Androgens, Ageing, Behavior and Cognition: Complex interactions and novel areas of inquiry

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This article reviews the complex relationship between androgens and behavior, changes that occur with ageing and in particular hormone effects on cognitive abilities. Androgens are steroid hormones that exert both anabolic and androgenic effects which masculinize the developing organism and brain structure. Throughout the lifespan, androgens continue to exert notable effects on behavior and cognition beyond reproductive functions. As men age, they undergo a natural decline in circulating testosterone which can effect muscle mass, bone density, sexual activity and cognition. Neural effects of testosterone mediated through the androgen receptor are widespread and complex but may have specific effects on spatial navigation and memory. In humans, testosterone may underlie gender differences on cognitive tasks with evidence for men outperforming women on spatial tasks. Studies of exogenous testosterone administration in men have yielded mixed results, some demonstrating improvements in spatial tasks and others failing to find improvements. Preliminary results for an ongoing study are included which suggest improvements in spatial and verbal memory in a group of healthy older men from robustly elevated testosterone levels. Overall, the effects of androgens on behavior are complex with numerous modulators producing context dependent interactions and bi-directional interactions as well as effects on cognition.

Androgens and their effects on behavior have been an area of study for hundreds of years. In 1889, Dr. Brown-Sequard using himself as case study, injected an extract from crushed animal testicles. He felt this treatment gave him increased energy, muscular strength, stamina and mental agility (Brown-Sequard, 1889). Although crude, this approach led the way to the discovery of androgens. Since then, the focus of most androgen research has been in the area of reproductive function. More recently, hormones have become a focus for ageing researchers due to the potential anti-ageing effects of hormone replacement therapy. This article will explore the complex relationship between hormones and behavior, changes that occur with ageing, and in particular hormone effects on cognitive abilities. Although a complete discussion of hormone influences on ageing would include all gonadal steroids including estrogen, this article will focus on androgens which have received less popular and scientific attention compared to estrogen.

What are Androgens?

Androgens are steroid hormones which exert both anabolic effects such as increasing lean muscle mass and androgenic effects such as development of genitalia and beard, lower voice and libido (Matsumoto, 1991). Gonadal hormones are present in the early stages of development, even as early as the perinatal period and act to masculinize or feminize the developing organism. These early effects of hormones are termed organizational effects because they tend to be enduring or permanent changes in the organism and can result in sexual dimorphisms. For example, in certain bird species such as the canary, the presence of steroid hormones at a critical point in development gives males the ability to sing, a necessity for attracting a female during mating season. By administering testosterone to female canaries, the ability to produce song develops (Brown & Bottjer, 1993). In humans, there is some evidence for sexual dimorphisms in brain structure (Moffat & Hampson, 1996) and cognitive abilities as reviewed below.

Gonadal steroids also have activational effects which are responsible for continuing effects throughout the lifespan or which initiate behavior or organ maturation as in the case of puberty. Traditionally, most research on the activational effects of hormones has focused on sexual functioning and

sexual behaviors. For example, in humans, castration eliminates or interferes with expression of male sexual behavior but this type of dysfunction can be restored with androgen replacement (Matsumoto, 1991).

Androgen effects on behavior in animals

Androgens have numerous and complex effects on behavior ranging from highly androgen dependent behaviors to those which are moderately or minimally influenced. Studies examining the effects of steroid hormones on behavior have used multiple research methods such as castration with subsequent hormone replacement, androgen receptor blockers and examination of natural sexual dimorphisms. Aggressive behavior in numerous animal species has been shown to be related to testosterone (Bouissou, 1983). Males in many species tend to be more aggressive than females with increases in aggressive behavior during breeding season when testosterone levels are high. Female rats generally do not display increased aggression with testosterone administration unless it is administered neonatally with subsequent oophorectomization (ovaries removed) (Bronson & Desjardins, 1968). However, females of other animal species such as deer and cows do demonstrate increased male type aggression with androgen administration as adults (Fletcher, 1978).

