Menopausal hot flashes and the default mode network

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Objective: To test whether more physiologically assessed hot flashes were associated with more connectivity in the default mode network (DMN), the network of brain regions active during rest. We particularly focus on DMN networks supporting the hippocampus as this region is rich in estrogen (E) receptors (ER) and has previously been linked to hot flashes.
Design: Women underwent 24 hours of physiologic and diary hot flash monitoring, functional magnetic resonance imaging (MRI), 72 hours of sleep actigraphy monitoring, a blood draw, questionnaires, and physical measures.
Setting: University medical center.
Patient(s): Twenty midlife women aged 40–60 years who had their uterus and both ovaries and were not taking hormone therapy (HT).
Intervention(s): None.
Main Outcome Measure(s): The DMN functional connectivity.
Result(s): Controlling for age, race, and education, more physiologically-monitored hot flashes were associated with greater DMN connectivity (beta, B [SE] = 0.004 [0.002]), particularly hippocampal DMN connectivity (B [SE] = 0.005 [0.002]). Findings were most pronounced for sleep physiologic hot flashes (with hippocampal DMN, B [SE] = 0.02 [0.007]). Associations also persisted controlling for sleep, depressive symptoms, and serum E_2 concentrations.
Conclusion(s): More physiologically-monitored hot flashes were associated with more DMN connectivity, particularly networks supporting the hippocampus. Findings were most pronounced for sleep hot flashes. Findings underscore the importance of continued investigation of the central nervous system in efforts to understand this classic menopausal phenomenon. (Fertil Steril® 2015;103:1572–8. ©2015 by American Society for Reproductive Medicine.)
Key Words: Hot flashes, vasomotor symptoms, brain, hippocampus, default mode network

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Hot flashes are the classic symptom of the menopausal transition, experienced by more than 70% of women at some point during the menopausal transition (1). Hot flashes are associated with impairments in quality of life (2), depressed mood (3), reported sleep disturbance (4), and possibly even poorer memory function (5). Hot flashes are a leading driver of medical treatment-seeking at midlife for women (6, 7).

Despite their prevalence and impact on women's lives, the understanding of the physiology of hot flashes remains incompletely understood. Leading models conceptualize hot flashes as originating in the central nervous system (8), yet there has been limited data investigating relations between the brain and hot flashes. Some data support changes in brain regions associated with awareness of bodily sensation, such as the insula and prefrontal cortex, acutely during hot flashes and the involvement of brainstem areas in the triggering of hot flashes (9, 10). However, little research has investigated brain network differences associated with hot flashes.

Hot flashes occur in the context of estrogen (E) withdrawal, and the effects of E on brain structure and function in humans remains controversial (11, 12). However, some prior studies (13–15) have suggested decrements in verbal memory during the perimenopause, a time when hot flashes are common. Although subjective hot flashes have not been associated with cognitive function, physiologically-measured hot

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flashes, particularly those occurring during sleep, have been linked to poorer verbal memory performance (5). Furthermore, brain regions involved in verbal memory including the hippocampus and prefrontal cortex are rich in E receptors (ER) (16, 17). Acute doses of E_2 are associated with greater functional connectivity between the hippocampus and the prefrontal cortex (18).

The default mode network (DMN) is a recently discovered network of brain regions that are active during rest in the absence of external stimuli (19, 20). Activity of this neural network is distributed across brain regions and occurs spontaneously. Suppression of the DMN is associated with better memory formation, and less suppression of the DMN predicts poorer attention to later tasks (21, 22). The DMN appears to be involved in a range of psychiatric and medical conditions, and DMN hyperactivity appears characteristic of major depressive disorder (23).

We tested whether self-reported and physiologically assessed hot flashes were associated with altered functional connectivity in the DMN, particularly networks supporting the hippocampus. We hypothesized that a higher frequency of physiologically assessed (but not self-reported) hot flashes would be associated with greater functional connectivity in the DMN, particularly networks supporting the hippocampus. We tested these hypotheses in a sample of midlife women who underwent brain imaging and detailed ambulatory physiologic hot flash monitoring. Physiologic assessment of hot flashes is particularly important to testing relations between hot flashes and the brain, as prior work has indicated that it is physiologically-detected hot flashes rather than self-reported hot flashes that are most related to cognition (5) and peripheral nervous system physiology (24, 25).

