Reduction in menopause-related symptoms associated with use of a noninvasive neurotechnology for autocalibration of neural oscillations

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Abstract

Objective: Increased amplitudes in high-frequency brain electrical activity are reported with menopausal hot flashes. We report outcomes associated with the use of High-resolution, relational, resonance-based, electroencephalic mirroring—a noninvasive neurotechnology for autocalibration of neural oscillations—by women with perimenopausal and postmenopausal hot flashes.

Methods: Twelve women with hot flashes (median age, 56 y; range, 46-69 y) underwent a median of 13 (range, 8-23) intervention sessions for a median of 9.5 days (range, 4-32). This intervention uses algorithmic analysis of brain electrical activity and near real-time translation of brain frequencies into variable tones for acoustic stimulation. Hot flash frequency and severity were recorded by daily diary. Primary outcomes included hot flash severity score, sleep, and depressive symptoms. High-frequency amplitudes (23-36 Hz) from bilateral temporal scalp recordings were measured at baseline and during serial sessions. Self-reported symptom inventories for sleep and depressive symptoms were collected.

Results: The median change in hot flash severity score was −0.97 (range, −3.00 to 1.00; $P = 0.015$). Sleep and depression scores decreased by −8.5 points (range, −20 to −1; $P = 0.022$) and −5.5 points (range, −32 to 8; $P = 0.015$), respectively. The median sum of amplitudes for the right and left temporal high-frequency brain electrical activity was 8.44 μV (range, 6.27-16.66) at baseline and decreased by a median of −2.96 μV (range, −11.05 to −0.65; $P = 0.0005$) by the final session.

Conclusions: Hot flash frequency and severity, symptoms of insomnia and depression, and temporal high-frequency brain electrical activity decrease after High-resolution, relational, resonance-based, electroencephalic mirroring. Larger controlled trials with longer follow-up are warranted.

Key Words: Menopause – Hot flashes – Neurotechnology – Brain adaptation – Brain electrical activity – High-resolution, relational, resonance-based, electroencephalic mirroring.

Up to 88% of perimenopausal and postmenopausal women in the United States experience hot flashes or night sweats[1] and disturbances in mood and sleep.[2–4] With hormone therapy use in decline because of safety concerns,[5,6] there is a persistent need for effective, safe, and tolerable ways to support symptom reduction.

Relaxation-oriented interventions may impact mechanisms of autonomic hyperarousal implicated in hot flashes, and trials of mind-body techniques have shown promise.[7] In an early and thoughtfully designed study, paced respiration training was found to confer significant reductions in hot flash frequency during muscle relaxation and α-wave electroencephalography (EEG) biofeedback given as placebo.[8] In contrast, a recent study from the MsFLASH (Menopause Strategies: Finding Lasting Answers for Symptoms and Health) Network showed that yoga was not superior to usual care in reducing hot flash frequency or bother and showed only a small improvement in insomnia symptoms.[9] A multicomponent strategy—relaxation training to reduce sympathetic arousal combined with cognitive-behavioral techniques to manage stress and negative thoughts—may be needed to reduce the physiological and psychological components of menopausal symptoms.[10]

Because the brain is the substrate common to physiological and psychological symptoms, an intervention that can facilitate relaxation through the brain itself could theoretically be more efficient and more efficacious than multicomponent approaches. Estrogen is an important modulator of noradrenergic

and serotonergic systems; the transition from regular rhythms in estrogen levels to irregular fluctuations and, finally, to an absolute reduction has been described as a prolonged process of "brain resetting" or "brain adaptation" that produces the various symptom clusters of menopause.[11,12]

High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM) is a noninvasive closed-loop neurotechnology that identifies dominant brain frequencies through high-resolution spectral analysis of noninvasively recorded brain electrical activity. Those dominant frequencies are reflected by translating them into auditory tones of varying pitch and timing, based on mathematical algorithms, which are presented bilaterally, simultaneously, to the recipient through earphones, with a delay of as little as 8 milliseconds. This acoustic stimulation paradigm is intended to allow an opportunity for the brain to relax and to self-optimize (improved capacity for adaptation) and for neural oscillatory patterns to shift, on their own, toward improved balance or reduced hyperarousal. Although an exact mechanism awaits confirmation, there is presumed to be resonance between neural oscillatory frequencies and auditory tones reflected in near real time.[13] HIRREM is described as an allostatic ("stability through change") technology through which an individual tends to self-adjust toward greater hemispheric symmetry and more optimal amplitudes across different frequency ranges of brain electrical activity in recipient-unique ways. HIRREM differs from EEG biofeedback in that there is no intention to learn voluntary control of brain activity, nor does it rely on EEG databases to define normality.

