Influence of endogenous estradiol, progesterone, allopregnanolone, and dehydroepiandrosterone sulfate on brain resting state functional connectivity across the menstrual cycle

Sabrina K. Syan, H.B.Sc.,[a,b] Luciano Minuzzi, M.D., Ph.D.,[a,b,c,d] Dustin Costescu, M.D.,[e] Mara Smith, M.D.,[d] Olivia R. Allega, M.Sc.,[a,b] Marg Coote, B.Sc.,[d] Geoffrey B. C. Hall, Ph.D.,[a,f] and Benicio N. Frey, M.D., M.Sc., Ph.D.[a,b,c,d]

[a] MiNDS Neuroscience Graduate Program, McMaster University; [b] Women's Health Concerns Clinic, St. Joseph's Healthcare Hamilton; [c] Mood Disorders Program, St. Joseph's Healthcare Hamilton; [d] Department of Psychiatry and Behavioural Neurosciences, McMaster University; [e] Department of Obstetrics and Gynecology, McMaster University; and [f] Department of Psychology, Neuroscience and Behaviour, McMaster University, Hamilton, Ontario, Canada

Objective: To [1] study brain resting state functional connectivity (Rs-FC) in a well-characterized sample of healthy women in the mid-follicular and late luteal phases of the menstrual cycle; and [2] examine the correlation between endogenous E_2, P, allopregnanolone, and DHEAS and patterns of Rs-FC across the menstrual cycle.

Design: We studied the Rs-FC of the default mode network, salience network, meso-paralimbic network, fronto-parietal network, visual network, and sensorimotor network in the mid-follicular and late luteal phases. Serum levels of E_2, P, allopregnanolone, and DHEAS were correlated to patterns of functional connectivity.

Setting: University medical center.

Patient(s): Twenty-five healthy women with regular menstrual cycles.

Intervention(s): None.

Main Outcome Measure(s): Functional connectivity of key brain networks at rest and correlations of hormones to Rs-FC in the mid-follcuar and late luteal menstrual phases.

Result(s): There were no differences in Rs-FC between the mid-follicular and late luteal menstrual phases using either independent component analysis or seed-based analysis. However, specific correlations between each hormone and patterns of functional connectivity were found in both menstrual cycle phases.

Conclusion(s): It seems that the association between female sex hormones and brain Rs-FC is menstrual cycle phase–dependent. Future studies should examine the cognitive and behavioral correlates of this association in regularly cycling women. (Fertil Steril® 2017;107:1246–55. ©2017 by American Society for Reproductive Medicine.)

Key Words: fMRI, hormones, ICA, menstrual cycle, SBA

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Estradiol and P mediate a cascade of neuroendocrine functions, with structural and functional implications to the central nervous system. Previous studies have shown that E_2 and P regulate the availability and function of monoamines, neurogenesis, inflammatory processes, and also play a role in regulating cognitive and affective processes (1–4). Sex hormones also have been suggested to play a role in functional cerebral asymmetries by influencing interhemispheric inhibition of the dominant on the nondominant brain hemisphere (5).

Estradiol and P are present in various regions of the central nervous system: postmortem studies investigating estrogen receptor-α and estrogen receptor-β messenger RNA expression have found greatest localization in the hippocampal formation, claustrum, cerebral cortex, amygdala, hypothalamus, subthalamic nucleus, and the thalamus (4, 6–8). Although there is no literature that investigates messenger RNA expression in the human brain, a postmortem study reported high concentrations of P in the amygdala, hypothalamus, and cerebellum (9). In regularly cycling women allopregnanolone (ALLO), a neuroactive metabolite of P, also varies across the menstrual cycle; with the corpus luteum serving as the primary site of contribution, and a modest amount being synthesized in the brain (10, 11). Allopregnanolone is hypothesized to regulate mood and cognition through the modulation of γ-aminobutyric acid (GABA)-a receptors and by exerting regulatory effects on serotonin and noradrenaline (12, 13). Another important moderator of neurotransmitter systems and thereby emotion and cognition is Dehydroepiandrosterone sulfate, a neuroactive metabolite of DHEA (14). DHEAS also modulates GABA-a receptors and influences serotonin neuron firing and availability (14). Administration of both DHEAS and ALLO have been associated with decreased resting state functional connectivity (Rs-FC) between brain areas involved in mediating anxious and depressive behavior (15). Studies using task-based functional magnetic resonance imaging (fMRI) and structural MRI have found changes in regions critical to emotional regulation and cognition throughout the menstrual cycle, emphasizing the influence of sex hormones on the central nervous system (for review see references [3, 11, 16]). The influence of sex hormones on Rs-FC has been less investigated and may be useful in providing a picture of intrinsic brain activation patterns in response to endogenous hormones free of task related bias.