Recent evidence suggests that for some complex behaviors or for species with more complex social behaviors, interactions between environment and hormone levels occur in both directions to affect behaviors. Breedlove (1997a) found seasonal variation in the size of the spinal nucleus of the bulbocavernosus (SNB) a region of the brain which enervates the penis. This seasonal variation corresponded to optimal times for mating and also correlated with testes size and circulating androgen levels. However, decreases in SNB size can be reversed when castrated males kept on a low dose replacement androgen are presented with a receptive female and copulatory behavior increases (Breedlove, 1997b). In baboons, dominant males demonstrate increasing testosterone levels in response to a stressor whereas submissive male baboons demonstrate decreasing testosterone levels in response to the same stressor (Sapolsky, 1982). Similarly, mice who are castrated following aggressive encounters with other mice demonstrate negligible effects from castration. However, if castration occurs prior to exposure or experience with aggressive encounters, castration effectively reduces aggression (Palmer, Hauser, & Gandelman, 1984). Other factors which affect androgen levels and/or modulate behaviors include age, circadian rhythm and individual metabolism differences. In summary, the relationship between androgens and behavior is complex, interactive and can vary greatly between species. In general, the higher one goes up the evolutionary ladder the more complex the relationship becomes with recent evidence indicating hormone and behavioral effects can be bi-directional.

Androgen effects on behavior in humans

In humans, androgens have effects on libido, sexual thoughts, feelings and activity. The most consistent findings demonstrate that when circulating androgens dip below a threshold (hypogonadism), decreases in libido and sexual functioning are found and can be treated with androgen replacement therapy (Matsumoto, 1991). However increasing circulating levels of androgens do not appear to exponentially or significantly increase libido or sexual functioning and erections in response to erotic stimuli do not appear to be androgen dependent (Anderson, Bancroft, & Wu, 1992; Bagatell, Heiman, Matsumoto, Rivier, & Bremner, 1994; Bancroft & Wu, 1983). Decreasing circulating testosterone and estradiol levels in healthy young males to induce hypogonadism decreases but does not abolish sexual desire and activity (Bagatell, Matsumoto, Christensen, Rivier, & Bremner, 1993). The relationship of testosterone to aggression in humans is complex with studies demonstrating a positive relationship between circulating androgens and outward aggression as well as negative findings demonstrating no relationship between the two (Christiansen & Kussmann, 1987; Inoff-Germain et al., 1988). Studies in which testosterone is administered to hypogonadal or eugonadal men in general find no increases in aggression but instead find improvement in mood and decreases in depression (Bagatell et al., 1994; Wu, Bancroft, Davidson, & Nicol, 1982). As with animals, the effects of androgens on behavior in humans are complex and context dependent.

Neural and Cognitive Effects of Testosterone in Animals

The effects of testosterone (T) and other androgens are mediated through the androgen receptor which is widely, but selectively distributed throughout the brain (Janne, Palvimo, Kallio, & Mehto, 1993). Testosterone replacement in castrated male rats results in neuroregulatory effects in frontal cortex, hypothalamus, amygdala, bed nucleus of stria terminalis, brainstem and hippocampus (Rubinow & Schmidt, 1996). The effects of testosterone vary depending on which region sampled but include decreased dopamine release, increased GABA turnover, and increased choline acetyltransferase levels (Rubinow & Schmidt, 1996). Effects may be long term or rapid, affecting both brain structure and receptor sensitivity.

T effects on the hippocampus may be particularly important since several lines of evidence suggest the hippocampus mediates spatial memory (Bouffard & Jarrard, 1988; Cammalleri et al., 1996; Jarrard, 1986; Jarrard & Hyko, 1994; Morris, Schenk, Tweedie, & Jarrard, 1990). The hippocampus is influenced by androgens both early in development and throughout the life span. Male rats demonstrate larger and more asymmetrical cell layers in the dentate gyrus compared with females and neonatal exposure of female rats to T results in a more "masculine" hippocampus (Roof, 1993; Roof & Havens, 1992). Circulating androgens undergo a natural process of aromatization into estradiol both in the brain and peripherally. The hippocampus contains both T receptors and estradiol receptors, thus making it a potential target for

