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

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ABSTRACT

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.

and 10 men not included in this study using PowerMap software package (Joyce and Hayasaka, 2012), developed specifically for neuroimaging studies. Power calculations indicated at least 80% power to detect between-group effects in subcortical regions for a sample size of 20 subjects in each group. The study was approved by the Hadassah Hebrew University Medical Center Ethics Committee. All participants provided written informed consent prior to inclusion in the study and the study was carried out in compliance with the Declaration of Helsinki.

2.2. Study design and fMRI protocol

Each woman completed two MRI scans: once during the mid-follicular phase (6–12 days after onset of menses) and once in the late-luteal phase (1–7 days before onset of menses). The luteal phase scanning sessions were scheduled according to a positive luteinizing hormone (LH) assay, confirmed by estradiol and progesterone serum concentrations and onset of the next menstrual bleeding. To counterbalance test order effects across the menstrual cycle, half of the women were scanned first in the mid-follicular phase and half were scanned first in the late-luteal phase. A blood sample was collected from each woman on the day of each MRI scan or the day before/after the scan, to measure estradiol and progesterone serum concentrations. All blood samples were collected between 7–9 AM. Men underwent one MRI scan. Each MRI scan included the following sequence: (i) two versions of the emotional face matching task (negative, positive) to test neural reactivity and (ii) emotion experience task: mood induction of prolonged states of sadness and amusement to test neural functional connectivity. The order of the two versions of the emotional matching task (negative, positive) was counterbalanced across each group of subjects (men, women). The order of the mood induction states (sadness, amusement) was also counterbalanced across each group of subjects (men, women).

2.3. Experimental paradigms

2.3.1. Emotion perception: emotional face matching task

Two versions of the emotional face matching task (Hariri et al., 2002) were used: a negative emotional matching task, identical to Hariri's original task, and a positive emotional matching task completed by a subset of the subjects (19 men, 11 women). In both versions, the block-design paradigm consisted of five blocks of a perceptual face processing task interleaved with six blocks of a sensorimotor control task. During the emotion blocks, a target face was presented at the top of the screen and subjects were instructed to select one of two faces presented at the bottom which showed the same emotional expression as the target face. During the sensorimotor blocks, a target ellipse was presented at the top of the screen and subjects were instructed to select one of two ellipses presented at the bottom which was at the same orientation as the target ellipse. Facial stimuli were derived from Ekman's Pictures of Facial Affect (POFA) (Ekman and Friesen, 2003). Each block consisted of six trials, each presented for 4 s, and started with an instruction ('match the emotion in the face' or 'match the orientation of the shape') presented for 2 s. Each emotion trial consisted of faces of the same sex and the identity of all three faces was different. Each emotion block had an equal mix of the sex of the actors. Subjects responded by pressing one of two possible buttons with their right hand and subject accuracy and reaction time were collected for each trial.

The first version of the task, the "negative emotional matching task", used angry and fearful facial expressions as in Hariri's original task. Each emotion block had three trials of anger as the target emotion and three trials of fear as the target emotion. The second version of the task, the "positive emotional matching task", used happy and neutral facial expressions and the happy facial expression was always the target face. Both tasks were designed to analyze neural activity.

2.3.2. Emotion experience: prolonged mood induction

This paradigm was designed to measure functional connectivity during discrete, intense and realistic emotions. The paradigm included two mood induction states: a continuous exposure to sad films (10 min) and a continuous exposure to amusing films (10 min). Each mood induction state was composed of four film clips (2–3 min each) presented in a row. A continuous exposure to four neutral film clips (10 min) was presented between the mood states and was not analyzed here. Film clips were preferred on other types of stimuli from the following reasons. Films were shown to elicit intense activations across many response systems associated with emotion (Rottenberg et al., 2007). In addition, in contrast to other types of available stimuli such as the International Affective Picture System (IAPS) (Lang et al., 2008) that were designed to provoke mainly negative or positive valence with different levels of arousal, films enable to induce specific emotion categories (e.g. sadness and amusement). Before the MRI scan, subjects were instructed to allow themselves to feel in a whole and free manner whatever feelings or emotions that come up without trying to suppress them. Passive viewing was chosen without any cognitive task such as rating of the stimuli since constraining attention or involvement in a task has been shown to reduce the intensity of the emotional response (Monk et al., 2008; Phan et al., 2002). Immediately after the MRI scan, subjects rated outside the scanner each mood induction state separately using a similar questionnaire to that of Gross and colleagues (Rottenberg et al., 2007). Each questionnaire included ratings of 18 discrete emotions, valence and arousal on a 1-to-8 Likert scale. Subjects were encouraged to report honestly their emotions during the films and try to separate them from their general mood that day, from what they think other people felt or what they believe people should feel in reaction to the films. It was emphasized that there are great individual differences in reactions to films.

The film clips were taken from sets of films previously validated to generate mood induction (Farb et al., 2010; Gross and Levenson, 1995; Rottenberg et al., 2007; Schaefer et al., 2010) (see Supplementary Table S1 for the full list of film clips used). The films were first tested in a separate behavioral study on an independent group of 20 undergraduate Israeli students, to examine and assure their ability to selectively induce the targeted discrete emotion (i.e. sadness and not a mixture of sadness and fear) with a high level of intensity. Of the tested films, the best film clips (i.e. the ones inducing the most intense and discrete target emotions of sadness or amusement) were chosen to be shown in the MRI scanner. The behavioral testing procedure was conducted as described previously by Gross and Levenson, 1995 and Schaefer et al. (2010) (see Supplementary Methods for detailed description of the behavioral experiment and its results). The films were matched for duration, number of actors and social interaction. All film clips were in English and Hebrew subtitles were added.

2.4. fMRI data acquisition

Magnetic resonance images were acquired with a 3T MR scanner (Magnetom Skyra, Siemens, Germany). Functional images were acquired using T_2^*-weighted gradient-echo echo-planar imaging (GE-EPI) sequence with TR = 2 s, TE = 30 ms, image matrix = 64 × 64, field of view = 192 x 192 mm, flip angle = 90°, resolution = 3 × 3 × 3 mm, interslice gap = 0.45 mm. High resolution anatomical images were acquired using a sagittal T1-weighted MP-RAGE sequence with TR = 2.2 s, TE = 2.43 ms, resolution = 1 × 1 × 1 mm. The T1-weighted images were acquired for coregistration and normalization of the functional images.