MATERIALS AND METHODS

Study Sample

Twenty women who were a subsample of a larger parent study of 300 women focused on menopause and cardiovascular function underwent brain imaging. At study entry, 9 women reported having daily hot flashes and 11 reported having no hot flashes in the past 6 months. Parent study inclusion criteria included being age 40–60 years; having a uterus and at least one ovary; not pregnant; being late perimenopausal (amenorrhea, >2–<12 months) or postmenopausal status (amenorrhea, ≥12 months) in accordance with STRAW+10 criteria (26); without a history of heart disease, stroke, arrhythmia, or breast cancer; and not taking hormone therapy (HT), selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitor antidepressants, clonidine, beta blockers, calcium channel blockers, gabapentin, or insulin within 3 months. Additional criteria for inclusion in the brain imaging substudy included no metal in the body and no history of chronic migraines, concussion, stroke, brain injury, dementia, or Parkinson's disease. Of the 20 women who underwent the brain imaging protocol, one woman completed only part of the imaging protocol due to time limitations and an additional subject experienced hot flash monitor failure; therefore 18 women are included in these analyses.

Design and Procedures

The parent study protocol included anthropometric measures, questionnaires, blood specimens, and a 3-day ambulatory hot flash and actigraphy sleep assessment protocol. Women in the brain imaging substudy additionally underwent magnetic resonance imaging (MRI) on a separate day. Procedures were approved by the University of Pittsburgh Institutional Review Board. All participants provided written informed consent.

Hot Flashes

Hot flash monitoring was conducted with an ambulatory sternal skin conductance monitor and an electronic diary. Sternal skin conductance was recorded with the VU-AMS monitor, a portable device worn in a pouch around the waist. This device measures sternal skin conductance sampled at 1 Hz from the sternum with a 0.5-V constant voltage circuit passed between two Ag/AgCl electrodes (UFI) filled with 0.05 M KCl Velvachol/glycol paste (27). Participants were instructed to avoid exercising and showering during monitoring. Physiologic hot flashes were classified by standard methods, with a skin conductance increase of 2 μmho in 30 seconds (28) flagged automatically by UFI software (DPSv3.6) and edited for artifact (29). Given that some women show submaximal hot flashes failing to reach the 2-μmho criterion (30, 31), all potential hot flash events were also visually inspected, and events showing the characteristic hot flash pattern of <2 μmho/30 s increase were coded as hot flashes. This coding has been shown to be reliable ($\kappa = 0.86$) (30, 31). A 20-minute lockout period was implemented after the start of the flash during which no hot flashes were coded. To report hot flashes, participants were instructed to [1] complete a portable electronic diary (Palm Z22; Palm, Inc.) during waking hours and [2] press event mark buttons on their wrist actigraph and hot flash monitor (waking and sleeping hours) when experiencing a hot flash.

MRI Acquisition

Imaging data were collected at the University of Pittsburgh Magnetic Resonance Research Center (MRRC) using a 3-T Siemens Trio machine and a 12-channel Siemens head coil. A standard high-resolution T_1-weighted volumetric magnetization prepared rapid gradient echo scans (MPRAGE) sequence was acquired in axial orientation (160 slices, 256 × 240, 1 mm isotropic). For the resting state scan, T_2^*-weighted BOLD acquisition was done using a gradient-echo echo planar imaging sequence: TR = 2,000 milliseconds, TE = 34 milliseconds, matrix = 128 × 128 × 29, voxel size = 2 × 2 × 3 mm^3, oblique axial acquisition, integrated parallel acquisition techniques = 2. Images were acquired during 5 minutes (150 volumes). Subjects were instructed to lie still with their eyes open, look at a fixation cross, think of nothing in particular, and not to fall asleep.

MRI Processing

A seed-based region of interest (ROI) analysis method was carried out in SPM8 (Wellcome Department of Imaging

Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Resting state functional images were slice time corrected, realigned, normalized to MNI space (using the MPRAGE), spatially smoothed with a 6-mm kernel, and temporally band-pass filtered (0.009 of 0.08 Hz). Functional connectivity analysis was performed using a seed-driven approach with the Conn toolbox (32). A component-based noise correction method (aCompCor) was used to remove physiologic and other spurious sources of noise (33). In addition, significant principle components of the signals from white matter and cerebrospinal fluid regions were removed together with movement-related covariates. The REX (http://web.mit.edu/swg/software.htm) was used to extract the primary eigenvariate time-series of each ROI and then the Conn toolbox was used to extract network connectivity strength for the DMN, using the ROIs defined by Tzourio-Mazoye et al. (34). These ROIs include the medial prefrontal cortex, anterior cingulate cortex, orbitofrontal cortex, superior frontal gyrus, midcingulate cortex, posterior cingulate cortex, precuneus, angular gyrus, thalamus, and hippocampus. A correlation map was produced for each subject by extracting the residual BOLD time course from the ROIs and computing Pearson's correlation coefficients between that time course and the time course of all other voxels. Correlation coefficients were converted to normally distributed z-scores using Fisher's transform. The mean DMN strength was defined as the mean z score across all nodes of the DMN. The mean hippocampal DMN score was the mean z score for connectivity between the hippocampus and all the other nodes of the DMN.

