications to hormone therapy (eg, vascular disease, uncontrolled hypertension, abnormal vaginal bleeding, history of blood clots, diabetes, abnormal mammogram); (4) use of antidepressants, selective estrogen-receptor modulators, and bisphosphonates; and (5) major systemic illness. Additional exclusion criteria for the ancillary cognitive study included (1) diagnosis of an Axis I psychiatric disorder, (2) any medical condition that affects cognitive function (eg, stroke, traumatic brain injury), (3) use of prescription or over-the-counter medications that affect cognitive function (eg, ginkgo biloba), (4) first language other than English, and (5) participation in clinical trials other than the parent trial within 30 days.

The data in this report were obtained after the initial screening visit, before treatment initiation, in women who volunteered to participate in this ancillary study focusing on the effects of the four treatments on objective measures of hot flashes and cognitive outcomes. At screening, 59 women were approached regarding participation, and subsequently 37 women agreed to participate. From this pool of 37 women, three women withdrew before cognitive testing due to lack of time or personal reasons, one woman completed cognitive testing but was excluded because she did not meet the study criterion (did not experience a minimum of 35 hot flashes per week on prospective diaries completed after cognitive testing), and four women completed cognitive testing but had invalid hot flash data because of equipment failure. Twenty-nine healthy early postmenopausal women were included in this analysis. Of these 29 women, 28 women were followed as part of the parent trial evaluating treatments for menopausal symptoms, and as part of the parent trial, they were randomized to one of four treatment arms after the baseline cognitive evaluation reported here. The other participant withdrew before randomization. Participants received a total of \$100.00 for time and travel for this ancillary evaluation.

Blood assays

Blood was obtained at the screening visit for the ancillary study from each participant to validate menopausal stage. Serum measures of estradiol, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were obtained through the University of Illinois Pathology Laboratory (n = 25) and Northwestern Medical Faculty Foundation shared laboratories (n = 4). At the University of Illinois at Chicago, each of these three assays was measured using a Beckman Coulter Access kit performed on D×I immunoassay. The estradiol assay had a measurable range of 20 to 3600 pg/mL, a manufacturer claim of an intra-assay coefficient of variation (CV) of 20% at 39 pg/mL and 5% at 2,918 pg/mL, and an observed CV of 10% at 90 pg/mL and 5% at 350 pg/mL. Estradiol levels below the lower limit of detection (20 pg/

mL) were assigned a value of 19 pg/mL for the present study. The FSH assay had a measurable range of 1 to 1000 IU/L, with a manufacturer claim of an intra-assay CV of approximately 4%, a manufacturer claim of an interassay CV of approximately 5%, and an observed CV of 4% at 11 IU/L and 5% at 50 IU/L. The LH assay had a measurable range of 1 to 1000 IU/L, a manufacturer claim of an intra-assay CV of approximately 5%, a manufacturer claim of an interassay CV of approximately 6%, and an observed CV of 5% at 2 IU/L and 5% at 58 IU/L. At Northwestern, each of the three assays was measured using an Immulite 1000 kit. The Immulite estradiol assay had a manufacturer claim of a lower sensitivity of 15 pg/mL and an intra-assay CV of 15% at a mean of 46 pg/mL. The Immulite 1000 FSH assay had a manufacturer claim of a lower sensitivity of 0.1 mIU/mL and an intra-assay CV of 6.1% at 58 mIU/mL and 6.7% at 87 mIU/mL. The Immulite 1000 LH assay had a manufacturer claim of a lower sensitivity of 0.1 mIU/mL and an intra-assay CV of 4.8% at 29 mIU/mL and 5.9% at 54 mIU/mL. Estrone assays for both University of Illinois at Chicago and Northwestern sites were performed at ARUP Laboratories using a Diagnostic Systems Laboratory double-antibody radioimmunoassay with a lower limit of sensitivity of 1.2 pg/mL and an intra-assay CV of 5.7% at a mean of 102 pg/mL.

