# Effects of Testosterone on Cognitive and Brain Aging in Elderly Men

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**ABSTRACT: Older age is associated with functional declines throughout the body, including some aspects of cognitive performance. While dementia develops in only some elderly individuals, declines in cognitive functioning have an impact on daily living for many others. There are individual differences in age-related cognitive changes, however, and the factors that contribute to this variability have not been well-characterized. Recent evidence suggesting that age-related alterations in the endocrine environment may modulate cognitive changes has generated considerable interest. Currently, there is a discordance between the rapidly expanding number of studies of the possible neuroprotective effects of estrogens in postmenopausal women, and the relative dearth of analogous research on the putative effects of testosterone on cognitive and brain function in older men. This paper reviews the extant literature and reports new findings on the effects of testosterone loss and supplementation on cognitive and brain function in elderly men. Preliminary evidence suggests that testosterone loss may be a risk factor for cognitive decline and possibly for dementia. Conversely, the maintenance of higher testosterone levels either endogenously or through exogenous supplementation may prove beneficial for cognitive and brain function in elderly men. However, most studies are associational in nature and the intervention studies are of short-duration testosterone exposure in small samples of subjects. Large-scale placebo-controlled intervention studies are required to resolve ambiguities in the literature. Testosterone intervention to ameliorate cognitive decline may be warranted only when the efficacy and safety of longer-term use is firmly established.**

**KEYWORDS: testosterone; androgen; Alzheimer's disease; dementia; memory; aging; hippocampus**

Older age is associated with functional declines throughout the body, including some aspects of cognitive performance. However, there are marked individual differences in age-related cognitive changes, and the factors that

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contribute to this variability have not been well-characterized. Recent evidence suggests that the hormonal environment may modulate these age-related cognitive changes. For example, there is some evidence that postmenopausal hormone replacement therapy (HRT) may exert beneficial effects on specific cognitive functions, but this remains controversial. In men, testosterone (T) levels decline precipitously between the ages of 30 and 80; results from both epidemiologic research and T replacement studies suggest that this progressive decline in testosterone secretion in aging men contributes to selective losses in memory and cognitive function. In order to fully understand the neurocognitive effects of steroid hormones, it is imperative that the cognitive and neural effects of testosterone loss and its subsequent replacement be fully characterized. Evidence for the possible neurotrophic and neuroprotective effects of testosterone come from investigations in humans and in non-human species.

## EFFECTS OF TESTOSTERONE ON BEHAVIORAL AND NEURAL SYSTEMS

In non-human species, a number of behavioral systems are responsive to gonadal steroids in both adult and developing animals. Among the diverse behavioral systems whose development and expression are sensitive to gonadal steroids include sexual and maternal behavior, overall activity levels, open field activity, aggression, juvenile play, feeding and taste preferences, motor behavior, and song production in songbirds.[1–3] An important element in understanding the effects of testosterone on the nervous system is that many of its behavioral and anatomical effects occur after it has been converted to its metabolically active derivatives, estradiol (E) or dihydrotestosterone (DHT) by means of the enzymes aromatase and 5-$\alpha$ reductase, respectively. Thus, testosterone may interact not only with androgen receptors, but also with E receptors, and hence, its administration may in some circumstances parallel the effects of E throughout the nervous system.

Of particular interest to researchers investigating hormonal contributions to human abilities is the observation that regions of the rat brain thought to subserve aspects of spatial learning and memory, including the hippocampus, have been shown to be affected by gonadal hormones. The hippocampus contains high concentrations of androgen receptors[4] and administration of testosterone to females during critical periods of development enhances spatial learning while castration in males impairs maze learning.[5–8]