Resting state functional connectivity is commonly studied through the use of seed-based analysis (SBA) and independent component analysis (ICA). Seed-based analysis is a hypothesis-driven approach, through which the blood oxygen level–dependent (BOLD) signal of a predefined seed region is correlated with the BOLD signal of other regions in the brain. On the other hand, ICA is an exploratory, data-driven approach, which maximizes statistical independence by highlighting patterns of BOLD signal that are independent from one another (17). Both SBA and ICA approaches are commonly used to visualize the functional connectivity of resting state networks (RSNs). The synchronous use of both methods provides visualization of the functional connectivity of RSNs, and the connectivity of a priori seed regions integral to their function and maintenance.

Resting state functional connectivity literature examining the effects of hormonal fluctuations across the menstrual cycle is sparse and largely inconsistent. Two studies using repeated measures across the follicular, ovulatory, and mid-luteal phases found no differences in the functional connectivity of RSNs between menstrual phases (18, 19). Petersen et al. (20) scanned two different groups of women, one in the early follicular and the other in the late luteal phase, and found increased functional connectivity of the angular gyrus of the default mode network (DMN) (20). Further, a recent study examining volume and functional connectivity of the hippocampus across the menstrual cycle scanned the same group of women at four points of their menstrual cycle (early follicular, late follicular, ovulation, and late luteal). They reported increased functional connectivity of both the right and left hippocampus in the late follicular phase compared with the early follicular and late luteal phases (21). A longitudinal study scanned the same woman (n = 1) 32 times over the course of four menstrual cycles and reported a correlation of P levels with intrinsic connectivity changes in the right dorsolateral prefrontal cortex (dlPFC) and bilateral sensorimotor cortex (22). Finally, a SBA study found sex- and estrogen level–dependent influences in Rs-FC in the left and right laterobasal and centromedial amygdala (23). Here it is important to note that none of these studies assessed or controlled for the presence of premenstrual symptoms or premenstrual dysphoric disorder (PMDD). This may be problematic because PMDD has been associated with alterations in brain functional connectivity and in affective and cognitive processing during the late luteal phase (24–28).

The influence of sex hormones on functional networks involved in cognitive, emotional, and self-referential processing is vital to our understanding of brain activity during periods of endogenous hormonal fluctuation. Numerous RSNs have been identified. Among those, six commonly studied networks include the default mode network (DMN), salience network (SN), fronto-parietal network (FPN), meso-paralimbic network (MPN), visual network (VN), and sensorimotor network (SMN) (Table 1) (29–32).

The objectives of the present study were to examine [1] the Rs-FC of the six RSNs mentioned above, and [2] the influence of E_2, P, ALLO, and DHEAS on Rs-FC during the mid-follicular and late luteal menstrual phases in a well-defined sample of healthy, naturally cycling women with no PMDD. We hypothesized that sex hormones will correlate with Rs-FC in brain regions that are dense in hormone receptors, such as the limbic system and prefrontal cortical regions specific to each menstrual phase. On the basis of previous studies with repeated-measures design (18, 19), we also hypothesized that there would be no differences in Rs-FC of the six networks studied through either ICA or SBA between menstrual phases.

MATERIALS AND METHODS
Participants

This study was approved by the Hamilton Integrated Research Ethics Board and adhered to the tenets of the Declaration of