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Hippocampal volume and functional connectivity changes during the female menstrual cycle☆

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ABSTRACT

Hippocampal volume has been shown to be sensitive to variations in estrogen and progesterone levels across rodents' estrous cycle. However, little is known about the covariation of hormone levels and brain structure in the course of the human menstrual cycle. Here, we examine this covariation with a multi-method approach that includes several brain imaging methods and hormonal assessments. We acquired structural and functional scans from 21 naturally cycling women on four time points during their cycles (early follicular phase, late follicular phase, ovulation and luteal phase). Hormone blood concentrations and cognitive performance in different domains were assessed on each of the measurement occasions. Structural MRI images were processed by means of whole-brain voxel-based morphometry and FreeSurfer. With either method, bilateral increases in hippocampal volume were found in the late follicular phase relative to the early follicular phase. The gray matter probability in regions of hippocampal volume increase was associated with lower mean diffusivity in the same region. In addition, we observed higher functional connectivity between the hippocampi and the bilateral superior parietal lobe in the late follicular phase. We did not find any reliable cycle-related performance variations on the cognitive tasks. The present results show that hormonal fluctuations covary with hippocampal structure and function in the course of the human menstrual cycle.

Introduction

The variations of female sex hormones over the menstrual cycle in mammals are connected to neural changes, including structural as well as functional transformations in different brain regions (e.g., Czoty et al., 2009; Desmond and Levy, 1997; Olmos et al., 1989; Qiu et al., 2013; Woolley, 1998; Woolley and McEwen, 1993). Estrogen and progesterone, the two main ovarian steroids, have received most attention in this research field. A multitude of animal studies has revealed detailed insights into hormone-related structural brain alterations. However, only a few studies investigated this topic in humans, and many of the previous studies lack adequate hormonal assessments or hypothesis-free whole-brain neuroimaging methods.

Basic knowledge about the association between the estrous cycle of female rats and neuroplasticity comes from a number of studies conducted by Woolley and colleagues. Naturally occurring variations in estrogen and progesterone have been shown to covary with spine density in the cornu ammonis 1 (CA1) hippocampal pyramidal cells (Woolley and McEwen, 1990). Increasing estrogen levels were accompanied by increasing spine density. In further experiments it was documented that not only spine density in the hippocampus increases following rise of estrogen, but that new synapses are built and the sensitivity of the synapses (to NMDA receptor-mediated input) is increased (Woolley et al., 1996, 1997). Estrogen effects on the brain are altered by progesterone and might vary between species (Pawluski et al., 2009; Woolley and McEwen, 1993). Following up on these seminal studies, researchers explored estrogen-dependent variations in cognitive function. Because the hippocampus has been demonstrated to be one of the main hormone-sensitive targets in the brain, hippocampus dependent cognitive functions, such as spatial-memory tasks, were investigated. Results are mixed, showing differences in associations to endogenous and exogenous hormonal variation, dose-and duration-specific reactions, and interactions between different gonadal hormones on cognitive functions (e.g., Bimonte and Denenberg, 1999; Chesler and Juraska, 2000; Gibbs, 2000; Korol and Kolo, 2002; O'Neal et al., 1996; Stackman et al., 1997). Some studies find evidence for decreased spatial abilities (i.e., spatial learning and spatial recognition memory) in high-estrogen phases during the cycle (e.g., Galea and Kavaliers, 1995; Lacreuse et al., 2001). Other studies revealed that

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estrogen administration in ovariectomized rats results in better spatial performance (i.e., spatial working memory; Fader et al., 1998; O'Neal et al., 1996). Lastly, some researchers report stable spatial-memory performance across the estrous cycle (Stackman et al., 1997). Results are more convergent for spatial strategies used to solve navigation tasks: rats prefer allocentric (hippocampal-based) strategies when exposed to high estrogen levels and egocentric (striatal-based) strategies when exposed to low levels (Hussain et al., 2014; Korol et al., 2004; Qiu et al., 2013). The different degrees to which spatial memory tasks rely on these learning strategies make comparisons between studies difficult.

More recently, hormone-related variations in cognition and neural plasticity in human females have come under empirical investigation. Compared to the five-day estrous cycle in rats, the human menstrual cycle takes about 28 days, and can be subdivided into four phases: first, the early follicular phase (EFP) during menses, where the steroid concentrations are low; second, the late follicular phase (LFP), where estrogen is at its highest levels and progesterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are low; third, the ovulation, with LH and FSH at their peaks; fourth, the luteal phase, in which estrogen and progesterone are both at high levels. Most studies so far compared the luteal with the early follicular phase to arrive at a high estrogen/progesterone vs low estrogen/progesterone contrast. Looking at cognitive performance, a number of studies have reported lower spatial (e.g., mental rotation) performance during cycle phases with high estrogen/progesterone levels (e.g., Hampson, 1990; Hausmann et al., 2000; Silverman and Phillips, 1993). In contrast, other studies show no overall influence of varying estrogen/progesterone levels on those abilities (e.g., Epting and Overman, 1998; Rosenberg and Park, 2002). In opposition to spatial abilities, verbal memory performance was shown to improve with high estrogen levels (Rosenberg and Park, 2002), but again, not all studies have found effects of menstrual cycle phases in this domain (Mihalj et al., 2014). The difficulty to separate memory and spatial skills in cognitive tasks hampers the comparison of results across studies.