Measures of cognitive function

Each participant met one-on-one with a trained test administrator and completed a cognitive battery. The cognitive test battery was modeled after the cognitive test battery used in the Cognitive Complaints in Early Menopause Trial, a study comparing the cognitive effects of combination hormone therapy and placebo in recently menopausal women with subjective cognitive complaints.¹⁷ Each battery lasted approximately 1.5 hours and was administered at the Center for Cognitive Medicine of the University of Illinois at Chicago (n = 25) or Northwestern University (n = 4). The primary outcome of interest was verbal memory, and we included two measures of verbal memory as described in the next section.

Primary cognitive outcome variables: verbal memory

Logical memory subtest of the Wechsler Memory Scale—Revised: This test yields a measure of immediate and delayed recall of a short story.¹⁸ Participants are read a brief story and are instructed to recall the story both immediately and after a 20-minute delay. Outcome measures included standardized scores of story recall accuracy both immediately after presentation and after a 20-minute delay, where the total scores range from 0 to 25.

California Verbal Learning Test (CVLT-Modified): This modified version of the CVLT was used in recent hormone therapy trials, including the Women's Health Initiative Study of Cognitive Aging and the Cognitive Complaints in Early Menopause Trial.^{17,19,20} The test provides measures of verbal learning and short- and long-delay verbal recall. On each of three successive verbal learning trials, the examiner reads aloud a target list of 16 words from four semantic categories (eg, articles of clothing) and instructs the participant to recall as many words as possible. The examiner then reads aloud a different "interference" list of 16 words from overlapping and different semantic categories and instructs the participant to recall as many words as possible from that list. Next, the participant is instructed to recall as many words as possible from the original target list (short-delay free recall), first without any categorical cues and then with categorical cues. After a 20-minute delay, the participant is instructed to recall the original target list (long-delay free recall), first without any categorical cues and then with categorical cues. Outcome measures included total verbal learning across trials 1 to 3 and short- and long-delay free recall.

Secondary cognitive outcomes

Benton Visual Retention Test: This is a test of short-term figural memory.²¹ In each of 10 trials, participants view a line drawing for 10 seconds and then immediately attempt to reproduce the drawing from memory on a blank sheet of paper. Stimulus complexity increases across the 10 trials. The dependent measure is the total number correct.

Modified Card Rotations test: This is a paper-and-pencil test that provides a brief measure of visuospatial ability.²² In each trial, participants view a target line drawing of a geometric figure and eight alternatives representing two- or three-dimensional rotations of the target. Participants are instructed to mark the alternatives that show the sample drawing rotated in two dimensions (ie, picture plane) as “same” and to mark those that show the sample drawing item rotated in three dimensions (ie, mirror images) as “different.” The dependent measure was the number of correct responses minus the number of incorrect responses across two trials of 3 minutes each, with a maximum possible score of 160.

Letter Fluency: This test provides a measure of verbal fluency.²¹ Participants are given 1 minute on each of three successive trials to generate as many words as possible that begin with a particular letter (ie, F, A, S). They are instructed to refrain from saying proper names, such as the names of people or places, and from saying multiple variations of the same word (eg, eat, eating). The outcome measure is the total number of words produced across three trials.

Digit Span Forward and Backward: This test provides measures of attention and working memory.¹⁸ In the first set of trials, the examiner reads a series of number strings aloud and instructs participants to repeat the string in the order presented (forward). In the next set of trials, the examiner reads a series of numbers aloud and instructs participants to repeat the string in the reverse order (backward). Outcome measures include the number of trials correctly recalled for the forward and backward trials.

Brief Test of Attention—Modified: This test measures auditory attention.^{23,24} On each trial, the examiner reads aloud a string of letters and numbers and instructs the participant to state aloud the number of numbers that were presented in each string. The strings increase in length across 10 trials, and the outcome measure is the total number of correct responses out of 10.

Finding A’s test: This is a test measuring visuoperceptual speed.²⁵ Participants are shown five columns of words on a sheet of paper and are instructed to cross out as many words containing the letter A as possible in 2 minutes. The outcome measure is the total number of correct responses made in 2 minutes.