2.5. Data analysis

2.5.1. Behavioral data analysis

Subject accuracy and reaction time were calculated separately for each version of the emotional face matching task. Group differences in

performance between men and women (men vs. women in the mid-follicular phase, men vs. women in the late-luteal phase) were evaluated by using two-sample two-tailed *t* tests. Group differences in performance between women's menstrual phases were evaluated by using paired two-tailed *t* tests.

For the subjective ratings of emotion experience during the mood induction, group differences were tested for the following measures: valence, arousal and intensity of the target emotion (sadness or amusement). The intensity of sadness was calculated as the average rating for "sadness" and "sorrow" and the intensity of amusement was calculated as the average of "amusement" and "pleasure". Group differences between men and women (men vs. women in the mid-follicular phase, men vs. women in the late-luteal phase) in each measure were evaluated by two-way mixed ANOVA models with sex (women, men) and emotion (sadness, amusement) factors. Group differences between women's menstrual phases were evaluated by a two-way repeated measures ANOVA model with menstrual phase (mid-follicular, late-luteal) and emotion (sadness, amusement) factors. Significant interactions were further analyzed using Tukey's HSD tests. Note that the measure of arousal was added to the original post-film questionnaire after the beginning of the study, thus arousal ratings were missing from 9 women.

2.5.2. Hormonal analyses of blood samples

Blood samples were collected via venipuncture in vacutainer tubes containing no anticoagulant. Blood was immediately centrifuged for 10 min at 1500 RPM, with no brake to stop centrifugation. The supernatant (serum) was aspirated into Eppendorf tubes and stored at −80 °C. Serum samples were subjected to capture sandwich immunoassay using commercial ADVIA Centaur Progesterone and Enhanced Estradiol (the most potent estrogen) assays at the Hadassah Ein-Kerem Biochemistry Lab. The assay was performed according to the manufacturer's protocol. The fluorescent intensity was acquired using ADVIA Centaur XP systems reader.

2.5.3. VBM analysis

Previous studies have highlighted the importance of accounting for individual gray matter (GM) volume when analyzing functional neural differences between the sexes (Filippi et al., 2013). For this purpose, voxel-based morphometry (VBM) analysis was conducted using VBM8 toolbox implemented in Statistical Parametric Mapping (SPM8, Wellcome Trust Centre for Neuroimaging, London, United Kingdom, http://www.fil.ion.ucl.ac.uk/spm/software/spm8). The total GM, white matter (WM), cerebrospinal fluid (CSF) and intracranial volumes were calculated for each subject. The following steps were performed: (1) normalization of T1-weighted images to the Montreal neurological institute (MNI) space using affine transformation; (2) segmentation of the affine transformed images into GM, WM and CSF; (3) normalization of each segment to its template using Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL); (4) using the deformation fields created in the third step to normalize the original T1-weighted images into the MNI space using DARTEL and (5) adjusting for volumetric confounds introduced by normalization (i.e. modulation). The default VBM8 settings were used except for sampling distance which was assigned a value of 1 for greater accuracy. The GM volume obtained from the VBM analysis was used as a nuisance regressor in all second level analyses to account for differences in GM volume between subjects.

2.5.4. Emotional face matching task analysis

Standard initial preprocessing of functional MRI data used SPM8 software. Functional images were spatially realigned, coregistered to T1 anatomical images, normalized to MNI space and resampled at an isotropic voxel size of 2 mm. The normalized images were smoothed with an isotropic 8 mm full-width-at-half-maximum Gaussian kernel. First and second level analyses were conducted in SPM8. Single subject activation maps were computed with the general linear model (GLM) on the blood oxygenation level dependent (BOLD) contrast signals. One regressor for each condition (emotion and sensorimotor) was convolved with the canonical hemodynamic response function combined with the time derivative. For each subject, contrast maps of the beta values of the regressor for emotional stimuli subtracted by the beta values for the sensorimotor stimuli were obtained. These contrast maps were then used for group comparisons. Three separate one-way ANCOVA models were implemented by a GLM to test for the following between-group differences: (i) men vs. women in the mid-follicular phase, (ii) men vs. women in the late-luteal phase and (iii) women in the mid-follicular vs. late-luteal phase, all models including the GM covariate. A statistical threshold of uncorrected voxel-level $p < 0.001$, FDR cluster-extent corrected for multiple comparisons at $p < 0.05$ was used. The relationships between neural clusters showing between-group differences and female sex hormones were assessed using Pearson's correlation. MRIcroGL (http://www.mccauslandcenter.sc.edu/mricrogl/) was used for visualization of the results.

2.5.5. Functional connectivity during mood induction analysis

After initial preprocessing steps in SPM8 (realignment, coregistration, normalization, smoothing), functional MRI data during mood induction states were further preprocessed for functional connectivity analysis using CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012). Censoring was done according to the method of Power et al. (2014) to remove motion-related artifacts. In addition, the six motion parameters and their first order derivatives were regressed out and potential effects of the beginning of each emotional state were removed by a step function convolved with the hemodynamic response function. Furthermore, the aCompCor method (Behzadi et al., 2007) was applied to regress out the first two principal components (PCAs) of the CSF and white matter signals. This was done to minimize the effects of potential physiological non-neuronal signals such as cardiac and respiratory signals, without the risk of artificially introducing anticorrelations into the functional connectivity estimates. Prior to regression of PCAs, the white matter and CSF masks were eroded to ensure only pure white matter or CSF signal were regressed from the data. Last, linear detrending and band-pass filtering (0.009–0.08 Hz) were applied. This frequency band was chosen based on studies showing greater effects of motion for frequencies above 0.08 Hz and specifically in the range of 0.08–0.1 Hz (Satterthwaite et al., 2013). Region of interest (ROI)-ROI functional connectivity analysis was done using the 90 cerebral Automated Anatomical Labeling (AAL) (Tzourio-Mazoyer et al., 2002) regions as ROIs. The average BOLD signal was computed from each ROI. Pearson's correlations were computed between each pair of ROIs and Fisher's transform was applied to the correlation values.