In a controlled clinical pilot trial, use of HIRREM was associated with improved sleep and reduced depressive symptoms among individuals with insomnia,[13] and a trend for reduced amplitudes in a high-frequency range (23-36 Hz) of brain electrical activity was observed. In the Study of Women's Health Across the Nation Sleep Study, a relationship between higher-amplitude brain electrical activity in a high-frequency range (16-32 Hz) and menopause status and hot flash frequency was found.[14] These studies point to the possible clinical significance of amplitude changes in the high-frequency range of brain electrical activity. Here, we report on changes in menopause-related symptoms and high-frequency brain electrical activity in an open-label cohort of women who undertook HIRREM.

METHODS

Twelve women (median age, 56 y; range, 46-69 y; 9 white and 3 African American) were enrolled in an ongoing, open-label, single-site feasibility study of HIRREM for individuals with diverse psychophysiological conditions. Procedures were approved by the Wake Forest University Health Sciences Institutional Review Board, and all participants provided a written informed consent form. Hot flash symptoms were reported by all participants and documented by use of a daily hot flash diary. Participants had a variety of self-reported comorbidities (Table 1). Individuals with a history of known sleep apnea, restless legs/periodic leg movement disorder, seizure disorder, or severe hearing impairment; a need for

TABLE 1. *Self-reported comorbidities*

Condition	Participants
Attention deficit disorder/attention deficit hyperactivity disorder	3 (25.00)
Depression	4 (33.33)
Fibromyalgia	2 (16.67)
Headaches/migraine	2 (16.67)
Hyperlipidemia	2 (16.67)
Hypertension	4 (33.33)
Hysterectomies	5 (41.67)
Insomnia	5 (41.67)
Stress/anxiety disorder	3 (25.00)

Data are presented as n (% of total).

ongoing treatment with opiates, benzodiazepines, or antipsychotic medications; or ongoing use of recreational drugs or alcohol were excluded. After meeting eligibility criteria, each participant completed a pre-HIRREM visit for enrollment and data collection, a baseline HIRREM assessment, a series of HIRREM sessions, and a post-HIRREM data collection visit. Procedures for the provision of HIRREM have been discussed in detail previously.[13]

HIRREM process

Before starting the HIRREM sessions, each participant underwent a baseline HIRREM assessment, which obtained information regarding brain electrical frequencies and amplitudes. The baseline assessment consisted of very brief recordings of brainwaves obtained from at least six standard locations on the scalp (F3/F4, C3/C4, P3/P4, T3/T4, FZ/OZ, and O1/O2), with the recipient at rest and carrying out a task. The assessment includes 1-minute recordings at each location with eyes closed, eyes partially open, and eyes open while performing a specific mental task appropriate for the location (ie, recalling numbers, reading a passage, etc). This assessment (45 min) allows for identification of the relative balance between homologous brain regions and for the proportionation or distribution of amplitudes among different frequency bands at each location. Data from the assessment are used to identify protocols for the initial HIRREM session.

HIRREM was received as a series of sessions lasting approximately 90 minutes (range, 54-102 min), consisting of four to nine individualized protocols, and addressing multiple brain locations and frequencies. Each protocol lasted from 6 to 30 minutes. Some protocols were performed with eyes closed and some with eyes open, with the participant sitting or reclining comfortably in a chair. The HIRREM sessions were scheduled to maximize frequency and efficiency, with participants generally completing two sessions in half a day separated by a 20- to 30-minute break. Because HIRREM is a unique, individualized process for each recipient, the specific protocols and session lengths vary between participants. Certified HIRREM technologists set session frequency and identified protocols (a combination of sensor montage and specific software design to address multiple locations and frequency bands during each session) to facilitate balance and proportionation between and within cortical regions, based on

data from the initial assessment or the preceding HIRREM sessions, as previously reported.[15]

During protocols, a proprietary mathematical algorithm selected the specific auditory tone to be reflected back to the participant by identifying the dominant frequency through high-resolution spectral analysis of noninvasively recorded real-time brain electrical activity. The dominant frequency was translated into an auditory tone and presented bilaterally, simultaneously, to the participant through earphones (Creative EP-630 or Sony Stereo Headphones MDR-EX58V) with a delay of as little as 8 milliseconds.

