MENSTRUAL CYCLE EFFECTS ON SELECTIVE ATTENTION AND ITS UNDERLYING CORTICAL NETWORKS

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Abstract

It was the aim of the present study to investigate menstrual cycle effects on selective attention and its underlying functional cerebral networks. Twenty-one healthy, right-handed, normally cycling women were investigated by means of functional magnetic resonance imaging using a go/no-go paradigm during the menstrual, follicular and luteal phase. On the behavioral level there was a significant interaction between visual half field and cycle phase with reaction times to right-sided compared to left-sided stimuli being faster in the menstrual compared to the follicular phase. These results might argue for a more pronounced functional cerebral asymmetry toward the left hemisphere in selective attention during the menstrual phase with low estradiol and progesterone levels. Functional imaging, however, did not reveal clear-cut menstrual phase-related changes in activation pattern in parallel to these behavioral findings. A functional connectivity analysis identified differences between the menstrual and the luteal phase: During the menstrual phase, left inferior parietal cortex showed a stronger negative correlation with the right middle frontal gyrus while the left medial frontal cortex showed a stronger negative correlation with the left middle frontal gyrus. These results can serve as further evidence of a modulatory effect of steroid hormones on networks of lateralized cognitive functions not only by interhemispheric inhibition but also by affecting intrahemispheric functional connectivity.

Abbreviations: ACC, anterior cingulate cortex; ANOVA, analysis of variance; DLPFC, dorsolateral prefrontal cortex; ER, error rates; FCA, functional cerebral asymmetry; fMRI, functional magnetic resonance imaging; FWE, family wise error; IPL, inferior parietal lobe; ISI, interstimulus interval; PPI, psychophysiological interaction; RT, reaction times; SD, standard deviation; TC, Talairach coordinates

Key words: fMRI; selective attention; go/no-go; menstrual cycle; steroid hormones; functional cerebral asymmetry

Introduction

Functional cerebral asymmetries (FCAs) in the human brain have been described for several higher cognitive functions, such as language and spatial processes, and have been found to be more pronounced in men than in women (McGlone, 1978; Jansen et al., 1992; Shaywitz et al., 1995; Hausmann et al., 1998; Hausmann and Gunturkun, 1999). Several studies have shown that FCAs vary across the menstrual cycle (Hampson, 1990; Bibawi et al., 1995; Rode et al., 1995) while they are relatively stable in postmenopausal women (Hausmann and Gunturkun, 2000). This suggests that sex hormones (in particular estradiol and progesterone) might modulate FCAs. However, the exact mechanism is not yet fully understood and results are partly contradictory. Some studies found largest asymmetries during the menstrual phase (Rode et al., 1995; Mead and Hampson, 1996) which is characterized by low levels of estradiol and progesterone while others found more pronounced FCAs during cycle phases with high steroid hormone concentrations such as the midluteal phase (Hampson, 1990; Bibawi et al., 1995). It remained an open question whether hormonal effects on FCAs are mediated by (i) activation of the superior hemisphere for a given task, (ii) suppression of the non-dominant hemisphere or (iii) modulation of the interaction between hemispheres. The latter has first been proposed by a menstrual cycle study (Hausmann and Gunturkun, 2000) which found interactions between cycle phase and FCAs for both right- and left-hemispheric dominant tasks. The authors proposed that both hemispheres act as partially independent systems and that interhemispheric information transfer (in particular interhemispheric inhibition) is the central mechanism which

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generates and maintains FCAs (Kinsbourne, 1970; Cook, 1984; Hoptman and Davidson, 1994; Chiarello and Maxfield, 1996). Specifically, they assumed that interhemispheric inhibition via the corpus callosum is diminished by progesterone through its glutamatergic and GABAergic effects (Hausmann and Gunturkun, 2000; Hausmann et al., 2002) and therefore FCAs vary during the course of the menstrual cycle (Hausmann and Gunturkun, 2000). The hypothesis of progesterone-modulated interhemispheric decoupling has subsequently been extended, taking into account more recent results showing that estradiol also plays an important role in modulating FCAs (Hausmann, 2005; Hollander et al., 2005; Weis et al., 2008; Hausmann and Bayer, 2010).

Only few functional magnetic resonance imaging (fMRI) studies have directly investigated menstrual cycle effects on FCAs. Dietrich et al. (2001) used a left-lateralized word-stem-completion task and a mental rotation task and found that the size of activated regions generally increased with elevated estradiol levels. FCAs, however, did not change across cycle phases. Fernandez et al. (2003) showed that gonadal steroid levels, and progesterone levels in particular, correlated with bilateral superior temporal and medial superior frontal recruitment in a semantic task but not with brain activity related to a perceptual task. Weis et al. (2008) studied the effects of estradiol in a word-matching task by means of a connectivity analysis and found that the inhibitory influence of the inferior frontal gyrus of the language dominant left hemisphere on the homotopic area of the right hemisphere fluctuated across the menstrual cycle with a stronger interhemispheric inhibition during the menstrual phase than during the follicular phase. In line with this observation, it was found that

estradiol levels were negatively correlated to the degree of interhemispheric inhibition which may explain reduced FCAs in error rates and response times during the follicular phase as compared to menses. A recent study by Weis et al. (2011) has shown that hormonal modulation is not restricted to interhemispheric inhibition between homotopic areas but can also affect functional connectivity between heterotopic areas of both hemispheres as well as intrahemispheric connectivity. The authors found cycle-related behavioral changes in the right hemisphere an advantage for a figure-matching task. On the functional imaging level, there were cycle-related changes specifically in the activation of the right hemisphere (dominant for figure matching) and in the functional connectivity between heterotopic areas of both hemispheres.