Between-group analyses were done in CONN. To test for the following between-group differences: (i) men vs. women in the mid-follicular phase and (ii) men vs. women in the late-luteal phase, two separate two-way mixed ANCOVA models were implemented by a GLM with sex (men, women) as a between-subject factor, emotion (amusement, sadness) as a within-subject factor and GM volume as a covariate. Significant interactions were further analyzed using Tukey's HSD tests. To test for differences between women's menstrual phases, a two-way repeated measures ANCOVA model was implemented by a GLM with menstrual phase (mid-follicular, late-luteal) and emotion (amusement, sadness) as within-subject factors and GM volume as a covariate. A statistical threshold of $p < 0.05$, FDR corrected for multiple comparisons was used. Following the above analysis, we further assessed the relationships between functional connections showing between-group differences and female sex hormones using Pearson's correlation. BrainNet Viewer (Xia et al., 2013) was used for visualization of the results.

3. Results

3.1. Sex hormones serum concentrations

The mid-follicular and late-luteal menstrual phases of women were verified by serum concentrations of sex hormones: (i) mid-follicular: estradiol: 318.03 ± 256.33 pmol/L, progesterone: 2.68 ± 1.64 nmol/L; (ii) late-luteal: estradiol: 394.94 ± 191.24 pmol/L, progesterone: 19.9 ± 17.18 nmol/L. Due to technical limitations (serum separation, kit sensitivity, amount of serum), hormone levels were missing for six women for the mid-follicular phase and for seven women for the late-luteal phase. The menstrual cycle phases differed significantly in levels of progesterone ($t = 3.45$, $p = 0.005$) but not in estradiol ($t = 1.11$, $p = 0.29$).

3.2. Emotion perception: emotional face matching task

3.2.1. Reaction time and accuracy

There were no significant differences in reaction time or accuracy between the three groups (men, women in mid-follicular phase, women in late-luteal phase) during performance of the emotional face matching task, for either the negative or positive version.

3.2.2. The negative emotional matching task- functional MRI analysis

Compared to women in the mid-follicular phase, men showed increased neural activity in response to negative emotional faces in the right hippocampus and parahippocampal gyrus (MNI: [22 −16 −16], $t = 4.504$, cluster size: 409 voxels) (Fig. 1a). Compared to women in the late-luteal phase, men showed increased neural activity in response to negative emotional faces in the right cerebellum: paravermal lobules VI, Crus I and Crus II and the dentate nucleus (MNI: [17–79 −34], $t = 5.702$, cluster size: 384 voxels) (Fig. 1b). No greater activity was found for women relative to men. No significant differences were found between women's menstrual phases. There was no correlation between neural clusters showing sex differences and female sex hormones.

3.2.3. The positive emotional matching task- functional MRI analysis

No differences in neural activity were found between the three groups.

3.3. Emotion experience: prolonged mood induction

3.3.1. Subjective ratings of emotion experience

3.3.1.1. Intensity of target emotion. A main effect of emotion was found when comparing men to women in the mid-follicular phase, where both sexes reported greater amusement than sadness [$F(1,38) = 14.07$, $p = 0.00058$] (Fig. 2a). There was no significant main effect of sex or interaction. When comparing men to women in the late-luteal phase, a sex-by-emotion interaction was found where women in the late-luteal phase reported less amusement and greater sadness compared to men [$F(1,38) = 6.8$, $p = 0.01263$] (Fig. 2b). There were no significant main effects. A significant menstrual phase-by-emotion interaction was found, where women in the late-luteal phase reported less amusement and greater sadness compared to women in the mid-follicular phase [$F(1,19) = 17.24$, $p = 0.00054$] (Fig. 2c). There were no significant main effects.

3.3.1.2. Valence. For all group comparisons, a significant main effect of emotion was found, with higher valence for amusement compared to sadness, as expected [women mid-follicular vs. men: $F(1,38) = 70.23$, $p = 3.6{\cdot}10^{-10}$, women late-luteal vs. men: $F(1,38) = 41.31$, $p = 1.6{\cdot}10^{-7}$, women mid-follicular vs. women late-luteal: $F(1,18) = 39.48$,

