Hormonal contraceptives dependency of quantitative diffusion kurtosis parameters in the limbic system: a voxel based approach

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Target audience: Neuroscientists and behavioral scientists

Purpose: MR studies show both morphological and functional alternations in the female brain as a function of menstrual cycle phase and hormonal concentrations. However, the use of hormonal contraceptives is discarded in these studies. A recent DTI tractography study suggests that this may have an influence on brain white matter microstructure.[1] In this work, we examined changes in diffusion kurtosis measures with a voxel based method. The goal was to elucidate localized differences in the quantitative diffusion parameters of the more extended DKI model, which provides more accurate description of the diffusion weighted signal. In addition we try to reproduce results of the DTI study.

Methods: A group of 30 healthy female subjects was assembled (age: 18-28y), from which 15 had a natural menstrual cycle, and 15 used combined oral contraceptives pill (COCP). All subjects underwent 2 MR experiments, one in follicular phase or stopweek in the COCP group, and one in luteal phase. We used a 3T Trio Siemens MR system. DKI acquisition consisted of 3 different b-values (700, 1000 and 2800 s/mm²) along 15, 40 and 75 non-collinear directions respectively. In addition 10 b0 reference scans were acquired. Voxel based image analysis was performed by methods described in Van Hecke et al.[2] and Veraart et al.[3], using high dimensional image registration techniques and a population specific DKI atlas. In order to extract the white matter, only voxels with FA>0.2 were considered for statistical analysis.

Results: Resulting maps were statistically analyzed using t-tests in SPM8. Voxels were considered significant when p-value was lower than 0.005, uncorrected. A comparison was made between 2 phases with highly different levels of estradiol and progesterone, who are known to be strong neuromodulators. More specifically, we compared the natural cycle group in luteal phase (high hormone) with women on COCP (low hormone). We found several clusters of statistically significant differences in the cingulum. Both radial diffusivity (RD) and mean diffusivity (MD) were found to be higher in the COCP group, and axial kurtosis (AK) was lower in the COCP group, compared to the natural cycle group (Figure 1).

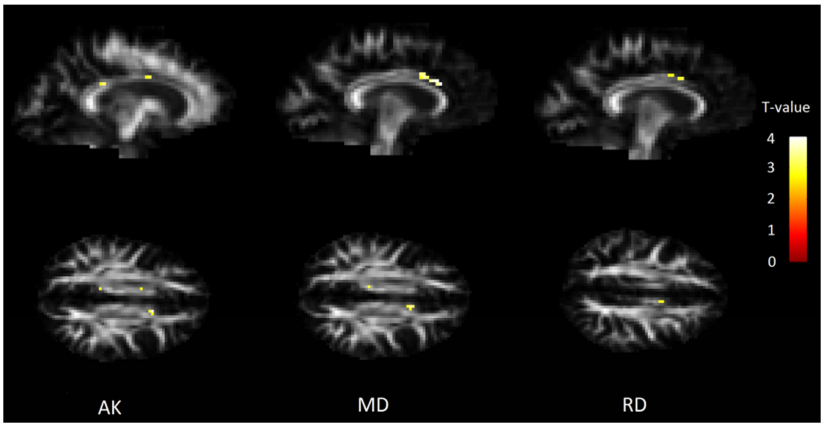

Figure 1: Sagittal and axial view of axial kurtosis, mean diffusivity and radial diffusivity significant voxels overlaid on an FA map in the population specific atlas.

Discussion: The result of the tractography study[1], an elevated MD in the COCP fornix, was not reproduced. However, additional localized differences were found in the cingulum, which together with the fornix, is the main white matter structure in the limbic system. Because of the considerable amount of voxels of the reconstructed cingulum in the tractography result, one loses the sensitivity to detect local differences as described here. Not reproducing the difference in MD in the fornix is most likely due to small registration errors which are a consequence of partial volume effects, an artifact for which the fornix is known to be prone to.

Conclusion: When designing a diffusion MRI study, the factor of hormonal contraception and menstrual cycle phase should be taken into account. Moreover, further studies might shed light on possible behavioral alternations introduced by hormonal contraceptives use.

References: [1] De Bondt T, Van Hecke W, Veraart J, et al. Does the use of hormonal contraceptives cause microstructural changes in cerebral white matter? Preliminary results of a DTI and tractography study. Eur Radiol. 2012; Epub. [2] Van Hecke W, Sijbers J, De Backer S, et al. On the construction of a ground truth framework for evaluating voxel-based diffusion tensor MRI analysis methods. Neuroimage. 2009; 46:692-707. [3] Veraart J, Van Hecke W, Sijbers J. Constrained maximum likelihood estimation of the diffusion kurtosis tensor using a Rician noise model. Magn Reson Med. 2011; 65:138-45.