Psychoneuroendocrinology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Metabolic and hormone influences on emotion processing during menopause

Alison Berent-Spillson[a,*], Courtney Marsh[b], Carol Persad[a], John Randolph[c], Jon-Kar Zubieta[d], Yolanda Smith[c]

[a] Department of Psychiatry, University of Michigan, Ann Arbor, MI 48109, USA
[b] Department of Obstetrics & Gynecology, University of Kansas, Kansas City, KS 66160, USA
[c] Department of Obstetrics & Gynecology, University of Michigan, Ann Arbor, MI 48109, USA
[d] Department of Psychiatry, University of Utah, Salt Lake City, UT 84108, USA

ARTICLE INFO

Article history:
Received 23 April 2016
Received in revised form 29 July 2016
Accepted 30 August 2016
Available online xxx

Keywords:
Menopause
Perimenopause
Emotion regulation
fMRI
Metabolism

ABSTRACT

Disturbances of emotion regulation and depressive symptoms are common during the menopause transition. Reproductive hormone levels are not directly correlated with depressive symptoms, and other factors may influence mood symptoms during menopause. In this study, we sought to determine the role of metabolic function in mood symptoms during menopause, hypothesizing an association with menopause status and long-term glucose load. We studied 54 women across three menopause transition stages (15 premenopause, 11 perimenopause, and 28 postmenopause), examining effects of age, hormones, and metabolism on mood and neural activation during emotional discrimination. We assessed participants using behavioral and functional MRI measures of negative emotion and emotion discrimination, and glycated hemoglobin A1c, to assess long-term glucose load. We found that emotionally unpleasant images activated emotion regulation (amygdala) and cognitive association brain regions (prefrontal cortex, posterior cingulate, temporal-parietal-occipital (TPO) junction, hippocampus). Cognitive association region activity increased with menopause stage. Perimenopausal women had left TPO junction activation, and postmenopausal women had prefrontal cortex, posterior cingulate, and TPO junction activation. Negative affect was associated with decreased amygdala activation, while depression symptoms and negative mood were associated with increased TPO junction activation. Hemoglobin A1c was associated with negative interpretation bias of neutral images and cognitive region recruitment during emotion discrimination. FSH levels, indicating menopause stage, were associated with negative mood. Age was not associated with any behavioral measures or activation patterns during the emotion task. Our results suggest that an interaction between metabolic and hormonal factors may influence emotion regulation, leading to increased risk for depression during menopause.

1. Introduction

During the transition to menopause, fluctuating hormone levels contribute to a variety of symptoms across multiple systems. In addition to vascular and metabolic effects, variable estrogen concentrations can impact neurological regulation of cognitive and emotional function (Rettberg et al., 2014). Women are more susceptible to depression than men during all stages of life, and are at particular risk of developing depressive symptoms during the menopause transition (Cohen et al., 2006; Llaneza et al., 2012; Weber et al., 2013).

Changes in estrogen concentrations within the central nervous system have the most profound effects in regions with dense estrogen receptors, with corresponding effects on the functions regulated by those regions. Disregulated estrogen signaling can impact cognitive and mood functions regulated by prefrontal, hippocampal, amygdala, and cingulate regions, but can also promote compensatory use of alternative neural networks (Brinton et al., 2015). During the menopause transition, fluctuations in the lev-

* Corresponding author at: 2409 Rachel Upjohn Building, University of Michigan, 4250 Plymouth Rd. Ann Arbor, MI 48109, USA.
E-mail address: berent@umich.edu (A. Berent-Spillson).

http://dx.doi.org/10.1016/j.psyneuen.2016.08.026
0306-4530/

els of both estradiol and FSH have been associated with depressive symptoms (Brinton et al., 2015; Freeman et al., 2014, 2006). However, there is no direct association between circulating hormone concentrations and depression (Henderson et al., 2013; Ryan et al., 2009), suggesting that other factors may contribute to the increased risk of depression during the menopausal period (Gibbs et al., 2012). Unlike changes to cognitive function during menopause, which are likely mediated in part by age, there is no clear relationship between age or time past menopause and depression (Freeman et al., 2014; Henderson et al., 2013).

Metabolic disturbances (insulin resistance, metabolic syndrome, and diabetes) frequently accompany menopause (Carr, 2003; Janssen et al., 2008; Polotsky and Polotsky, 2010), and are independently associated with increased risk of mood disorders (McIntyre et al., 2009). In menopausal women, a higher BMI has been associated with depression, suggesting that a relationship between hormonal and metabolic factors may influence the development of depressive symptoms (Bromberger and Kravitz, 2011).

