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