

REVIEW

Testosterone and the brain

MICHAEL ZITZMANN

Institute of Reproductive Medicine, University of Münster, Münster, Germany

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Abstract

Gender differences in spatial recognition, and age-related declines in cognition and mood, point towards testosterone as an important modulator of cerebral functions. Testosterone appears to activate a distributed cortical network, the ventral processing stream, during spatial cognition tasks, and addition of testosterone improves spatial cognition in younger and older hypogonadal men. In addition, reduced testosterone is associated with depressive disorders. The relationship between depression and testosterone appears to partly depend upon the androgen receptor genotype of the patient, and in appropriate patients with low testosterone levels, testosterone substitution can increase positive mood and decrease negative mood. The much publicized link between testosterone and aggression is probably only of importance in athletes who supplement their testosterone levels to excessively high levels, whereas in hypogonadal men, testosterone supplementation only enhances the positive aspects of aggression such as vigour and energy. Current data suggest that testosterone supplementation in hypogonadal men of all ages will enhance many aspects of mood and cognition.

Keywords: *Testosterone, hypogonadism, cognition, depression*

Introduction

Various dimensions of cognition differ between the sexes – for example, men generally perform spatial tasks better than women [1], whereas women outperform men in some verbal tasks [2]. It has been shown that, for example, during phonological tests, in which women excel, men have lateralized inferior frontal gyrus activation in the brain but women have more bilateral activation [3]. However, for spatial tasks, functional MRI shows that men have greater activation mainly in the right lateral inferior parietal and planum temporale regions but also show some left lateralized changes, whereas women have lower activity and no evidence of bilateral activity [4].

In addition to these gender differences in spatial cognition, many aging men have a decline in cognitive abilities as well as adverse mood shifts. It has therefore been postulated that spatial cognition and mood are negatively influenced by a decrease in androgen levels with age or with hypogonadism. Indeed, hypogonadism is associated with impaired spatial cognition [5] and depression [6,7].

Until recently, the effect of testosterone variation within the normal range on spatial cognition and mood was unclear. Measuring the possible effect of testosterone is complicated by the fact that estradiol (produced by the aromatization of testosterone) can

also modulate some cerebral functions and these effects must be separated from the effects of testosterone. There is evidence that testosterone secretion is impaired during depressed mood, even if the patient is not clinically depressed [8]. Similarly, some studies indicate a clear positive relationship between testosterone levels and spatial cognition [5], while others appear to show the converse [9]. One recent study with 59 healthy men once again confirmed a positive relationship between mean testosterone levels and performance in spatial cognition tests [10]. The authors suggested that testosterone helped in the spatial recognition task if the task was difficult, but when easier tasks are done, the level of testosterone may actually have a negative effect (possibly by interfering with concentration). Importantly, this report showed no relationship between spatial cognition and estradiol levels [10].

These pieces of information may not be conclusive but they do suggest that when testosterone levels are significantly reduced, as in men with late-onset hypogonadism, cognitive abilities and other cerebral functions may be impaired. By the same reasoning, supplementation with testosterone should help enhance mood and cognitive function in aging men with reduced testosterone. In this article, the relationship between testosterone and hypogonadism with

cognition and mood is discussed and the role of testosterone replacement therapy is summarized.

Hypogonadism, testosterone and spatial cognition

The relationship between testosterone and spatial cognition is more clearly illustrated in patients with very low testosterone levels, such as in hypogonadism, than when testosterone levels are in the normal range expected for healthy men.

Men with androgen deficiency have lower visuo-spatial abilities than eugonadal men [5]. A recent study clearly showed the link between hypogonadism, testosterone levels and spatial cognition [11]. Six men with marked androgen deficiency due to idiopathic hypogonadotropic hypogonadism performed a 21-item, standardized 3-dimensional mental rotation task before and after treatment with intramuscular testosterone (250 mg bi-weekly). The mean score on the test increased after 12 weeks' treatment with testosterone by an average of 32.6%, and this increase was significantly greater ($p = 0.001$) than increases seen with healthy individuals (which is presumably a result of learning).