direct T effects as well as estradiol effects following T aromatization (Luine, 1994; Roof & Havens, 1992). Such estradiol effects may be particularly relevant to cognition and ageing, given that estradiol administration causes increased spine density on CA1 apical dendrites, and distinct firing patterns of place, landmark and reference cells during spatial behavior have been recorded in the CA1 region (Gothard, Skaggs, Moore, & McNaughton, 1996; Gould, Woolley, Frankenfurt, & McEwen, 1990; Luine, 1994; Woolley, Gould, & McEwen, 1990). Testosterone administered to both male and female rats improved performance on spatial memory tasks (Flood, Farr, Kaiser, La Regina, & Morley, 1995; Rivas-Arancibia & Vazquez-Pereyra, 1994; Roof, 1993; Roof & Havens, 1992; Vazquez-Pereya, Rivas-Aranciba, Castillo, & Schneider-Rivas, 1995). In summary, while the effects of testosterone in the brain are numerous and complex, T may have specific effects on spatial navigation ability, a special form of spatial memory.

Neural and Cognitive Effects of Testosterone in Humans

Testosterone effects on brain development and function are thought to underlie gender differences in certain cognitive abilities. For example, in humans, some evidence suggests men on average may outperform women on spatial tasks while women on average may outperform men on verbal tasks. Correlations between endogenous T levels and spatial abilities in men range from near zero to .53. (Gordon & Lee, 1986; McKeever & Deyo, 1990) Males and females may also differ in the manner by which they solve spatial navigation tasks. For example, men on average tend to use a Euclidean (distance) approach to spatial navigation whereas women on average tend to use landmark references, tendencies that may reflect differential effects of gonadal hormones on place and landmark systems in the hippocampus (Galea & Kimura, 1993; Wilson, Riches, & Brown, 1990).

However, studies examining the relationship between endogenous androgen levels and cognitive performance have produced inconsistent results. In healthy young men, positive relationships have been found between circulating or endogenous T levels and visuospatial orientation (Gordon & Lee, 1986), spatial form comparison (Christiansen & Kussmann, 1987), and composite visuospatial scores (Errico, Parsons, Kling, & King, 1992). Positive relationships have also been found for tactual spatial tasks (Christiansen, 1993; Tan, 1991). Other studies examining endogenous T levels have failed to find such a relationship between circulating androgen levels and visuospatial abilities (Kampen & Sherwin, 1996; McKeever, Rich, Deyo, & Conner, 1987). Low T levels in men have also been found to be associated with better performance on spatial ability tasks (Gouchie & Kimura, 1991; Kampen & Sherwin, 1996; Moffat & Hampson, 1996; Shute, Pellegrino, Hubert, & Reynolds, 1983). In contrast, when male and female subjects are divided into high and low T level groups, the high T women and low T men typically demonstrate better spatial abilities (Gouchie & Kimura, 1991). Further, when a group of female to male transsexuals were administered testosterone, spatial abilities improved whereas verbal abilities worsened. These findings have led some to suggest that the beneficial effects of T may be found in a curvilinear relationship such that low to moderate T levels improve cognitive abilities but higher levels result in no further improvements or even decrements in some abilities (e.g., verbal) (Gouchie & Kimura, 1991; Moffat & Hampson, 1996).

Testosterone effects on spatial ability have also been examined by studies which manipulate testosterone levels or treatment studies for hypogonadal (low or absent T) individuals. In Kallmann's syndrome (idiopathic hypogonadism), deficits in spatial attention, spatial construction and spatial memory have been reported (Cherrier et al., 1998c; Kertzman, Robinson, Sherins, Schwankhaus, & McClurkin, 1990), and these deficits may improve with replacement T treatment (Cherrier et al., 1998c). In healthy men, T administration has been found to improve performance on a spatial rotation task and a spatial working memory task but decrease performance on a verbal fluency task (Janowsky, Orwoll, & Chavez, 1997; Van Goozen, Cohen-Kettenis, Gooren, Frijda, & Van De Poll, 1994). While these findings support the notion of testosterone having specific effects on spatial abilities and spatial memory, as will be discussed later, results have not been consistent in humans and in particular older adults, with some studies demonstrating no change following T administration or an inverse relationship between estradiol levels and spatial performance (Janowsky, Oviatt, & Orwoll, 1994; Sih et al., 1997).