Testosterone exerts an early organizational effect on the development of the hypothalamus,[9] the cerebral cortex,[10] the hippocampus,[5] and other cerebral structures, and several observations suggest that testosterone is also capable of modulating neural systems in adult animals. For example,

testosterone loss in aging mice is associated with spatial learning deficits, which are reversed by administration of testosterone.[11] Moreover, the physiological effects of testosterone strongly suggest that it may serve as an important neuroprotective and neurotrophic factor. These properties of testosterone make it a possible candidate for the prevention and/or amelioration of cognitive decline. For example, androgen treatment prevents *N*-methyl-D-aspartate (NMDA) excitotoxicity in hippocampal neurons[12] and may facilitate recovery after injury by promoting fiber outgrowth and sprouting.[13] Administration of testosterone increases nerve growth factor (NGF) levels in the hippocampus, and induces an upregulation of NGF receptors in the forebrain. [14] Testosterone may also have important inhibitory effects on the expression of amyloid, one of the principal neuropathologic hallmarks of Alzheimer's disease (AD). Testosterone decreases amyloid secretion from rat cortical neurons[15] and reduces amyloid-induced neurotoxicity in cultured hippocampal neurons.[16]

Although work investigating the *neurophysiological* effects of testosterone in humans is in its infancy, preliminary work supports the findings from the animal literature. In humans, suppression of testosterone for treatment of prostate cancer resulted in a two-fold *increase* in plasma amyloid concentrations in elderly men, suggesting that higher levels of endogenous testosterone may reduce plasma amyloid concentrations in humans.[17] In another important study, Hammond *et al.*[18] found that testosterone was protective of human primary neurons in culture, providing the most direct evidence for neuroprotective effects of testosterone on human neural tissue.

Taken together, these findings suggest that testosterone may exert important neurotrophic and neuroprotective effects, making it a potential therapeutic agent for the treatment of cognitive decline in elderly men. Additionally, studies in non-human species compellingly demonstrate that testosterone affects various aspects of behavior including learning and memory. It is, therefore, reasonable to investigate whether such effects may be present in humans as well.

## EFFECTS OF TESTOSTERONE ON HUMAN COGNITIVE FUNCTION

The large and expanding literature investigating the effects of hormone replacement therapy in women contrasts sharply to the state of science of the endocrinology of men's aging. There is a comparative dearth of research elucidating the effects of testosterone on cognitive and neural function. However, as with the research undertaken in non-human species, there is evidence that testosterone may have important behavioral and cognitive effects in humans. Among younger adults, the effects of testosterone on visuo-spatial performance has been suggested by enhanced performance in females ex-

posed prenatally to excess androgens[19,20] and reduced spatial performance in young males with hypogonadism.[21] The majority of investigations examining the association between testosterone levels and cognition have been studies in young adult men and women. Our own data[22] indicated that females with higher testosterone levels outperform those with lower levels of testosterone, while the reverse may be true in young males. Results from other[23–25] but not all [6,27] studies have reported a similar inverted U-shaped relationship between testosterone and spatial cognition in samples of young adults. Language-related measures such as verbal fluency show no significant relationship to testosterone. These correlational studies in young adults relating naturally occurring individual differences in testosterone to cognitive abilities reliably implicate spatial cognition as the domain of cognitive function most sensitive to testosterone concentrations.

Several studies have now examined the association between testosterone and cognition in older men. The progressive decline in testosterone levels with age[28,29] raises the question of whether hypoandrogenism is associated with age-related declines in cognitive functions. Morley *et al*. assessed androgen levels and cognitive performance in a sample of 56 men aged 21–84 years and found that age-related decreases in bioavailable testosterone predicted age-related decline in visual and verbal memory.[30] This study is one of the few studies to report *longitudinal* findings relating testosterone to rates of cognitive decline. Longitudinal designs are particularly important in this field as this is the only way to acquire data on within-individual *rates of change* in cognitive function, which may be a very important factor for assessing who may be a greatest risk for later acquisition of AD. In one epidemiologic study of 547 men age 59–89 years,[31] higher bioavailable testosterone concentrations were found in men who scored better on a measure of long-term verbal memory. In a second study, the relationship between endogenous steroid levels and cognitive performance was investigated in 383 women, aged 55 to 89 years.[32] Women with higher scores on mental status had significantly higher total and bioavailable testosterone levels.

