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Metabolic and hormone influences on emotion processing during menopause

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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.

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Contributors

Alison Berent-Spillson collected and analyzed study data, interpreted results, and drafted the manuscript
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Jon-Kar Zubieta contributed to study design, data interpretation, and manuscript review
Yolanda Smith developed study design, interpreted data, and contributed to drafting manuscript for publication
All authors have approved the final article.

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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.

Keywords

Menopause; perimenopause; emotion regulation; fMRI; metabolism

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 levels of both estradiol and FSH have been associated with depressive symptoms (Brinton et al., 2015; Freeman et al., 2014; Freeman et al., 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 1.5s 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 Tesla GE MRI scanner. Localizer scans were acquired to identify landmarks, including the anterior commissure (AC) and the posterior commissure (PC), then 30 3mm-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=500ms, TE=8ms, FOV=20cm, 256x192 matrix). Magnetic field uniformity was achieved through high-order shimming, then functional imaging was performed using a T2*-weighted pulse sequence with parameters: single-shot combined spiral in/out acquisition, gradient echo, TR=2000ms, TE=30ms, FA=90, FOV=20cm, 64x64 matrix. Slice thickness and locations were matched to the T1-weighted images. The entire volume of 30 slices was acquired once every 2 seconds and scan duration was matched to the duration of the tasks. Images were reconstructed using the iterative approach and placed in NIfTI (Neuroimaging Informatics Technology Initiative) format for post-processing. First, the data were sync-interpolated in time to correct for staggered slice acquisition. Next, a motion correction algorithm was applied to realign functional data to the first image acquired during scanning. The data were thresholded to exclude extra-parenchymal voxels and the scan-wise global signals and power spectra were derived. For group comparisons, the preprocessed images were first coregistered into standard stereotactic space and anatomically normalized by non-linear warping to a common “reference” anatomical MR data set. The anatomical

T1-weighted MR data were warped using the ICBM (Montreal Neurological Institute) atlas template as a reference, and the transformation matrix was applied to the realigned functional images. After anatomical normalization, functional images were smoothed with a 6mm Gaussian filter to reduce residual interindividual anatomical variability. Following pre-processing, image analysis was undertaken using MATLAB (Mathworks, Inc.) and Statistical Parametric Mapping packages (SPM8; Wellcome Department of Cognitive Neurology).

2.7 Data analysis: Statistical parametric mapping

Statistical parametric maps (SPM) of significant differences between longitudinal time points, within subjects, were obtained from the fMRI data using SPM8 on the preprocessed T2*-weighted images. The data were fit in two stages, a first-level intrasubject model for task effects and a second-level within subjects model that addressed the effects of interest. At the first level, a general linear model (GLM) was fit at voxel level for each subject, and orthogonal contrasts constructed for the main comparisons of interest (negative images – neutral images, to isolate circuitry activated by emotionally negative stimuli). Second-level analyses were based on anatomically-standardized contrast images of each subject's first-level analysis. A whole-brain effect-of-task analysis was performed with the entire sample (1-sample t test). Data from whole brain images were corrected for multiple comparisons by setting the False Discovery Rate (FDR) threshold at 0.05, and beta values were extracted from regions meeting this criteria for significant activation for use in secondary analyses. Subsequent whole-brain analyses were performed separately for each group, and regions were reported if present in the effect-of-task analyses and met FDR significance threshold of 0.05.

2.8 Data analysis: Clinical & behavioral

Clinical, demographic, and behavioral variables were compared between menopause stage groups using ANOVA analyses. Associations between clinical, behavioral, and regional activation were determined using Pearson correlational analyses. Because age significantly differed between groups, we performed comparisons between groups with and without age covariate. As age was not correlated with behavioral or imaging measures, age was not included as a covariate in Pearson correlation analyses.