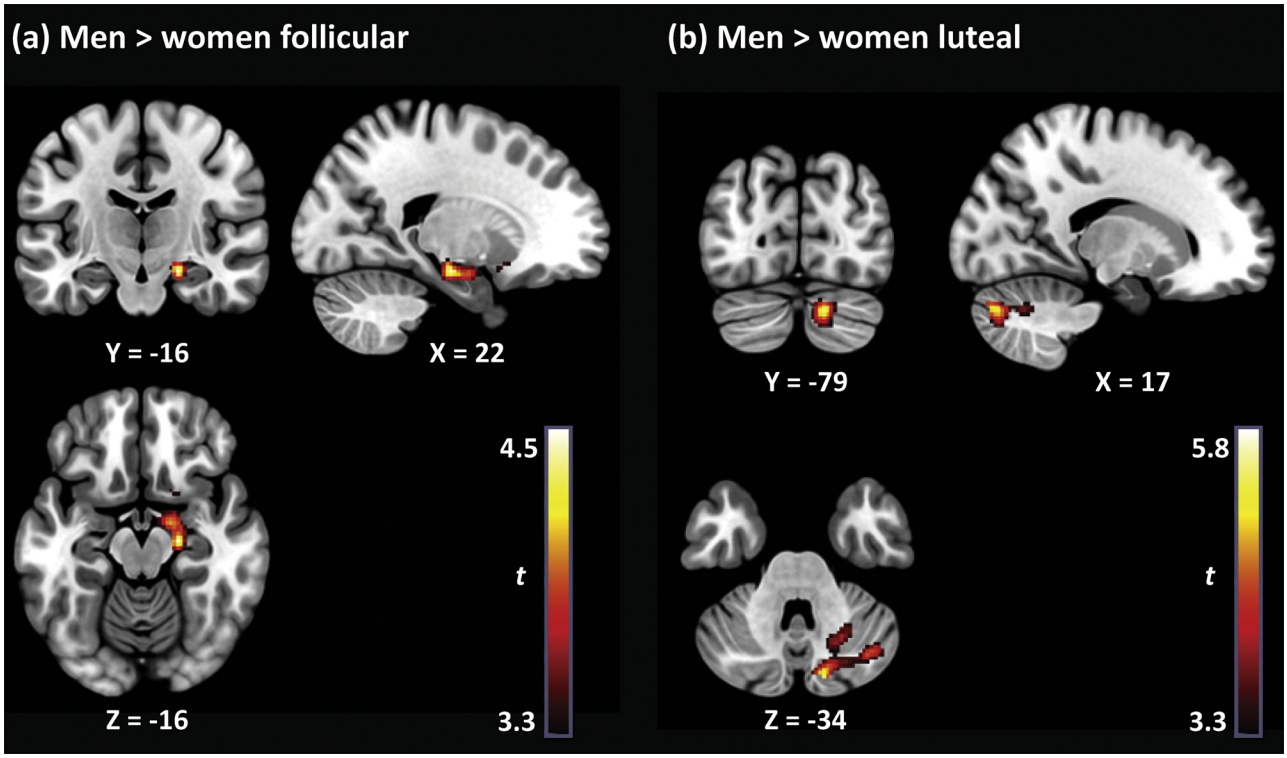

Fig. 1. Menstrual phase-dependent sex differences in neural activity during negative emotion perception. During the negative emotional face matching task **(a)** men showed increased neural activity in the right hippocampus and parahippocampal gyrus relative to women in the mid-follicular phase. **(b)** Men showed increased neural activity in the right cerebellum: paravermal lobules VI, Crus I and Crus II and the dentate nucleus, relative to women in the late-luteal phase. There was no greater activity found for women relative to men. Coordinates are presented in MNI space and *t* values are indicated by the color bar. Between-group differences were tested using one-way ANCOVA models implemented by a GLM controlling for gray mater volume. Uncorrected voxel-level $p < 0.001$, FDR cluster-extent corrected for multiple comparisons at $p < 0.05$.

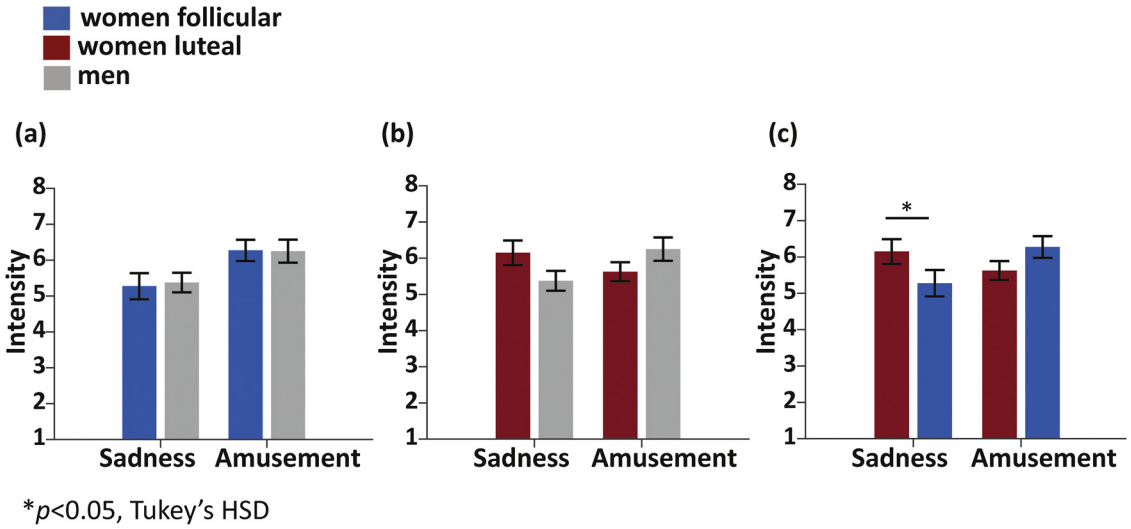

Fig. 2. Subjective behavioral report of emotion intensity during the emotion experience task. The y axis indicates the intensity of the target emotion rated on a 1-to-8 Likert scale. Subject groups (men, women in the mid-follicular phase, women in the late-luteal phase) are indicated by colors. Between-group differences were tested using two-way ANOVA models. **(a)**When comparing men to women in the mid-follicular phase, a main effect of emotion was found where both sexes reported greater amusement than sadness [$F(1,38) = 14.07, p = 0.00058$]. **(b)** When comparing men to women in the late-luteal phase, a sex-by-emotion interaction was found where women in the late-luteal phase reported less amusement and greater sadness relative to men [$F(1,38) = 6.8$, $p = 0.01263$]. **(c)** When comparing women between menstrual phases, a menstrual phase-by-emotion interaction was found [$F(1,19) = 17.24$, $p = 0.00054$]. Post hoc Tukey's HSD tests revealed significant greater sadness and marginally significant less amusement during the late-luteal phase. * denotes $p < 0.05$, Tukey's HSD test.

$p = 6.3{\cdot}10^{-6}$]. No main effects of sex/menstrual phase or interaction were found.

3.3.1.3. Arousal. A main effect of emotion was found when comparing men to women in the mid-follicular phase, where both sexes reported greater arousal during amusement compared to sadness [$F(1,29) = 8.72$, $p = 0.0061$]. There was no significant main effect of sex or interaction. No significant effects were found when comparing men to women in the late-luteal phase or for women between the menstrual phases.

3.3.2. Between-group differences in ROI-ROI functional connectivity

3.3.2.1. Men compared to women in the mid-follicular phase. A main effect of sex across emotional states was found for the following functional connections. Men showed stronger functional connectivity between the right inferior parietal gyrus and the left opercular inferior frontal gyrus ($p = 0.0329$, FDR corrected). Women in the mid-follicular phase showed a tendency for stronger functional connectivity between the left posterior cingulate cortex and the left orbital superior frontal gyrus ($p = 0.0529$, FDR corrected). No interaction between sex and emotional state was found.