Postintervention outcome data were collected after completion of the HIRREM sessions. The primary outcomes for this analysis included changes in hot flash scores from baseline to post-HIRREM and serial values for the sum of high-frequency amplitudes at T3 and T4. Secondary outcomes included self-report insomnia (Insomnia Severity Index [ISI]) and depression (Center for Epidemiological Studies—Depression Scale [CES-D]) questionnaires at baseline and after the HIRREM intervention.

Primary outcome measures
Hot flash diaries

Hot flash diaries provide a valid and reliable approach to understanding a participant's experience of hot flashes.[16] Diaries measure the daily frequency (number of hot flashes) and severity of each hot flash. Hot flash severity categories are as follows: 1, mild; 2, moderate; 3, severe; 4, very severe. The hot flash severity score for each day was calculated as the sum of the number of hot flashes within each severity category, multiplied by the severity score for that category, with the resulting sum divided by the total number of hot flashes. Participants were asked to complete a paper-and-pencil hot flash diary for up to 1 week before beginning the HIRREM sessions to provide a more accurate reflection of the baseline pattern of hot flashes. Postintervention hot flash scores were derived from the final day of reporting available for each individual participant.

High-frequency amplitudes

Serial values for the sums of high-frequency amplitudes (23-36 Hz) at T3/T4 (μV) were evaluated by analysis of 1-minute epochs of brain electrical data recorded during the HIRREM assessment at baseline and during the penultimate minute of the first four HIRREM sessions and the last four HIRREM sessions. Analysis focused on high-frequency amplitudes at the temporal regions (sum of amplitudes at T3 and T4) owing to their proximity to underlying cortical regions implicated in autonomic regulation, with notation of change in values from baseline to the final HIRREM session.

Secondary outcome measures
Insomnia Severity Index

The ISI is a seven-item survey that assesses the severity, nature, and impact of insomnia symptoms on quality of life in the previous 2 weeks.[17] It is scored on a five-point Likert scale from 0 (*no problem*) to 4 (*very severe problem*) on a composite score range from 0 to 28. Composite scores can be stratified into the following clinical severities of insomnia: absent (0-7), subthreshold (8-14), moderate (15-21), and severe (22-28).[18] The internal consistency for ISI was 0.74, and a correlation with sleep diaries was also established.[19]

Center for Epidemiological Studies—Depression Scale

The CES-D is a 20-item survey that assesses affective depressive symptoms to screen for risk of depression.[20] Each question identifies a depressive symptom and is scored on a four-point Likert scale from 0 (*rarely*; <1 d/wk) to 3 (*most or all of the time*; 5-7 d/wk). Participants were instructed to respond based on how they have felt during the past week. Four questions have positive valence with reverse scoring. The cumulative score ranges from 0 to 60, with a score of 16 commonly used as a clinically relevant cutoff.[21] Its internal consistency varies by demographics, with α coefficients between 0.60 and 0.90 and with 3-month test-retest validity higher than 0.60.[22,23]

Autonomic cardiovascular control

Continuous blood pressure and heart rate data were acquired from noninvasive finger arterial pressure measurements for a minimum of 5 minutes while participants were in supine position. Systolic blood pressure and R-R interval files (BIOPAC acquisition software; BIOPAC Systems, Santa Barbara, CA) acquired at 1,000 Hz were analyzed using Nevrokard Baroreflex Sensitivity software (Medistar, Ljubljana, Slovenia) for measures of baroreflex sensitivity (as low-frequency and high-frequency α indices; sequence baroreflex sensitivity), heart rate variability, and blood pressure variability as power of systolic blood pressure spectra calculated as low-frequency systolic arterial pressure and SD of the mean arterial pressure. Specific heart rate variability measures included the power of R-R interval spectra in low and high frequency ranges, the SD of beat-to-beat R-R interval, and the root mean square of successive beat-to-beat differences in R-R interval duration.

