Psychoneuroendocrinology (2009) 34, 110—117

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Androgen treatment effects on memory in female-to-male transsexuals

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Received 9 May 2008; received in revised form 21 July 2008; accepted 21 August 2008

KEYWORDS
Androgen;
Sex hormones;
Transsexual;
Gender identity disorder;
Memory;
Cognition

Summary
Introduction: It has been hypothesized that cognitive and memory-related brain function in transsexuals during cross-sex hormonal treatment might be activated towards that of the subjective gender. However, research on this topic has produced inconsistent results, and to the best of our knowledge no studies have investigated memory changes in androgen-treated female-to-male (FM) transsexuals.
Methods: A total of 33 FM transsexuals underwent neuropsychological testing in order to examine the effects of androgen on memory. We used a longitudinal design in which 14 FM transsexuals were tested twice, before and after receiving 6 months of testosterone treatment. In addition, a cross-sectional design was used to compare 10 individuals off treatment versus 9 individuals on testosterone treatment for at least 6 months.
Results: Participants tested before and after 6 months of androgen treatment improved significantly their performance on a visual memory task (visual paired associates, immediate recall, WMS-R). The cross-sectional design confirmed that patients on androgen treatment for at least 6 months performed better than subjects off treatment on the same task and also on another visual memory task (Rey—Osterrieth complex figure test, ROCF; copy and delayed recall). No differences were found in any verbal memory test for either design.
Conclusions: The results indicate that androgen has an influence on visual memory, but not on verbal memory. Therefore, for FM transsexuals the data support an activating effect for androgens on visual memory, a domain that generally tends to favour males.

1. Introduction

Although men and women do not differ in general intelligence, sex differences in some cognitive functions have been widely established in the literature. Men tend to

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doi:10.1016/j.psyneuen.2008.08.017

outperform women on some visuo-spatial tasks (Linn and Petersen, 1985). In contrast, women generally perform better than men on verbal fluency (Halpern, 1992) and perceptual speed tasks (Mann et al., 1990). A similar pattern of differences has also been described in regard to memory, another cognitive domain. Females tend to excel on certain verbal memory tasks, such as verbal learning and story recall tests (Bleecker et al., 1988; Basso et al., 2000), whereas males generally excel on certain visual memory tests, such as reproducing designs from memory (Basso et al., 2000; Lewin et al., 2001). Nevertheless, there is a considerable overlap in cognitive performance between men and women, and it is difficult to find sex differences in small populations (Kimura, 1996, 2002; Torres et al., 2005). In fact, the most stable sex difference found in many studies of normal populations is on mental rotation tasks, which favours men (Hampson, 1995).

It has been suggested that these cognitive differences are related to sex hormonal mechanisms. In this regard it has been proposed that endogenous sex hormones, estrogen or androgen, affect cognitive functioning through both pre- and perinatal permanent organisational effects on brain structures, as well as through the reversible postnatal activational effects that are thought to occur during puberty or in adulthood (Hampson, 1995; Kimura, 2002).

The possible activational effects of androgen on cognitive functioning have not, however, been widely reported. In men, experimental studies suggest beneficial changes in cognitive function induced by testosterone supplementation (Shute et al., 1983; Gouchie and Kimura, 1991; Moffat and Hampson, 1996; Barret-Connor et al., 1999; Cherrier et al., 2007). Moreover, higher free testosterone levels have been related to better visuo-spatial abilities and semantic memory (Sherwin, 2003; Thilers et al., 2006). In women, the available data suggest that high testosterone levels are associated with better performance on mental rotation and visuo-spatial abilities (Shute et al., 1983; Imperato-McGinley et al., 1991; Gouchie and Kimura, 1991; Moffat and Hampson, 1996; Hausmann et al., 2000; Aleman et al., 2004), and that they have a negative influence on verbal fluency and verbal memory (Hogervorst et al., 2004; Thilers et al., 2006; Schattmann and Sherwin, 2007). However, inconsistent results have been obtained both in women (Wolf and Kirschbaum, 2002; Hines et al., 2003; Halari et al., 2005; Malouf et al., 2006; Shah et al., 2006) and in men (McKeever et al., 1987; Wolf et al., 2000; O'Connor et al., 2001; Wolf and Kirschbaum, 2002; Kenny et al., 2004; Halari et al., 2005). Further research is needed to establish whether androgen hormones have an activational influence on cognitive functions in men and women.