3.3.2.1.1. Relationship between functional connections showing sex-differences and female sex hormones. During sadness, female functional connections showing a main effect of sex described above were correlated with sex hormones: right inferior parietal - left opercular inferior frontal gyrus was positively correlated with estradiol ($r = 0.564$, $p = 0.0443$), and left posterior cingulate - left orbital superior frontal gyrus was negatively correlated with progesterone ($r = -0.562$, $p = 0.0456$) (Fig. 4a). During amusement, no correlations were found between functional connectivity strength and sex hormones.

3.3.2.2. Men compared to women in the late-luteal phase. No main effect of sex across emotional states was found. Significant sex-by-emotion interactions were found for several ROI-ROI functional connections and presented in Figs. 3 and 4 and Table 2. The majority of functional connections showing an interaction effect were of the bilateral putamen (85% of connections, 17/20) (Fig. 3a). Most of the connections of the putamen were with the prefrontal cortex (94% of putamen connections, 16/17), particularly with the inferior frontal gyrus (50% of prefrontal connections, 8/16) and the dorsomedial prefrontal cortex, i.e. the bilateral anterior cingulate and medial superior frontal gyrus (31% of prefrontal connections, 5/16). Post hoc analysis (Tukey's HSD tests, $p < 0.05$) indicated that while men had stronger functional connections during amusement compared to sadness, women had either stronger functional connections during sadness compared to amusement or no difference in connectivity between emotional states (Fig. 3b). Since behavioral differences in the subjective report of emotion were also found between men and women in the late-luteal phase (Fig. 2b), we repeated the whole brain functional connectivity analysis while controlling for these differences in the subjective report. Significant sex-by-emotion interactions were found for 7 out of the 20 ROI-ROI functional connections that were significant without controlling for behavior (Supplementary Table S2). When using a 0.08 FDR corrected threshold, significant sex-by-emotion interactions were found for 11 out of the original 20 ROI-ROI functional connections.

3.3.2.2.1. Relationship between functional connections showing sex-differences and female sex hormones. During amusement, female functional connections showing sex-by-emotion interactions described above were negatively correlated with estradiol (significant correlations were found for 30% of connections (6/20), Fig. 4b) and progesterone (significant correlations were found for 15% of connections (3/20), Fig. 4c). Namely, for women in the late-luteal phase, higher levels of estradiol or progesterone indicated weaker functional connectivity during amusement. These correlations were found for putamen-dorsomedial prefrontal cortex connectivity and connections of the amygdala with the orbitofrontal cortex and calcarine gyrus. During sadness, no correlations were found between functional connectivity strength and sex hormones.

3.3.2.3. Women between different menstrual phases. No main effect of menstrual cycle phase or interaction between emotional state and menstrual phase were found.