Hormone Changes In Ageing and Dementia

Serum levels of total testosterone and bioavailable T (T that is not bound to sex hormone-binding globulin) decrease with ageing in men (Tenover, 1992; Tenover, Matsumoto, Plymate, & Bremner, 1987). Although this decrease is gradual, it can result in decreased muscle mass, osteoporosis, decreased sexual activity and changes in cognition (Swerdloff & Wang, 1993). Androgen replacement therapy in normal older men has demonstrated benefits on bone mass, muscle strength, and sexual functioning (Tenover, 1994). However, these benefits may result from direct effects of T or from increased estradiol levels following aromatization of T. Recent evidence in the case of a patient with genetic aromatase deficiency suggests that bone mass changes and other physiological effects may in fact be attributable to changes in estradiol levels rather than to direct T effects (Carani et al., 1997).

In addition to peripheral physiological effects, age-related declines in T levels appear to affect spatial memory. Ageing mice show a progressive impairment of spatial learning and memory related to decreases in plasma testosterone which can be reversed with T administration (Flood et al., 1995). In healthy older men, endogenous T levels are significantly correlated with both visual and verbal memory and verbal fluency (.53, .52 and .45, respectively) (Morely et al., 1997). However, studies which have

examined exogenous T administration in older men have produced mixed results. Sih et al. (1997) using a double-blind placebo controlled design, gave older, hypogonadal men bi-weekly injections of 200mg testosterone cypionate. Although grip strength improved, memory measures remain unchanged. Several reasons may account for lack of significant findings in this study: First, T levels did not change significantly from baseline levels consistently during the course of T administration. Second, it is unclear when cognitive testing occurred relative to the T injection and thus T levels may not have been sufficiently elevated (i.e., trough level) at the time of cognitive testing. In contrast, Janowsky et al. (1994) found improvements in spatial abilities, in a double-blind study using daily 15 mg T skin patches. However, in this study it is not clear to what degree changes in T or estradiol resulted in improved cognition, since improvement was inversely correlated with estradiol levels and unrelated to T levels. Therefore, it is possible that T exerted its effects indirectly through estradiol and/or estradiol exerted effects independent of T levels. More recently, Janowsky et al. (1997) found testosterone enanthate 150mg/weekly injections reversed spatial working memory deficits in healthy older males. In this more recent study, a higher dose of testosterone was used and testing occurred within 24-48 hours of injection to capture peak T levels.

In summary, these previous studies suggest that T administration may improve spatial memory, particularly for older males who have age-related decreases in endogenous testosterone levels. In my own laboratory, we have attempted to explore the relationship between exogenous testosterone administration and spatial abilities in a healthy older male population. Preliminary findings from a pilot study are reported below.

Preliminary findings

This study attempted to examine whether exogenous testosterone administration affects cognition in healthy older men. Based on previous research, we hypothesized that testosterone administration would improve spatial memory. A randomized, placebo-controlled, double-blind design was used with six weeks of treatment followed by six weeks of washout. Subjects were thoroughly screened prior to entry into the study on physical and cognitive measures. Treatment phase included weekly injections of 100mg testosterone enanthate or placebo (saline). Cognitive testing was conducted at baseline (week 0) and repeated at weeks 3 and 6 of treatment within 48 hours of injection to capture peak T levels. The cognitive battery consisted of measures of spatial and verbal memory, language, and attention.

At the time of this paper the project was not yet complete. Therefore, initial results are presented here with a full report of the completed study will be available in the future. Initial results were available for nineteen healthy older males ranging in age from 59 to 76 years with nine subjects in the treatment group and 10 in the placebo group (Table 1).