Estimate of verbal intelligence

Primary Mental Abilities Vocabulary test (PMA): This is a paper-and-pencil vocabulary test that was included to estimate individual differences in verbal knowledge at baseline.²⁶ In African Americans, verbal knowledge varies with acculturation, and accounting for acculturation improves the diagnostic accuracy of neuropsychological tests.²⁷ In each of 75 trials, participants read a target word and circle its synonym out of four alternative responses. The outcome measure was the total number of correctly identified synonyms identified in 5 minutes, with a deduction of 0.33 for each incorrect answer to correct for guessing.

Self-report questionnaires

Greene Climacteric Scale (GCS)—This is a 21-item questionnaire that measures a variety of menopausal symptoms on a 4-point Likert scale (0 = “not at all” to 3 = “extremely”).²⁸ The scale yields four categorical symptom measures: psychological symptoms, somatic symptoms

(eg, feeling dizzy or faint, headaches), vasomotor symptoms (eg, hot flushes, night sweats), and sexual dysfunction (eg, loss of interest in sex).

Modified Pittsburgh Sleep Quality Index (PSQI)—This is a modified version of the PSQI²⁹ and provides information regarding sleep latency (number of minutes it takes to fall asleep: ≤ 15 min = 0; 16–30 min = 1; 31–60 min = 2; > 60 min = 3), sleep duration (actual number of hours of sleep during the night), and sleep disturbances (not being able to fall asleep within 30 min, waking up in the middle of the night or early in the morning, having trouble sleeping, other reasons). These three items correspond to components 2, 4, and 5a, 5b, and 5j of the original sleep inventory. For sleep disturbances, participants rate them on a Likert scale ranging from 0 to 3, where 0 is “not during the past month” and 3 is “three or more times a week.” A total sleep score was calculated using a previously published scoring scheme.²⁹ For all sleep measures, higher scores indicate greater sleep disturbance.

Positive and Negative Affect Scale—This is a paper-and-pencil self-report measure of positive and negative mood states.³⁰ Participants rate a list of 10 pleasant mood states and 10 unpleasant mood states on a 5-point Likert scale based on the extent to which they experienced each state during the previous 2 weeks. Ratings for each item range from 1 to 5, with 1 indicating “very slightly” and 5 indicating “extremely.” Positive and negative scales are scored separately and the total score is divided by 10 to yield a maximum score of 5 for each scale.

Hot flash assessments

Participants were fitted with an ambulatory sternal skin conductance monitor (Biolog model 3991x/2-HFI, UFI, Morro Bay, CA), with two skin conductance electrodes (UFI) connected to the sternum by adhesive electrode pads (UFI, 1081-HFD) prepared with electrode gel (CustomMed Apothecary). The monitor was placed inside a small pouch for participants to attach to their belt or sling over their shoulder for easy maneuvering throughout the recording session. Participants were instructed to wear the monitor for 24 hours and to refrain from immersing the electrodes in water during the recording period (eg, by showering, swimming, bathing). Both objective (ie, > 2 - μ mho increase in 30 s) and subjective (button press) hot flashes were recorded with the monitor according to standard procedures and criteria.² Participants were instructed to indicate when they subjectively experienced a hot flash by simultaneously pressing two buttons on the hot flash monitor, resulting in a time stamp, and by recording the time of occurrence, severity, bother, and activity at the time of the perceived hot flash in a diary. In each diary entry, severity and bother were recorded for each subjective hot flash. Participants rated hot flash severity and bother on a Likert-scale ranging from 0 (“no bother/not severe”) to 10 (“very bothersome/very severe”). Activity at the time of each subjective hot flash was recorded by self-report in a diary. For the purposes of this investigation, only frequency data were used because severity data are not available for hot flashes that were not subjectively detected.