The majority of studies have looked at verbal and spatial tasks because of the well-know cognitive sex differences in these cognitive domains. Another top down process which has not yet been systematically studied in this research area is attention, although sub-functions of this basic cognitive function have been shown to be lateralized and differentially organized in the male and female brain (e.g. Jansen et al., 1992). Furthermore, attention processes are supposed to play a mediating role in the hormonal effects on lateralization of other cognitive domains (Hausmann, 2005; Hollander et al., 2005; Hausmann et al., 2006; Weis et al., 2008; Hjelmervik et al., 2012). According to a model by Posner and colleagues (Posner and Boies, 1971; Posner and Rafal, 1987; Posner and Petersen, 1990), which has been modified later on by Van Zomeren and Brouwer (1994) as well as Sturm (2008), attention is regarded as a complex function that comprises intensity aspects (i.e., alertness and sustained attention) and

selectivity aspects (i.e., selective and divided attention). Intensity aspects which are normally measured by simple reaction time or vigilance tasks have been consistently shown to be primarily based on right hemisphere brain activity (Posner and Petersen, 1990). Sturm et al. (1999), Sturm and Willmes (2001) and Langner et al. (2012) found a modality nonspecific right lateralized network for alerting, including the anterior cingulate gyrus, dorsolateral prefrontal and inferior parietal cortex as well as thalamic and brainstem structures.

In contrast, findings on functional neuroanatomy of selective attention are more heterogeneous and comprise left and right hemisphere regions. In an fMRI study using an auditory selective attention task, Sturm et al. (2011) found a bilateral, albeit left accentuated, network comprising activity in various frontal areas including middle and inferior frontal lobe, the anterior cingulate cortex (ACC), the inferior parietal lobe (IPL), temporal lobe and cerebellum. These results were in line with previous neuroimaging studies of attention showing that a frontoparietal network was associated with a great diversity of attention functions (Pessoa et al., 2003). It can be assumed that the frontoparietal activations of the right hemisphere in selective attention tasks represent the intensity aspects which are a prerequisite of any attention process, while left hemisphere brain activity (particularly of left frontal and parietal areas) is associated with the specific selectivity aspect of the task (Corbetta et al., 1991; Sturm et al., 1999; Sturm et al., 2004; Sturm et al., 2011; Mottaghy et al., 2006). This lateralization to the left hemisphere has been shown previously in various selective attention studies in healthy subjects (Bisiach et al., 1982; Jansen et al., 1992) and patients (Dee and Van Allen, 1973; Sturm and Bussing, 1986). A

recent fMRI study (Hirose et al., 2012) found brain activity in multiple regions of the left frontal and parietal cortex to be positively related with the efficiency of response inhibition in a go/no-go task. Apart from this fronto-parietal network, the ACC has been suggested to play a specific role in rapid detection and selection of targets (Fernandez-Duque and Posner, 2001) and accordingly has been found consistently activated in studies using go/no-go paradigms (Watanabe et al., 2002; Garavan et al., 2003; Hester et al., 2004; Nakata et al., 2008a; Nakata et al., 2008b). Most of these studies additionally found activation of further medial frontal structures like the SMA (Watanabe et al., 2002; Nakata et al., 2008a; Nakata et al., 2008b), pre-SMA (Garavan et al., 2003; Hester et al., 2004) or medial frontal cortex (Jaffard et al., 2008).

It was the aim of the present study to investigate menstrual cycle effects on selective attention, its underlying cerebral networks and its functional organization by carrying out an fMRI experiment with a go/no-go paradigm. According to the above-mentioned studies on other cognitive domains, we expected that FCAs in selective attention fluctuate over the menstrual cycle, presumably caused by modulating effects of estradiol and/or progesterone. Therefore, we assessed healthy women not taking any hormonal medication repeatedly with a go/no-go task during three different cycle phases: menstrual phase (low estradiol/low progesterone), follicular phase (high estradiol/low progesterone) and luteal phase (high estradiol/high progesterone). We assumed a left hemisphere advantage in selective attention during the menstrual phase and an attenuation or abolition of this effect in the follicular and/or luteal phase due to elevated concentrations of the steroid hormones estradiol and

progesterone. Furthermore, the present study aimed to investigate the effects of estradiol and progesterone on intra- and interhemispheric functional connectivity in the fronto-parietal selective attention network across hormonally distinct cycle phases. We assumed that according to the hypothesis of steroid hormone modulated interhemispheric decoupling, there might be a stronger negative correlation between left and right hemisphere attention areas during the low-steroid menstrual phase. We focused on left (medial) frontal and inferior parietal areas as seed regions for this analysis, as these regions have been identified as central for selective attention in the above-mentioned studies.

Experimental procedures

Subjects

Twenty-one right-handed, spontaneously cycling women were tested. The mean age was 24.8 years (standard deviation [SD] 3.5 years; range 18–34 years). Women who had taken hormonal contraceptives during the last 6 months before testing were excluded. All subjects were consistent right-handers, according to the Edinburgh Handedness Index (Oldfield, 1971): mean lateralization quotient = 84.1; SD = 12.5; range 57.1–100. They had normal or corrected-to-normal vision and were native speakers of German. Following approval by the Local Ethics Committee, all subjects gave their written informed consent according to the Declaration of Helsinki (1991). Subjects were paid for their participation.

