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Research Report

Stability of resting state networks in the female brain during hormonal changes and their relation to premenstrual symptoms

Timo De Bondt[a,*], Dirk Smeets[b], Pim Pullens[a], Wim Van Hecke[b], Yves Jacquemyn[c], Paul M. Parizel[a]

[a]Department of Radiology, Antwerp University Hospital & University of Antwerp Belgium, Belgium
[b]icometrix, Leuven, Belgium
[c]Department of Obstetrics and Gynaecology, Antwerp University Hospital & University of Antwerp, Belgium

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ABSTRACT

Resting-state fMRI is a promising imaging technique to evaluate functions in the human brain in health and disease. Different hormonal stages of the female menstrual cycle and hormonal contraceptives use affect results in task-based fMRI; it is however not yet clarified whether resting state networks are also altered. A population of 18 women with a natural cycle, and 19 women using hormonal contraceptives was examined in a longitudinal study-design. The natural cycle group was scanned at 3 time-points (follicular phase, ovulation, luteal phase), and the contraceptives group was scanned twice (inactive pill-phase, active pill-phase). Blood samples were acquired to evaluate hormonal concentrations, and premenstrual symptoms were assessed through daily record of severity of problems questionnaires. Results show no major alterations in the default mode network and the executive control network between different hormonal phases, across or within groups. A positive correlation of functional connectivity in the posterior part of the default mode network (DMN) was found with premenstrual-like symptoms in the hormonal contraceptives group. Using the current methodology, the studied resting state networks seem to show a decent stability throughout menstrual cycle phases. Also, no effect of hormonal contraceptive use is found. Interestingly, we show for the first time an association of DMN alterations with premenstrual-like symptoms, experienced during the inactive pill-phase by a sub-population of women.

*Corresponding author.
E-mail addresses: timo.debondt@uantwerpen.be (T. De Bondt), dirk.smeets@icometrix.com (D. Smeets), pim.pullens@uantwerpen.be (P. Pullens), wim.vanhecke@icometrix.com (W. Van Hecke), yves.jacquemyn@uza.be (Y. Jacquemyn), paul.parizel@uantwerpen.be (P.M. Parizel).

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1. Introduction

Blood oxygen-level dependent (BOLD) contrast has been used for studying the brain in-vivo, through functional magnetic resonance imaging (fMRI), for more than 2 decades now (Belliveau et al., 1991). In the absence of a task, spontaneous low frequency (<0.1 Hz) fluctuations of BOLD signal occur throughout the brain. This signal exhibits temporal correlations in spatially distinct regions of the brain. Some patterns appear consistently and are referred to as resting state networks (RSN). It is hypothesized that these networks are related with unconstrained mental activity (Biswal et al., 1995; Mason et al., 2007; Raichle, 2011; Barkhof et al., 2014). Functional connectivity as measured by RS-fMRI is a new potential biomarker for several pathologies. Using RS-fMRI, alterations in RSNs have been described in a series of different diseases, showing the sensitivity of this technique. Examples of pathologies, which were recently studied using RS-fMRI are: Alzheimer's disease (Dennis and Thompson, 2014), Parkinson's disease (Baggio et al., 2015), obsessive compulsive disorder (Beucke et al., 2014), bipolar disorder (Magioncalda et al., 2015), depression (Sambataro et al., 2013; Sundermann et al., 2014), attention deficit hyperactivity disorder (ADHD) (dos Santos Siqueira et al., 2014), and anorexia nervosa (Boehm et al., 2014). However, different diseases seem to affect the same RSN, so specificity of RS-fMRI is lower. It is important to note that menstrual cycle phase and use of hormonal contraceptives is almost never controlled for in these studies, while it is not yet confirmed that it is justified to do so.

