



GABAergic neuroactive steroids and resting-state functional connectivity in postpartum depression: A preliminary study

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ABSTRACT

Postpartum depression (PPD) affects up to 1 in 8 women. The early postpartum period is characterized by a downward physiological shift from relatively elevated levels of sex steroids during pregnancy to diminished levels after parturition. Sex steroids influence functional brain connectivity in healthy non-puerperal subjects. This study tests the hypothesis that PPD is associated with attenuation of resting-state functional connectivity (rs-fc) within corticolimbic regions implicated in depression and alterations in neuroactive steroid concentrations as compared to healthy postpartum women. Subjects ($n = 32$) were prospectively evaluated during pregnancy and in the postpartum with repeated plasma neuroactive steroid measurements and mood and psychosocial assessments. Healthy comparison subjects (HCS) and medication-free subjects with unipolar PPD (PPD) were examined using functional magnetic resonance imaging (fMRI) within 9 weeks of delivery. We performed rs-fc analysis with seeds placed in the anterior cingulate cortex (ACC), and bilateral amygdala (AMYG), hippocampi (HIPPO) and dorsolateral prefrontal cortices (DLPFCs). Postpartum rs-fc and perinatal neuroactive steroid plasma concentrations, quantified by liquid chromatography/mass spectrometry, were compared between groups. PPD subjects showed attenuation of connectivity for each of the tested regions (i.e. ACC, AMYG, HIPPO and DLPFC) and between corticocortical and corticolimbic regions vs. HCS. Perinatal concentrations of pregnanolone, allopregnanolone and pregnenolone were not different between groups. This is the first report of a disruption in the rs-fc patterns in medication-free subjects with PPD. This disruption may contribute to the development of PPD, at a time of falling neuroactive steroid concentrations.

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1. Introduction

Depression is the leading cause of disease burden and years lost to disability for women in their childbearing years (World Health Organization, 2008). Postpartum depression (PPD) affects 1 in 8

women (Cox et al., 1993) and negatively impacts infant attachment, neurocognitive development and behavior (Feldman et al., 2009). Women may be at increased risk for developing depression during the postpartum period (Vesga-Lopez et al., 2008), a time of a downward physiological shift in sex steroid levels. Current nosology (American Psychiatric Association, 2000) defines PPD as a specifier of a major depressive episode. It is not known if PPD is a distinct neurobiological entity compared to non-puerperal depression (Payne et al., 2009).

Derivatives of progesterone, neuroactive steroids (NAS) alter excitability of the central nervous system through their actions at the γ -aminobutyric acid A (GABA_A) receptor (Mostallino et al., 2009; Stell et al., 2003). Times of NAS withdrawal may represent a time of disease vulnerability, as seen in epilepsy (Reddy et al., 2012) and possibly in women predisposed to developing PPD (Bloch et al., 2005). Differential regulation of NAS during the perinatal period (Bloch et al., 2000; Nappi et al., 2001), may be involved in the pathophysiology of PPD.

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Alternatively, the GABA_A receptor may undergo NAS induced changes in the perinatal period, acting as a risk factor (Concas et al., 1998; Follsea et al., 1998; Maguire and Mody, 2008, 2009).

NAS concentrations are altered in depression (Girdler et al., 2011; Klatzkin et al., 2006) and influence the regulation of emotional responses and affective states in premenstrual syndrome (Schmidt et al., 1998), and premenstrual dysphoric disorder (PMDD) (Epperson et al., 2002; Girdler et al., 2001). Altered steroid concentrations may reflect abnormalities in the steroid metabolic pathway as elevated ratios of progesterone-derived NAS metabolites to its precursor progesterone have been demonstrated in PMDD and women with a history of depression (Girdler et al., 2011, 2001; Klatzkin et al., 2006).

Steroids are an important modulator of corticocortical and corticolimbic functional connectivity (Berman et al., 1997; Dreher et al., 2007; Goldstein et al., 2005; van Wingen et al., 2008). Essential to cognitive processing, progesterone and estradiol modulate functional cerebral asymmetries (Weis et al., 2008). Progesterone modulates amygdala reactivity (Gingnell et al., 2012; Ossewaarde et al., 2010; van Wingen et al., 2008) and its connectivity with the prefrontal cortex (Amin et al., 2006; Protopopescu et al., 2008). Progesterone, at high levels may reduce amygdala activity (van Wingen et al., 2007), but its effects in the postpartum, as levels precipitously decline is unknown.

Although neuroimaging studies in PPD are few, depressive symptomatology in the postpartum period is associated with reduced amygdala responsivity to positive stimuli (Barrett et al., 2011), threat-related stimuli (Silverman et al., 2011) and negatively valenced stimuli (Moses-Kolko et al., 2010; Silverman et al., 2007). Additional studies have shown abnormalities in ventral striatal response to reward (Moses-Kolko et al., 2011), increased glutamate levels in the medial prefrontal cortex (McEwen et al., 2012) and reduced post-synaptic serotonin-1A receptor binding, in particular in the ACC and mesiotemporal cortices (Moses-Kolko et al., 2008). A single study (Epperson et al., 2006) measured NAS. Allopregnanolone and cortical GABA concentrations were low in the postpartum compared to healthy follicular phase women (Epperson et al., 2006).

