Effects of hormonal contraception on the default mode network: a resting-state MRI study

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Target Audience: Neuroscientists and behavioral scientists

Purpose: In the last decade, attention has been brought to sex-differences, but also the non-negligible effect of female hormonal fluctuations on human behavior and results of several advanced MRI brain-imaging techniques. In the present study, we aim to evaluate the effects of hormonal contraceptives use on the resting state activity of the default mode network (DMN).

Methods: A time serie of 140 resting state fMRI images was acquired in groups of healthy 16 hormonal contraceptives (HC) users and 13 women with a natural cycle (NC), ages between 18 and 28, using a Siemens Trio 3T scanner. The HC group was scanned during intake of the contraceptive pill, the NC group was scanned in the follicular and luteal phase of their menstrual cycle. The data are processed according to the pipeline presented in Figure 1.

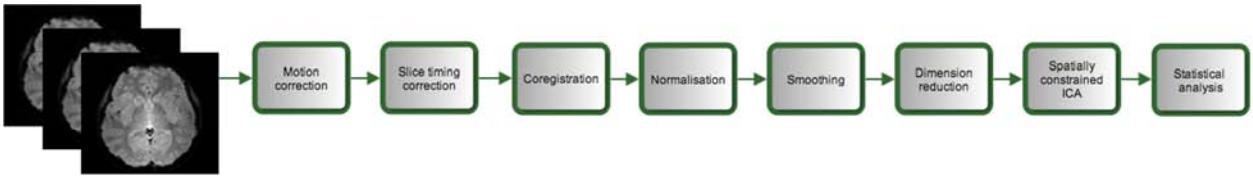

Figure 1: General pipeline for processing the resting state-fMRI images.

First, subject movement is corrected using a six parameter rigid body spatial transformation with a least squares approach. Before performing a slice timing correction, all images are registered towards the chronologically first scan. For the normalization of the images to MNI space, the mean image of the fMRI sequence is registered towards the anatomical T1-weighted image with an affine transformation. The resulting transformation is applied to all images. The T1-weighted image is used to estimate the affine and non-rigid transformation to the atlas. This transformation is applied to all fMRI images to place them in the atlas-space, including a resampling to a 2 mm isotropic resolution. To decrease the effects of noise, the images are smoothed by Gaussian kernel with a FWHM of 4 mm. Next, the high dimensional fMRI data are reduced to 20 dimensions with principal component analysis (PCA). To extract the default mode network from the fMRI images, a semi-blind spatial independent component analysis (ICA) algorithm with spatial constraints is used [1]. It extracts independent components per subject, corresponding to the DMN. Finally, 2-sample t-tests were performed using SPM8. Statistical significance was set to $p < 0.001$ uncorrected.

Results: Figure 2 shows that the resting state activity is decreased in a cluster of 105 voxels of the posterior cingulate cortex (PCC) in the HC group, compared to the NC group. A large part (85 voxels) of the cluster survives a multiple comparison correction (FDR = 0.05) Results were similar in both phases of the NC cycle. Figure 2 shows the comparison in the luteal phase.

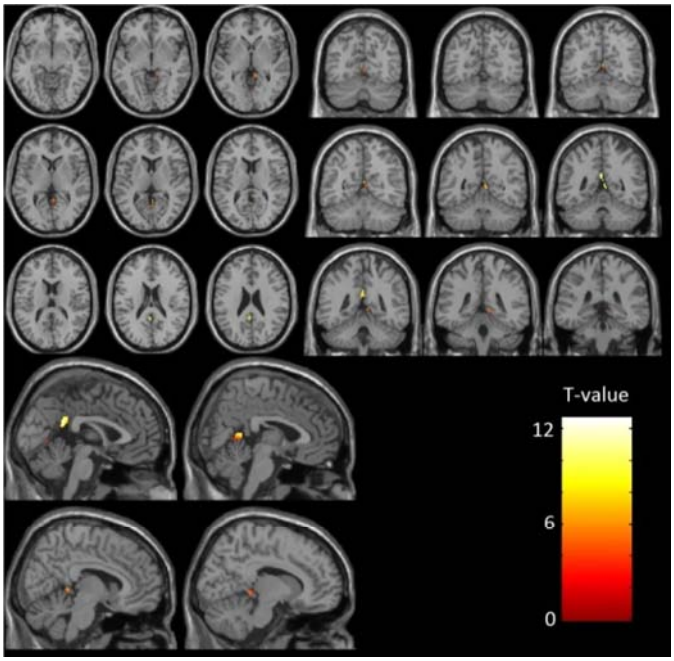

Figure 2: Transversal, coronal and sagittal images showing decreased resting state activity in the posterior cingulate cortex (PCC) in hormonal contraceptive users (HC), compared to women with a natural menstrual cycle (NC). P-value < 0,001 uncorrected.

Discussion: The PCC has been described as a key node in the DMN which is highly connected and metabolically active. It plays a role in emotional processing, as well as cognition, awareness [2] and self-reference ("getting caught up in…")[3]. Failing of appropriately deactivating the DMN is associated with inefficient cognitive functioning in these various contexts. It has been shown before that the use of HC alters the process of emotional memory. More specifically, HC users tend to retain more central information from an emotional story than NC women do. In contrast, NC women retain more of the peripheral details than HC women [4]. This shows that there is a difference between HC users and NC women in handling these kinds of ruminative emotional thoughts. For the best of our knowledge, the effect of HC use on the DMN has not been described before, and we believe that our findings support previously described literature regarding emotional memory processing.

Conclusion: Our results show that the PCC activation in the DMN is significantly reduced in the HC group when compared to the NC group. Since the PCC is commonly studied through fMRI in a wide range of pathologies including Parkinson's disease, schizophrenia, autism, depression and ADHD, our findings are of interest for behavioral scientists. However, more importantly, they implicate that heterogeneity is introduced in data when not accounting for HC use. This inevitably leads to loss of accuracy, and reduction of statistical power.

References: [1] Lin QH, Liu J, Zheng YR, et al. Semiblind spatial ICA of fMRI using spatial constraints. Human brain mapping. 2010 Jul;31(7):1076-88. [2] Leech R, Sharp DJ. The role of the posterior cingulate cortex in cognition and disease. Brain : a journal of neurology. 2013 Jul 18. [3] Brewer JA, Garrison KA, Whitfield-Gabrieli S. What about the "Self" is Processed in the Posterior Cingulate Cortex? Frontiers in human neuroscience. 2013;7:647. [4] Nielsen SE, Ertman N, Lakhani YS, et al. Hormonal contraception usage is associated with altered memory for an emotional story. Neurobiology of learning and memory. 2011 Sep;96(2):378-84.