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Sex differences during emotion processing are dependent on the menstrual cycle phase

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A B S T R A C T

Sex differences in the neural processing of emotion are of special interest considering that mood and anxiety disorders predominant in females. However, these sex-related differences were typically studied without considering the hormonal status of female subjects, although emotion processing in the brain was shown to differ between phases of the menstrual cycle. In this functional MRI study, we demonstrated the influence of the menstrual cycle phase on sex differences in brain activity and functional connectivity during negative and positive emotions, using two different paradigms: emotion perception and emotion experience. Twenty naturally cycling healthy women without premenstrual symptoms were scanned twice: during the mid-follicular and late-luteal menstrual phases, and compared to a matched group of twenty healthy men. During negative emotion perception, men showed increased neural activity in the right hippocampal formation relative to women in the mid-follicular phase, and increased activity in the right cerebellum relative to women in the late-luteal phase. During experience of amusement, reduced putamen-ventrolateral prefrontal cortex and putamen-dorsomedial prefrontal cortex functional connectivity were observed for women in the late-luteal phase relative to men and associated with levels of sex hormones. These neural and hormonal findings were complemented by behavioral reports of reduced amusement and increased sadness in late-luteal women. Our results demonstrate menstrual phase-dependent sex differences in emotion perception and experience and may suggest a biological tendency for a deficient experience of pleasure and reward during the late-luteal phase. These findings may further shed light on the underlying pathophysiology of premenstrual dysphoric disorder.

1. Introduction

Sex differences in the neural processing of emotions have been increasingly demonstrated across the brain (Filkowski et al., 2017). These distinctions between the sexes in emotion processing are of special interest considering the known female predominance in the prevalence of mood and anxiety disorders (Steel et al., 2014). However, sex-related neural differences are typically studied while neglecting the hormonal status of female subjects. The menstrual cycle is typically divided to follicular and luteal phases, in which the follicular phase refers to the period after menstruation and until ovulation and the luteal phase refers to the period between ovulation and menses-onset. During the menstrual cycle, endogenous levels of estrogen and progesterone show considerable fluctuations (Sakaki and Mather, 2012). Both estrogen and progesterone levels are low during the early-follicular phase, with a marked rise in estrogen during the late-follicular phase. Progesterone levels increase during the early-luteal phase and peak in the mid-luteal phase, in parallel to a second peak in estrogen. These sex hormones cross the blood-brain barrier and were shown to influence nearly all neurotransmitter systems and mood regulatory circuits (Rubinow and Schmidt, 2006).

Several studies indicated changes in brain reactivity to emotional stimuli in women across phases of the menstrual cycle (Comasco and Sundström-Poromaa, 2015; Toffoletto et al., 2014). In response to negative emotional linguistic stimuli, activity in the anterior-medial orbitofrontal cortex was increased during the late-luteal relative to the

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mid-follicular phase with the inverse pattern shown in the lateral orbitofrontal cortex (Protopopescu et al., 2005). Increased hippocampal and amygdala activity during the mid-luteal relative to the early-follicular phase was shown in response to negative emotional images (Andreano and Cahill, 2010). In response to negative emotional faces, progesterone administration during the follicular phase to reach luteal levels resulted in increased amygdala activity (van Wingen et al., 2008), while another study found the opposite results, with increased amygdala activity during the follicular compared to the luteal phase (Derntl et al., 2008b).

While the influences of sex or menstrual cycle on emotion have been studied separately, studies considering both sex and menstrual phase are scarce. In response to negative images, greater neural sex differences were found when women were in the late-follicular compared to the early-follicular phase (Goldstein et al., 2010). These differences were most pronounced in the medial and ventromedial prefrontal and orbitofrontal cortices. A recent event-related potentials (ERP) study found an indication for less suppression of negative emotion in mid-luteal women than in men with no sex differences during the follicular phase (Lusk et al., 2017). Taken together, these findings suggest that overlooking the menstrual cycle phase of women may potentially lead to partial information or distorted observations of sex differences in emotional responses.

Functional connectivity refers to the level of temporal synchronization between distinct brain regions and is thought to play a key role in complex brain processes such as emotion, by integration of the computation occurring in distributed regions (van den Heuvel and Hulshoff Pol, 2010). While most of the studies on neural sex differences in emotion have examined brain activity, hardly any explored functional connectivity during emotion processing. Among the few that did, sex differences in fronto-limbic functional and effective connectivity were demonstrated during negative emotion processing (Lungu et al., 2015; Mareckova et al., 2016). In another study (Moriguchi et al., 2014), enhanced functional connectivity in men between the dorsal anterior insula and the dorsal anterior cingulate cortex was found across negative and positive stimuli. These studies highlight the possible importance of examining not only neural activity but also functional connectivity during emotion processing. Most importantly, no study to date has tested the influence of the menstrual cycle on sex differences in functional connectivity during emotional states.