4. Discussion

In this study, we demonstrated the influence of the menstrual cycle

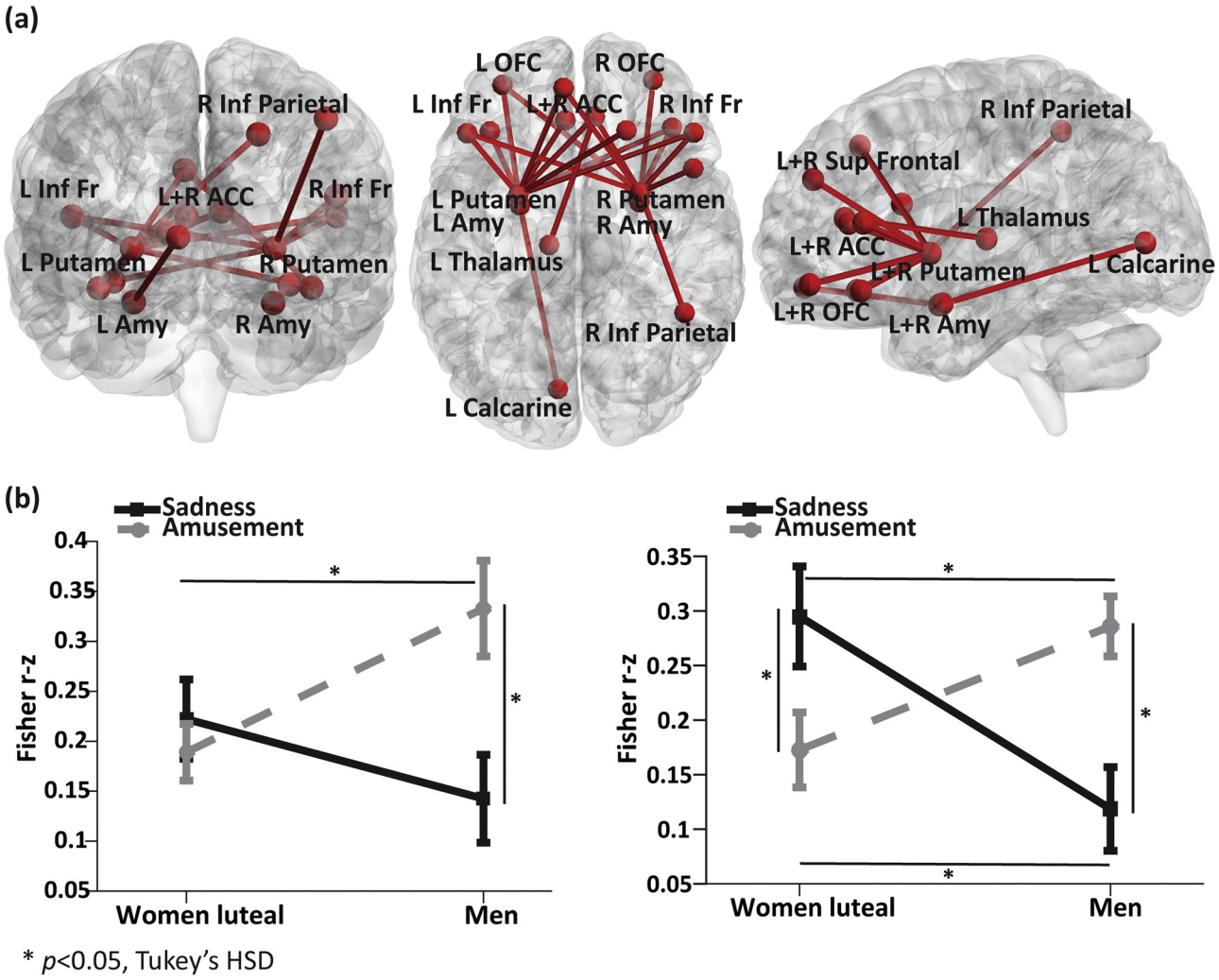

Fig. 3. Sex-by-emotion interaction between men and women in the late-luteal phase during emotion experience. **(a)** ROI-ROI functional connections showing sex (men, women in the late-luteal phase) by emotion (sadness, amusement) interactions. The majority of significant connections were between the putamen-ventrolateral prefrontal cortex and putamen-dorsomedial prefrontal cortex. Between-group differences were tested using a two-way mixed ANCOVA model implemented by a GLM controlling for gray mater volume. A statistical threshold of $p < 0.05$, FDR corrected for multiple comparisons was used. Abbreviations: ACC, anterior cingulate cortex; Amy, amygdala; Inf fr, inferior frontal gyrus; Inf parietal, inferior parietal gyrus; OFC, orbitofrontal cortex; Sup frontal, medial superior frontal gyrus. L, left; R, right. **(b)** Examples for two functional connections showing significant sex-by-emotion interaction. Fisher's transformed values (i.e. functional connectivity strength) are indicated by the y axis. While men had stronger functional connections during amusement, women had either no difference in connectivity between emotional states (left graph, left putamen – right anterior cingulate connection) or stronger functional connections during sadness (right graph, right putamen – left inferior frontal gyrus connection). Sadness is indicated by black solid lines and amusement by dashed gray lines. * denotes $p < 0.05$, Tukey's HSD test.

phase on behavioral and neural sex differences during different types of emotion processing (emotion perception and emotion experience). Namely, our results indicated that sex differences are not constant over the menstrual cycle but rather depend on the specific menstrual phase. Specifically, sex differences during emotion experience were examined in terms of functional connectivity between brain regions. Functional connectivity analysis was conducted during emotional states, as opposed to the commonly used "resting state", i.e. without external stimuli. By averaging over the mood induction, we aimed to characterize the relative "steady" brain state for each emotion.

The most important and novel finding of the current study was that sex differences in functional connectivity during emotion experience were dependent on the menstrual cycle phase, with greater sex differences indicated during the late-luteal phase. Sex-by-emotion interactions were found mainly for functional connections between the bilateral putamen and the inferior frontal gyrus, i.e. the ventrolateral prefrontal cortex (VLPFC) and between the bilateral putamen and the dorsomedial prefrontal cortex (DMPFC). The interactions were driven by stronger putamen-PFC connectivity during amusement for men, whereas women in the late-luteal phase did not show a difference in connectivity strength between amusement and sadness or had stronger connectivity during sadness. We argue that this finding reflects a tendency for a deficient experience of pleasure and reward during the late-luteal phase, based on the following complementing behavioral and hormonal results and previous published evidence.

Similarly to the functional connectivity findings, in the behavioral reports of emotion a sex-by-emotion interaction was found where women in the late-luteal phase reported less amusement and greater sadness relative to men. Moreover, men and women in the mid-follicular phase exhibited increased arousal and emotion intensity for amusement relative to sadness, not found for women in the late-luteal phase. Furthermore, associations were found between functional connections showing sex differences and female levels of estradiol and progesterone. During the late-luteal phase, estradiol and progesterone were negatively correlated with functional connections between subcortical (the putamen and amygdala) and prefrontal regions. During the