Sleep

Participants wore a wrist actigraph and completed a sleep diary each day during the monitoring period. Actigraphy data were collected with a Minimitter Actiwatch-2 (Respironics, Inc.) in 1-minute epochs and analyzed with the Actiware (version 6.0.1) software program. Sleep diary data for bedtime and rise time were entered for calculation of sleep–wake variables. Actigraphy outcome variables included total sleep time (within the bedtime and rise time interval), sleep latency (bedtime to first sleep period), wakefulness after sleep onset (total minutes of wakefulness between sleep onset and final wake time), and sleep efficiency (100% * total sleep time/time in bed). Participants also completed the Pittsburgh Sleep Quality Index (35), a well-validated questionnaire measure of sleep quality.

Covariates

Demographics, menstrual history, and health behaviors were assessed by questionnaires and interview. Menopausal status was obtained from reported bleeding patterns, categorized as perimenopausal (amenorrhea, >2–<12 months), or postmenopausal (amenorrhea, ≥12 months). Race/ethnicity was self-reported by the participant. Education was assessed as years of completed education and due to small cell sizes was classified as less than or more than a college degree for analysis. Depressive symptoms were assessed by the Center for Epidemiologic Studies Depression Scale (36) and trait anxiety via the Spielberger State-Trait Anxiety Inventory (37). Concentrations of E_2 were obtained from a morning fasting blood sample and assessed using liquid chromatography–tandem mass spectrometry, with interassay and intra-assay coefficients of variation (CV) of 5.0% and 8.1%, respectively, and a lower limit of detection of 0.5 pg/mL.

Statistical Analysis

Variables were examined for distributions, outliers, and cell sizes. Average DMN was log and square transformed due to skew. To account for variations in monitoring times, hot flash rates were calculated, with the number of hot flashes (either physiologically-detected or self-reported) divided by monitoring time and standardized to a 24-hour period. Hot flash rates were set to 0 for women without hot flashes. Associations between hot flashes and DMN variables were tested in linear regression models, controlling for a priori selected covariates age, race/ethnicity, and education. Additional covariates depressive symptoms, trait anxiety, and E_2 concentrations were separately added into multivariable models in secondary models. All tests were two-tailed with an alpha set to 0.05. Analyses were conducted using SAS v9.4 (SAS Institute).

RESULTS

Participants were on average 55 years old and approximately a quarter of the women were African American, with the remainder non-Hispanic white (Table 1). Most of the women (85%) were postmenopausal. Nine women reported having

TABLE 1

Sample characteristics.

Characteristic	Data
N	18
Age (y), mean (± SD)	54.9 (3.5)
Race, N (%)	
White	13 (72.2)
Nonwhite	5 (27.8)
Education, N (%)	
<College	6 (33.3)
≥College	12 (66.7)
Menopause status, N (%)	
Perimenopausal	3 (16.7)
Postmenopausal	17 (83.3)
BMI (kg/m^2), mean (± SD)	29.0 (4.9)
CESD score, mean (± SD)	7.6 (7.7)
Trait anxiety, mean (± SD)	32.1 (8.6)
Serum E_2 (pg/mL), mean (± SD)	10.9 (16.9)
Actigraphy-assessed sleep time (h), mean (± SD)	6.3 (1.3)
Physiologic hot flash rate, mean (± SD)	
24 h	7.2 (6.6)
Wake[a]	5.3 (5.5)
Sleep[a]	1.9 (1.9)
Self-report hot flash rate, mean (± SD)	
24 h	2.3 (2.9)
Wake[a]	1.5 (2.2)
Sleep[a]	0.7 (0.8)

Note: BMI = body mass index; CESD = Center for Epidemiologic Studies Depression; N = number of patients.

[a] Standardized to sleep and wake periods of 17 and 7 h, respectively, for ease of interpretation.