In a series of comprehensive studies from the Baltimore Longitudinal Study of Aging (BLSA), we have investigated the cognitive and neural consequences of testosterone loss in aging men. In the first study,[33] we investigated age-associated decreases in endogenous testosterone concentrations and declines in neuro-psychological performance among 407 men aged 50 to 91 years. The men in the study were followed *longitudinally* for an average of 10 years, with assessments of multiple cognitive domains and contemporaneous determination of total serum testosterone, sex hormone–binding globulin (SHBG), and a calculated free testosterone index. In this study, higher free testosterone was associated with higher scores on visual and verbal memory and visuospatial functioning and with a reduced rate of decline in visual memory. No relations were observed between testosterone and measures of verbal knowledge, general mental status, or depressive symptoms.

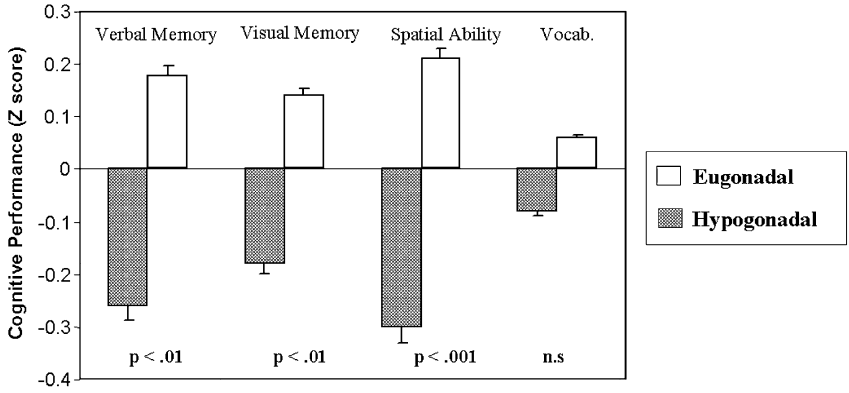


**FIGURE 1.** Cognitive performance in hypogondal and eugonadal men in four domains of cognitive performance. All cognitive test results are presented in standard scores. After age and other relevant factors (see text) were controlled, hypogonadal men performed more poorly than eugonadal men on measures of verbal and visual memory and spatial cognition.

In a second component of the same study, we classified men as either hypogonadal (less than the 2.5 percentile of men under 40), or eugonadal based on established guidelines.[29] Comparison of the two groups of men revealed higher spatial cognition, verbal memory, and visual memory function among the eugonadal men (FIG. 1). In addition, in longitudinal analyses, we observed a reduced rate of decline in visual memory among eugonadal men (FIG. 2). The effect sizes from these comparisons were substantial. For example, the difference between hypogonadal and eugonadal men on spatial cognition was one-half of a standard deviation (d = 0.52). These results demonstrate a possible beneficial effect of high circulating free testosterone concentrations in older men on specific domains of cognitive performance and cognitive decline. Although these data cannot confirm a causal impact of testosterone on neuropsychological outcome, we took every measure to control health-related factors that may potentially affect testosterone concentrations or cognitive performance, including smoking, alcohol use, body mass index, heart disease and diabetes status, age, and education levels. Moreover, individuals with cancer, dementia, or other neurologic or psychiatric problems were excluded from the study. Nevertheless, because of the associational nature of our and other studies, we cannot eliminate the possibility that low T/free T levels may serve as a marker for, rather than a causative factor in, age-related cognitive decline.