Procedure

Before the experiment started, participants were informed about the general procedure and data about their menstrual cycle were collected. Subjects were tested during three different cycle phases: menstrual phase (cycle day 1–3), follicular phase (cycle day 10–12) and luteal phase (cycle day 20–22). Time points for the examinations were estimated for each woman according to the onset of menstruation (cycle day 1). This estimation also took the individual mean length of each woman's menstrual cycle into account. To balance the design, the testing order was randomized across subjects in a way that all three cycle phases were equally distributed across the three time points. Blood samples were taken directly before each experimental session and progesterone and estradiol levels were assessed by Electrochemiluminescence Immunoassay to verify the cycle phase. If hormone levels were outside the reference range of the cycle phase, the examination was repeated during the next cycle. To control for circadian rhythm effects, every experimental session was performed at the same time of the day. The fMRI session contained a selective attention paradigm. Before each fMRI session, the task was explained and practiced in a short practice session outside the MRI scanner.

Materials and tasks

The task was presented as a block design. Each subject performed two identical runs of the experiment, responding with the left hand in one run and with the right hand in the other one. Each run lasted for 12.5 min and consisted

of two experimental conditions: "selective attention" and "control". Additionally, we collected data on alertness which are not reported here. The order of hands and conditions was balanced across subjects but remained stable within subjects. Before each condition, an instruction appeared for 3 s that indicated which condition was following. Each condition comprised of eight experimental blocks of 31-s duration. Experimental blocks were separated by baseline blocks of 15-s duration, during which a central fixation cross ("+") was shown.

Each experimental block of the selective attention condition started with the presentation of the combination "x X x" or "X x X" indicating that stimuli (white squares, visual angle 1.7°) of the following block were to be presented centrally or lateralized respectively. Each block contained 10 stimuli which were presented at a jittered interstimulus interval (ISI) between 2 and 4 s resulting in a mean ISI of 3 s. The white squares were presented on a black background either centrally (odd blocks) or lateralized by 7° from a central fixation cross (even blocks). Each lateralized block contained 50% left and 50% right visual field stimuli in randomized order. Squares were either orientated with outlines parallel to the screen or rotated at 45° (in the following referred as "squares" and "rhombuses" respectively).

In the selective attention condition, participants were instructed to press a response button as fast as possible with the index finger selectively whenever a rhombus appeared. No response had to been given when a square appeared. In the control condition, each experimental block contained only one single stimulus (of the type described above) continuously presented for the entire

block. Participants were instructed to look at this permanent stimulus and press the button about every 2–3 s without counting or keeping a rhythm.

Behavioral data analysis

Median reaction times and percentage error rates of the selective attention condition were determined for each single participant. Subsequently, mean reaction times and error rates were calculated for the group and were subjected to a 2 × 3 within subjects ANOVA (analysis of variance) with factors "cycle phase" and "stimulus position". Only trials with lateralized stimulus presentation were included in this analysis. Significant effects and statistical trends were subsequently investigated by 2 × 2 within subjects ANOVAs and t-tests. According to our directed hypotheses, one-tailed testing was conducted.

fMRI data acquisition

fMRI was performed on a 3-Tesla MRI scanner (Philips Systems Achieva) using an eight-channel SENSE head coil and T2∗-weighted axial EPI sequences. Each run comprised 300 scans (including three initial dummy scans) with the following parameters: number of slices: 37 continuous slices parallel to the AC–PC line comprising the whole brain; slice thickness: 3 mm; no interslice gap; matrix size: 64 × 64; field of view: 192 × 192 mm; echo time: 30 ms; repetition time: 2500 ms; flip angle: 81°.

fMRI data analysis

Statistical analysis of the fMRI data was done by using statistical parametric mapping software (SPM8, Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB version R2010a (The Mathworks Inc., Natick, MA, USA). After discarding the first three volumes (dummy scans), functional images were realigned to the first scan to correct for head movement. Slices within each volume were synchronized to the middle slice to correct for differences in slice acquisition time. Volumes were normalized to a standard EPI template based on the Montreal Neurological Institute reference brain using default settings for normalization in SPM8 with 16 nonlinear iterations. Finally, all images were smoothed with a Gaussian kernel of 8-mm full-width half-maximum.

To investigate the selective attention network, the two experimental conditions (selective attention and control condition) were compared with each other in individual first-level contrasts within subjects. Contrary to the behavioral analyses, besides the lateralized also the centrally presented stimuli were included into the fMRI analyses since lateralization of selective attention can be measured by fMRI regardless of lateralization in primary visual stimulus processing. First-level contrasts were taken to the second level to perform random effects analyses by means of repeated measurement ANOVA. In this way, selective attention effects during each single cycle phase were tested. Based on these analyses, the common network across cycle phases was detected by a conjunction analysis. This was done to examine brain regions involved with selective attention independent of cycle phase. Furthermore, results of this

analysis were used to determine appropriate seed regions for the psychophysiological interaction (PPI) analysis (see Section "Functional connectivity analysis"). In a second step, differences between cycle phases were investigated post hoc by paired t-tests.

Second-level analyses were performed with a predefined threshold of p < 0.05 FWE (family wise error)-corrected. Only clusters comprising at least 10 voxels are reported. Analyses which failed to show significant brain activity following this criterion were repeated with a procedure that has a higher sensitivity while still correcting for multiple comparisons. Therefore, an appropriate voxel contiguity threshold was determined by employing a Monte-Carlo simulation of the whole brain volume (Slotnick et al., 2003). Based on 10.000 simulations, an extent threshold of 24 resampled voxels was determined for a threshold at the voxel level of p = 0.001. This procedure prevented a false positive rate above 5% due to multiple testing. Brain activations were projected onto an SPM template.