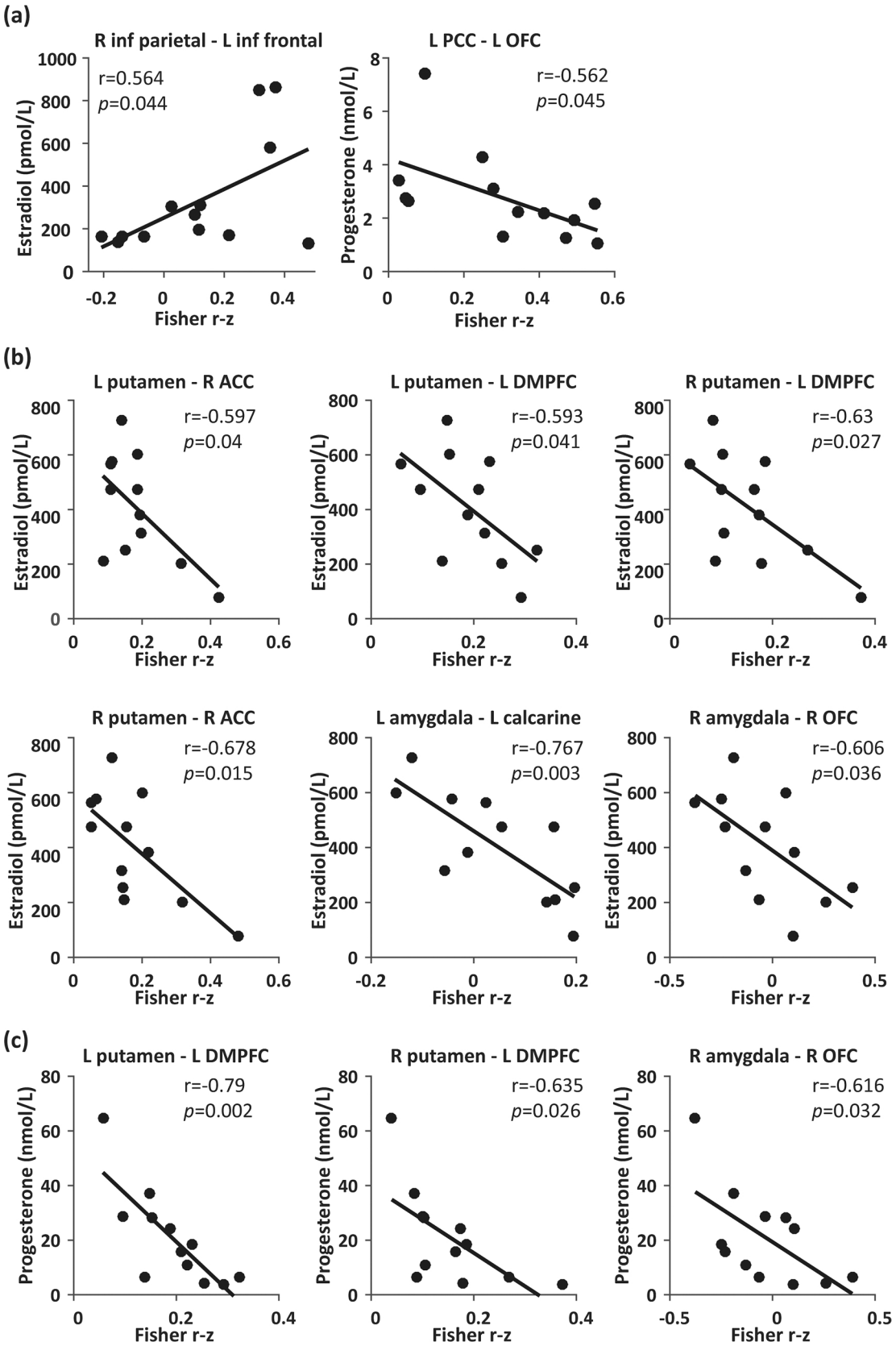

Fig. 4. Correlations between female sex hormones and functional connections showing sex differences. Female sex hormones (y axis) are plotted against Fisher's transformed values, i.e. functional connectivity strength (x axis). **(a)** During the mid-follicular phase, female functional connections showing a main effect of sex were correlated with estradiol (left) and progesterone (right) during sadness. **(b,c)** During the late-luteal phase, female functional connections showing sex-by-emotion interactions were negatively correlated during amusement with **(b)** estradiol and **(c)** progesterone. Namely, for women in the late-luteal phase, higher levels of estradiol or progesterone indicated weaker functional connectivity during amusement. Abbreviations: ACC, anterior cingulate cortex; DMPFC, dorsomedial prefrontal cortex (medial superior frontal gyrus); inf frontal, opercular inferior frontal gyrus; inf parietal, inferior parietal gyrus; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex. L, left; R, right.

Table 2
Functional connections showing sex-by-emotion interaction between men and women in the late-luteal phase during experience of sadness and amusement.

ROI-ROI functional connection	*t* statistic (df = 37)	*p* value (FDR corrected)[a]
L putamen – R anterior cingulate	5.53	0.0056
R putamen – L inferior frontal gyrus, triangular part	5.52	0.0056
L putamen – L superior frontal gyrus, medial part	5.17	0.011
R putamen – L superior frontal gyrus, medial part	5.08	0.011
L putamen – L inferior frontal gyrus, triangular part	4.94	0.0136
R putamen – R inferior frontal gyrus, triangular part	4.77	0.0193
R putamen – R inferior frontal gyrus, orbital part	4.61	0.0269
L putamen – L anterior cingulate	4.45	0.0378
L putamen – R inferior frontal gyrus, orbital part	4.37	0.0392
L putamen – R inferior frontal gyrus, triangular part	4.32	0.0392
R putamen – R anterior cingulate	4.29	0.0392
R putamen – R inferior frontal gyrus, opercular part	4.26	0.0392
L amygdala – L calcarine sulcus	4.26	0.0392
L putamen – L middle frontal gyrus, orbital part	4.24	0.0392
R putamen – L middle frontal gyrus, orbital part	4.23	0.0392
L thalamus – R anterior cingulate	4.19	0.0412
L putamen – L inferior frontal gyrus, orbital part	4.16	0.0426
R putamen – R inferior parietal gyrus	4.13	0.0426
R amygdala – R middle frontal gyrus, orbital part	4.12	0.0426
L putamen – R superior frontal gyrus, dorsolateral part	4.11	0.0426

L = left; R = right.
[a] *p* values are FDR corrected and adjusted to enforce monotonicity.

mid-follicular phase, estradiol was positively correlated with a parietal-prefrontal functional connection and progesterone negatively correlated with a posterior cingulate-orbitofrontal functional connection. Few studies have examined the influence of sex hormones on brain functional networks. Recently, an imaging study found menstrual phase-dependent correlations between functional networks and female sex hormones (Syan et al., 2017).

The following studies support our claim for a reduction in the reactivity for reward during the late-luteal phase. Greater activity in the striatum during reward delivery was found for women in the follicular relative to the luteal phase, in addition to greater activity in the striatum and prefrontal cortex for men relative to women (Dreher et al., 2007). The putamen, dorsomedial and orbitofrontal cortices are key regions of the reward system (Haber et al., 2000; Sescousse et al., 2013) The putamen was shown to code different types of reward, including social interaction (Kawamichi et al., 2016), pleasure (Berridge and Kringelbach, 2008) and hedonic amusement (Franklin and Adams, 2011). Animal and human studies suggested that estrogen enhances reactions to reward, and that progesterone opposes these facilitative effects of estrogen (Sakaki and Mather, 2012), resulting with greater reward sensitivity during the follicular phase.

Additional evidence comes from imaging data on the functional roles of the prefrontal cortex and its relation to the striatum. The VLPFC plays a crucial role in emotion and emotion regulation (Mitchell, 2011). Evidence suggest that the VLPFC detects or encodes both negative and positive stimuli (Grimm et al., 2006; Nielen et al., 2009) and modulates the impact of stimuli on subjective emotional states (Mitchell, 2011). The DMPFC has consistently been implicated in many types of emotion processes (Etkin et al., 2011) including evaluation and generation of emotion, attribution of mental states to self and others and cognitive control of emotion (Ochsner and Gross, 2005). Some of the above functionalities of the VLPFC and DMPFC were suggested to be supported by their structural connections with the striatum (Ferry et al., 2000). In depression, weaker frontal-striatal functional connectivity has been linked to anhedonia, dysphoria and reduced ability to sustain positive emotion (Heller et al., 2013; Sabatinelli et al., 2015). It is noteworthy that the anterior cingulate cortex (part of the DMPFC) and orbitofrontal cortex (part of the VLPFC) are both regions of the salience network (Seeley et al., 2007) or affective network (Sheline et al., 2010), that features extensive subcortical and limbic connectivity including to the putamen. This network is involved in emotion regulation and monitoring of the salience of motivational stimuli and has reciprocal connections to autonomic and endocrine systems (Sheline et al., 2010). Namely, women in the late-luteal phase showed reduced connectivity relative to men within the salience/affective network during amusement.