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hot flashes, yet on physiologic monitoring 15 women showed physiologic hot flashes, a finding that is consistent with prior findings that women tend to under-report hot flashes relative to physiologic monitoring (38). For the sample as a whole, women reported an average of two hot flashes/24 hours, and showed seven hot flashes/24 hours on physiologic monitoring.

We first tested the relation between hot flashes and DMN connectivity. More physiologic hot flashes were associated with greater total DMN connectivity, as well as greater hippocampal DMN connectivity (Table 2; Fig. 1; Supplemental Fig. 1, available online). Associations were most pronounced for the left hippocampus and for physiologic hot flashes occurring during sleep, and associations persisted after covarying for age, race, and education. We next examined relations between hot flashes and a priori selected frontal–hippocampal connectivity, finding that physiologically-monitored sleep hot flashes were positively associated with connectivity in five of the six regions in multivariable models (Table 3). No significant associations were observed between self-reported hot flashes and DMN connectivity.

Given that relations between hot flashes and DMN connectivity were observed most strongly for sleep hot flashes, we examined whether sleep characteristics accounted for observed relations. None of the relations between hot flashes and DMN connectivity were accounted for by the sleep variables assessed, including sleep time, sleep efficiency, wake after sleep onset, or questionnaire-sleep quality (e.g., relations between physiologic sleep flashes and DMN outcome controlling for actigraphy assessed sleep time, for total DMN: B [SE] = 0.01 [0.006], P=.048; hippocampal DMN: B [SE] = 0.02 [0.007], P=.01; left hippocampal DMN: B [SE] = 0.03 [0.009], P=.007). Notably, the sleep indices were weakly or largely unrelated to the DMN outcomes (data not shown).

We considered several additional analyses. In models of relations between physiologic hot flashes and DMN outcomes, we additionally adjusted for covariates such as depressive symptoms, trait anxiety, and serum E_2 concentrations. Results were unchanged (data not shown).

DISCUSSION

This study was the first to investigate the relation between menopausal hot flashes and resting state connectivity, showing that more physiologically-monitored hot flashes (but not self-reported hot flashes) were associated with greater activity in the DMN. Findings were most striking for DMN connectivity to the hippocampus. In addition, relations were most pronounced for physiologically-monitored hot flashes occurring during sleep as compared with waking.

The DMN is an organized network in the brain that is active during rest. Data indicate that hyperconnectivity and hyperactivity of the DMN, as well failure to deactivate components of the DMN, is associated with maladaptive emotional states such as major depressive disorder (23, 39). Elevated DMN activity has also been linked to rumination (23), and alterations in DMN activity have been linked to chronic pain (40) and possibly insomnia (41). It is notable that these findings were for physiologically-assessed hot flashes and not subjectively-experienced hot flashes, arguing against a purely symptom-perception or somatic focus explanation of links between hot flashes and the DMN. In addition, depressive and anxious symptoms were measured and did not account for observed associations. Notably, suppression of the DMN is associated with better memory formation (21, 22). However, why the DMN is linked to hot flashes is not entirely clear and requires further investigation.

The current study pointed to DMN connectivity to the hippocampus, in particular as related to hot flashes. A numerous literature indicates that the hippocampus may be sensitive to changing E levels in the menopause transition and possibly to hot flashes (42). The abrupt declines in endogenous E_2 that mark the menopause transition may negatively impact the hippocampus, which is a region rich in ERs (16). Memory problems are a leading cognitive change that women report during the menopause transition; in one study (43) 60% of women transitioning through the menopause reporting unfavorable memory changes. Reproductive hormones may be important to these relations. A longitudinal study of women transitioning through the menopause indicated that perimenopausal women who used HT had improved verbal

TABLE 2

Relation between hot flashes and default mode network activity.

	Average DMN[d]	Average hippocampal DMN	Average left hippocampal DMN	Average right hippocampal DMN
Hot flash rate	**B (SE)**	**B (SE)**	**B (SE)**	**B (SE)**
Physiologic				
24 h	0.004 (0.002)[b]	0.005 (0.002)[b]	0.006 (0.003)[b]	0.004 (0.003)
Sleep	0.01 (0.006)[b]	0.02 (0.007)[c]	0.03 (0.008)[c]	0.02 (0.01)
Wake	0.004 (0.002)[b]	0.005 (0.003)	0.006 (0.003)[a]	0.005 (0.003)
Self-report				
24 h	0.00006 (0.005)	0.0007 (0.006)	0.002 (0.007)	−0.0007 (0.008)
Sleep	0.002 (0.02)	0.004 (0.02)	0.01 (0.02)	−0.005 (0.03)
Wake	−0.0003 (0.006)	0.0005 (0.008)	0.002 (0.010)	−0.0006 (0.01)

Note: Covariates are age, race, education. DMN = default mode network.
[a] P< .10.
[b] P< .05.
[c] P< .01.
[d] Log transformed.