3. Results

3.1 Demographic and clinical characteristics

Demographic and clinical characteristics are provided in Table 1. Menopause stage groups significantly differed in age ($p<0.000$), estradiol ($p<0.000$), FSH ($p<0.000$), and HbA1c ($p<0.020$), but had similar IQ ($p=0.519$) and BMI ($p=0.108$).

While age differed between groups, introducing age as a covariate to the analyses had little impact on clinical differences between groups. With age held constant at the mean of 52.01 years, significant differences between groups remained for estradiol (91.97±9.62 pg/mL premenopause, 42.33±8.84 perimenopause, and 13.76±6.46 postmenopause, $p<0.000$), FSH (7.82±6.43 mIU/mL premenopause, 30.04±5.95 perimenopause, and 84.17±4.36

postmenopause, p<0.000), and HbA1c (5.36±0.14% premenopause, 5.73±0.12% perimenopause, and 5.57±0.094% postmenopause, p=0.042). Groups remained similar in IQ (p=0.209), education (p=0.088), and BMI (p=0.214).

3.2 Brain regions activated during emotion task

Regional activation during the emotion task is provided in Table 2. To determine the regional activation effects of the emotion images task, we performed a 1 sample T test of whole-brain activation in all women, without considering menopause stage or age (Table 2A). We found that emotionally unpleasant images elicited significant regional activity in the medial prefrontal cortex (MNI coordinates *x,y,z* (mm)= −6, 52, 18; T=5.72; p (FDR corrected) =0.009; size 16392 mm^3), posterior cingulate (2, −60, 28; T=8.93; p<0.000; size 188808 mm^3), right temporal/parietal/occipital (TPO) junction (54, −64, 0; T=9.94, p<0.000, size 166696 mm^3), left TPO junction (−52, −72, 4; T=8.94; p<0.000, size 21856 mm^3), right amygdala (16, −4, −16; T=4.30; p=0.052; size 3904 mm^3), left amygdala (−20, −6, −18; T=4.55; p=0.031; size 360 mm^3), and left hippocampus (−24, −20, −18; T=4.90; p=0.012; size 3632 mm^3).

While ANOVA comparisons did not reveal significant differences in regional activation between menopause stage groups at the stringent criteria of p<0.05 after FDR correction for multiple comparisons, 1-sample T tests performed in each group independently revealed distinct activation patterns within each group. When analyzed by menopause stage group (Table 2B), no regions met the stringent significance criteria of p<0.05 after FDR correction for multiple comparisons in premenopausal women. In perimenopausal women there was activation in the right TPO junction (*x,y,z*= 52, −62, −4; T=5.49; p=0.036, size 4736 mm^3), and in postmenopausal women there was activation in the left prefrontal cortex (−8, 58, 20; T=5.59; p=0.004; size 15016 mm^3), posterior cingulate (0, −58, 26; T=5.59; p<0.000; size 11528 mm^3), right TPO junction (52, −42, 10; T=8.09; p<0.000; size 21016 mm^3), and left TPO junction (−44, −70, 4; T=9.78; p<0.000; size 24880 mm^3). Because mean age differed between menopause stage groups, we included age as a covariate when analyzing each group individually, however analyses without age covariate had similar results (data not shown).

3.3 Behavioral and imaging task measures

Women had similar scores on measures of mood and affect across menopause stage groups (Table 3). The entire group had a mean Beck depression score of 4.14±3.80 (SD), with premenopausal women scoring 3.53±2.86, perimenopause 3.47±4.21, and postmenopause 4.62±4.09 (p=0.490). The entire group had a mean PANAS-X negative affect score of 2.00±2.65, premenopausal women scored 1.22±1.17, perimenopause 2.15±2.48, and postmenopause 2.48±3.29 (p=0.289). The entire group had a POMS negative mood score of 3.66±22.88, premenopausal women scored −3.37±15.84, perimenopause 1.13±17.39, and postmenopause 7.56±27.71 (p=0.244).