Here, we aimed to examine the dependency of sex differences in neural functional connectivity and activity during emotion perception and experience on the menstrual cycle phase. To this end, we carried out an fMRI study of healthy young men and women, with each woman measured twice: during the mid-follicular and late-luteal phases of the menstrual cycle. Two different emotion paradigms were used, one for emotion perception and the other for emotion experience. Note, that female subjects did not take any hormonal contraceptives and were carefully chosen so that they have no premenstrual symptoms according to daily prospective evaluations.

Based on the previous literature discussed and recent reviews pointing to overlapping networks for the processing of positive and negative emotions (Guillory and Bujarski, 2014; Touroutoglou et al., 2015), we predicted that behavioral and neural sex differences in emotion processing will be more pronounced during the late-luteal phase for both positive and negative emotions and found in limbic and prefrontal regions.

2. Materials and methods

2.1. Subjects

The sample was composed of 20 women (age: 24.45 ± 2.28 years) and 22 men (age: 23.82 ± 2.8 years). Subjects were recruited among undergraduate students at the Hebrew University of Jerusalem as part of a larger study on biological and psychological factors in reactive psychiatric disorders. Before inclusion, subjects were evaluated by a psychiatrist using the Structured Clinical Interview for DSM-IV (SCID-CV) to exclude past or present psychiatric, neurological or hormonal disorders. One male subject was excluded due to family history of schizophrenia and another male subject was excluded due to anxiety during the MRI scan, which yielded a final sample of 20 men (age: 23.75 ± 3 years). Additional exclusion criteria for women were: use of hormonal contraceptives, pregnancy, breast-feeding or premenstrual symptoms. Premenstrual symptoms were evaluated based upon daily, prospective symptom ratings on the Daily Record of Severity of Problems (DRSP) (Endicott et al., 2006) scale during at least two menstrual cycles prior to inclusion. Inclusion criteria on the DRSP were: an average score ≤ 2 for all DRSP items during the mid-follicular phase, an average score ≤ 2 for all DRSP items during the late-luteal phase and no core mood symptoms or functional impairment score > 2 on any day during the late-luteal phase. In addition, DRSP scores of the whole cycle were evaluated to rule out mood changes occurring outside the mid-follicular and late-luteal phases. Women were required to have no core mood symptom or functional impairment score > 3 on any day of the menstrual cycle. Out of 84 female subjects clinically evaluated that satisfied the initial inclusion criteria, 20 fulfilled the DRSP inclusion criteria and were included in the study. Note, that 63% (53 out of 84) of our initial female sample were found to have some degree of premenstrual mood fluctuations and taken out of the study, in congruent with previous reported rates of premenstrual symptoms (Robinson and Swindle, 2000; Wittchen et al., 2002).

Women and men were matched for age, education, religion, socio-economic status, marital status, birth country and handedness (Table 1). All subjects were instructed not to consume caffeine or nicotine at least 3 h prior to the MRI scan as it was shown these may affect blood flow and fMRI measures (Newhouse et al., 2011; Wong et al., 2012). FMRI-based power analysis was done on pilot data of 10 women

Table 1
Demographic characteristics of female and male subjects.

Demographic variables	Female subjects (n = 20)	Male subjects (n = 20)	Statistics
Age, years	24.45 ± 2.28 (21–29)	23.75 ± 3 (19–29)	$t = 0.82, p = 0.412$[c]
Education, years	13.75 ± 1.06 (12–16)	14.4 ± 2.23 (12–20)	$t = 1.17, p = 0.25$[c]
Marital status	19 single, 1 married	16 single, 4 married	$\chi^2 = 2.05, p = 0.151$[d]
Socio-economic status[a]	3.5 ± 0.61 (2–4)	3.7 ± 0.47 (3–4)	$t = 1.11, p = 0.274$[c]
Religion	8 religious, 3 traditional[b], 9 secular	8 religious, 3 traditional, 9 secular	$\chi^2 = 0, p = 1$[d]
Birth country	18 Israel, 2 USA	19 Israel, 1 USA	$\chi^2 = 0.36, p = 0.548$[d]
Handedness	18 right, 2 left	13 right, 7 left	$\chi^2 = 3.58, p = 0.058$[d]

[a] Socio-economic status was evaluated by a self-administered questionnaire, where 1 indicates great economic difficulties and lack of basic commodities and 4 indicates good economic welfare without any economic difficulties.
[b] Traditional is an Israeli common term of self-definition that describes those who perceive and define themselves as neither strictly religious nor secular.
[c] p values were obtained using two-sample two-tailed t tests.
[d] p values for marital status, religion, birth country and handedness distributions between the groups were obtained using Pearson's chi-squared test.