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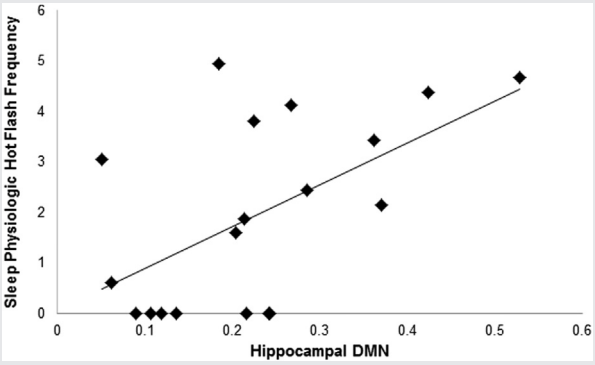
FIGURE 1



Scatterplot of relation between sleep physiologic hot flashes and hippocampal default mode network. Values of horizontal axis represent mean of the normalized correlations between the hippocampus and all the other nodes of the default mode network.

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memory and increased activation in the left hippocampus during this memory task relatively to their counterparts who had never used HT (11). Furthermore, experimental suppression of the reproductive axis in young women results in changes in verbal memory encoding, which can be restored with restoration of ovarian function (44, 45). Finally, prior work has shown more overnight physiologic hot flashes related to poorer verbal memory function (5). This body of literature points to adverse changes in the hippocampus and the functions it serves during the menopause transition and with its characteristic symptoms. Our findings for hippocampal DMN connectivity and hot flashes are consistent with this work. However, it is notable that endogenous E_2 concentrations, measured with state of the art methods, did not account for these relations, suggesting that other physiologic processes, such as hypothalamic-pituitary-adrenal axis activity linked to both hot flashes and hippocampal function, may be important to investigate in future research on hot flashes and DMN activity.

Findings were most pronounced for physiologically-monitored hot flashes, particularly hot flashes during sleep compared with those during waking hours. These findings are consistent with other research showing that physiologically-monitored hot flashes, rather than self-reported hot flashes, were associated with verbal memory (5). Physiologically-monitored hot flashes differ from self-reported hot flashes in several important ways. Like the results observed, most studies that use physiologic hot flash measures in the ambulatory setting detect more hot flashes than are reported (5, 25, 38). Although these measures merit continued refinement for use in large studies (46), physiologic hot flash measures have the advantage of not relying on attention, perception of hot flashes, emotional influences on hot flash perceptions, or adherence to reporting (47, 48). These issues are particular prominent in the ambulatory setting when distracting factors, emotional experiences, and competing activities are common. Physiologic hot flashes show a circadian rhythm (49) and may be more related to other physiologic indices such as cardiac vagal control than are self-reported hot flashes (24, 25). Physiologic hot flash measures may be particularly useful for measuring hot flashes during sleep, when hot flash reporting may be particularly difficult and influenced by the quality of sleep itself (50, 51).

Notably, in the present study the strongest associations were for hot flashes detected during sleep. Why associations between hot flashes and DMN connectivity were most pronounced for sleep rather than waking hot flashes is not entirely clear, but these findings are consistent with prior work showing overnight hot flashes most related to verbal memory (5). The associations between sleep physiologic hot flashes and DMN connectivity were not accounted for by sleep characteristics such as sleep time, waking during the night, or subjective sleep quality, broadly consistent with prior work (5). In fact, sleep indices were weakly or unrelated to DMN connectivity in this study. Whether sleep hot flashes (aka "night sweats") and waking hot flashes have different underlying physiologies is not known, although it is notable that other work has found that reductions in cardiac vagal control with hot flashes were particularly large for sleep physiologic hot flashes (25). Furthermore, investigation of the unique role of sleeping hot flashes in relation to brain function is warranted with more intensive measures (e.g., polysomnography) of sleep.

This study has several limitations. The main limitation of the study was its small size, which may have limited power to detect associations, although it is notable that such consistent findings were noted between DMN activity and hot flashes

TABLE 3

Relation between physiologically-monitored hot flashes and specific dorsal DMN regions.

