Long-term estradiol treatment induces changes in brain activation during cognitive task performance in fMRI

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Introduction

Estradiol is the main female sex steroid hormone implied in the regulation of several reproductive functions. It is also used as a therapeutic drug in multiple indications such as the treatment of postmenopausal osteoporosis or as an oral contraceptive. Several functional magnetic resonance imaging (fMRI) studies demonstrated that estradiol can affect distinct cognitive functions such as visuo-spatial processing [1]. Here, we evaluated estradiol effects on a mental rotation task 1) in healthy subjects; and 2) male-to-female transsexuals before and after 4 months of hormone treatment using fMRI.

Methods

SUBJECTS

Twenty healthy female controls (FC) (26.9 ± 6.0 years) and 5 male-to-female transsexuals (MfT) (33.7 ± 6.6 years) were included in this study. FCs were measured once, MfTs were measured at the beginning and after four months of estradiol treatment.

fmRI IMAGE ACQUISITION TECHNICALITIES

All subjects underwent fMRI using a Siemens Magnetom 7T scanner (EPI-sequence: TE=23ms, TR=1.4s).

fmRI PARADIGM

All subjects performed a mental rotation task (Figure 1) in an event-related design. During this task, 48 pairs of 3D geometrical figures in different degrees of rotation with three levels of difficulty were presented randomly to the subjects [2]. The goal was to mentally rotate one of the figures and thus bring them into mutual alignment. The mental rotation task is one of the most sexually dimorphic paradigms known [1]. The FCs were measured only once and their BOLD signal activity during the task (Figure 2) was correlated with circulating plasma estradiol levels (Figure 3). The MfT-transsexuals were measured twice, once medication free and the second time after 4 months of treatment with estradiol (estradiol 100μg transdermal twice a week).

PREPROCESSING

The fMRI scans were preprocessed in SPM8: slice timing correction, realignment, normalization to MNI space using an in-house custom EPI template created for 7T EPI, 9mm Gaussian kernel smoothing.

QUANTIFICATION

For each subject, the different levels of mental rotation difficulty were modeled by three regressors. The contrast relevant for this study comprised the mental rotation regressors compared against baseline. The influence of estradiol on individual activations during mental rotation was evaluated 1) by linear regression for healthy controls; and 2) paired t-test for MfT subjects comparing treatment against baseline condition.

Results

Correlation of plasma estradiol with fMRI signal in 20 healthy female controls: Significant negative correlations of individual deactivations with plasma estradiol level were found in parieto-occipital sulcus (T=7.24, p<0.05 FWE, cluster extent > 10 voxels), and the neighboring cuneus and precuneus cortical areas (Broadman areas 7,17-19), see Figure 3 top left. Mean model parameter estimates from the peak cluster (MNI 47,18,39, extent 17 voxels) were plotted against plasma estradiol levels (Figure 3 top right) and a linear fit was performed. R² value was 0.82, that is the regression model explains 82% of the variance.

Paired t-test in 5 MfT-transsexuals:

Comparing task-specific activations four months after estradiol treatment to baseline revealed stronger deactivations after treatment in the parieto-occipital sulcus and adjacent Brodmann areas (7,17-19, T=7.17, p<0.001 uncorrected), see Figure 3 bottom left. Furthermore, plasma estradiol levels of FmT transsexuals were measured at the beginning and after four months of hormonal therapy with estradiol. Figure 3 bottom right shows a box car plot. A two sample t-test was performed in which unequal variance was assumed (df=8.87,t=4.08,p=0.003).

Discussion

The assessment of estradiol effect in two independent subject groups showed consistent results, i.e. stronger deactivations in cortical areas neighboring the parieto-occipital sulcus under the influence of estradiol. The adjacent Brodmann areas (7,17-19) are implied in the processing of visuo-spatial information [3]. The observed estradiol-dependent modulation of brain activation in these regions might at least partially explain the known differences in mental rotation task between males and females.

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References: