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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.

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 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).

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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.

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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, 2004, 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,b). Most of these studies additionally found activation of further medial frontal structures like the SMA (Watanabe et al., 2002; Nakata et al., 2008a,b), 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