In the current study, we examined affective state, depressive symptoms, and neural activation driving emotion response, in the context of the hormonal and metabolic environments of women spanning the menopause transition. We expected to find differing patterns of neural network activation during an emotion task across the menopause stages. We hypothesized that premenopausal women would have the greatest activation in the emotion regulating amygdala region, with increasing activation of compensatory cognitive association regions (hippocampus, parietal/temporal/occipital (PTO) junction) in the perimenopause and postmenopause groups. We also hypothesized that perimenopausal and postmenopausal women would exhibit more depressive symptoms than premenopausal women. We further expected to find that affective symptoms and alternative neural activation patterns would be associated with higher levels of glycated hemoglobin (HbA1c), a measure of long-term glucose load.

2. Research methods

2.1. Study protocol

This was a cross-sectional study of women at 3 stages of the menopause transition. Women underwent a clinical evaluation including assessment of reproductive hormones, behavioral assessments of depression symptoms, mood, and affective state, and fMRI to observe neural activation patterns during an emotional images task. All procedures were approved by the University of Michigan Institutional Review Board, and written informed consent was obtained from all participants.

2.2. Participants

54 women, aged 42–61 years, were recruited from a population-based longitudinal study of the menopause transition. Women were divided into three menopause stage groups based on hormones and menstrual cycle criteria: (1) premenopause (regular menstrual cycles and FSH <11 IU/L); (2) perimenopause (at least one cycle in the previous year and FSH between 11 and 45 IU/L); and (3) postmenopause (no cycles in previous year and FSH >40 IU/L). Women with a previous hysterectomy but at least one intact ovary were categorized using hormonal criteria. Women were excluded for acute illness, uncorrected thyroid disease, diabetes, neurological or psychiatric illness, current or past substance abuse, claustrophobia, contraindications to magnetic resonance imaging (pacemakers, surgical clips, and metallic surgical devices), smoking within 3 years, and hormone use within 3 months. Left-handed women were also excluded because potential hemispheric variability in cognitive function between right- and left-handed people, including differences in hemispheric lateralization particularly noted in women, can impede accurate comparisons of regional brain activation (van der Kallen et al., 1998).

2.3. Hormone and metabolic assays

We measured the reproductive hormones estradiol and FSH for use in determining menopause status and to characterize hormonal environment, and HbA1c, a measure of long-term glucose homeostasis, to represent overall metabolic function. Fasting serum was collected in the morning during the longitudinal study yearly visit, during follicular days 2–7 in cycling women. Estradiol concentrations were measured with a modified off-line ACS:180 E_2-6 immunoassay (Bayer Diagnostics Corp., Norwood, MA). FSH concentrations were measured with a two-site chemiluminometric immunoassay using 2 monoclonal antibodies with specificity for intact FSH (Bayer Diagnostics). Glycated hemoglobin A1c (HbA1c) was measured with a non-porous ion exchange column and high performance liquid chromatography (HPLC), using a Tosoh G7 HPLC Analyzer (Tosoh Biosciences Inc., South San Francisco, CA), and calculated as a percent of total hemoglobin.

2.4. Behavioral assessment of emotion regulation

Measures were chosen to specifically reflect state and trait measures of mood, emotion regulation, and depressive symptoms. Negative affective state and mood were assessed using the Positive and Negative Affect Schedule – Expanded (PANAS-X) (Watson et al., 1988) and the Profile of Mood States (POMS) total mood disturbance score (Nyenhuis et al., 1999). The Beck Depression Index was used to assess the severity of depressive symptoms even in the absence of frank Major Depression (Beck et al., 1961). Potential IQ differences between groups were assessed using the Shipley Insititute of Living Scale (Shipley, 1946).

2.5. fMRI emotion paradigm

During the fMRI scanning session, women performed an emotion identification task designed to engage limbic emotion regulation circuitry. During the task, women were presented with a series of images previously validated as emotionally neutral or unpleasant by a normative female sample. Participants indicated their interpretation of each image as “unpleasant” (negative) or “neutral”. Each picture was presented for 3.5s, with a 1.5 s inter-stimulus interval. The task was presented in blocked design across four runs, with 12 pictures per block and four blocks per run. Response times and accuracy scores were recorded. Prior to scanning, participants practiced the task, using a separate set of images with similar emotional valence, to minimize performance differences attributable to unfamiliarity with the task. Stimuli were presented through display goggles, and responses made by response box button-press.

2.6. MRI acquisition & reconstruction protocols

We used blood oxygen level dependent (BOLD) contrast imaging. Scans were acquired on an FDA-approved 3 T GE MRI scanner. Localizer scans were acquired to identify landmarks, including the anterior commissure (AC) and the posterior commissure (PC), then 30 3 mm-thick oblique axial slices were prescribed parallel to the AC-PC line covering the entire cerebral cortex. These first two data sets were acquired using a T1-weighted pulse sequence (TR = 500 ms, TE = 8 ms, FOV = 20 cm, 256 × 192 matrix). Magnetic field uniformity was achieved through high-order shimming, then functional imaging was performed using a T2*-weighted

Please cite this article in press as: Berent-Spillson, A., et al., Metabolic and hormone influences on emotion processing during menopause. Psychoneuroendocrinology (2016), http://dx.doi.org/10.1016/j.psyneuen.2016.08.026