Statistical analysis

Data are summarized as sample frequencies and median/interquartile ranges. Changes from baseline to the post-HIRREM data collection visit were evaluated using Wilcoxon signed rank test. "Spaghetti" plots were used to illustrate longitudinal trajectories for the diary-based hot flash scores during the course of the HIRREM intervention.[24] All analyses were performed using the R Statistical Computing Environment.[25]

RESULTS

Participants had a median of 13 (range, 8-23) HIRREM sessions (90 min each) administered for a median of 9.5 days (range, 4-32 d). All participants returned for a follow-up data collection visit at a median of 10 days (range, 0-20 d) after completion of their final HIRREM session.

Participants maintained the hot flash diary for a median of 3.5 days (range, 1-11 d) before starting the HIRREM sessions. The median change in hot flash severity score was −0.97
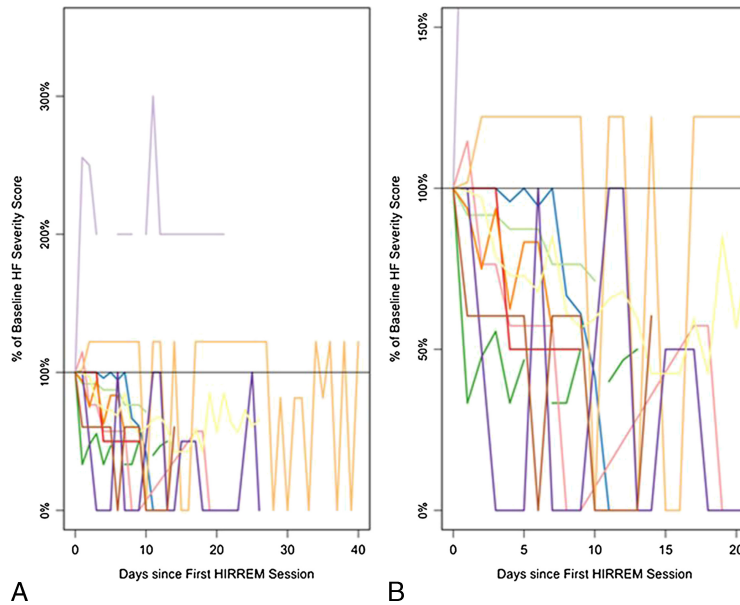
FIG. 1. Changes in hot flash (HF) severity scores across time as a percentage of baseline score for the entire cohort (**A**) and with focus on the 0% to 150% range that included most participants (**B**). The *y* axis indicates the percentage of baseline score. The *x* axis indicates the number of days since the start of High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM) sessions. Each line represents an individual participant in the study.

(range, −3.00 to 1.00; *P* = 0.015). Figure 1A, B illustrates changes in hot flash severity score for each individual participant during the period of her diary recordings. General inspection shows that much of the benefits associated with HIRREM accrued quickly, within the first 7 days of the beginning of the intervention.

The median total T3/T4 high-frequency amplitude was 8.44 µV (range, 6.27-16.66 µV) at baseline, decreasing by a median of −2.96 µV (range, −11.05 to −0.65; *P* = 0.0005) by the final HIRREM session. Figure 2A, B provides an example (from one study participant) of the type of changes generally seen in high-frequency amplitudes, with initially high amplitudes in high-frequency ranges (Fig. 2A) and with decreased amplitudes in a subsequent HIRREM session (Fig. 2B). No statistically sig-

nificant changes in measures of autonomic cardiovascular control were noted.

Symptom scales for insomnia and depression saw a decrease in median scores post-HIRREM. At baseline, participants had a median ISI score of 16 (range, 4-27) and a median decrease of −8.5 (range, −20 to −1; *P* = 0.022). Ten of 12 participants reported at least subthreshold insomnia (ISI score ≥8) at baseline. Eight of these 10 participants reported no insomnia post-HIRREM (Table 2). No participants reported an increase in symptoms of insomnia after treatment.