One RSN that is particularly studied is the default mode network (DMN), first described in 2001 (Raichle et al., 2001). It includes the medial prefrontal cortex, posterior cingulate cortex, lateral temporal cortex and inferior parietal lobule, and is attenuated during task performance (Buckner et al., 2008). The DMN is believed to be related to introspective and self-referential thought processes, and becomes deactivated during goal-directed behavior (Barkhof et al., 2014). In addition, significant gender differences are found in cognition related networks, like the executive control network (ECN) (Filippi et al., 2013). Hormonal factors are a plausible explanation for sex-differences, and hormones might influence the formation of these RSNs.

Previous task-based fMRI research has revealed several gender (Wrase et al., 2003; Schoning et al., 2007; Konrad et al., 2008; Weis et al., 2008; Pletzer et al., 2013), menstrual cycle (Fernandez et al., 2003; Gizewski et al., 2006; Konishi et al., 2008; Roberts et al., 2008; Rupp et al., 2009; Guapo et al., 2009; Zhu et al., 2010), and hormonal contraceptives (HC) (Bonenberger et al., 2013; Abler et al., 2013; Mareckova et al., 2014) effects on the BOLD signal. The amount of the literature on these hormonal effects on RS-fMRI is however significantly smaller. Aside from gender differences (Tomasi and Volkow, 2012; Filippi et al., 2013; Wetherill et al., 2014; Agcaoglu et al., 2015), only recently some authors evaluated the effect of menstrual cycle phase (Petersen et al., 2014; Hjelmervik et al., 2014), and use of HC (Petersen et al., 2014). Unfortunately, regarding the menstrual cycle effects on RSNs, the results of these studies are inconsistent; Petersen et al. (2014) found differences with cycle phase in the DMN and ECN, Hjelmervik et al. (2014) only assessed the ECN and did not find any differences. Regarding HC use, Petersen et al. (2014) did not find differences between the active and inactive pill phase, but did record alterations when comparing the natural menstrual cycle (NC) follicular phase with the inactive pill phase.

The purpose of this work was to evaluate the influence of both menstrual cycle phase, and HC use on the DMN and the ECN, in a longitudinal design. For the NC group, we included the time-point of ovulation, which was not assessed in previous studies. In the HC group we corrected for generation of the synthetic progestin component contained in the HC, as this may influence results or introduce heterogeneity within the HC group (Pletzer and Kerschbaum, 2014). Additionally, since the association of the DMN with mood disorders like depression and bipolar disorder (Sambataro et al., 2013; Sundermann et al., 2014; Magioncalda et al., 2015), we acquired data regarding premenstrual symptoms (PMS) in both our groups, through completion of a “daily rating of severity of problems” (DRSP) questionnaire (Endicott et al., 2006) during 2 cycles. To the best of our knowledge, it is the first time that possible PMS effects on RSNs are evaluated.

2. Results

As described in more detail in Section 4, data quality control was performed on both hormonal data, and MR data. Temporal SNR maps are used to assess RS-fMRI data quality. What we describe in this section results from the remaining data after quality control (NC group=18 subjects; HC group=19 subjects).

2.1. *Hormonal assays*

Concentrations of follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol and progesterone are shown in Fig. 1. Means with standard deviations of the concentrations of all hormones are listed in Table 1. Cycle phase is confirmed by comparing the measured hormonal values to the literature data. Natural cycle hormonal data was compared to the dataset of Stricker et al. (2006). The HC hormonal data in the pill-free week is similar to the NC follicular phase (Seidman et al., 2014), and the use of HC suppresses endogenous estradiol and progesterone levels (Sahlberg et al., 1987). All hormonal values follow the expected pattern for a regular natural menstrual cycle, and HC cycle.

2.2. *Premenstrual symptoms*

Normalized somatic and psychological premenstrual symptom (sPMS and pPMS) values in all groups were found not to deviate significantly from a Gaussian distribution (all K–S tests show p-Value>0.366). Values are illustrated in boxplots in Fig. 2. In the NC group, sPMS and pPMS values with standard deviations were 0.84 ± 0.77 and 0.64 ± 0.63 respectively. In the HC groups these values were 0.80 ± 0.68 and 0.57 ± 0.45. A t-test revealed no significant group-differences