This study also investigated brain activity during these tests. Importantly, during each test, cerebral glucose metabolism (measured using 18-FDG-PET) was enhanced after 12 weeks of testosterone treatment (Figure 1). There was considerable interindividual variability in the location of this increase, with increased glucose metabolism in the right inferior occipital gyrus, the right inferior frontal gyrus, the right middle temporal gyrus or the left primary visual cortex, depending on the individual. Furthermore, individuals who did not improve their score on the mental rotation task after testosterone treatment showed no signs of increased cerebral glucose metabolism [11]. Although these changes are located in one functional cortical entity (ventral processing stream), the variability in the areas of enhanced glucose metabolism and the small number of patients studied make firm conclusions difficult.

Other studies have recently indicated that testosterone supplementation may also improve cognition, and in particular spatial cognition, in patients with hypogonadism and Alzheimer's disease [12]. Intramuscular testosterone (200 mg every 2 weeks) improved scores on the Alzheimer's Disease Assessment Scale cognitive subscale (ADAScog) and the Mini Mental Status Examination (MMSE) after 12 months, whereas placebo-treated patients declined in these measures [12]. This effect was confirmed recently when patients with Alzheimer's disease or mild cognitive impairment showed improvements in spatial memory ($p < 0.05$) and constructional abilities ($p < 0.05$) when they received intramuscular testosterone (100 mg weekly) for 6 weeks [13].

As mentioned in the Introduction, some effects of testosterone supplementation on the brain are probably secondary to the increase in estradiol (formed by aromatization of testosterone) – for example, the improvement in spatial and verbal memory observed when testosterone is given to healthy but older men [14]. However, improvements in spatial memory have been shown to occur at a similar level in healthy elderly individuals given intramuscular testosterone (100 mg once weekly) for 6 weeks in the presence or absence of anastrozole, an aromatase inhibitor (Figure 2) [15]. This confirms that the effects of testosterone on spatial cognition are not mediated by estradiol. However, the precise mechanism by which testosterone enhances spatial cognition is not known.

Hypogonadism, testosterone and depression

Spatial cognition is not the only cerebral function that testosterone has been shown to affect. Although the larger scale epidemiological studies (the Massachusetts Male Aging Study (MMAS) [16] and the Veteran's Experience Study (VES) [17]) failed to show a clear correlation between depression and testosterone levels, other studies have provided good evidence that low free testosterone levels can be associated with depression [6,7,18].

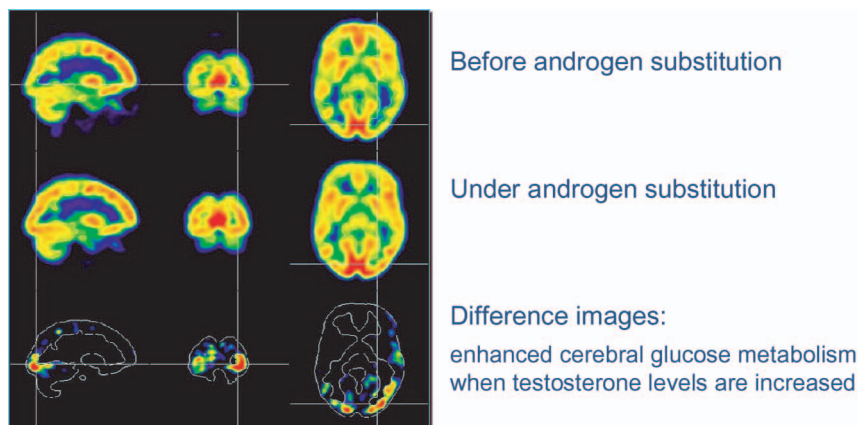


Figure 1. Cerebral glucose metabolism measured using 18-FDG PET during the mental rotation task in an individual with hypogonadism before and after 12 weeks of testosterone substitution [11].