ANOVA analyses revealed that women in each menopause stage group were similarly accurate in identifying negative emotional images during the fMRI scanning session, however perimenopausal women were significantly less accurate at identifying neutral

images than the other groups, suggesting a negative bias in this group. The entire group correctly identified 87±11% of emotionally negative images, with premenopausal women correctly identifying 86±10%, perimenopause 91±7%, and postmenopause 87±12% (p=0.494). The group identified the negative images at a mean speed of 1.42±0.23 seconds, premenopausal women at 1.43±0.27s, perimenopause 1.35±0.19s, and postmenopause 1.44±0.23s (p=0.558). The entire group correctly identified 84 ± 9% of the emotionally neutral images, with premenopausal women correctly identifying 86 ± 8%, perimenopause 77±12%, and postmenopause 85±9% (p=0.048). The group identified the neutral images at a mean speed of 1.53±0.22 seconds, premenopausal women at 1.43±0.19s, perimenopause 1.53±0.22s, and postmenopause 1.57 0.22s (p=0.172).

3.4 Correlations between clinical, behavioral, and imaging measures

We performed correlation analyses to determine associations between regional activation patterns, hormonal and metabolic environments, and behavioral measures of emotion regulation in all women (Table 4). We found associations between activation of cognitive association regions during the emotional images task and metabolic and behavioral measures, but not with FSH or estradiol (Table 4A). Activation in the TPO junction was correlated with HbA1c levels (R=0.345, p=0.011 right; R=0.279, p=0.041 left), and activation in the prefrontal cortex was inversely correlated with BMI (R=−0.274, p=0.045). Posterior cingulate activation was correlated with accurate identification of negative images (R=0.439, p=0.001), and inversely correlated with accurate identification of neutral images (R=−0.402, p=0.003), and associated with time spent identifying negative images (R=0.410, p=0.003). TPO junction activation was correlated with depressive symptoms (R=0.283, p=0.038, right), with POMS negative mood score (R=0.310, p=0.023 right; R=0.330, p=0.015 left), and with accurate identification of neutral images (R=0.311, p=0.025 left). Activation of the emotion regulation amygdala region was inversely activated with PANAS-X negative affect score (R=−0.297, p=0.036).

We also found associations between clinical and behavioral measures (Table 4B). FSH levels were correlated with POMS negative mood score (R=0.355, p=0.009), and HbA1c levels were inversely associated with accurate identification of neutral images (R=−0.334, p=0.014), and correlated with time spent identifying neutral images (R=0.300, p=0.031).

Age was not associated with any neurobiological, clinical, or behavioral measures.

To determine if relationships between metabolic function and imaging or behavioral measures were driven by higher HbA1c levels, we divided women into “lower” (mean HbA1c = 5.23%) and “higher” (mean HbA1c = 5.77%) HbA1c groups based on a median split at 5.47%. In the lower HbA1c group, activation in the TPO junction was not correlated with HbA1c levels (R = 0.219, p = 0.283 right; R = 0.052, p = 0.799 left), while TPO junction activation was correlated with HbA1c in the higher HbA1c group (R = 0.456, p = 0.015 right; R = 0.466, p = 0.013 left). Accurate identification of neutral images was not correlated with HbA1c in either group when calculated separately, time spent identifying neutral images was correlated with HbA1c in the higher HbA1c group (R = 0.465, p = 0.013), but not the lower HbA1c group (R = 0.092, p = 0.667).