Transsexual patients are interesting model for investigating the effects of varying hormonal levels on cognitive function because they receive supraphysiological doses of cross-sex hormonal treatment in the course of the sex reassignment procedure. Transsexualism (ICD Classification of Mental and Behavioural Disorders, ICD-10), also known as gender identity disorder (GID) of adulthood or adolescence (diagnostic and statistical manual of mental disorders, DSM-IV-TR), is characterized by a strong and persistent cross-gender identification, accompanied by persistent discomfort with the biological sex or sense of inappropriateness in the gender role of that sex (American Psychiatric Association, 2000), and it is usually accompanied by the wish to make the body as congruent as possible with the preferred sex through hormone treatment and sex reassignment surgery (World Health Organization, 1993). As part of their sex reassignment, female-to-male (FM) transsexuals are treated with androgens to promote masculinization and male-to-female (MF) transsexuals are treated with estrogens in combination with antiandrogens to promote feminization (Gómez-Gil and Esteva de Antonio, 2006). After 3 months of hormone treatment, sex hormone levels of transsexuals are in the range of those of the opposite sex (Meyer et al., 1986).

Studies investigating cognitive changes in transsexual patients receiving hormonal treatment are scarce and have produced inconsistent results. A number of studies have provided support for the idea that cross-sex hormone treatment skews the cognitive performance of transsexual patients towards the pattern of the desired sex. For instance, in MF patients, Van Goozen et al. (1995) found impaired visuo-spatial abilities and an improvement on some verbal fluency tasks after receiving cross-sex hormones. However, the deleterious effect on visuo-spatial functions was not replicated in several longitudinal studies (Slabbekoorn et al., 1999; Van Goozen et al., 2002; Haraldsen et al., 2005; Miles et al., 2006) or in studies with normal controls (Wisniewski et al., 2005). Similarly, in FM patients, initial studies reported improved visuo-spatial performance (Van Goozen et al., 1994, 1995; Slabbekoorn et al., 1999) and impaired verbal fluency (Van Goozen et al., 1994, 1995) after 3 or more months of testosterone treatment. These findings could not, however, be replicated in subsequent studies for either visuo-spatial abilities (Van Goozen et al., 2002; Haraldsen et al., 2005) or verbal fluency (Slabbekoorn et al., 1999; Haraldsen et al., 2005).

Memory functioning has received little attention in research on cognition in transsexual patients. Cohen-Kettenis et al. (1998) found in transsexuals who were not yet hormonally treated that FM patients performed worse on a verbal learning task than the female control group, whereas MF patients obtained better results than did the male control group. Miles et al. (1998) compared MF transsexuals taking estrogens with a transsexual control group awaiting treatment and reported that the former showed enhanced performance on a verbal learning test. However, in a recent study by the same authors these results were not replicated (Miles et al., 2006). A study about visual memory in a sample of MF patients receiving cross-sex hormone treatment did not find any differences with respect to male controls (Wisniewski et al., 2005). Similarly, Miles et al. (2006) failed to find a deleterious effect of estrogenic treatment on several visual memory tests in MF transsexuals. To our knowledge, there are no studies about changes in memory functioning in FM transsexuals receiving androgenic treatment.

The aim of the present study was to examine the effects of androgens on memory in FM transsexuals. We used a longitudinal design in which FM transsexuals were tested twice, before and after 6 months of androgen treatment. We also used a cross-sectional design to compare groups of individuals on versus off androgen treatment. The hypothesis was that FM transsexuals receiving androgens would show enhanced visual memory and impaired verbal memory.