Functional connectivity analysis

To gain further insights into the hormonal modulation of the selective attention network, we calculated PPI analyses (Friston et al., 1997), examining the functional connectivity between and within the dominant (left) and non-superior (right) hemisphere and its variation across cycle phases. Seed regions for the connectivity analyses were selected from the conjunction analysis across cycle phases. We chose two areas which were consistently activated in each of

the three cycle phases and furthermore in accordance with the present literature concerning selective attention networks: the left medial frontal cortex (group maximum at Talairach coordinates [TC] −6 1 53) and the left inferior parietal lobule (group maximum at TC −53 −53 36 (Talairach and Tournoux, 1988)). For each subject, the individual seed regions were determined by selecting circular spheres with a radius of 5 mm around the individual activation maxima closest to the overall group maxima. The psychological variable was determined by the time course of the experiment in order to set up a PPI regressor for calculating correlations during the selective attention condition in contrast to the control condition. To investigate hormone-related modulations of inter- and intrahemispheric inhibitory influences, we examined negative correlations with each seed region for each subject in a first-level statistical analysis. Subsequently, a second-level random effects analysis was performed on these contrast images using repeated measurements ANOVA to identify differences in functional connectivity between cycle phases. These contrasts were controlled for deactivation by using an inclusive masking procedure, i.e., regions which were e.g. stronger correlated in the menstrual than in the luteal phase were only reported if they were also significantly ($p < .05$ FWE-corrected) negatively correlated with the seed region in the menstrual phase alone. Identical to the fMRI data analyses, we used a Monte-Carlo simulation of the whole brain volume to determine an appropriate voxel contiguity threshold (resulting in 24 resampled voxels for a threshold at the voxel level of $p = 0.001$) and results were projected onto an SPM template.

Results

Hormone assays

Hormone levels of each subject were within the reference range of the follicular and luteal phases (for the menstrual phase no reference range exists). The mean serum hormone levels and SDs for each cycle phase are presented in Table 1. A within subjects ANOVA for mean serum estradiol levels revealed significant differences between cycle phases ($F_{(2,40)} = 22.44$; $p < .001$). Post hoc paired t-tests revealed significant differences between any two cycle phases (follicular > menstrual: $t_{(20)} = 4.11$; $p < .001$; luteal > follicular: $t_{(20)} = 3.01$; $p < .005$; luteal > menstrual: $t_{(20)} = 5.95$; $p < .001$). A within subjects ANOVA for mean serum progesterone levels also revealed significant differences between cycle phases ($F_{(2,40)} = 31.54$; $p < .001$). Post hoc paired t-tests showed significant higher progesterone levels in the luteal phase compared to the other two phases (luteal > follicular: $t_{(20)} = 5.68$; $p < .001$; luteal > menstrual: $t_{(20)} = 5.56$; $p < .001$), however, no significant difference between the follicular and menstrual phase was found ($t_{(20)} = 1.02$; $p = .16$).

Table 1. Mean hormone levels (SD) and reference ranges

	Estradiol pmol/l		Progesterone nmol/l	
	Mean (SD)	Reference range	Mean (SD)	Reference range
Menstrual	110 (59)		2.1 (0.9)	
Follicular	324 (260)	46-607	1.9 (0.7)	0,6-4,7
Luteal	478 (310)	161-774	30.1 (22.5)	5,3-86

Behavioral data

Mean error rates (ER) and reaction times (RT) were determined for each cycle phase and stimulus position (see Table 2 and Table 3). Due to the overall very low ER (mean = 1.4–3.0, SD = 1.9–3.2) these data were not statistically analyzed. RTs were subjected to a 2 × 3 repeated measures ANOVA with visual field (LVF/RVF) and cycle phase (menses, follicular, luteal) as within-subject factors. No main effects were found for visual field ($F(1,20) = 0.48$; $p = .50$) and cycle phase ($F(2,40) = 0.42$; $p = .66$), however the interaction between both factors showed a statistical trend ($F(2,40) = 2.25$; $p = .06$). In a subsequent 2 × 2 ANOVA, the interaction of the visual field and cycle phase was significant ($F(1,20) = 3.94$; $p = .03$) for the menstrual compared to the follicular phase. This interaction was congruent with our hypothesis of a left hemisphere advantage in selective attention during the menstrual phase and an abolition of this effect in the follicular phase. The other interaction tests for the remaining pairs of menstrual cycle phases × LVF/RVF revealed no significant interaction effects (mens/lut × LVF/RVF: $F(1,20) = 1.89$; $p = .18$; fol/lut × LVF/RVF: $F(1,20) = 0.60$; $p = .45$). For further exploration of the interaction terms, post hoc one-tailed paired t-tests were computed. A trend was found for the following comparisons: fol LVF < RVF; $t(20) = 1.62$; $p = .06$; RVF mens < fol; $t(20) = 1.36$; $p = .09$; RVF mens < lut; $t(20) = 1.69$; $p = .05$.

Table 2. Mean error rates (SD) in %

	Stimulus position	
	LVF	RVF
Menstrual	1.4 (1.9)	2.4 (2.4)
Follicular	2.4 (3.2)	3.0 (3.0)
Luteal	2.1 (2.9)	2.0 (2.7)

Table 3. Mean reaction times (SD) in ms

|	Stimulus position	
	LVF	RVF
Menstrual	412 (63)	401 (66)
Follicular	402 (67)	417 (74)
Luteal	412 (78)	418 (76)

Imaging results

Selective attention networks. To determine a general selective attention network, activations were examined for each single cycle phase and across all cycle phases by means of a conjunction analysis (Table 4 and Fig. 1). This analysis revealed a left accentuated cortical network that included bilateral medial frontal gyri, superior temporal gyri and the insula as well as left lateralized brain activity of the inferior parietal lobule and occipital lobe. Furthermore, brain activity was found in the cerebellum, thalamus and basal ganglia.