4. Discussion

Depression is universal, but occurs more frequently in women, particularly after menopause (Cohen et al., 2006; Llaneza et al., 2012; Weber et al., 2013). There is evidence that the hormonal environment plays some role in the etiology of depression – variability of estradiol levels was found to be associated with depressive symptoms in women who had recently experienced stressful life events (Gordon et al., 2015), and greater lifetime exposure to endogenous estrogens, assessed by age at menopause and length of reproductive period, is associated with lower risk of depression (Georgakis et al., 2016; Jung et al., 2015). However there is not a direct relationship between depressive symptoms and reproductive hormone levels (Henderson et al., 2013; Ryan et al., 2009), and studies of postmenopausal hormone therapy have found variable effects on depression symptoms (Gleason et al., 2015; Jung et al., 2015; Schmidt et al., 2015). Despite the increased risk of depressive symptoms during the menopausal period of hormonal instability, the relationship seems to be driven by factors other than reproductive hormone levels. In the current study, we examined the effects of age, reproductive hormone levels, and metabolic function on depressive symptoms, mood, affective state, and emotion processing in healthy women across the menopause transition. We found that FSH levels were associated with negative mood, and HbA1c, a measure of long-term glucose load, was associated with a tendency toward negative interpretation of emotionally neutral images, and with increased recruitment of cognitive association regions during emotion processing. Age was not associated with any behavioral measures of mood or emotion regulation or with neural activation patterns during the emotional images task. Our results indicate relationships between menopause status, metabolic profile, and regional brain activation during emotional decision-making, which may lead to increased risk for depression during menopause.

In our entire sample, viewing emotionally unpleasant images activated both emotion regulation and cognitive association regions in the brain. When we separated the whole-brain analyses by menopause status group, a pattern emerged where activation in the cognitive association regions became more pronounced with advancing menopause stage. Perimenopausal women had significant activation in the left TPO junction, and postmenopausal women had activation in the prefrontal cortex, posterior cingulate, and TPO junction. This complexly interconnected region of the brain regulates visual information processing, with direct and indirect connections between visual cortex and limbic emotion regulation regions (De Benedictis et al., 2014). The posterior cingulate is also a highly interconnected cognitive association region, and has been implicated in memory retrieval of emotionally salient events (Maddock et al., 2003; Riegel et al., 2015). While women in all three menopause stage groups had similar measures of mood and affective state, women in the perimenopausal group were most likely to interpret emotionally neutral images as unpleasant, suggesting a negative interpretation bias.

Across our entire sample, negative affective state, which may be associated with future risk for depression in older adults (Harralson and Lawton, 1999), was associated with decreased activation in the amygdala, while depression symptoms and negative mood were associated with increased activation in the TPO junction. This pattern of results suggest that increased negative symptomology is associated with less activation in emotion regulation regions and

increased activation in cognitive association regions during emotion processing, a potential proxy for ruminative processes and negative cognitive bias. This conclusion is further supported by an association between posterior cingulate activation and accurately identifying emotionally unpleasant images, and also with a tendency to misidentify emotionally neutral images as unpleasant, while taking a longer time to make this decision. Higher levels of HbA1c, a measure of long-term glucose homeostasis, were associated with increased activation in the TPO junction, and with lower accuracy, and longer reaction time, at correctly identifying emotionally neutral images. Interestingly, the range of HbA1c values in our sample, and particularly the perimenopausal group, fall near the 5.7% cut-off for pre-diabetes determined by the U. S. National Health and Nutrition Examination Survey (NHANES) (Zhang et al., 2015). When we divided our group into “higher” and “lower” HbA1c levels, relationships between HbA1c and TPO junction activation and reaction time to emotionally neutral images were found to exist only in women with higher HbA1c levels, with mean HbA1c falling within pre-diabetic range. Similar threshold effects have been found for other relationships between metabolic measures and neural outcomes, for example glucose levels are associated with reduced cortical thickness in Alzheimer’s Disease only in patients with glucose levels in the diabetic range (Wennberg et al., 2016). Our results suggest that the negative interpretation bias associated with increased recruitment of cognitive association regions during emotional decision-making may be driven by metabolic dysfunction during menopause.

