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REVIEW

Emotional and cognitive functional imaging of estrogen and progesterone effects in the female human brain: A systematic review

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Summary Ovarian hormones are pivotal for the physiological maintenance of the brain function as well as its response to environmental stimuli. There is mounting evidence attesting the relevance of endogenous ovarian hormones as well as exogenous estradiol and progesterone for emotional and cognitive processing.

The present review systematically summarized current knowledge on sex steroid hormonal modulation of neural substrates of emotion and cognition revealed by functional magnetic resonance imaging (fMRI). Twenty-four studies of healthy naturally cycling and combined oral contraceptives (COC) user women, or women undergoing experimental manipulations, during their reproductive age, were included. Furthermore, six studies of premenstrual dysphoric disorder (PMDD), a hormonally based mood disorder, and three of gender dysphoria (GD), which provides an intriguing opportunity to examine the effect of high-dose cross-sex hormone therapy (CSHT) on brain functioning, were included. Globally, low (early follicular and the entire follicular phase for estrogen and progesterone, respectively) and high (COC, CSHT, late follicular and luteal phase for estrogen; COC, mid- and late-luteal phase for progesterone) hormonal milieu diversely affected the response of several brain regions including the amygdala, anterior cingulate cortex, and inferior frontal gyrus, but their functional recruitment across groups and domains was scattered.

The constellation of findings provides initial evidence of the influence of sex steroid hormones on cortical and subcortical regions implicated in emotional and cognitive processing.

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Further well-powered and multimodal neuroimaging studies will be needed to identify the neural mechanism of functional brain alterations induced by sex steroid hormones.

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1. Introduction

Ovarian hormones establish and maintain a specific neuroendocrine milieu through which the brain structure and function is modulated across the woman's life span. However, the neurobiological underpinnings of ovarian hormones-related modulation of brain function remain largely unknown and speculative. Recently, functional magnetic resonance (fMRI) studies have begun elucidating ovarian hormones influences on the activation of the female brain during reproductive age induced by emotional and cognitive processing.

Both estradiol and progesterone exert structural and functional trophic effects from the early brain development, and throughout adolescence and adulthood, by acting via classical nuclear receptors as well as non-classical membrane-associated receptors. The well-characterized estrogen receptors (ER) and progesterone receptors (PR) are localized in brain regions involved in emotional and cognitive regulation (Brinton et al., 2008; Wharton et al., 2012). The ERα isoform is highly expressed in the amygdala and hypothalamus, whereas the ERβ isoform is highly expressed in the claustrum, cerebral cortex and hippocampal formation (Osterlund et al., 2000a,b). Moreover, the hypothalamus, preoptic area and substantia nigra of human post-mortem brain are characterized by elevated E2 levels (Bixo et al., 1995). Likewise, PRA and PRB are most abundant in the amygdala, cerebellum, cortex, hippocampus, and hypothalamus of rats (Kato et al., 1994), whereas the highest P4 and allopregnanolone (THP) levels have been found, respectively, in the amygdala, cerebellum, hypothalamus and in the substantia nigra and basal hypothalamus of human post-mortem brain (Bixo et al., 1997). Additional non-classical receptors have emerged as potential mediators of rapid non-genomic effects of E2 and P4 in rodent brain, G protein-coupled estrogen receptors (GPERs) are responsive to E2 in the hippocampus, hypothalamus, isocortex and substantia nigra (Hazell et al., 2009), while progesterone has been reported to bind to the progesterone receptor membrane component 1 (PGRMC1) in the cerebellum, cortical regions, hippocampus, and hypothalamic nuclei (Intlekofer and Petersen, 2011). The widespread distribution of all these receptors in the brain may indicate a non-specific pattern of ovarian hormones modulation of the brain. However, the localization of classical and non-classical signaling pathways in emotion- and cognition-related brain