Hot flash scoring

Raw hot flash data were transmitted from the Biolog monitor to a PC using the Biolog Interface Box. Skin conductance time series data in μ mho units were read and displayed in a time-locked graph using specialized software (DPS v. 1.5, UFI). Raw objective hot flash data were analyzed by a combination of automated computer software and data analysts trained by a national expert in this area (Janet Carpenter, PhD). Both the software and analysts defined an objective hot flash as a rapid increase in skin conductance of at least 2 μ mho over a 30-second period according to standard criteria.² Once an objective hot flash was coded, no other hot flashes were coded for the next 15 minutes according to standard procedures.³¹ Each participant’s time series was double-scored for the number of true-positive hot flashes (objective hot flashes that were subjectively detected within 5 min), number of false-positive hot flashes (subjectively

detected hot flashes that were not accompanied by an objective hot flash within 5 min) and false-negative hot flashes (objective hot flashes that were not subjectively detected within 5 min) that occurred either during wake time or sleep. Any discrepancies were discussed and resolved by the two coders before entry of coded data into the database. All coded data were then double-entered into an SPSS database. Total numbers of objective and subjective hot flashes during sleeping and waking hours were scored based on reports in hot flash diaries of the time that participants went to bed and the time that they woke up while wearing the monitor.

Some women wore the monitor for slightly less than 24 hours (37% of sample; recording hours ranged from 22.10 to 23.98), and each had complete data for hot flashes during sleep. For those women, the total number of daytime hot flashes was estimated by (1) first estimating the average number of hot flashes per hour awake by dividing the total number of objective hot flashes during waking hours by the total number of hours of recording time during waking hours and then (2) multiplying that average by the total hours awake. This method of prorating hot flashes was validated by correlating the total number of objective hot flashes with the prorated total of objective hot flashes (24 h), which was $r = 0.96$, $P < 0.001$. A more detailed discussion of the Biolog specifications and scoring procedures is available.³¹

Statistical analyses

Computations—Sensitivity was calculated by dividing the total number of true-positive hot flashes (ie, objectively determined hot flashes that were subjectively detected) by the sum of the total number of objectively measured hot flashes (ie, true positives and false negatives).

Analyses—Correlations and multivariate regressions were used to evaluate the extent to which objective hot flashes predicted verbal memory performance, the primary cognitive outcome. First, Pearson's correlations were conducted to evaluate the unadjusted relationship between six estimates of hot flashes (ie, total objective and subjective hot flashes in a 24-h period, during waking hours, and during sleeping hours) and verbal memory performance. Next, regression analyses were conducted when warranted by the correlational analyses to assess the extent to which hot flashes accounted for memory performance when other relevant and significant predictors of cognition such as demographic information (eg, age, race), verbal knowledge (PMA vocabulary), sleep quality (modified PSQI total score, duration, latency, and disturbances), and mood (Positive and Negative Affect Scale) were included in the model. A similar series of correlations and regressions was conducted on secondary cognitive outcomes to test the hypothesis that hot flashes would not predict performance on secondary outcomes. Hormone values (ie, estradiol, estrone, LH, and FSH) were not included as predictors in the regression analyses because the hormone values collected were not always collected at the time of cognitive testing. All statistical analyses were conducted using SPSS statistical software (version 14.0 for Windows, SPSS, Chicago, IL). Before conducting correlational analyses, we first examined the distribution of each cognitive outcome to ensure normality of the distribution and check for statistical outliers (ie, values >3 SD above or below the mean). For statistical outliers that were deemed to be valid measures of performance, we substituted the outlier value with the next most extreme value in the variable distribution.³² Definitions of small, medium, and large effect sizes for correlational analyses were based on Cohen, using r values of 0.1, 0.3, and 0.5, respectively.³³ To determine whether any significant correlation between hot flashes and verbal memory (ie, the test of the primary hypothesis) remained significant after controlling for other variables that also correlated with verbal memory, we conducted follow-up regression analyses using any demographic or menopausal symptom variable that also correlated with that verbal memory outcome.

RESULTS

Characteristics of the participants

Table 1 shows the demographic information, hormone levels (estradiol, estrone, FSH, and LH), primary cognitive outcomes (ie, verbal memory), secondary cognitive outcomes, menopausal symptoms, sleep quality, and mood for the 29 participants. The minimum, maximum, and mean hormone levels across the two sites were similar, so we averaged the University of Illinois at Chicago (n = 25) and Northwestern (n = 4) values together. Participants ranged in age from 44 to 62 years (mean = 53.13), and 62% were African American, 35% white, and 3% Asian. There was one statistical outlier on verbal fluency (ie, >3 SD above the mean).

