European Neuropsychopharmacology (2008) **18**, 215–221

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Effects of cross-sex hormones on cerebral activation during language and mental rotation: An fMRI study in transsexuals

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Received 27 June 2007; received in revised form 25 September 2007; accepted 1 October 2007

KEYWORDS
Cerebral lateralization;
Sex steroids;
fMRI;
Gender identity disorder;
Transsexualism;
Testosterone

Abstract

Androgens and estrogens affect the performance on certain cognitive tests, particularly those measuring verbal fluency and mental rotation. Their effects on cognition have frequently been attributed to changes in cerebral lateralization. This study tested the impact of a reversal of the sex steroid milieu on cerebral activation and lateralization during verbal and spatial tasks in transsexuals.

fMRI scans were obtained from 6 female-to-male and 8 male-to-female transsexuals at baseline and after cross-sex steroid treatment. Activation was measured during language and mental rotation tasks. Language activation increased after sex steroid treatment in both groups ($F(1,12) = 3.7$, $p = 0.08$), and total language activity was correlated to post-treatment estradiol levels (rho = 0.54, $p = 0.05$). Lateralization was not affected by the reversal of sex steroid milieus ($F(1,12) = 1.47$, $p = 0.25$). Activation during mental rotation did not increase during treatment ($F(1,12) = 0.54$, $p = 0.34$), but post-treatment testosterone levels correlated to total activation during mental rotation (rho = 0.64, $p = 0.01$). Findings suggest that sex steroids may influence cerebral activation, but lateralization remains stable.

1. Introduction

Sex hormones (estrogens and androgens) may affect cognitive functions both in males and females. For example, Aleman et al. (2004) found significantly improved performance on mental rotation tasks in healthy young females after administration of a single dose of testosterone. In parallel, Cherrier et al. (2003) described improvement on

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doi:10.1016/j.euroneuro.2007.10.002

spatial memory in hypogonadal males receiving testosterone replacement therapy. In contrast, subjects treated with androgen blockade for prostate cancer showed a decrease in spatial abilities but increased performance on verbal memory (Cherrier et al., 2001). Hampson and Kimura (1988) found improved spatial skills in healthy women during the menstrual phase, when estrogen level is low and improved verbal skills in the midluteal phase, when estrogen level is high. Slabbekoorn et al. (1999) described decreased performance on verbal fluency tasks and increased performance on mental rotation tasks in female-to-male transsexuals treated with androgens, while male-to-female transsexuals treated with androgen blockade and estrogen addition showed the opposite changes in cognitive performance (but see van Goozen et al., 2002). These results suggest that androgen administration improves performance on mental rotation tests with decreasing performance on verbal fluency tests, whereas anti-androgen and estrogen administration appears to induce the opposite effects. Precisely how sex steroids act on the brain to affect performance on cognitive tasks is currently unclear. Animal studies found effects of estrogen on synaptic density and transmission. For example, Yankova et al. (2001) demonstrated that increased estrogen concentrations induce synaptogenesis and alterations in synaptic transmission in hippocampal pyramidal cells in female rats. In the human brain, no analogues of these sex steroid-induced neural changes have been described.

Both language and spatial functions have an asymmetrical cerebral representation, with language activation predominantly in the left hemisphere and spatial activation predominantly in the right hemisphere (Kimura, 2000). Several dichotic listening and visual half-field studies have suggested that estrogens decrease cerebral lateralization for language (Herman et al., 1993; Wisniewski et al., 2005) while androgens are associated with increased language lateralization (Gadea et al., 2003). Low degrees of language lateralization are thought to induce competition between verbal and spatial functions in the right hemisphere, leading to reduced spatial functioning (Levy, 1969). However, evidence for this mechanism is lacking. Thus, though several studies have explored the effects of sex steroids on *performance* on verbal and spatial tasks (reviewed by Collear and Hines, 1995), the effects of sex hormones on the *neural representation* of these functions are unclear.

In this study, we aimed to investigate the effects of inversing the sex steroids milieu on cerebral activation and lateralization of language and spatial functioning. For this purpose, we obtained functional Magnetic Resonance Imaging (fMRI) scans of both male-to-female transsexuals and female-to-male transsexuals, at baseline and after three months of cross-sex hormone administration.

2. Experimental procedures

2.1. Subjects

Subjects were eight male-to-female transsexuals (22 ± 3 years old, and education of 10 ± 3 years) and six female-to-male transsexuals (29 ± 9 years old, education of 12 ± 3 years) eligible for cross-sex hormone treatment. All subjects gave their informed consent to the research protocol which had been approved by the ethical review board of the institution. They were scanned a few days before the start of hormonal treatment and again, after approximately 3 months of hormonal treatment. Male-to-female transsexuals received treatment with the anti-androgen cyproterone acetate (Androcur) 100 mg/day and estrogens: oral ethinyl estradiol (Lynoral 100 μg/day) or transdermal 17β-estradiol (Estraderm TTS 100, 100 μg twice a week). Female-to-male transsexuals received parenteral testosterone esters (Sustanon) 250 mg/14 days. Serum testosterone and 17β-estradiol were measured at the day of the scans.

2.2. Activation paradigms

All subjects completed two language tasks while being scanned: a paced verb-generation task with covert articulation and a paced categorical decision task, in which subjects indicated by button presses whether the presented word was an animal or not. In the control condition of the verb-generation task, visual objects matched for size and light intensity to letters were shown, without any instructions. During the control condition of the semantic decision task, the subjects were shown the same visual objects and asked to press the button in response to five small figures. Only the number of errors was recorded, but no reaction times, since we applied a paced-task design. The patients engaged in language tasks for a total time of 20 min (Ramsey et al., 2001).

The Mental Rotation Task, originally described by Shepard and Metzler (1971) was presented in the version of two three-dimensional figures, from which the participant had to indicate whether they are identical or different (i.e. mirror-images). The control condition for the mental rotation task was an abstract figure that appeared similar to the figures shown in the experimental condition, but that lacked three-dimensional information. The control condition also included a button press response, since subjects had to press the right or left button depending on the direction of an arrow. The control condition for this task thus included a visual and a motor component, but no spatial component. Only the number of errors was recorded, no reaction times. The patients engaged in the mental rotation task (activation and baseline) for 20 min. All tasks were presented in blocks of 30 s activation paradigm alternated with 30 s baseline condition.

2.3. fMRI scan protocol

Functional scans were acquired with a Philips ACS-NT 1.5 Tesla clinical scanner, using the blood oxygen level dependent (BOLD) sensitive, navigated 3D PRESTO pulse sequence (Ramsey et al., 2001), with the following parameter settings: TE/TR 35/24 ms, flip angle 9°, FOV 225×180×77 mm, matrix 64×52×26, voxel size 3.51 mm isotropic, scan time per fMRI volume 2.4 s. Following the fMRI procedure an anatomical scan was acquired (3d-FFE, TE/TR 4.6/30 ms, flip angle 30°, FOV 256×256×180 mm, matrix 128×128×150, slice thickness 1.2 mm) to permit detailed localisation of the functional maps.

2.4. Statistical analysis of the fMRI data

All data were analyzed with custom-written software, which is based on the algorithms described by Worsley and Friston (1995). Functional images were analyzed individually on a voxel by voxel basis using multiple regression analysis with one factor coding for activation (task versus rest), and three for signal drift (due to scanner hardware). The regression coefficient for activation was converted to a *t*-value for each voxel, yielding a *t*-map. Significant activation was then determined in each voxel by applying a threshold of 4.0, corresponding to a *p*-value of 0.05 after Bonferroni correction for the number of voxels in the volumes of interest.