	MPC-ACC-OC—LH	MPC-ACC-OC—RH	RSFG—LH	RSFG—RH	MCC—LH	MCC—RH
Physiological hot flash rate	**B (SE)**	**B (SE)**	**B (SE)**	**B (SE)**	**B (SE)**	**B (SE)**
24 h	0.008 (0.009)	0.01 (0.006)[b]	0.008 (0.008)	0.003 (0.006)	0.02 (0.006)[b]	0.009 (0.006)
Sleep	0.06 (0.03)[b]	0.07 (0.02)[c]	0.06 (0.02)[b]	0.03 (0.02)	0.08 (0.02)[c]	0.05 (0.02)[b]
Wake	0.004 (0.01)	0.01 (0.008)	0.006 (0.009)	0.0009 (0.007)	0.02 (0.008)[a]	0.008 (0.007)

Note: Covariates are age, race, education. DMN = default mode network; LH = left hippocampus; MCC = midcingulate cortex; MPC-ACC-OC = medial prefrontal cortex, anterior cingulate cortex, orbitofrontal cortex; RH = right hippocampus; RSFG = right superior frontal gyrus.

[a] $P<.10$.
[b] $P<.05$.
[c] $P<.01$.

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despite this small sample. However, these findings should be replicated in future work. Primarily postmenopausal women were included here and thereby any differences by menopausal stage could not be investigated. Although the sleep measures used were extensive, future work should further expand the sleep battery given the particular importance of nocturnal hot flashes.

This study had several strengths. This is the first study to investigate resting state connectivity in relation to menopausal hot flashes. Hot flashes were investigated via rigorous methods: physiologic monitoring and prospective diary report and during wake and sleep as a woman went about her daily activity. These methods allowed investigation of any similarities or differences in the patterns of associations across indices and states. Sleep was measured by actigraphy, an improvement over prior work that has largely used self-reported sleep. In addition, other related important indices, including depression, anxiety, and rigorously-measured endogenous E_2 concentrations were assessed and their roles considered.

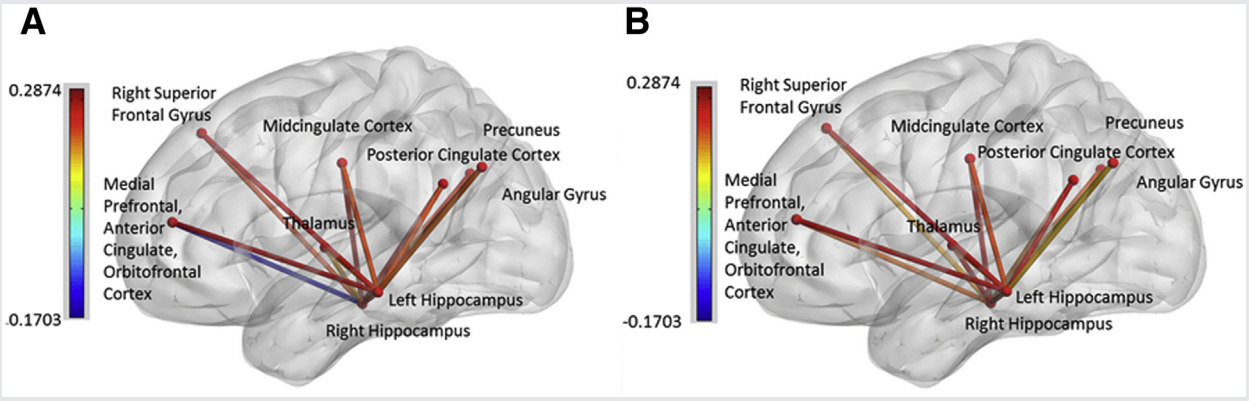
In conclusion, more menopausal hot flashes were associated with greater DMN connectivity, particularly to the hippocampus. These associations were most pronounced for physiologically-monitored hot flashes occurring during sleeping hours. As opposed to prior work showing changes in brain function acutely during hot flashes, the current data support differences in DMN connectivity that distinguish women with varying degrees of hot flash burden. Most investigations have focused on peripheral physiology in attempting to understand the physiology of hot flashes. These findings underscore the importance of continued investigation of central nervous system function in considering the propensity toward and underlying physiology of hot flashes.