Hot flashes

A total of 548 objective hot flashes were recorded. Twenty-four percent of participants wore the monitor on the day before cognitive testing, 69% on the day of testing, and 7% on the day after cognitive testing. Twenty-four percent of the total sample experienced between 6 and 13 objective hot flashes during the 24-hour monitoring period, 34% experienced 15 to 19 hot flashes, 24% experienced 21 to 24, and 20% experienced 25 to 35 hot flashes. The mean number of subjective and objective hot flashes per day were 18.59 (SD = 7.67; range, 6-34) and 19.46 (SD = 7.66; range, 6-35), respectively. The average number of subjective hot flashes during waking hours was 15.13 (SD = 6.38; range, 5-28) and during sleeping hours was 3.46 (SD = 2.43; range, 0-8), compared with an average number of objective hot flashes during waking hours of 15.28 (SD = 6.31; range, 6-35) and during sleeping hours of 4.18 (SD = 2.87; range, 0-9).

The similarity in these mean values for subjective and objective hot flashes might suggest a high concordance between objective and subjective hot flashes for any given participant. However, as shown in Figure 1, the mean sensitivity during a 24-hour period was 57% (range, 22%-100%), indicating an underreporting of objective hot flashes by 43%. The mean sensitivity during waking hours was 60% (range, 25%-100%), indicating an underreporting of objective daytime hot flashes by 40%. Of the 29 participants, 23 had objective hot flashes during sleeping hours. The mean sensitivity during sleeping hours was 40% (range, 0-100%), indicating an underreporting of objective nighttime hot flashes by 60%.

Cognitive function

Primary cognitive outcome: verbal memory—The total number of objective hot flashes over a 24-hour period significantly correlated with delayed paragraph recall, $r(28) = -0.40$, $P < 0.05$ and showed a trend for immediate paragraph recall, $r(28) = -0.36$, $P = 0.054$. There was a significant relationship between the number of objective hot flashes during sleep and immediate paragraph recall, $r(28) = -0.43$, $P < 0.05$, and delayed paragraph recall, $r(28) = -0.48$, $P < 0.01$. By contrast, the number of hot flashes while awake did not correlate with immediate or delayed paragraph recall, $r(28) = -0.24$, NS, and $r(28) = -0.27$, NS, respectively. Subjective hot flashes did not correlate significantly with verbal memory performance.

Next, a series of stepwise regression analyses was conducted to characterize the relationship between objective and subjective hot flashes and verbal memory, while controlling for other significant correlates of verbal memory, including demographics (eg, age, education), verbal knowledge (a proxy for acculturation, an important factor for interpretation of neuropsychological outcomes in African American women²⁷), and menopausal symptoms (eg, sleep, mood). In addition to objective hot flashes during sleep, race ($r = -0.45$, $P < 0.05$), age ($r = 0.41$, $P < 0.05$), vocabulary score ($r = 0.56$, $P < 0.05$), total sleep score ($r = 0.42$, $P < 0.05$), and sleep duration ($r = -0.41$, $P < 0.05$) were significant correlates of immediate paragraph recall. As shown in Table 2, in regression analyses, PMA vocabulary score was a significant

(positive) predictor of immediate paragraph recall, but objective nighttime hot flashes just missed significance as a negative predictor of memory ($P = 0.053$). For delayed paragraph recall, in addition to objective hot flashes, significant correlates included race ($r = -0.44$, $P < 0.05$), age ($r = 0.44$, $P < 0.05$), PMA vocabulary ($r = 0.73$, $P < 0.01$), total sleep score ($r = -0.43$, $P < 0.05$), and sleep duration ($r = -0.57$, $P < 0.01$). In regression analyses, verbal knowledge measured by the PMA vocabulary test, total number of objective hot flashes during sleep, and sleep duration were each significant predictors. Figure 2 shows the significant negative relationship between delayed paragraph recall and the total number of objective hot flashes while asleep, controlling for verbal knowledge and sleep duration. Hot flashes did not predict performance on any CVLT outcome measure but higher positive affect scores predicted better recall after a long delay.