Only few studies so far have looked at hormone-related structural plasticity in the female brain. Hagemann et al. (2011) investigated short-term whole-brain volume changes in total gray matter (GM) across the menstrual cycle. They found a GM volume peak along with a reduction of cerebrospinal fluid at time of ovulation. Individual differences in the magnitude of these volume changes were not reliably related to changes in estrogen or progesterone hormone levels between the respective phases. Ossewaarde et al. (2011) restricted their analysis to changes in the amygdala. Measuring the participants on two different time points during the cycle (follicular and luteal phase), they found an increase in the dorsal part of the left amygdala in the luteal phase. In a recent voxel-based morphometry (VBM) study, De Bondt et al. (2013) found structural changes in a number of frontal and temporal regions when comparing the follicular and luteal phase of 15 young, naturally cycling women. Larger GM volumes during the follicular phase were found inter alia in the anterior cingulate cortex (ACC) and fusiform gyrus. In addition, a negative correlation between estrogen and GM volume in the ACC was found during the luteal phase. The authors discuss these neural changes in relation emotional processing in women across the menstrual cycle. The results of two other studies applying VBM (Pletzer et al., 2010; Protopopescu et al., 2008) are in line with findings from the animal literature. Both studies show evidence for structural changes in the hippocampal formation during the menstrual cycle. Pletzer et al. (2010) found an increase in a right fusiform/parahippocampal gyrus region of interest (ROI) during the early follicular (low hormonal) phase, compared to the mid-luteal (high hormonal) phase. In contrast Protopopescu et al. (2008) found a right hippocampal GM increase during the peak estrogen late follicular phase, compared to the late luteal (low hormonal) phase. Furthermore, Protopopescu et al. (2008) found that verbal memory was increased during the peak-estrogen phase, pointing to a connection between cognitive and brain structural changes. In both studies, participants were measured at two time points during their cycle, but the exact cycle phases measured differ between the studies, rendering direct comparisons difficult. In addition, neither of the two studies assessed hormonal levels, which further weakens the conclusions that can be drawn from these studies. It remains unclear, whether the knowledge about cycle-related hippocampal plasticity can be transferred from animal studies to humans. The animal pattern predicts that the hippocampal volume follows the estrogen increase from early to late follicular phase and stays high until the luteal phase, where it starts decreases again due to elevated progesterone levels. This pattern would suggest more strongly that the same mechanisms underlying hormone-related hippocampal plasticity in animals come in consideration in humans.

To summarize, the human structural magnetic resonance imaging (MRI) literature provides some initial evidence that structural changes over the menstrual cycle are present in women. Almost all of the available studies are restricted to two time points only, and hence give a very impoverished picture of the hormonal changes during the menstrual cycle and their potential relations to the structure and function of the brain. In addition, actual hormone levels are often not measured. Finally, differences in the timing of measurements in relation to the menstrual cycle additionally hinder comparisons across studies. Reliable within-subject differences in brain structure and function of women during the menstrual cycle would have important implications for neuroimaging research. A proportion of observed between-subject variance might be explained by within-person fluctuations and this cycle-related variability could distort cross-sectional and longitudinal neuroimaging findings.

With the present study we aimed at investigating structural and functional brain changes over the female menstrual cycle by measuring young women at four different occasions according to the four cycle phases. Following up on the studies by Pletzer et al. (2010) and Protopopescu et al. (2008), we expected that the hippocampus is especially sensitive to hormonal variation. To test this assumption most conservatively, we applied whole-brain voxel based comparisons that are uninfluenced by our a priori hypotheses. Based on animal results (Woolley, 1998), we hypothesized hippocampal structure and connectivity to increase from low to high estrogen phases. We mainly expected hippocampal differences when contrasting early and late follicular phase. This contrast compares a high and low estrogen phase, while being relatively unaffected by progesterone levels. In the luteal phase, effects of progesterone might attenuate the effects of estrogen. Based on this main phase contrast, we wanted to investigate the pattern of hippocampal variation across the whole menstrual cycle. Corresponding to estrogen levels, we expected to find increased volume in late follicular, ovulatory and luteal phase, but volume at ovulation and luteal phase might be lower compared to late follicular phase, indicating oppositional effects rising progesterone levels. We also included cognitive variables to explore whether cognitive performance would vary across cycle phases, and covary with changes in estrogen levels.

Methods

Participants

Twenty-five right-handed, healthy women were included in the initial study sample after written informed consent. The study was conducted according to the Declaration of Helsinki, with approval of the German Psychological Society ethics committee. All women reported regular menstrual cycles (mean 28 days, range 26–30 days). We recruited women who did not use hormonal contraceptives during the three months preceding the study. All participants reported no history of neurological or psychiatric conditions or of drug/alcohol abuse. Four women participated in only two of the four measurement occasions and were excluded from the analyses, because information on the