When comparing women between menstrual phases, differences were found in behavior without any in functional connectivity. This result is in line with previous claims for the stability of resting-state functional connectivity networks across menstrual phases (De Bondt et al., 2015; Hjelmervik et al., 2014; Syan et al., 2017), yet variations were also found (Petersen et al., 2014). Regarding the behavioral findings, previous studies have reported a wide range of differences between menstrual phases related to emotion processing. For example, women in the luteal phase reported reduced accuracy in emotion recognition compared to the follicular phase (Derntl et al., 2008a; Guapo et al., 2009), longer time for resolving emotional conflict (Hoyer et al., 2013) and more intrusive recollections after exposure to emotional films (Ferree et al., 2011).

It is recognized that women in the late-luteal phase are susceptible for symptoms of depression, anxiety and anhedonia (Yonkers et al., 2008). Of those women suffering from premenstrual symptoms, 3–8% meet the clinical definition of premenstrual dysphoric disorder (PMDD). Importantly, in this study the influence of the menstrual phase on the subjective experience of emotional stimuli was found for women that underwent rigorous screening to confirm the absence of premenstrual symptoms. Hence, although in the daily prospective records of symptoms women reported no change in measures such as anxiety, sadness or irritability during the days before the menses, when exposed to external emotional stimuli (e.g. films) their experience differed. We speculate that the intensity of the emotional manipulation unmasked an existing tendency for increased sadness and reduction in pleasure during the late-luteal phase.

The second type of emotion processing examined in this study was emotion perception that was measured using the emotional face matching task. In this paradigm, sex differences in neural activity during negative emotion were found during both menstrual phases, but varied depending on the phase. Men showed increased activity in the right hippocampal formation compared to women in the mid-follicular phase, and increased activity in the right cerebellum: paravermal lobules VI, Crus I and Crus II and the dentate nucleus, compared to women in the late-luteal phase. Sex differences in emotion perception

were found specifically for negative emotions and not positive emotions. However, caution needs to be taken, as indicated by the power analysis, since only a subgroup of subjects completed the positive emotion perception task (19 men, 11 women). In congruent with our results, it has been previously suggested that men exhibit greater activity than women in several brain regions during perception of aversive stimuli (Kret and De Gelder, 2012). Note, that during emotion perception, no correlations were found between neural clusters showing sex differences and female sex hormones, despite previous studies linking hippocampal activity and levels of ovarian hormones (Arélin et al., 2015; Bayer et al., 2018).

The right parahippocampal gyrus was found in several meta-analyses to show greater activation in men during emotion perception, across different emotions (Filkowski et al., 2017). Notably, the hippocampus is one of the most prominent regions known to show sex differences in its structure and function (Cahill, 2006). It is also one of the key regions most strongly affected by sex hormones with a high expression of receptors of estrogen and progesterone. The hippocampus undergoes substantial neuroplasticity in response to exposure to sex hormones, and this hormonally modulated plasticity also differs between the sexes (Galea et al., 2013).

Substantial evidence exists for the role of the cerebellum in many aspects of emotion, including perception (Adamaszek et al., 2017). The functional topography of emotion processing in the cerebellum was recently mapped, with all five primary emotions (happiness, anger, disgust, fear and sadness) evoking distinct patterns of activity in the posterior cerebellar lobe (Baumann and Mattingley, 2012). Specifically, anger and fear induced activations in right paravermal lobules VI, Crus I and Crus II, in congruent with our findings for sex differences during perception of those emotions in these regions. Furthermore, a previous study found sex differences in emotion processing in the cerebellum, with men showing greater activity in the left cerebellum during positive emotion and greater activity in the right cerebellum during negative emotion (Hofer et al., 2006), the latter in line with our findings. In summary, in addition to indicating the importance of the hippocampal formation, our emotion perception results highlight the need to consider the cerebellum when studying sex differences in emotion processing.

4.1. Limitations

Whilst this study addresses an important gap in the literature, there are several limitations. The relatively modest sample size may limit the generalizability of the findings and studies with greater number of subjects are needed to strengthen the results. There were marginally significant differences between women and men in handedness (Table 1, $p = 0.058$). The lack of assessing masculine and feminine traits may also be a limitation (Rippon et al., 2014). Moreover, this study addressed sex differences in functional connectivity during specific emotions, namely sadness and amusement. It remains to be determined if these sex-related differences are characteristic of the specific emotions or general to negative/positive valence. This may be tested in future studies examining emotions that are of the same valence but of a different emotion category (e.g. sadness, fear, disgust).

5. Conclusions

To the best of our knowledge, this is the first study to demonstrate that sex differences in neural functional connectivity during emotion experience are dependent on women's menstrual cycle phase, with greater differences indicated during the late-luteal phase. Diminished putamen-VLPFC and putamen-DMPFC functional connectivity during experience of amusement were observed for women in the late-luteal phase relative to men and associated with levels of sex hormones. These neural findings were complemented by behavioral reports of less amusement and greater sadness in late-luteal women. We suggest that our results indicate a tendency for a deficient experience of pleasure and reward during the late-luteal phase, and may further shed light on the underlying mechanisms of premenstrual dysphoric disorder.

Conflict of interest

The authors report no conflict of interest.

Contributors

RD, LC, RS, MW, IR, OB, GG: study conception and design, review of manuscript.

RD: design and preparation of experiments, acquisition of data, analysis of data, writing of the manuscript.

TK: contributed to analysis of data.

RD, IR, LC: subject recruitment.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2018.09.032.

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