Secondary cognitive outcomes—Only one secondary outcome measure correlated with either objective or subjective hot flashes. Verbal fluency correlated positively with the number of objective hot flashes during the day ($r = 0.41$, $P < 0.05$), but not with any other predictor variable. Sleep parameters from the PSQI significantly predicted performance on tests of verbal memory, working memory, and attention. Sleep duration was a significant predictor of attention, as measured by Digit Span Forward ($B = -1.56$, $SE = 0.41$, $P < 0.001$) and the Brief Test of Attention ($B = -0.81$, $SE = 0.37$, $P < 0.05$). Overall sleep quality, as measured by PSQI total score, was a significant predictor of working memory as measured by Digit Span Backward ($B = -0.59$, $SE = 0.23$, $P < 0.05$). In addition to sleep parameters, education predicted performance on the Brief Test of Attention ($B = 0.33$, $SE = 0.16$, $P < 0.05$) and Digit Span Backward ($B = 0.46$, $SE = 0.22$, $P < 0.01$).

DISCUSSION

The goal of this investigation was to explore the relationship between objective hot flashes and verbal memory performance in midlife women with moderate to severe hot flashes. We predicted that objective hot flashes would be a negative predictor of verbal memory but not of other cognitive abilities. Results supported this prediction. Objectively measured hot flashes, particularly nighttime hot flashes, correlated negatively with immediate and delayed paragraph recall as measured by the Logical Memory subtest. In regression analyses of the primary cognitive outcomes, nighttime hot flashes, sleep duration, and general verbal ability were significant predictors of delayed paragraph recall scores. Objective hot flashes during sleep tended to predict immediate paragraph recall ($P = 0.053$), although this effect did not reach significance. Consistent with previous studies,¹²⁻¹⁴ subjective hot flashes did not predict verbal memory performance. In analyses of secondary cognitive outcomes, objective daytime hot flashes predicted verbal fluency, and sleep quality predicted poorer attention and working memory. Women in the present study underreported the number of objectively measured hot flashes by 43%. The high proportion of undetected objective hot flashes, coupled with the strong relationship between only objective hot flashes and memory performance, suggests that physiological rather than psychological correlates/mediators of hot flashes are related to memory disturbance in symptomatic women.

Of the two measures of verbal memory, the modified CVLT and Logical Memory, only Logical Memory was related to objective hot flashes. The two verbal memory tests are frequently thought to be interchangeable, although they differ procedurally in a number of ways and appear to differentially rely on executive/frontal lobe functions (eg, attention, strategies, organization).^{34,35} Logical Memory is presented once as a structured story, whereas the modified CVLT is presented three times as an unstructured 16-item word list composed of four words from four semantic categories. Both tests include a 20-minute delay before the delayed recall trial. Tests of executive/frontal lobe function predict performance on the CVLT but not Logical Memory,^{34,35} suggesting that the difference between the two memory tests in the

extent to which the presented verbal material is organized appears to place different demands on cognitive abilities that are dependent on frontal lobes. One interpretation of the present findings is that objective hot flashes impair memory for verbal material that is organized into logical units but do not affect performance on tests that require strategic/organizational skills dependent on frontal lobe systems.

Evidence from neuroimaging studies suggest that performance on Logical Memory relates more to temporal lobe function than to frontal lobe function.³⁶ The sex difference in verbal memory in favor of women has been reported to be greater for the Logical Memory subtest, particularly for the delayed trial, than for the CVLT.³⁶ Furthermore, Logical Memory scores correlated significantly with resting cerebral blood flow in the left temporal lobe in women but not men.³⁶ That pattern of neuroimaging findings was interpreted as reflecting women's greater facility in retrieving "gestalt-like mental representation of story concepts"³⁷ via a brain area involved in retrieval of multimodal associations in semantic memory. The left temporal pole has been shown to be thicker in women compared with men. In the context of those neuroimaging findings, objectively measured hot flashes might be thought of as interfering with women's native advantage over men in retrieving story concepts, perhaps due, at least in part, to temporal lobe dysfunction.