Table 4. Selective attention networks (p < .05 FEW corrected); selected seed regions for PPI analyses in bold

Region	Side	BA	Menstrual					Follicular					Luteal					Conjunction				
			RS	z	TC			RS	z	TC			RS	z	TC			RS	z	TC		
					x	y	z			x	y	z			x	y	z			x	y	z
Medial frontal gyrus	L/R	6, 32	2205	6.93	−4	8	47	2680	7.07	−2	−3	61	1799	6.69	−6	1	53	**1627**	**6.66**	**−6**	**1**	**53**
Cingulate gyrus	L	23	223	6.25	−6	−14	27															
	R	23	44	5.08	10	−22	25															
Middle frontal gyrus	R	10	87	5.49	34	36	18															
	R	6						139	5.39	51	2	42										
Precentral gyrus	L	6	89	5.57	−40	0	42	139	6.07	−38	−9	48										
Inferior frontal gyrus	L	47	17	4.84	−24	11	−12															
	R	13											12	4.90	30	5	−10					
Superior temporal gyrus	L	22	1510	7.65	−48	4	0	2438	7.75	−48	4	0	880	7.11	−48	4	0	240	7.11	−48	4	0
	R	22	1495	6.83	48	6	−2	2414	6.71	50	8	−4						15	4.89	63	−36	18
	L	39	188	7.10	−48	−52	10	191	6.73	−48	−52	10	53	5.54	−48	−52	14	48	5.54	−48	−52	14
	R	13											79	5.14	59	−42	15					
Middle temporal gyrus	R	21	52	5.04	50	−42	9															
Insula	L	13	232	5.37	−48	−39	26											315	5.73	−34	18	8
	R	13											978	6.54	32	22	4	611	6.17	32	22	4
Inferior parietal lobule	**L**	**40**						352	6.35	−55	−47	30	84	5.41	−55	−53	36	**60**	**5.16**	**−53**	**−53**	**36**
	R	40						978	5.81	63	−36	22	129	5.56	57	−45	34					
Postcentral gyrus	L	40						108	5.92	−50	−24	20										
Superior occipital gyrus	L	19	17	5.47	−30	−69	22															
Middle occipital gyrus	L	18,19	310	5.82	−24	−87	4	82	5.52	−22	−91	6	55	5.36	−24	−87	4	42	5.22	−24	−87	4
	R	18	12	5.03	22	−89	14	124	6.03	20	−95	12										
Inferior occipital gyrus	L	19						253	5.96	−38	−74	0	40	5.14	−40	−68	−5	19	4.92	−40	−68	−3
Cerebellum			424	7.11	0	−59	−9	300	6.68	0	−59	−11	132	5.94	0	−59	−11	132	5.94	0	−59	−11
Thalamus	L												46	5.35	−10	−16	1	21	4.87	−12	−16	−1
Thalamus	R												93	5.28	12	−17	5					
Brainstem	R		37	5.31	4	−18	−14															
Lentiform nucleus/Putamen	R																	68	5.22	26	−3	9

TC: Talairach coordinates; BA: Brodmann area; RS: region size (number of voxels, cluster size ≥10); FEW: familywise error rate.
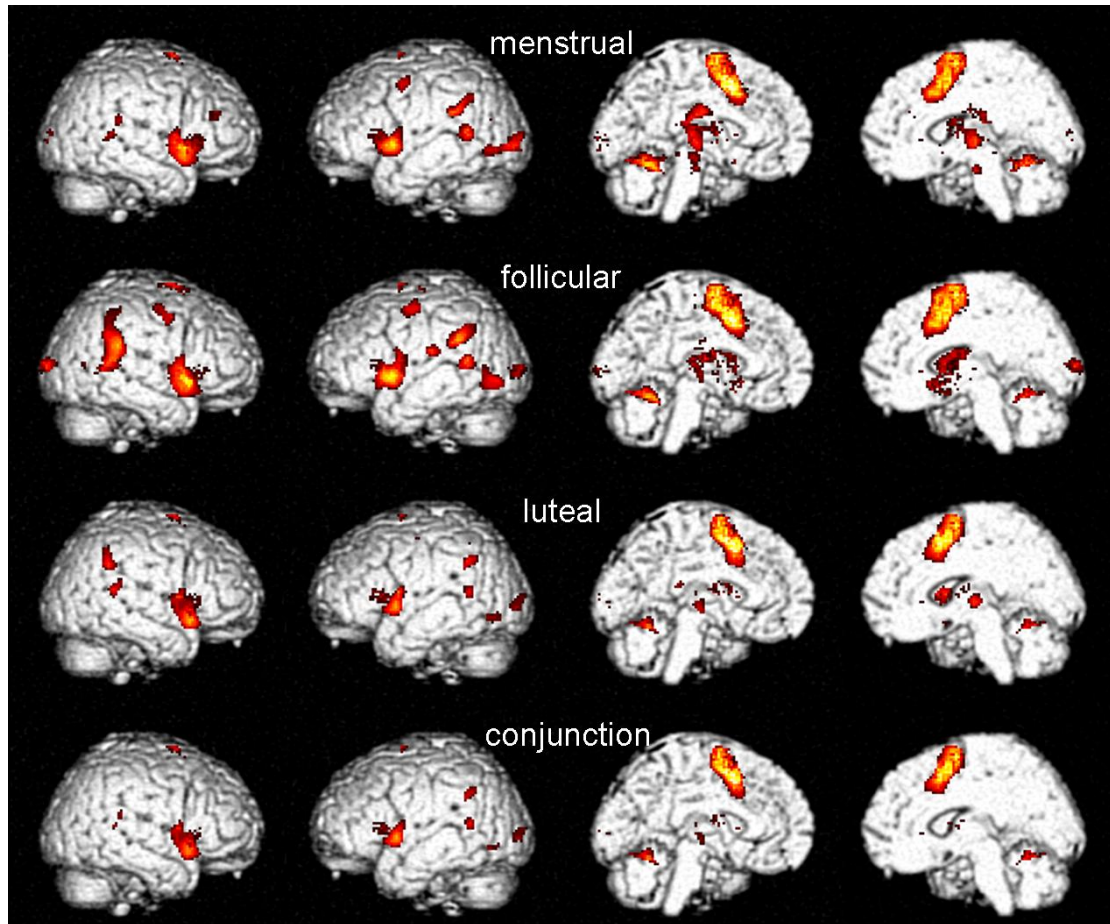
Figure 1. Selective attention network in each single cycle phase (line 1-3) and conjunction analysis over all cycle phases (line 4); FWE p < .05; k > 10.

Cycle-related differences. To investigate cycle-related differences in the selective attention network, post hoc paired t-tests between cycle phases were calculated. No significant brain activity was found for the strict criterion of FWE-correction. Therefore we repeated the analyses by using the more sensitive Monte-Carlo-correction as described above.

These analyses revealed significant differences for the following contrasts: menstrual > follicular, follicular > luteal and menstrual > luteal (Table 5 and Fig. 2). In these contrasts, differential brain activity was found in several cortical and subcortical areas. Most interestingly, the ACC, one of the core regions of selective attention especially with go/no-go tasks, was significantly less activated in the luteal phase than during both the menstrual and follicular phases.

Table 5. Differential brain activity between cycle phases (p < .001 MC corrected)

Region	Side	BA	RS	z-value	TC		
					x	y	z
mens > fol							
Precuneus	R	19	100	3.81	42	-70	40
mens > lut							
Anterior cingulate	R	24	60	3.65	12	20	19
Fusiform gyrus	L	37	28	3.70	-32	-45	-10
Thalamus (Pulvinar)	L		108	4.16	-20	-35	5
Caudate	R		37	4.06	34	-31	3
Mammillary body	R		28	3.38	2	-10	-15
fol > lut							
Anterior cingulate	R	24	58	3.92	2	23	-1
Middle frontal gyrus	L	6	95	3.90	-22	-16	60
Insula	L	13	30	3.52	-44	-7	6
Postcentral gyrus	R	3	28	3.37	26	-28	64

TC: Talairach coordinates; BA: Brodmann area; RS: region size (number of voxels, cluster size ≥10); MC: Monte Carlo simulation.
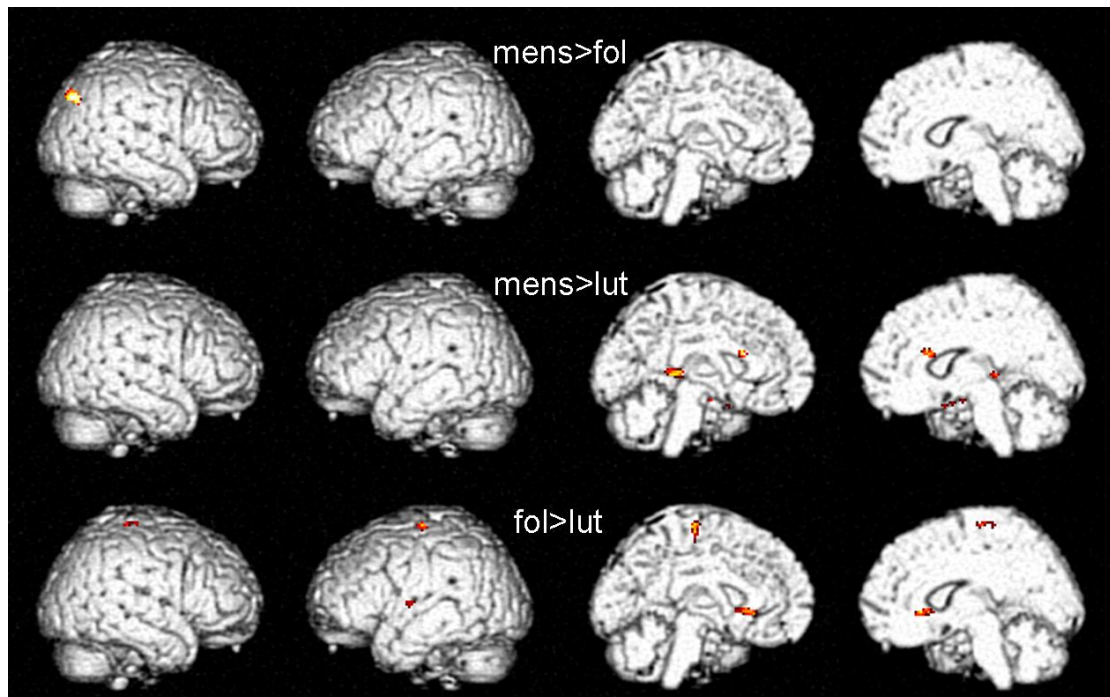
Figure 2. Differential brain activity between cycle phases; p < .001 MC corrected.
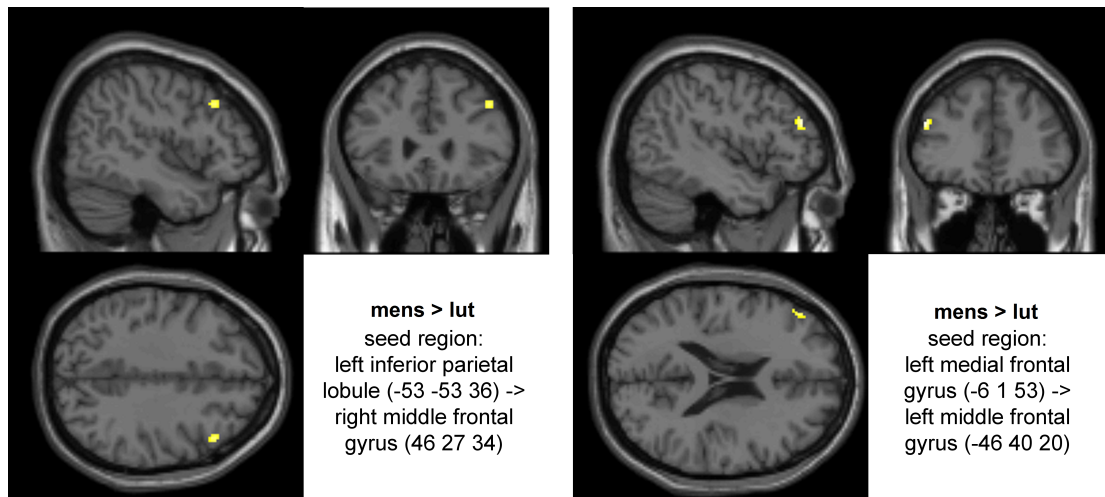
PPI analyses