While disturbances of emotion regulation and depressive symptoms are common during the menopause transition, it is not clear what mechanisms underlie this phenomenon. In this study we found evidence of altered emotion regulation in peri- and postmenopausal women, with women in these groups displaying recruitment of cognitive association regions during an emotion discrimination task, and evidence of negative interpretation bias in perimenopausal women. This pattern echoes that found in studies of individuals with depression, where a negative bias is associated with increased connectivity between emotion and cognitive regulating regions (Zhou et al., 2010). In our study, neither hormonal variables nor age appear to be driving these outcomes in our study sample. On the contrary, our data suggest that metabolic factors may play a role.

Evidence from the literature supports metabolic influences on limbic function and emotion regulation, with disrupted emotion regulation in the context of metabolic dysfunction. Insulin has neurotransmitter-like functions within the CNS, and insulin receptors are abundant throughout interior brain structures (Adamo et al., 1989; Werner and LeRoith, 2014). Insulin signaling through receptors located within the hippocampus are thought to regulate cognitive processes, while those in the amygdala and other limbic regions have roles in emotion regulation functions (Akintola and van Heemst, 2015). In addition to signaling through insulin receptors, interactions with other neurotransmitter systems can affect emotion regulation and influence behavioral outcomes. In a previous study of insulin resistant women with polycystic ovary disease, we found evidence of decreased opioid tone, an emotion and stress-regulatory mechanism, in limbic regions compared to non-insulin resistant controls, which was associated with greater brain regional activation during the emotional images task, mood disturbances, and measures of metabolic dysfunction (Berent-Spillson et al., 2011; Marsh et al., 2013). These results are consistent with studies finding

high prevalence of insulin resistance in depressed patients, with suspected brain glucose metabolism deficiencies secondary to central insulin resistance (Baxter et al., 1985; Okamura et al., 2000; Rasgon and Kenna, 2005). This hypothesis is supported by animal studies, where decreased limbic responsiveness was noted after chronic hypoglycemia in rats (Hurst et al., 2012). Interestingly, an earlier set of similar studies found that estradiol administration preserved limbic activation response after chronic hypoglycemia in ovariectomized rats (Nedungadi et al., 2006), supporting an interactive effect of metabolic factors with hormonal environment during menopause.

Strengths of this study include the inclusion of three distinct menopause stage groups, defined by a combination of hormonal environment and cycle patterns, which allowed us to examine the role of age, hormonal, and metabolic factors in emotion regulation not only between pre- and postmenopausal women, but also in women in the transitional period itself. We utilized glycated hemoglobin A1c as a measure of long-term metabolic homeostasis, which allowed us to assess metabolic function over a period of weeks to months, rather than using plasma glucose or insulin concentrations, which are subject to acute influences that may not reflect the longer-term metabolic environment. However we were limited by the cross-sectional nature of the study, which did not allow for detection of changes over time and through the menopause transition in each woman. We were also limited by the relatively small sample size of the perimenopausal group, primarily due to the transitional nature of this period. All neuroimaging analyses were performed using a stringent FDR correction for multiple comparisons. Because of the number of clinical and behavioral factors considered, it is possible that interpretation of these results may be limited by multiple comparison issues, however we minimized this possibility by assessing a distinct set of relevant variables for each outcome of the study. Because some of the variables differed between menopause stage groups, and due to the limited sample size of some groups, it is possible that violations of homogeneity of regression across subgroups may be a limitation to interpretation of these results.

The results of this study suggest a relationship between menopause status, metabolic function, and emotion regulation, in a sample of healthy women without clinical depression. Our results indicate a pattern of increasing cognitive regulation of emotional decision making through the menopause transition, accompanied by a negative interpretation bias that is especially prominent during the perimenopausal period. This relationship appears to be driven by metabolic factors rather than by age or the hormonal environment. This suggests a potential role for metabolic function and glucose regulation in the etiology of depressive symptoms during the menopause transition.