REFERENCES

1. Gold E, Colvin A, Avis N, Bromberger J, Greendale G, Powell L, et al. Longitudinal analysis of vasomotor symptoms and race/ethnicity across the menopausal transition: study of Women's Health Across the Nation (SWAN). Am J Public Health 2006;96:1226–35.
2. Avis NE, Colvin A, Bromberger JT, Hess R, Matthews KA, Ory M, et al. Change in health-related quality of life over the menopausal transition in a multiethnic cohort of middle-aged women: study of Women's Health Across the Nation. Menopause 2009;16:860–9.
3. Bromberger JT, Matthews KA, Schott LL, Brockwell S, Avis NE, Kravitz HM, et al. Depressive symptoms during the menopausal transition: the Study of Women's Health Across the Nation (SWAN). J Affect Disord 2007;103:267–72.
4. Kravitz HM, Zhao X, Bromberger JT, Gold EB, Hall MH, Matthews KA, et al. Sleep disturbance during the menopausal transition in a multi-ethnic community sample of women. Sleep 2008;31:979–90.
5. Maki PM, Drogos LL, Rubin LH, Banuvar S, Shulman LP, Geller SE. Objective hot flashes are negatively related to verbal memory performance in midlife women. Menopause 2008;15:848–56.
6. Nicholson WK, Ellison SA, Grason H, Powe NR. Patterns of ambulatory care use for gynecologic conditions: a national study. Am J Obstet Gynecol 2001;184:523–30.
7. Williams RE, Kalilani L, DiBenedetti DB, Zhou X, Fehnel SE, Clark RV. Healthcare seeking and treatment for menopausal symptoms in the United States. Maturitas 2007;58:348–58.
8. Freedman RR. Menopausal hot flashes: mechanisms, endocrinology, treatment. J Steroid Biochem 2014;142:115–20.
9. Diwadkar VA, Murphy ER, Freedman RR. Temporal sequencing of brain activations during naturally occurring thermoregulatory events. Cereb Cortex 2014;24:3006–13.
10. Freedman RR, Benton MD, Genik RJ 2nd, Graydon FX. Cortical activation during menopausal hot flashes. Fertil Steril 2006;85:674–8.
11. Maki PM, Resnick SM. Longitudinal effects of estrogen replacement therapy on PET cerebral blood flow and cognition. Neurobiol Aging 2000;21:373–83.
12. Wnuk A, Korol DL, Erickson KI. Estrogens, hormone therapy, and hippocampal volume in postmenopausal women. Maturitas 2012;73:186–90.
13. Epperson CN, Sammel MD, Freeman EW. Menopause effects on verbal memory: findings from a longitudinal community cohort. J Clin Endocrinol Metab 2013;98:3829–38.
14. Greendale GA, Huang MH, Wight RG, Seeman T, Luetters C, Avis NE, et al. Effects of the menopause transition and hormone use on cognitive performance in midlife women. Neurology 2009;72:1850–7.
15. Weber MT, Maki PM, McDermott MP. Cognition and mood in perimenopause: a systematic review and meta-analysis. J Steroid Biochem 2014;142:90–8.
16. Ishunina TA, Fischer DF, Swaab DF. Estrogen receptor alpha and its splice variants in the hippocampus in aging and Alzheimer's disease. Neurobiol Aging 2007;28:1670–81.
17. Osterlund MK, Gustafsson JA, Keller E, Hurd YL. Estrogen receptor beta (ER-beta) messenger ribonucleic acid (mRNA) expression within the human forebrain: distinct distribution pattern to ERalpha mRNA. J Clin Endocrinol Metab 2000;85:3840–6.
18. Ottowitz WE, Siedlecki KL, Lindquist MA, Dougherty DD, Fischman AJ, Hall JE. Evaluation of prefrontal-hippocampal effective connectivity following 24 hours of estrogen infusion: an FDG-PET study. Psychoneuroendocrinology 2008;33:1419–25.
19. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proceedings of the National Academy of Sciences of the United States of America 2005;102:9673–8.
20. Raichle ME. A paradigm shift in functional brain imaging. J Neurosci 2009;29:12729–34.
21. Daselaar S, Prince S, Cabeza R. When less means more: deactivations during encoding that predict subsequent memory. Neuroimage 2004;23:921–7.
22. Daselaar S, Prince S, Dennis N, Hayes S, Kim H, Cabeza R. Posterior midline and ventral parietal activity is associated with retrieval success and encoding failure. Front Hum Neurosci 2009;3:1–10.
23. Whitfield-Gabrieli S, Ford JM. Default mode network activity and connectivity in psychopathology. Annu Rev Clin Psychol 2012;8:49–76.
24. Thurston RC, Christie IC, Matthews KA. Hot flashes and cardiac vagal control: a link to cardiovascular risk? Menopause 2010;17:456–61.
25. Thurston C, Christie I, Matthews K. Hot flashes and cardiac vagal control during women's daily lives. Menopause 2012;19:406–12.
26. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, et al. Executive Summary of the Stages of Reproductive Aging Workshop (STRAW) + 10: addressing the Unfinished Agenda of Staging Reproductive Aging. J Clin Endocrinol Metab 2012;97:1159–68.
27. Dormire SL, Carpenter JS. An alternative to Unibase/glycol as an effective nonhydrating electrolyte medium for the measurement of electrodermal activity. Psychophysiology 2002;39:423–6.
28. Freedman RR. Laboratory and ambulatory monitoring of menopausal hot flashes. Psychophysiology 1989;26:573–9.
29. Carpenter JS, Andrykowski MA, Freedman RR, Munn R. Feasibility and psychometrics of an ambulatory hot flash monitoring device. Menopause 1999;6:209–15.
30. Thurston R, Matthews K, Hernandez J, de la Torre F. Improving the performance of physiologic hot flash measures with support vector machines. Psychophysiology 2009;46:285–92.
31. Thurston R, Hernandez J, del Rio J, de la Torre F. Support vector machines to improve physiologic hot flash measures: application to the ambulatory setting. Psychophysiology 2011;48:1015–21.

32. Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect 2012;2:125–41.
33. Behzadi Y, Restom K, Liau J, Liu TT. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. Neuroimage 2007;37:90–101.
34. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 2002;15:273–89.
35. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213.
36. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385–401.
37. Spielberger CD. Manual for the State-Trait Anxiety Inventory. Palo Alto: Consulting Psychologists Press; 1983.
38. Mann E, Hunter MS. Concordance between self-reported and sternal skin conductance measures of hot flushes in symptomatic perimenopausal and postmenopausal women: a systematic review. Menopause 2011;18:709–22.
39. Rive MM, van Rooijen G, Veltman DJ, Phillips ML, Schene AH, Ruhe HG. Neural correlates of dysfunctional emotion regulation in major depressive disorder. A systematic review of neuroimaging studies. Neurosci Biobehav Rev 2013;37:2529–53.
40. Farmer MA, Baliki MN, Apkarian AV. A dynamic network perspective of chronic pain. Neurosci Lett 2012;520:197–203.
41. Picchioni D, Duyn JH, Horovitz SG. Sleep and the functional connectome. Neuroimage 2013;80:387–96.
42. Greendale GA, Derby CA, Maki PM. Perimenopause and cognition. Obstet Gynecol Clin North Am 2011;38:519–35.
43. Woods NF, Mitchell ES, Adams C. Memory functioning among midlife women: observations from the Seattle Midlife Women's Health Study. Menopause 2000;7:257–65.
44. Craig MC, Fletcher PC, Daly EM, Rymer J, Brammer M, Giampietro V, et al. Reversibility of the effects of acute ovarian hormone suppression on verbal memory and prefrontal function in pre-menopausal women. Psychoneuroendocrinology 2008;33:1426–31.
45. Craig MC, Fletcher PC, Daly EM, Rymer J, Cutter WJ, Brammer M, et al. Gonadotropin hormone releasing hormone agonists alter prefrontal function during verbal encoding in young women. Psychoneuroendocrinology 2007;32:1116–27.
46. Miller HG, Li RM. Measuring hot flashes: summary of a National Institutes of Health workshop. Mayo Clin Proc 2004;79:777–81.
47. Hunter MS, Mann E. A cognitive model of menopausal hot flushes and night sweats. J Psychosom Res 2010;69:491–501.
48. Thurston RC, Blumenthal JA, Babyak MA, Sherwood A. Emotional antecedents of hot flashes during daily life. Psychosom Med 2005;67:137–46.
49. Freedman RR, Norton D, Woodward S, Cornelissen G. Core body temperature and circadian rhythm of hot flashes in menopausal women. J Clin Endocrinol Metab 1995;80:2354–8.
50. Thurston RC, Santoro N, Matthews KA. Are vasomotor symptoms associated with sleep characteristics among symptomatic midlife women? Comparisons of self-report and objective measures. Menopause 2012;19:742–8.
51. Thurston RC, Blumenthal JA, Babyak MA, Sherwood A. Association between hot flashes, sleep complaints, and psychological functioning among healthy menopausal women. Int J Behav Med 2006;13:163–72.

SUPPLEMENTAL FIGURE 1



Default mode network connectivity by physiologic hot flash frequency (median split). (**A**) None-low hot flashes; (**B**) medium-high hot flashes.

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