Differences in functional connectivity of the selective attention network between cycle phases were examined by calculating PPI analyses. For both the left inferior parietal and the left medial frontal seed regions, only the contrast between the menstrual and the luteal phase revealed significant differences in functional connectivity between components of the fronto-parietal selective attention network. In the menstrual phase, the left inferior parietal seed region showed a stronger negative correlation with the right middle frontal gyrus (TC 46 27 34) than in the luteal phase. Furthermore, in the menstrual phase, the left medial frontal seed region showed a stronger negative correlation with the left

middle frontal gyrus (TC −46 40 20) than in the luteal phase. Results are displayed in Table 6 and Fig. 3.

Table 6. PPI analyses, negative correlations menstrual > luteal (p< .001 MC corrected)

Region	Side	BA	RS	z-value	TC		
					x	y	z
Seed region: left inferior parietal lobule (TC -53 -53 36)							
Middle frontal gyrus	R	9	26	3.49	46	27	34
Seed region: left medial frontal gyrus (TC -6 1 53)							
Middle frontal gyrus	L	46	43	4.28	-46	40	20

TC: Talairach coordinates; BA: Brodmann area; RS: region size (number of voxels, cluster size ≥10); MC: Monte Carlo simulation.

Figure 3. PPI analyses, inhibitory effects mens > lut; p < .001 MC corrected.

Discussion

It has been reported previously that lateralization of brain activity and performance in higher cognitive functions can vary across menstrual cycle

phases, presumably caused by modulating effects of different steroid hormone levels (Dietrich et al., 2001; Fernandez et al., 2003; Weis et al., 2008; Weis et al., 2011) but this has not yet been shown for selective attention. Thus, it was the aim of the present study to investigate menstrual cycle effects on selective attention, its underlying cerebral networks and its functional connectivity. We carried out an fMRI experiment using a go/no-go task which has previously been shown to be processed by a predominantly left lateralized network.

To investigate lateralization on the behavioral level, stimuli were presented laterally and participants' performance of a selective attention task, including successful response suppression to stimuli defined as irrelevant, was measured by error rates and reaction times. It was hypothesized that during the menses the dominance of the left hemisphere for this kind of selective attention task should lead to a better performance for stimuli presented in the RVF (as compared to the LVF) and changes of the FCA across cycle phases should be reflected by a modulation of the left hemisphere advantage. Error rates in general were very low and were therefore not further analyzed. For reaction times, there was a significant interaction between visual field and cycle phase: participants responded faster to RVF compared to LVF stimuli in the menstrual compared to the follicular phase. In the luteal phase the reaction time pattern was similar to the follicular phase and stimuli in the RVF were detected slower than in the menstrual phase. These behavioral results corroborate the assumption that in the low-steroid menstrual phase the FCA for selective attention toward the left hemisphere is more pronounced than in the follicular or luteal phase. Conversely, one can assume that increasing estradiol and

progesterone levels lead to a diminishment of a left hemisphere advantage in selective attention.

In contrast to the behavioral analysis which only included LVF and RVF trials, all trials (left, right, and central) were included in the fMRI analyses. Here, a superordinate network for selective attention was assumed to be activated independently of the stimulus position. The analysis revealed that the right ACC was less activated in the luteal phase compared to both the menstrual and follicular phases. Previous studies have shown that the ACC plays a crucial role in attention processes, in particular for selective attention. Fernandez-Duque and Posner (2001) suggested a specific role of the anterior cingulate gyrus in rapid detection and selection of targets. Strong activation of the ACC has been found in go/no-go tasks (Watanabe et al., 2002; Garavan et al., 2003; Hester et al., 2004; Nakata et al., 2008a; Nakata et al., 2008b) as well as in the classical Stroop interference paradigm (Pardo et al., 1990; Carter et al., 1995). These activations have been found independently of input and output modality (Loose et al., 2003; Nakata et al., 2008a; Nakata et al., 2008b) and stimulus conditions (Sturm et al., 2011). The lower activation of the right ACC during the luteal phase is mirrored behaviorally by overall slowest response times during this phase. Besides selective attention, the right ACC also plays a dominant role in top down control of alertness (Sturm et al., 1999; Sturm et al., 2004; Mottaghy et al., 2006) and alertness is the prerequisite for higher attention functions including selective attention. A high level of alertness is represented in fast response times. Thus, higher progesterone and/or estradiol levels seem to relate to a lower level of alertness.