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Highlights

- Menopausal women use cognitive regions during emotional decision making
- Cognitive region activation for emotion processing is associated with negative mood
- HbA1c is associated with negative bias and cognitive region activation

Table 1

Clinical and demographic characteristics

	Whole Sample			Premenopause			Perimenopause			Postmenopause			ANOVA	
N	**54**			**15**			**11**			**28**				
	Mean	**±**	**SD**	**Mean**	**±**	**SD**	**Mean**	**±**	**SD**	**Mean**	**±**	**SD**	***F***	***p***
Age	52.01	±	4.18	47.49	±	2.78	52.66	±	3.43	54.38	±	2.70	286.793	.000
Education (years)	13.87	±	2.52	15.07	±	3.06	13.64	±	2.16	13.32	±	2.18	2.546	.088
Shipley IQ	106.73	±	8.14	107.47	±	6.74	108.33	±	5.67	105.63	±	9.71	.662	.519
Estradiol (pg/mL)	45.89	±	49.51	86.84	±	46.21	43.34	±	41.24	16.40	±	7.19	29.849	.000
FSH (mIU/mL)	51.03	±	40.48	8.13	±	3.04	29.99	±	14.08	84.00	±	28.20	84.663	.000
HbA1c (%)	5.50	±	0.39	5.31	±	0.20	5.74	±	0.64	5.60	±	0.46	4.185	.020
BMI	27.45	±	4.81	26.66	±	5.30	30.03	±	5.51	27.23	±	4.24	2.304	.108

Table 2

Regions activated during emotion task in all women (A) and by menopause status (B)

A

Region	Coordinates	T	P (FDR corr)	Size (mm^3)
Medial prefrontal cortex	−6, 52, 18	5.72	0.001	16392
Posterior cingulate	2, −60, 28	8.93	0.000	18808
R temp/par/oc junction	54, −64, 0	9.94	0.000	16696
L temp/par/oc junction	−52, −72, 4	8.94	0.000	21856
R amygdala	16, −4, −16	4.30	0.052	3904
L amygdala	−20, −6, −18	4.55	0.031	360
L hippocampus	−24, −20, −18	4.90	0.012	3632

B

Region	Coordinates	T	P (FDR corr)	Size (mm^3)
Premenopause				
no significant regions				
Perimenopause				
R temp/par/oc junction	52, −62, −4	5.49	0.036	4736
Postmenopause				
L prefrontal cortex	−8, 58, 20	5.59	0.004	15016
Posterior cingulate	0, −58, 26	6.82	0.000	11528
R temp/par/oc junction	52, −42, 10	8.09	0.000	21016
L temp/par/oc junction	−44, −70, 4	9.78	0.000	24880

Table 3

Behavioral measures by menopause stage group

	Whole Sample			Premenopause			Perimenopause			Postmenopause			ANOVA	
N	**54**			**15**			**11**			**28**				
	Mean	**±**	**SD**	**Mean**	**±**	**SD**	**Mean**	**±**	**SD**	**Mean**	**±**	**SD**	***F***	***p***
Beck depression	4.14	±	3.80	3.53	±	2.86	3.47	±	4.21	4.62	±	4.09	0.722	.490
PANAS negative affect	2.00	±	2.65	1.22	±	1.17	2.15	±	2.48	2.48	±	3.29	1.270	.289
POMS negative mood	3.66	±	22.88	−3.37	±	15.84	1.13	±	17.39	7.56	±	27.71	1.441	.244
Emotion task negative	0.87	±	0.11	0.86	±	0.10	0.91	±	0.07	0.87	±	0.12	.715	.494
Emotion task negative RT	1.42	±	0.23	1.43	±	0.27	1.35	±	0.19	1.44	±	0.23	.590	.558
Emotion task neutral	0.84	±	0.09	0.86	±	0.08	0.77	±	0.12	0.85	±	0.09	**3.237**	**.048**
Emotion task neutral RT	1.53	±	0.22	1.43	±	0.19	1.53	±	0.22	1.57	±	0.22	1.827	.172

