Effects of Sex Steroid Manipulation on Irritability and the Neural Reward System in Women with a History of Perinatal Depression

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Introduction

Irritability is defined as a reduced threshold for experiencing anger and control of temper and is a common symptom of perinatal depression (PND), especially during the postpartum period.

Background

• Prior research demonstrates that neuroendocrine factors play a role in the etiology of PND and distinguishes irritability as one of the most severe and prominent symptoms to come on the scene when a woman experiences distress.

• However, irritability as a symptom of PND is still understudied and overlooked by standard depression screening tools used across the US, leading to significant missed opportunities for early detection and intervention.

Primary aim: To characterize how reproductive hormones trigger irritability and alter neural reward responsivity among hormone-sensitive women. Here we present data from a pharmaco-fMRI study investigating the effects of experimentally controlled reproductive steroid exposure on mood and reward circuit activation.

Methods

Subjects: Healthy, euthymic women with a history of postpartum depression (PPD+, n=15) and those without such a history (PPD-, n=15).

Symptom assessment: PPD history was assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). Depressive symptoms were assessed using the Inventory of Depression and Anxiety Symptoms (IDAS) at baseline, hormone addback, and withdrawal.

fMRI sessions: The first functional magnetic resonance imaging (fMRI) session occurred during the early- to mid-follicular phase (i.e., “baseline”) and the second session occurred during the “hormone withdrawal” phase.

fMRI Task: Participants performed a monetary incentive delay task, to probe the neural response to reward anticipation and outcomes.

Analyses: Whole brain, task-based functional activation maps were generated using permutation analysis of linear models (PALM) toolbox, with significant effects identified through the threshold-free cluster enhancement (TFCE) method controlling for family-wise error (FWE) rate of p<0.05. A 2x2 mixed-effect ANOVA was used to examine the effect of phase (baseline vs. withdrawal) and interaction group (HS+ vs. HS-).

Mood Effects of Hormone Manipulation

At baseline, there were significant differences in mood symptoms between those with a history of PPD and controls as measured by the 11 IDAS scales. Women with a history of PPD+ (n=15) showed a significant increase in irritability during hormone addback and withdrawal, while PPD- (n=15) did not.

We defined hormone sensitivity as a 30% increase in IDAS mood symptoms during either hormone addback or withdrawal. 11 of the 15 PPD+ women were hormone sensitive, and 1 of the 15 PPD- was hormone sensitive.

Neural Effects of Hormone Manipulation

Neural response to reward gain and loss conditions were examined during anticipation and outcome of monetary incentives.

Reward Gain: When anticipating reward, participants had reduced activation in the right putamen and left postcentral-supramarginal gyri during hormone withdrawal, compared to baseline.

Reward Loss: No significant differences were found between groups or hormone phases (TFCE, z=2.3) during either task condition.

Irritability & Reward Responsivity During Hormone Withdrawal

When exploring associations between irritability and neural response to reward during hormone withdrawal, IDAS Ill Temper scores were significantly correlated with putamen activation.

Conclusions

• The significant increase in irritability during addback and withdrawal of estradiol and progesterone in PPD+, but not in PPD- shows that PPD+ have an aberrant response to fluctuations in gonadal steroids.

• These results also demonstrate that irritability, as a symptom of PND, often presents during pregnancy and could serve as an initial indicator for women more susceptible to postpartum depression.

• More research is needed to understand irritability onset during the postpartum period and how its association with reward response might affect maternal behavior regulation and caregiving interactions.

References