We found that the significant overall relationship between objective hot flashes and paragraph recall was primarily due to nighttime hot flashes. This relationship might suggest that impaired paragraph recall was attributable to sleep deprivation after hot flashes. Shorter sleep duration predicted worse verbal memory, but the number of nighttime hot flashes remained a significant predictor even when sleep duration and other subjective sleep parameters were modeled in the regression. Thus, sleep duration and nighttime hot flashes independently contributed to impaired verbal memory. Sleep deprivation has been shown to impair verbal memory performance and lower activity in brain regions critical for memory during verbal recall (eg, left temporal pole and parahippocampal gyrus).³⁸ Sleep complaints are common among midlife women with hot flashes,³⁹ yet the relationship between the two symptoms is not straightforward. Neither hot flashes nor menopausal stage was associated with differences in objective sleep parameters in a large polysomnography study.³⁹ A recent study revealed that hot flash—induced sleep disturbance occurs in the first half of the evening and that rapid eye movement sleep during the second half of the evening suppresses hot flashes and associated awakenings.⁴⁰ The first half of the evening is when most deep sleep (stages 3 and 4; slow wave sleep) occurs, and slow wave sleep is a critical determinant of memory performance.^{41,42} This gives rise to the hypothesis that objective hot flashes, particularly during the first half of the evening, may lead to a decrease in slow wave sleep and thereby lead to impaired verbal memory.

One potential mediator of the relationship between hot flashes and cognition is cortisol. Cortisol has been shown to increase 20 minutes after hot flashes.⁴³ Recent findings indicate that midlife women with higher urinary cortisol levels are more likely to have severe hot flashes compared with women with lower cortisol levels.⁴⁴ Cortisol administration produced a reversible, but negative, effect on verbal memory measured by the Logical Memory subtest, the same test shown to relate to objective hot flashes in this study.⁴⁵ Notably, exogenous administration of glucocorticoids during slow wave sleep has been shown to impair verbal memory.⁴² Nocturnal cortisol levels predict poor declarative memory performance in healthy individuals and individuals with chronic insomnia.⁴¹ In a healthy young population, 24-hour urinary cortisol levels and verbal fluency levels were both higher during the follicular phase compared with the luteal phase.⁴⁶ In the present study, objective daytime hot flashes were positively related to verbal fluency. Although that positive relationship may have been a chance finding, one possibility is that cortisol may mediate the relationship between objective hot flashes and cognitive performance in highly symptomatic women.

The present study has several limitations. First, the study is based on a correlational design, so a causal relationship between objective hot flashes and verbal memory disturbance cannot be directly inferred. Second, the results are based on a sample in which the majority of patients are African American. Although we controlled for race and used a measure of acculturation appropriate for African Americans, the results may not generalize to other ethnic groups. Third, our sample size provided 89% power to detect a significant correlation of 0.50, and larger samples are needed to explore relationships between hot flashes and other cognitive domains that are smaller in magnitude. Fourth, we studied as many as six predictor variables in a multiple regression, although we had only 29 participants. With small samples, the statistical regression solution might not generalize beyond the present sample. Our main goal was to ensure that the relationship between objective hot flashes and verbal memory remained significant when other significant correlates of verbal memory were included in the regression analyses. Fifth, we did not include objective measures of sleep disturbance to better understand the possible interplay between sleep disturbance and nighttime hot flashes on verbal memory.

CONCLUSIONS

In summary, to our knowledge, this is the first study to explore the relationship between objectively measured hot flashes and cognitive test performance. Our findings reveal that objective, rather than subjective, hot flashes are a negative predictor of verbal memory in midlife women with moderate to severe vasomotor symptoms. This relationship appears to be primarily due to nighttime rather than daytime hot flashes. Nighttime hot flashes predicted verbal memory even when sleep duration and other subjective sleep parameters were modeled in the regression. This indicates that sleep duration and nighttime hot flashes independently contributed to impaired verbal memory and suggests that some of the adverse influence of hot flashes on menopausal clinical outcomes may be unrelated to sleep disruption. Verbal memory performance relates significantly to the objective number of hot flashes women experience but not to the number of hot flashes that they report. These findings suggest that physiological, rather than psychological, factors associated with vasomotor symptoms relate to memory dysfunction in this group. Accordingly, our study suggests that interventions that lower vasomotor symptoms may provide cognitive benefit to symptomatic women. Larger studies are needed to evaluate the robustness of these pilot data and to fully evaluate their clinical significance.

