Short- and long-term effects of hormonal contraceptives use on the default mode network

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Target Audience: Neuroscientists and behavioral scientists

Purpose: Recently, attention has been brought to effects on brain function and structure, due to artificial hormonal fluctuations, by using hormonal contraception (HC). In the present study, we firstly aim to evaluate short-term effects of HC use on the resting state activity of the default mode network (DMN), comparing active and inactive pill-phases. Secondly, since not restarting a HC-cycle generally immediately results in a normal menstrual cycle [1], we compare the inactive pill phase and the follicular phase of the natural menstrual cycle to evaluate a long-term effect of HC use.

Methods: A time series of 140 resting state fMRI images was acquired in groups of healthy 27 second-generation HC users and 18 women with a natural cycle (NC), ages between 18 and 34, using a Siemens Trio 3T scanner. The HC group was scanned during the pill-free week and the active pill phase; the NC group was scanned in the follicular phase of their menstrual cycle. In order to exclude inter-subject variability, we only used HC subjects where all datasets were of adequate quality, as evaluated by temporal-SNR maps. This reduced the HC group to 19 subjects. All together, we analyzed 56 datasets. The data are processed according to the pipeline presented in Figure 1.
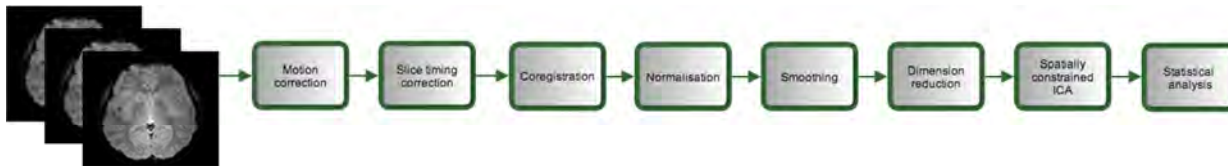

Figure 1: General analysis pipeline for the processing of the resting-state fMRI data.

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 [2]. It extracts independent components per subject, corresponding to the DMN. Finally, statistical analysis was performed using SPM8, age was introduced as a covariate of no interest. Statistical significance was set to p < 0.001 uncorrected.

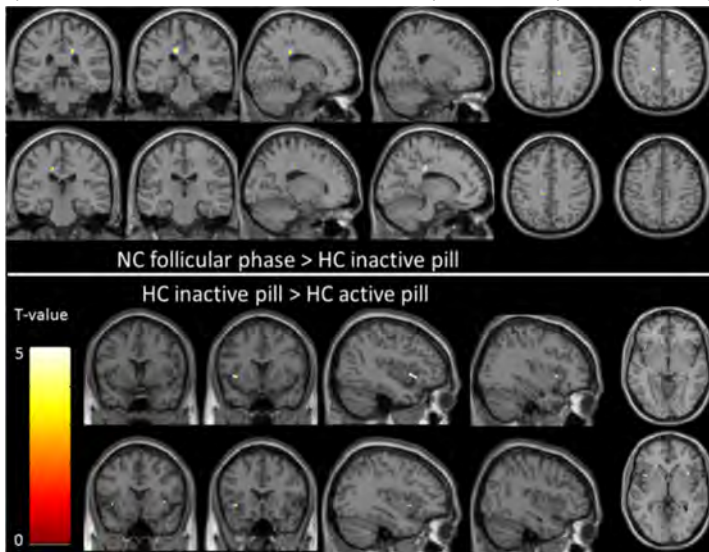Results: The upper pane of Figure 2 shows a decreased functional connectivity in bilateral cingulate gyrus in the inactive pill phase of HC users, as compared to the follicular phase of NC women. The lower pane of Figure 2 shows a short term HC effect within the HC use. Functional connectivity is decreased in bilateral.

Figure 2: Transversal, coronal and sagittal images increased functional connectivity in bilateral cingulate gyrus in the NC follicular phase compared to HC inactive pill phase (upper pane), and in bilateral insula in the HC inactive pill phase compared to active pill-phase (lower pane). P-value < 0,001 uncorrected.

Discussion: Both cingulate gyrus and the insula have been associated with emotional processing [3]. It has been shown that the use of hormonal contraception alters emotional memory formation; however active or inactive pill-phase was not controlled for [4]. Whether these findings have an underpinning in the resting-state DMN, is currently unknown. A recent study found an increased functional connectivity in the follicular phase, as compared to inactive pill phase in caudate nucleus and no differences between active and inactive pill phase [5]. Despite that we do not reproduce these results, findings consistently show *reduced* functional connectivity due to HC use. Since our study, unlike reference [5], is test-retest in the HC group, we believe that our data shows improved reliability regarding new within HC-group finding.

Conclusion: Our research describes DMN-alterations due to both short and long-term effects of HC use. We believe that our results support previous, non-resting-state fMRI based, literature. Moreover, areas for emotional processing are topic of interest in neuro-psychological research. Importantly, HC use is almost never corrected for in these fields. Consequently, researchers introduce heterogeneity in their data, which will lead to loss of accuracy and precision, enhancing or obscuring findings.

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