As expected, weekly T administration significantly ($F = 16.12$, $p<.01$) raised T levels in the active medication group as compared with placebo and this increase reached the range of healthy young males (Figure 1). Improvements in the T treatment group were found for spatial and verbal memory measures with most effects statistically significant and some measures demonstrating a trend toward significance. Interestingly, no significant improvements, or trends were noted on measures of verbal fluency or divided attention in either group. These initial results suggest that healthy older males demonstrate improvements in spatial and verbal memory in response to testosterone treatment (Cherrier et al., 1998a). While improvements in spatial memory have previously been reported, improvements in verbal memory have not suggesting T may have specific effects on memory. We are also currently conducting studies to address the potential cognitive effects of testosterone treatment for male AD patients who suffer from memory loss (Cherrier et al., 1998b). While these initial results are suggestive of a specific effect of testosterone on memory, a more complete and confident outcome awaits the completion of the study and further replication. Although these initial results are promising, the degree of functional improvement and the ultimate efficacy of testosterone replacement for older adults will need to be fully explored in future studies.

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Table 1. Demographics, Healthy Older Men

	N	Age (Years)	Years of Education	DRS Total Score	*Baseline T nmol/ L‡
T 100mg/ week Mean (s.d.)	9	67.11 (8)	15.36 (3)	139.67 (4)	16.7 (6)
Placebo Mean (s.d.)	10	68.00 (7)	16.29 (3)	139.89 (5)	16.4 (7)

* Mattis Dementia Rating Scale administered at baseline. (Mattis, 1988)

‡ Mean baseline serum total testosterone.

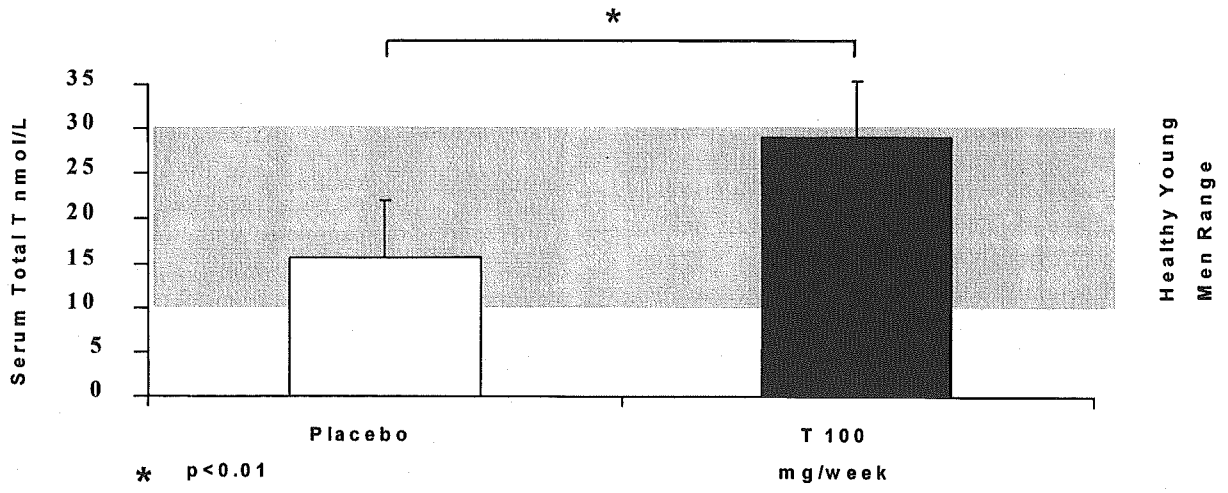

Figure 1. Mean of treatment period (6 weeks) serum total testosterone levels (nmol/L) for both treatment group (black bar) and placebo group (white bar). Normal range of serum total testosterone is indicated by gray area. Asterisk indicates significant differences between groups (.01 level) using a repeated measures ANOVA.

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