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Research report

Changes in spatial cognition and brain activity after a single dose of testosterone in healthy women

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HIGHLIGHTS

- We administered testosterone in a randomized, placebo-controlled design to 42 women.
- We performed fMRI during wayfinding tasks in a recently learned virtual environment.
- Testosterone improved some aspects of spatial abilities in women.
- Testosterone increased medial temporal lobe activity during virtual navigation.

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ABSTRACT

Studies have consistently shown that males perform better than females on several spatial tasks. Animal and human literature suggests that sex hormones have an important role in both establishing and maintaining this difference. The aim of the present study was to examine the effects of exogenous testosterone on spatial cognition and brain activity in healthy women. A cross-sectional, double-blind, randomized, placebo-controlled study was performed in 42 healthy young women who either received one dose of 0.5 mg sublingual testosterone or placebo. They then learned a virtual environment and performed navigation tasks during functional magnetic resonance imaging (fMRI). Subsequently, their knowledge of the virtual environment, self-reported navigation strategy, and mental rotation abilities were measured. The testosterone group had improved representations of the directions within the environment and performed significantly better on the mental rotation task compared to the placebo group, but navigation success and navigation strategy were similar in the two groups. Nevertheless, the testosterone group had significantly increased activity within the medial temporal lobe during successful navigation compared to the placebo group, and a positive correlation between testosterone load and medial temporal lobe activity was found. Fetal testosterone levels, measured as second-to-fourth digit length ratio, interacted significantly with parahippocampal activity and tended towards giving higher mental rotation task scores. These results demonstrated that testosterone had a limited effect pertaining specifically to spatial cognition involving 3D-visualization in healthy women, while complex behaviors such as navigation, relying more on learned strategies, were not altered despite increased neuronal activity in relevant brain regions.

1. Introduction

Performance on certain cognitive tasks, such as spatial navigation and mental rotation tasks (MRT), is unevenly distributed between men and women. Indeed, MRT and navigation are the two tasks with the most consistent and notable sex differences with men scoring higher than women [1–6]. Furthermore, performance on MRT is moderately correlated to navigation ability [7,8]. The underlying biological mechanism(s) underpinning this sexual dimorphic performance remain uncertain, but several lines of evidence point to testosterone levels playing a significant role. In general, increased testosterone levels are associated with improved MRT performance in women [9–11]. More ambiguous results are found for navigation using a virtual analogue of the Morris water

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task (vMWT), with one study indicating a positive association between endogenous testosterone and navigation performance in women [8], and other studies showing a neutral [7] or negative association [12]. Testosterone has both organizational and activational effects on the brain, which may both be involved in the emergence of sexual dimorphic performance [13]. The organizational effect takes place during development and results in permanent changes in brain morphology. Fetal testosterone levels are believed to be mirrored in the ratio between the length of the second and fourth digit (2D:4D) [14], which is used in some studies as a proxy for testosterone's organizational effects on the brain [15–19]. The activational effect of testosterone is more transient and depends on the current endogenous hormone level [20,21]. Both organizational and activational effects influence brain function, and interactions between organizational and activational effects are reported [22,23].

Navigation ability is subserved by several medial temporal lobe (MTL) structures [24], predominantly the hippocampus, entorhinal and parahippocampal cortices [25–28]. Both androgen and estrogen receptors are particularly densely expressed in the MTL [29,30], and sex hormones have been demonstrated to have major effects on hippocampal structure and function [8,31–33]. In the hippocampus, androgens can act on pyrmidal cells both directly via the androgen receptor, as well as via one of the estrogen receptors after convertion to estrogens by aromatase [34]. Activational effects of testosterone have been shown in women, as adult endogenous testosterone levels correlate positively with navigation abilities in both adult women and female rats [8,35]. In animal models, it has been shown that testosterone administration increases hippocampal pyramidal dendritic spine density in ovariectomized female rats [36]. Hippocampal pyramidal dendritic spine density is positively associated with memory [37–39], and thus possibly navigation performance. Moreover, women born with congenital adrenal hyperplasia, which is associated with excessive production of androgens in fetal life, perform better on spatial tasks than healthy controls [40] pointing to an organizational effect of testosterone on spatial cognition in women. Still, no study has assessed the effect of exogenous testosterone on navigation performance in women, nor examined possible interactions between testosterone's activational and organizational effects in navigation, and/or their separate contributions to navigation.