Table 4

Correlations between clinical, behavioral, and regional brain activation measures

A

	Prefrontal cortex		R amygdala		L amygdala		Post. cingulate		R TPO junction		L TPO junction	
	R	***p***	***R***	***p***	***R***	***p***	***R***	***p***	***R***	***p***	***R***	***p***
Age	−0.183	(0.185)	−0.089	(0.523)	−0.216	(0.120)	0.101	(0.469)	0.029	(0.838)	0.105	(0.449)
FSH	−0.183	(0.634)	−0.032	(0.822)	0.077	(0.588)	0.090	(0.519)	0.123	(0.378)	0.156	(0.266)
Estradiol	−0.183	(0.094)	0.069	(0.620)	0.179	(0.201)	−0.171	(0.217)	−0.072	(0.605)	−0.126	(0.365)
HbA1c	−0.052	(0.707)	−0.022	(0.872)	0.035	(0.802)	0.198	(0.151)	**0.345**	**(0.011)**	**0.279**	**(0.041)**
BMI	**−0.274**	**(0.045)**	−0.037	(0.788)	−0.141	(0.315)	−0.123	(0.374)	−0.250	(0.069)	−0.176	(0.204)
Beck depression	−0.011	(0.934)	−0.075	(0.592)	−0.091	(0.519)	−0.142	(0.305)	**0.283**	**(0.038)**	0.258	(0.059)
PANAS negative affect	−0.081	(0.574)	−0.223	(0.116)	**−0.297**	**(0.036)**	0.006	(0.964)	0.225	(0.113)	0.173	(0.224)
POMS negative mood	0.012	(0.930)	−0.076	(0.585)	0.036	(0.798)	−0.030	(0.830)	**0.310**	**(0.023)**	**0.330**	**(0.015)**
Emotion task negative	−0.028	(0.842)	0.171	(0.225)	0.037	(0.795)	**0.429**	**(0.001)**	−0.165	(0.244)	−0.263	(0.060)
Emotion task negative RT	0.137	(0.333)	0.006	(0.968)	−0.008	(0.957)	−0.124	(0.380)	0.014	(0.921)	0.262	(0.061)
Emotion task neutral	0.000	(0.999)	−0.151	(0.286)	0.054	(0.708)	**−0.402**	**(0.003)**	0.092	(0.518)	**0.311**	**(0.025)**
Emotion task neutral RT	0.177	(0.209)	0.106	(0.453)	−0.060	(0.676)	**0.410**	**(0.003)**	−0.116	(0.412)	0.055	(0.701)

B

	Age		FSH		Estradiol		HbA1c		BMI	
	R	***p***	***R***	***p***	***R***	***p***	***R***	***p***	***R***	***p***
Beck depression	−0.049	(0.697)	0.211	(0.093)	−0.032	(0.816)	−0.092	(0.464)	−0.105	(0.402)
PANAS negative affect	0.150	(0.261)	0.198	(0.135)	−0.165	(0.248)	0.068	(0.610)	−0.244	(0.065)
POMS negative mood	0.086	(0.493)	**0.355**	**(0.009)**	−0.190	(0.169)	−0.102	(0.414)	−0.064	(0.612)
Emotion task negative	0.245	(0.077)	0.106	(0.453)	−0.051	(0.719)	0.203	(0.144)	−0.189	(0.174)
Emotion task negative RT	−0.164	(0.245)	−0.081	(0.570)	−0.095	(0.504)	0.088	(0.533)	0.112	(0.428)
Emotion task neutral	−0.174	(0.211)	0.033	(0.818)	−0.129	(0.362)	**−0.334**	**(0.014)**	0.087	(0.536)
Emotion task neutral RT	0.155	(0.274)	0.095	(0.509)	−0.267	(0.055)	**0.300**	**(0.031)**	−0.088	(0.533)

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