Baseline CES-D scores showed a median value of 14 (range, 3-36) with a median change of −5.5 (range, −32 to 8; *P* = 0.015). Six of 12 participants reported clinically relevant depressive symptoms (CES-D score ≥16) at baseline. Four of
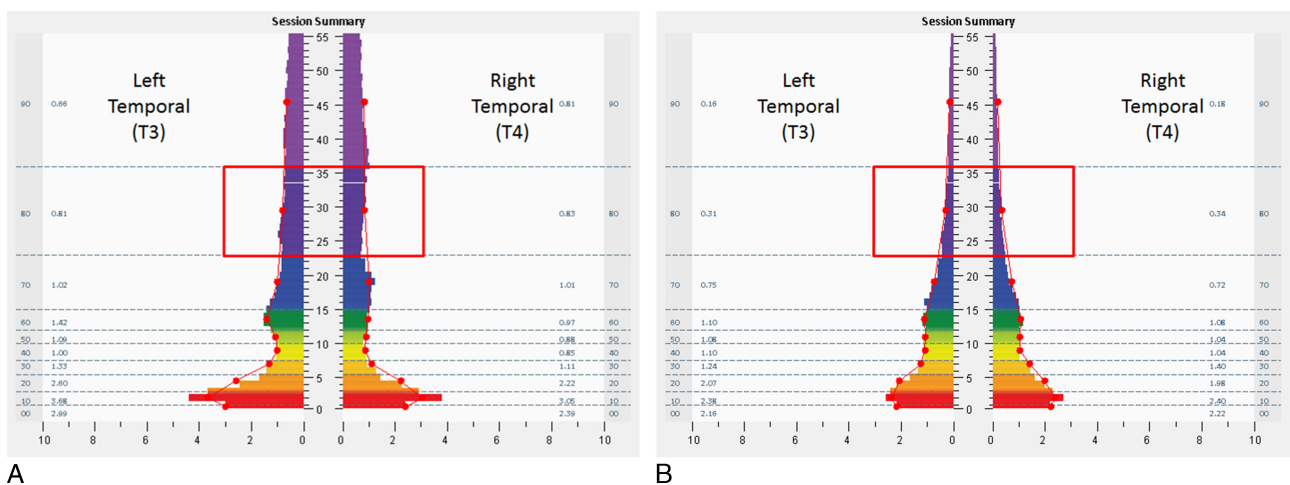

FIG. 2. A, B: Fast Fourier transform spectral display of electroencephalic data with frequency (Hz; central *y* axis) plotted against transformed amplitude (µV; *x* axis). Data represent 1 minute of data from the T3/T4 montage with eyes closed at baseline assessment (**A**) and at the penultimate minute of the final session (**B**) for one participant (a woman aged 47 y). Note the change in amplitudes in the range 23 to 36 Hz (dark purple) outlined by red boxes.

TABLE 2. *Changes in clinical category for insomnia after HIRREM, by ISI score*

Clinical category	ISI score	Baseline	Post-HIRREM
No clinically significant insomnia	0-7	2 (16.67)	10 (83.33)
Subthreshold insomnia	8-14	4 (33.33)	0 (0)
Moderate insomnia	15-21	3 (25.00)	2 (16.67)
Severe insomnia	22-28	3 (25.00)	0 (0)

Data are presented as n (% of total).
HIRREM, High-resolution, relational, resonance-based, electroencephalic mirroring; ISI, Insomnia Severity Index.

these six participants reported depressive symptoms below the clinically relevant threshold post-HIRREM. One participant who reported subthreshold depressive symptoms at baseline (CES-D score, 11) indicated clinically relevant symptoms of depression after the intervention (CES-D score, 19).

DISCUSSION

In this open-label study, use of HIRREM by perimenopausal and postmenopausal women was associated, on average, with significant reductions in hot flash frequency and severity, decreased symptoms of insomnia and depression, and decreased amplitudes in the high-frequency range of brain electrical activity, as measured from bilateral temporal scalp recordings. Interpretation of our findings is limited by the sample size of the study, the absence of a control group, and the lack of long-term follow-up.