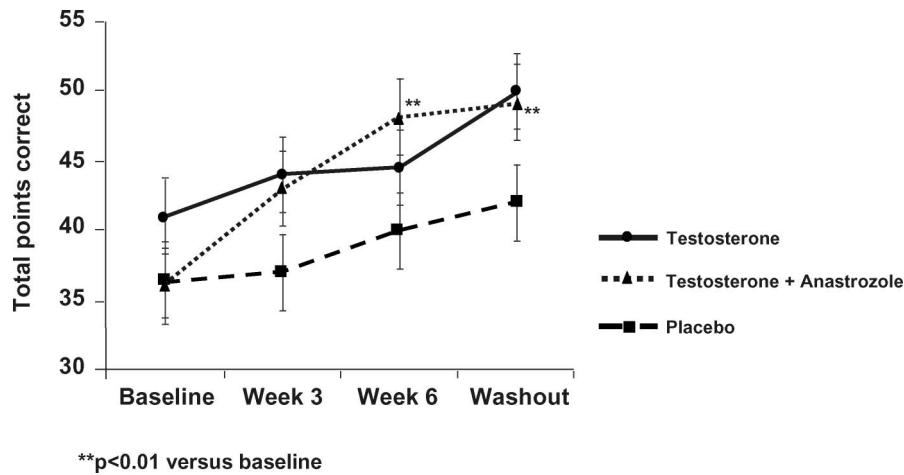


Figure 2. Improvements in spatial memory (measured by total points correct on a route test $\pm$ standard error – maximum possible score is 63) during treatment with testosterone in the presence or absence of anastrozole ($n=19$ and $n=20$, respectively), or placebo ($n=21$) in healthy men aged 50–90 years [15].

The Rancho Bernardo Study probably gave the best indication yet that depression increased with age (in the range 50–89 years), and this increase in depression was also clearly associated with lower bioavailable testosterone levels ($p=0.007$), independent of age, weight change and physical activity [18]. This phenomenon was measured using the Beck Depression Inventory (BDI) score, and the association was evident at the whole range of BDI scores and not only among those with categorically defined depression.

There have been several studies looking at a possible mechanism for the apparent link between testosterone and depression. One possible mechanistic link involves the CAG repeat sequences within the androgen receptor gene (the gene encoding the androgen receptor that mediates the effects of androgens on various cell types): The shorter the CAG-repeat tract in the androgen receptor gene, the shorter is the actually translated polyglutamine stretch of the actual androgen receptor protein. Co-activators are able to bind more easily to receptors with short repeat tracts; thus, men with long CAG repeats in the androgen receptor gene are less susceptible to androgen effects.

A smaller number of CAG repeat sequences in the androgen receptor gene is related to a faster age-related decline in testosterone over a 9-year period [19]. It seems that the number of CAG repeat sequences also influences the development of depression. In men with shorter CAG repeat sequences, total testosterone is inversely associated with depression, whereas in men with moderate or longer CAG repeat sequences, no such association exists [20]. Therefore, depending on an individual's genotype, even mild age-related reductions in testosterone levels may lead to depression or depressed mood **and men with shorter CAG repeats might benefit more in this regard from testosterone treatment than those with long repeats.** Nevertheless, as shorter CAG repeats facilitate enhanced

androgen action, **a correlation between a longer number of CAG repeats and feelings of depression and a desire to be dead was demonstrated** [21].

Depressed mood is a frequently observed phenomenon in patients with hypogonadism, and this can be managed by testosterone supplementation. Indeed, the most striking evidence that reduced testosterone can lead to increased depression comes from treatment studies in which mood is greatly enhanced by the use of testosterone supplementation. In 22 men (aged 30–65 years) with depression that was refractory to treatment with conventional antidepressants, treatment with testosterone 1% gel (10 g/day) for 8 weeks produced significantly greater reductions on depression scores than placebo (Figure 3) [22]. Interestingly, administration of testosterone gel benefited both psychological aspects of depression (such as depressed mood, guilt and psychological anxiety) and somatic aspects of depression (such as sleep, appetite, and libido). Although these men had low testosterone levels, many were within the normal range (generally testosterone levels were ≤ 350 ng/dl), and it is not known if the addition of testosterone to depressed men with higher endogenous testosterone levels would have the same effect. In addition, depression may be influenced by cerebrospinal fluid (CSF) levels of testosterone rather than plasma levels, which do not always correlate with each other. For example, one recent study showed that patients with post-traumatic stress disorder had normal plasma testosterone levels but low CSF testosterone levels [23]. Testosterone modulates brain monoamine levels [24], and therefore it may be the CSF levels of testosterone that affect mood.

The study by Pope et al. was relatively short-term and the authors concluded that longer-term studies were required [22]. A recent study therefore investigated the benefits of testosterone supplementation in hypogonadal men in the long-term, and assessed whether testosterone could also improve mood in