In a neuroimaging study of a subsample of these same men from the Baltimore Longitudinal Study of Aging, we quantified long-term testosterone con-

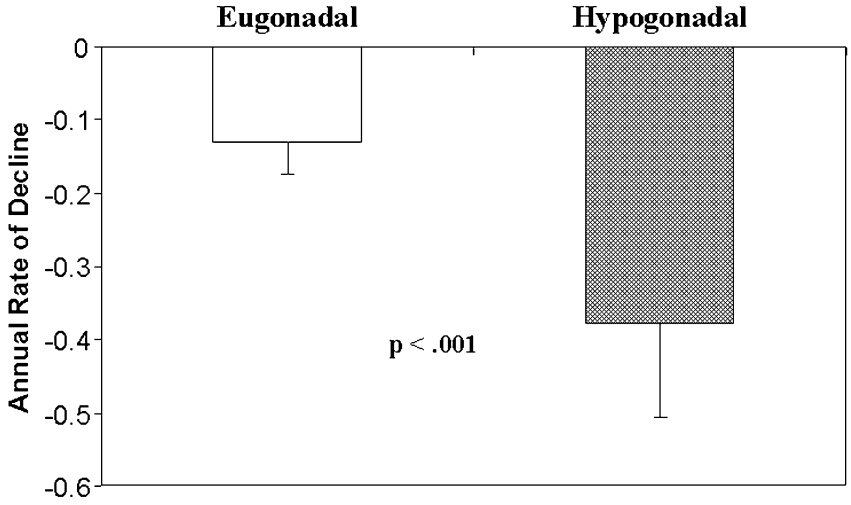


**FIGURE 2.** Annual rate of decline in visual memory as a function of hypogonadal or eugonadal status. Men classified as hypogonadal had a steeper rate of decline in visual memory than did eugonadal men.

centration in association with regional cerebral blood flow (rCBF) as determined by positron emission tomography (PET). We found that men with higher endogenous free T had increased blood flow in the hippocampus bilaterally. This study converges with our cognitive findings in the full BLSA sample in demonstrating that high levels of endogenous free testosterone is associated with improved memory and spatial cognition and increased resting activation of the hippocampus. This is significant as the hippocampus plays a critical role in memory and possibly in spatial cognitive processing. The latter neuroimaging study may provide the beginnings of physiological explanation for the possible beneficial effects of free testosterone on cognitive function.

A related question concerning cognitive aging is whether age-related testosterone decline may be a risk factor for the development and diagnosis of Alzheimer's disease (AD). Some recent cross-sectional studies have reported lower testosterone concentrations in men diagnosed with AD.[34–37] A problem with studies assessing androgen levels in individuals who have already been diagnosed with AD is that the depleted testosterone levels could be a consequence rather than a cause of the disease. For example, degnerative brain changes in AD could potentially alter hypothalamic-pituitary-gonadal axis function and result in altered steroid hormone levels. Thus, it is important to evaluate hormone levels *prior* to the diagnosis of AD to be more certain that lower androgen levels do not follow CNS changes in Alzheimer's disease.