A positive effect of exogenous testosterone administration on MRT performance in women is, on the other hand, well documented [10,41,42]. In contrast to navigation, mental rotation is not dependent on the hippocampus, but relies on frontal and parietal regions [43]. Since there are no experimental animal models of mental rotation, less is known about the possible neurobiological mechanism(s) behind testosterone's MRT enhancing effect. However, sex hormone receptors are located throughout the cortex [44], including frontal and parietal regions, and numerous effects have been ascribed to sex hormone receptor activation [33,45–49]. At the activational level, it has been shown both that endogenous testosterone levels correlate positively with MRT performance [9], and that a single dose of exogenous testosterone improves MRT performance in healthy women [10]. Moreover, prolonged androgen treatment in female-to-male transsexuals improves MRT performance even several weeks after cessation of testosterone administration [41]. There is conflicting evidence with regard to testosterone's organizational effects on MRT performance [15,16,18,19], but women exposed to higher intrauterine testosterone levels, i.e., women with congenital adrenal hyperplasia and female fraternal twins with male co-twins, perform better than controls on several spatial tasks, including MRT [11,40,50,51].

The neuronal correlates of testosterone's effect on behavior in healthy women have so far only been studied with paradigms probing social interaction, reward and mood, and only by comparing overall responses to stimulus presentation versus a passive baseline condition. A general finding across these studies is increased brain activity in task positive regions [52–57]. However, whether this increase in activity is related specifically to task performance or reflect a general increase in the BOLD signal due to the mere exposure to a stimulus, cannot be surmised from these results. In addition to increased brain activity, both increased and decreased functional connectivity has been described during task performance [54,58,59], but no study has examined if exogenous testosterone influences resting state functional connectivity. The described effects of exogenous testosterone on brain activity have always been measured after a delay of several hours, when serum levels have returned to normal, pointing to genomic mechanisms behind the changes in fMRI activity [23,52–55,57,60].

The primary aim of the current study was to explore the effect of exogenous testosterone administration on navigation ability and its neuronal correlates in women using an ecologically valid, large scale virtual environment (VE). Based on the above reviewed literature, we predicted that sublingual administration of a single dose of testosterone would increase spatial navigation performance in women. Furthermore, we predicted that testosterone administration would improve knowledge of the environment, i.e., improve judgments of direction and distance between landmarks and increase use of available shortcuts. The latter prediction was motivated by previous studies showing that men perform better than women when navigation requires accurate directions [5,6,61], have better pointing and navigation accuracy towards unseen targets [62,63], and better distance judgment compared to women [62,64].

We further predicted that testosterone administration induced changes in brain activity in certain regions of the MTL, and that these changes would be specific to successful navigation. Specifically, we predicted increased activity in the anterior hippocampus in the testosterone group, as activity in this area has been linked to the use of an allocentric strategy, i.e. a more male like navigation style [65], during VE navigation [25], and correlates with successful VE navigation [26]. The overall activity during navigation compared to baseline, on the other hand, would be similar in the two groups. As a control, the effect of exogenous testosterone on MRT performance was assessed to ascertain that the experimental setup allowed for reproduction of the earlier described performance effects of testosterone. Since some previous studies suggest an interaction between current testosterone level and fetal testosterone exposure on task performance [22,23], we investigated correlations and interactions between the 2D:4D ratio, navigation performance, MRT performance, and brain activity in the MTL during successful navigation. Lastly, we explored the effects of exogenous testosterone on resting state networks based on previous reports on increased functional connectivity in task positive regions following testosterone administration.

2. Materials and methods

2.1. Participants

53 healthy right-handed women (19–30 years, mean = 22.5 years) were recruited at the university campus. The local ethics committee only allowed the enrollment of participants that were on oral contraceptives. Moreover, the participants had to take a pregnancy test at the day of the experiment to ensure that pregnant women were not included. To control for menstrual cycle induced hormonal fluctuations and to ensure similar low endogenous hormone levels in all participants, the women were instructed to stop using oral contraceptives three to seven days prior to the study to ensure that they were in their early follicular phase [66]. At this time