A current model for the genesis of vasomotor symptoms focuses on changes in the thermoregulatory neutral zone, as defined by the hypothalamus.[26] In this model, vasomotor symptoms result from a narrowing between the upper limits and the lower limits of body temperature, producing sweating and shivering, respectively. Narrowing of the thermoregulatory neutral zone is in turn explained as a consequence of the changing rhythms of ovarian steroid circulation and their influence on neurotransmitter activity in the hypothalamus, serotonergic system, and noradrenergic system.[12]

Noradrenergic systems are demonstrated to contribute to hot flashes. Injection of yohimbine, an α_2 antagonist that increases norepinephrine availability, produces increased vasomotor symptoms.[27] In contrast, noradrenergic reuptake inhibitors have been shown to be efficacious for reducing vasomotor symptoms, suggesting that "restoring" norepinephrine levels is a way to stabilize thermoregulatory mechanisms.[11] These divergent effects seem to be further confirmation of the "brain adaptation" model for menopausal symptoms in that the role of brain norepinephrine in vasomotor symptoms may lie not on its absolute excess or deficiency but on irregular fluctuations in the dynamics of its availability and activity.

HIRREM helps the brain to self-optimize activity patterns toward more flexibly adaptive and recipient-unique set points, in contrast to pharmacological agents that stabilize the brain by clamping neurotransmitters at relatively fixed activity levels. The findings from this study are consistent with the idea that HIRREM may support symptom reduction by facilitating shifts in brain electrical activity patterns toward

adaptively lower amplitudes in the high-frequency range. Increased amplitudes in the high-frequency range of brain electrical activity are observed not only in menopause[14] but also in insomnia.[28] We did not find changes in autonomic cardiovascular control, although such changes may be more reliably detected by recording autonomic activity in direct association with a hot flash event, as has been performed by others.[29]

The speed with which clinical changes were reported by study participants stands in contrast with other studies of relaxation techniques, in which benefits were typically not measured or demonstrated for at least 4 weeks after the start of the intervention.[7] The rapidity of benefits in the current study was similar to our observations in a clinical trial of HIRREM for individuals with insomnia[13] and, preliminarily, may offer further evidence that self-optimization of brain activity at the cortex could be a viable "upstream" approach to achieving health objectives.

The current feasibility results do not allow for an evaluation of the duration of effects. Prior studies showed a persistent reduction in symptoms of insomnia at 1 month after HIRREM completion[13] and a clinically relevant reduction in probability of headache at 2 months after HIRREM completion in a cohort with episodic migraine.[30] Future controlled trials should include a delay in collection of primary outcomes to allow for resolution of placebo effect and to assess duration of benefits.

CONCLUSIONS

Recent null findings from studies of "alternative" techniques for reducing menopausal symptoms have led to a sense of frustration.[31] The data from this exploratory study suggest that HIRREM merits further study in controlled trials with longer follow-up to support the brain adaptation process undergone by women in menopause.

REFERENCES

1. Williams RE, Kalilani L, DiBenedetti DB, et al. Frequency and severity of vasomotor symptoms among peri- and postmenopausal women in the United States. *Climacteric* 2008;11:32–43.
2. Ensrud KE, Stone KL, Blackwell TL, et al. Frequency and severity of hot flashes and sleep disturbance in postmenopausal women with hot flashes. *Menopause* 2009;16:286–292.
3. Williams RE, Levine KB, Kalilani L, Lewis J, Clark RV. Menopause-specific questionnaire assessment in US population–based study shows negative impact on health-related quality of life. *Maturitas* 2009;62:153–159.
4. Avis NE, Crawford S, Stellato R, Longcope C. Longitudinal study of hormone levels and depression among women transitioning through menopause. *Climacteric* 2001;4:243–249.
5. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701–1712.
6. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321–333.
7. Innes KE, Selfe TK, Vishnu A. Mind-body therapies for menopausal symptoms: a systematic review. *Maturitas* 2010;66:135–149.
8. Freedman RR, Woodward S. Behavioral treatment of menopausal hot flushes: evaluation by ambulatory monitoring. *Am J Obstet Gynecol* 1992;167:436–439.
9. Newton KM, Reed SD, Guthrie KA, et al. Efficacy of yoga for vasomotor symptoms: a randomized controlled trial. *Menopause* 2014;21:339–346.

10. Kadakia KC, Loprinzi CL, Barton DL. Hot flashes: the ongoing search for effective interventions. *Menopause* 2012;19:719–721.

11. Deecher DC, Dorries K. Understanding the pathophysiology of vasomotor symptoms (hot flushes and night sweats) that occur in perimenopause, menopause, and postmenopause life stages. *Arch Womens Ment Health* 2007;10:247–257.

12. Rossmanith WG, Ruebberdt W. What causes hot flushes? The neuroendocrine origin of vasomotor symptoms in the menopause. *Gynecol Endocrinol* 2009;25:303–314.

13. Tegeler CH, Kumar SR, Conklin D, et al. Open label, randomized, crossover pilot trial of high-resolution, relational, resonance-based, electroencephalic mirroring to relieve insomnia. *Brain Behav* 2012;2:814–824.

14. Campbell IG, Bromberger JT, Buysse DJ, et al. Evaluation of the association of menopausal status with δ and β EEG activity during sleep. *Sleep* 2011;34:1561–1568.

15. Gerdes L, Gerdes P, Lee SW, Tegeler H. HIRREM: a noninvasive, allostatic methodology for relaxation and auto-calibration of neural oscillations. *Brain Behav* 2013;3:193–205.

16. Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl H. Methodologic lessons learned from hot flash studies. *J Clin Oncol* 2001;19:4280–4290.

17. Morin CM, Barlow DH, Dement WC. *Insomnia: Psychological Assessment and Management*. New York, NY: Guilford Press; 1993.

18. Morin CM, Belleville G, Belanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* 2011;34:601–608.

19. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* 2001;2:297–307.

20. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychol Meas* 1977;1:385–401.

21. Smarr KL. Measures of depression and depressive symptoms: the Beck Depression Inventory (BDI), Center for Epidemiological Studies—Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and Primary Care Evaluation of Mental Disorders—Mood Module (PRIME-MD). *Arthritis Care Res* 2003; 49:S134–S146.

22. Devins GM, Orme CM, Costello G, et al. Measuring depressive symptoms in illness populations: Reliability and factorial composition of the Center for Epidemiological Studies Depression (CES-D) scale. *Psychol Health* 1988;2:139–156.

23. Hann D, Winter K, Jacobsen P. Measurement of depressive symptoms in cancer patients: evaluation of the Center for Epidemiological Studies Depression Scale (CES-D). *J Psychosom Res* 1999;46:437–443.

24. Swihart BJ, Caffo B, James BD, Strand M, Schwartz BS, Punjabi NM. Lasagna plots: a saucy alternative to spaghetti plots. *Epidemiology* 2010;21:621–625.

25. R Core Team. *R: A Language and Environment for Statistical Computing [Computer Program]*. Vienna, Austria: R Foundation for Statistical Computing; 2013.

26. Freedman RR. Menopausal hot flashes: mechanisms, endocrinology, treatment. *J Steroid Biochem Mol Biol* 2014;142C:115–120.

27. Freedman RR, Woodward S, Sabharwal SC. α2-Adrenergic mechanism in menopausal hot flushes. *Obstet Gynecol* 1990;76:573–578.

28. Perlis ML, Merica H, Smith MT, Giles DE. β EEG activity and insomnia. *Sleep Med Rev* 2001;5:363–374.

29. Thurston RC, Christie IC, Matthews KA. Hot flashes and cardiac vagal control during women's daily lives. *Menopause* 2012;19:406–412.

30. Tegeler CH, Tegeler CL, Kumar SR, et al. Randomized, placebo-controlled pilot trial of a novel, noninvasive electroencephalic feedback-based intervention, HIRREM, for alleviation of episodic migraines. Cephalalgia: Abstracts of the 2013 International Headache Conference, June 27, 2013.

31. Richardson MK. Menopause Strategies: Finding Lasting Answers for Symptoms and Health: eliminating hot flashes—still not a slam dunk! *Menopause* 2014;21:321–322.