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FIG. 1.

Mean sensitivity (percentage of hot flashes correctly reported) during waking hours and overall. Sensitivity was calculated by dividing the total number of true-positive hot flashes (ie, objectively determined hot flashes that were subjectively detected) by the sum of the total number of objectively measured hot flashes (ie, true positives and false negatives). Of the 29 women in this study, 23 reported nighttime hot flashes, and therefore sensitivity measures were calculated only for those 23 women. Women underreport objective hot flashes by 40% during the day, 50% during the night, and 43% overall (ie, across the full 24 hours).

FIG. 2.
Relationship between Logical Memory delayed free recall and average objective hot flashes during sleeping hours controlling for verbal knowledge and sleep duration.

TABLE 1

Participant characteristics and outcomes (mean and SD)

Variables	Mean	SD
Demographics		
Age	53.13	4.38
Education	15.48	1.92
Body mass index	27.67	3.80
Months since final menstrual period	46.62	6.54
Verbal knowledge (PMA vocabulary)	38.36	14.34
Hormone levels		
Estradiol (pg/mL)	22.38	5.56
Estrone (pg/mL)	29.22	8.39
FSH (IU/L)	101.68	32.68
LH (IU/L)	37.87	12.55
Cognitive outcomes		
Primary outcome: verbal memory		
Logical Memory subtest		
Immediate recall	13.97	3.44
Delayed recall	13.76	3.70
California Verbal Learning Test		
Total words recalled across trials 1–3	29.59	5.80
Short-delay free recall	8.90	2.74
Long-delay free recall	9.72	2.67
Other secondary cognitive outcomes		
Benton Visual Retention Test	5.62	2.50
Card Rotations Test	54.14	40.85
Letter Fluency (FAS) ^a	44.72	14.06
Digit Span Forward	8.55	2.16
Digit Span Backward	6.52	2.52
Brief Test of Attention	8.34	1.80
Finding A's	29.97	7.06
Questionnaires	15.97	6.30
Green Climacteric Scale	8.62	3.85
Psychological	2.45	1.66
Somatic	3.86	1.83
Vasomotor	1.03	1.02
Sexual		
Pittsburgh Sleep Quality Index	4.28	1.79
Sleep latency	0.45	0.63
Sleep duration	1.55	0.83
Sleep disturbances	2.28	0.88
Positive and Negative Affect Scale		
Positive affect	3.36	0.72
Negative affect	1.75	0.55

Variables	Mean	SD
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PMA, Primary Mental Abilities Vocabulary Test; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

^aOne woman scored more than 3 SD above the mean on verbal fluency and was excluded from that analysis only.

Summary of the first-order correlations and results of stepwise regression analyses where menopausal symptom variables predicted verbal memory

TABLE 2

Primary outcome	Predictors	r	B	SE	β	ΔR^2	P
Logical Memory subtest							
Immediate recall	PMA	0.56	0.13	0.38	0.56	0.56	0.001
	Objective HFs during sleep ^a	-0.43	-0.32				0.053
Delayed recall							
	PMA	0.73	0.14	0.03	0.53	0.53	0.001
	Objective HFs during sleep	-0.48	-0.40	0.15	-0.31	0.10	0.013
	Sleep duration	-0.57	-1.24	0.56	-0.28	0.06	0.037

PMA, Primary Mental Abilities Vocabulary Test Total Score; HFs, hot flashes.

^aTrend for objective hot flashes during sleep predicting performance on immediate paragraph recall. For sleep measures, a higher score is indicative of worse sleep. *r* Values represent the first-order correlations between predictor and outcome variables.