Apart from the ACC, no further areas of the selective attention network showed variations across cycle phases. This is in line with previous fMRI studies, showing that the brain activation in specific areas involved in a particular cognitive task remains relatively stable (Dietrich et al., 2001; Weis et al., 2008) although the functional connectivity within specific cortical networks can fluctuate (Weis et al., 2008; Weis et al., 2011). Furthermore, as pointed out in the introduction, findings on functional neuroanatomy of selective attention are more heterogeneous and comprise left and right hemisphere regions (Pessoa et al., 2003; Sturm et al., 2011). The frontoparietal activations of the right hemisphere in selective attention tasks probably represent intensity aspects of attention, while left hemisphere brain activity (particularly of left frontal and parietal areas) is associated with the specific selectivity aspect of the task (Corbetta et al., 1991; Sturm et al., 1999; Sturm et al., 2004; Sturm et al., 2011; Mottaghy et al., 2006). This lack of clearcut a priori laterality might weaken effects of hormone-induced laterality changes.

Therefore we performed a PPI analysis on cycle-related fluctuations in the functional connectivity in the frontoparietal attention network with seed regions in the left medial frontal gyrus and the left inferior parietal lobule. The seed regions were identified in a conjunction analysis of our data. As described above, medial frontal areas play an important role in selective attention (Watanabe et al., 2002; Garavan et al., 2003; Hester et al., 2004; Jaffard et al., 2008; Nakata et al., 2008a; Nakata et al., 2008b) and the medial frontal gyrus was activated across all cycle phases with a local maximum of activation in the left hemisphere. As a second seed region, we chose the inferior parietal lobule which

was a clearly left-lateralized region in our conjunction analysis and has also been described frequently in the literature to be associated with selective attention (Hester et al., 2004; Jaffard et al., 2008; Nakata et al., 2008a; Nakata et al., 2008b; Sturm et al., 2011; Hirose et al., 2012). The PPI analysis revealed a higher negative correlation in the activation between seed regions and other cortical regions during the menstrual compared to the luteal phase.

In line with previous publications (Weis et al., 2008; Weis et al., 2011) we suggest that the negative correlation might reflect an increased inhibitory influence of seed regions on these cortical sites when sex hormone levels are low as compared to when they are high. It should be noted that PPI cannot provide information about the causality of the relationship between seed and target regions. However, in the context of the hypothesis of steroid hormone-modulated interhemispheric decoupling (Hausmann and Gunturkun, 2000) and its revised version (Hausmann et al., 2013), a negative correlation might be interpreted as an inhibitory process (Weis et al., 2008; Weis et al., 2011). Consistent with our hypothesis, this suggests a stronger inhibitory influence of the left inferior parietal seed region on the right middle frontal gyrus and of the left medial frontal seed region on the left middle frontal gyrus during the menstrual phase. Both frontal areas belong to the selective attention network. The middle frontal gyrus or dorsolateral prefrontal cortex (DLPFC) has been consistently found in fMRI studies using a go/no-go paradigm (Hester et al., 2004; Nakata et al., 2008a; Nakata et al., 2008b; Vallesi et al., 2009; Kramer et al., 2013). A stronger inhibitory effect on these areas during the menstrual phase compared to the luteal phase can also be interpreted as a reduced functional

connectivity in the fronto-parietal attention network during the luteal phase compared to the menstrual phase.

In the present study both a reduction of inter- and intrahemispheric inhibitory effects was found: reduced functional connectivity (weaker negative correlation) during the luteal phase was found between left-hemispheric frontal areas (left medial frontal and left middle frontal gyrus) and between the left inferior parietal region and the right middle frontal gyrus. The reduced functional connectivity occurred during the midluteal cycle phase, suggesting that high estradiol and/or progesterone levels mediated this effect. The results are both in line with a previous fMRI study investigating cycle-related effects on functional connectivity in a verbal task (Weis et al., 2008) which revealed a reduced interhemispheric inhibitory effect between homotopic areas in the inferior frontal lobe and with the results of a study using a spatial paradigm demonstrating cycle-related modulation of both intra- and interhemispheric inhibition (Weis et al., 2011).

Our findings of a disinhibited network in combination with reduced performance are in accordance with a review by Hester et al. (2004) who reanalyzed three fMRI studies using go/no-go paradigms and found slower responders showing significantly greater activation in parietal, lateral prefrontal and ACC regions. The connection between the left medial frontal gyrus and the left DLPFC is also in accordance with the present literature (e.g. Garavan et al., 2003) and possibly reflects error monitoring and response inhibition during the task which has been shown to be associated with midline brain activation. In a study by Amin et al. (2006) increased activation during response inhibition in an

emotional go/no-go task has been found in the ACC and DLPFC during the luteal, compared to the early follicular phase.

In summary, our study showed effects of menstrual cycle phase on lateralized reaction times in a go/no-go task. In the menstrual phase, women revealed the expected lateralization toward the left hemisphere reflected by a trend toward a reaction time advantage for the processing of RVF stimuli. This effect was abolished in the follicular and luteal phase when participants showed slower reaction times on RVF stimuli compared to the menstrual phase. In parallel to these behavioral results, the PPI analysis of functional connectivity revealed reduced negative correlations between left medial frontal cortex and IPL on left and right DLPFC areas respectively, during the luteal phase compared to the menstrual phase, possibly reflecting a reduction of inhibition of the left medial frontal cortex on these areas.

Author contributions

WS, MH, SW and MT designed research; MT performed research; MT and SW analyzed data; MT, WS, MH and SW wrote the paper.

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