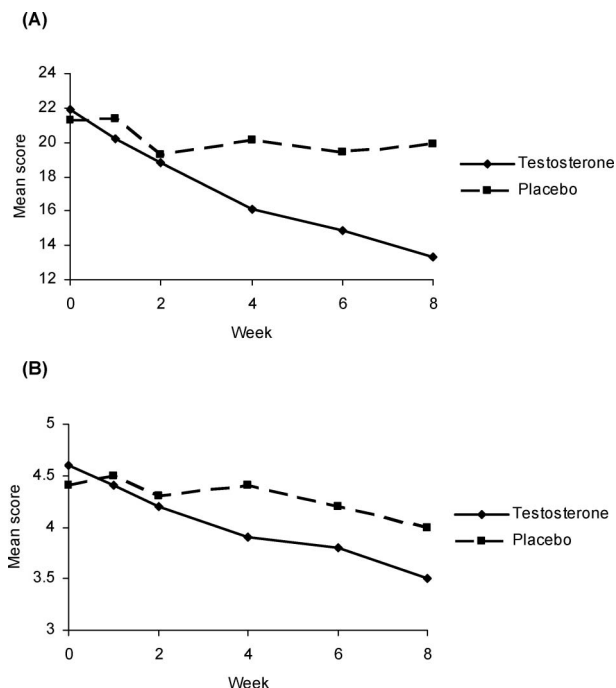


Figure 3. The effect of testosterone gel or placebo for 8 weeks on depression scores in men with treatment-refractory depression. (A) Hamilton Depression Rating Scale. (B) Clinical Global Impression severity rating [22].

this group of patients [25]. Mood change was assessed in 123 hypogonadal men receiving 1% testosterone gel (5, 7.5 or 10 g/day) for up to 42 months. The results confirmed that testosterone supplementation rapidly improved positive mood (and reduced negative mood), and these improvements were maintained for over 3 years ($p = 0.0022$) [25]. Similar results have been obtained with different testosterone gel formulations [26].

Increases in positive mood and decreases in negative mood with testosterone replacement therapy were confirmed in a study of 208 men with hypogonadism [27]. Interestingly, this study suggested that a gel formulation of testosterone may have greater effects on mood than a transdermal patch formulation because gel formulations significantly improved mood after 30, 60 and 90 days of treatment but the patch formulation induced non-significant changes [27].

These data provide evidence that many men with depression, who are refractory to antidepressant treatment, may benefit from testosterone supplementation. This would be especially true of the proportion of refractory patients with low testosterone (possibly up to 50%), but is also true for all men with hypogonadism who often suffer depressed mood. However, identifying the men who would benefit from testosterone supplementation may prove difficult because CSF levels of testosterone may be the crucial factor. Furthermore, there are potential risks with testosterone supplementation. For example, co-administration with tricyclic antidepressants may lead to paranoid symptoms [28].

Are there any negative effects on the brain?

The effect of testosterone on behaviour, and in particular aggression, has received high-profile publicity and may be considered an undesirable side effect of testosterone supplementation. However, most reports of aggression are in strength athletes who raise the level of androgens to well above normal [29–31] and there is little evidence that providing testosterone to restore levels in those with hypogonadism leads to aggression.

A recent study, in which eugonadal and hypogonadal men were given intramuscular testosterone (200 mg weekly for 8 weeks) supplementation, suggests that an increase in aggression is not inevitable with testosterone treatment and when it does occur there are many positive aspects to this increase [30]. In this study, the sub-dimensions of aggression were assessed separately (such as tension, anger, exhaustion, vigour and energy), and testosterone supplementation was shown to have no effect in eugonadal men. However in hypogonadal men, supplementation with testosterone significantly reduced many of the negative aspects of aggression (tension, anger and fatigue) while increasing positive aspects such as vigour [30]. It is possible that higher doses of testosterone could induce the more negative aspects of aggression.

Summary

In conclusion, testosterone clearly improves spatial cognitive abilities in androgen-deficient men. It also facilitates favourable shifts in mood in hypogonadal men by decreasing negative moods and increasing positive moods. The ability to improve mood even applies to patients with overt depressive disorders, especially if they have low testosterone. Furthermore, testosterone affects only the positive sub-dimensions of aggression when given to hypogonadal men and is therefore unlikely to cause violent aggression. These data highlight the beneficial effects testosterone has on the brain and explain the huge quality of life benefits that can be achieved by hypogonadal men receiving testosterone. The newer gel formulations of testosterone have as good efficacy in this respect as the older injectable formulations. These testosterone gel formulations offer some advantages over injectable forms (e.g., convenience) and avoid the potential hepatotoxicity of orally active synthetic androgens. The effects of testosterone on the brain, in addition to the other positive effects discussed in this supplement, highlight the fact that testosterone therapy should be considered in any men with hypogonadism and impairment of mood or cognition.

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