This investigation is the first to assess resting-state functional connectivity (rs-fc) and quantify NAS concentrations in healthy postpartum subjects and subjects who developed unipolar PPD. Functional connectivity analysis was performed using a hypothesis-driven seed-based approach based on findings in non-puerperal major depression and emerging task-based fMRI and PET findings in PPD described above. We investigated the rs-fc patterns of the anterior cingulate cortex (ACC), amygdala (AMYG), hippocampus (HIPPO) and dorsolateral prefrontal cortex (DLPFC). We measured plasma concentrations of two progesterone metabolites, allopregnanolone and pregnanolone and their precursors, progesterone and pregnenolone, to examine if there was an association between perinatal plasma concentrations and PPD or NAS/progesterone ratios and PPD. We tested the hypotheses: (1) PPD would be associated with attenuation of connectivity between the ACC and DLPFC, the ACC and AMYG and the DLPFC and HIPPO as compared to healthy postpartum women and (2) mean postpartum plasma concentration of the NAS allopregnanolone (i.e. 3 α , 5 α -tetrahydroprogesterone) and pregnanolone (i.e. 3 α , 5 β -tetrahydroprogesterone) would be lower in the PPD group and would be correlated to the postpartum depression total score, and that the ratio of progesterone-derived NAS to progesterone would be elevated in those subjects who developed PPD.

2. Materials and methods

2.1. Subjects

The University of Massachusetts Medical School (UMMS) Institutional Review Board (IRB) granted a waiver to review the medical

records of obstetrics patients at UMass Memorial Medical Center during the study period. Subjects who met inclusion/exclusion criteria were approached by study staff to assess interest and eligibility. Two-hundred and forty-three subjects were consented and screened with the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987) at 26–30 weeks gestational age. The EPDS is a well-validated self-report of depression and anxiety symptoms used to assess perinatal depression (Bergink et al., 2011; Cox et al., 1987). A total of 32 eligible subjects of 18–40 years of age enrolled in the prospective study. Sample size was limited by available funding for this preliminary study. Two groups were enrolled: (1) 12 healthy comparison subjects (HCS) who were at low-risk and (2) 20 subjects at high-risk for developing postpartum depression (PPD). The HCS group included women without a personal or family history of psychiatric illness, as ascertained by clinical and research interviews [Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) conducted by a board-certified psychiatrist (K.M.D.)] and who had an EPDS ≤ 5 throughout pregnancy and the postpartum, which indicated the absence of depressive or anxiety symptoms. At the time of the postpartum MRI scan, HCS continued to have no psychiatric symptoms. Since women with anxiety or depressive symptoms during pregnancy, or a history of PPD are at increased risk of future PPD episodes (Viguera et al., 2011), the PPD subject group included subjects who had a history of major depressive disorder (MDD) or PPD and an EPDS ≥ 10 at the first study visit (i.e. at 26–30 weeks gestation). The EPDS cut-off of 10 was chosen based on validation of the EPDS during pregnancy (Bergink et al., 2011). Subjects who had a score of 6–9 on the EPDS or had an EPDS ≥ 10 and met criteria for major depression at the time of screening were ineligible. All 32 subjects completed all four study visits. In the HCS group, 9/12 subjects consented to the MRI scan. In the high risk (PPD) group 12/20 subjects developed PPD. Of those 12 subjects, 8 subjects consented to the MRI scan. All data reported represents 9 HCS and 8 high-risk subjects who developed PPD and completed resting-state functional Magnetic Resonance Imaging (rs-fMRI).

Subjects were excluded if they had: a multiple gestation pregnancy, a current major depressive episode or lifetime history of manic episode or any psychotic disorder as determined by the MINI; elevated suicidal risk; alcohol, tobacco or substance abuse/dependence in the 6 months prior to study entry; positive urine benzodiazepine test; positive urine pregnancy test prior to MRI; pregnancy loss; active or history of serious medical, neurological or endocrine disorder; any contraindication to MRI; antidepressant or benzodiazepine use 4 weeks prior to study entry and at any time during the study; concomitant use of pharmacotherapy with known psychotropic, GABAergic or neurosteroidotropic activity at any time during the study.

2.2. Procedures

All subjects were evaluated during pregnancy (i.e. between 26 and 30 weeks gestation (visit 1) and 34–36 weeks gestation (visit 2), dates confirmed by first trimester ultrasound) and in the postpartum (i.e. <36 h after parturition (visit 3) and between 3 and 9 weeks after parturition (visit 4)). The 9-week postpartum cut-off was based on literature suggesting a postpartum onset definition of up to 6–8 weeks of delivery as optimal (Forty et al., 2006), with the additional week to allow research assessment completion. Serial mood and psychosocial assessments were completed at each of the four study visits. Blood samples for NAS analysis were obtained at antepartum study visit 2 and postpartum study visit 4 between 9 and 11 AM, whenever possible, and collected into tubes containing EDTA. Samples were centrifuged at 4000 rpm for 15 min and plasma was stored at -80°C until analysis was completed by collaborators blind to the mood outcome. Research assessments done at all 4 visits included: Edinburgh Postnatal Depression Scale (EPDS) (Cox et al.,

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