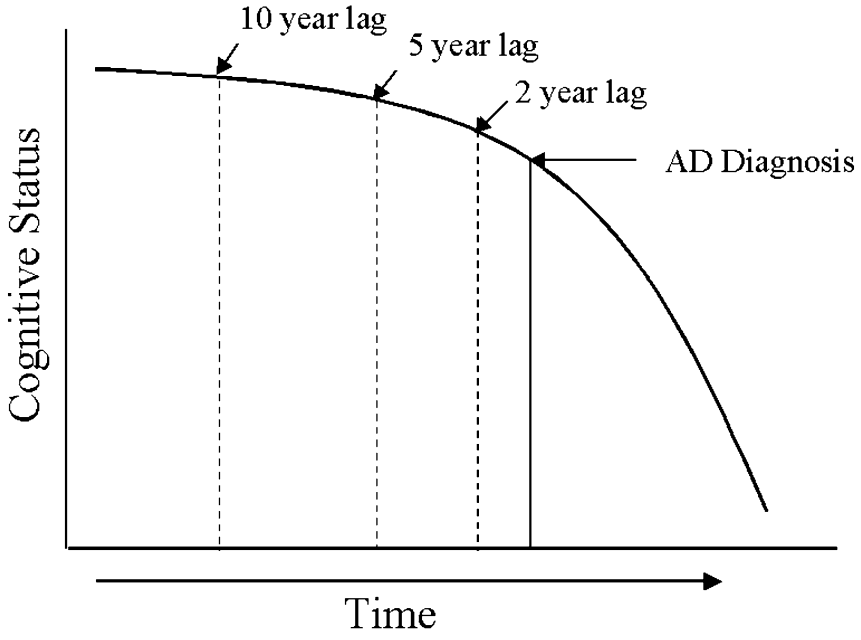


**FIGURE 3.** Schematic diagram illustrating a hypothetical cognitive trajectory in individuals who are ultimately diagnosed with Alzheimer's disease. In our study assessing testosterone levels in AD, we restricted our testosterone assays only to those serum samples that were collected *before* the date of AD diagnosis. We performed three analyses, restricting assays to those samples that were collected 2, 5 or 10 years prior to diagnosis. This was done to minimize the possibility that reduced testosterone levels in AD may be a consequence rather than a cause of the disease.

The most convincing study to date suggesting that testosterone could protect against AD and cognitive decline was part of the Baltimore Longitudinal Study of Aging. Importantly, in this prospective longitudinal study, we quantified long-term testosterone concentrations in individuals prior to the diagnosis of dementia.[38] This was done by restricting assays only to those blood samples that were provided 2, 5 and 10 years prior to the diagnosis of AD diagnosis (FIG. 3). Consistent with the results of other studies, we observed lower free testosterone levels in individuals diagnosed with AD compared to controls (FIG 4). More specifically, the results of this study revealed an approximately 10% reduction in the risk for AD for each unit increase in free testosterone. These results were robust with respect to restricting testosterone values to 2, 5 and 10 years prior to AD diagnosis. The restriction of testosterone observations to as long as 10 years *prior* to diagnosis of AD makes it very unlikely that the reduced testosterone concentrations observed in persons with Alzheimer's disease was a result of AD pathology. This study pro-

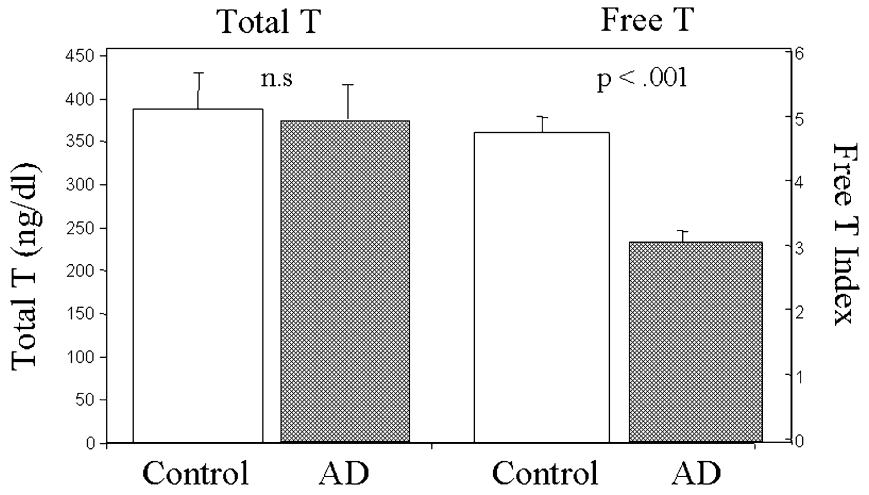


**FIGURE 4.** Mean total testosterone (T) and mean free T levels in individuals diagnosed with AD and non-demented controls. There was no difference between AD patients and controls in total T, but we observed significantly lower free T levels in patients with AD than in controls. There was an approximately 10% reduced risk for AD for each unit increase in free T.

vides the clearest evidence to date that altered testosterone levels in AD may precede rather than follow diagnosis. Indeed it suggests that lower testosterone levels may be evident quite early in those individuals who go on to develop dementia years later. Care was taken to control for health-related factors that may potentially affect testosterone concentrations or cognitive performance. Nevertheless, because of the associational nature of observational studies, the possibility that low T/free T levels may serve as a co-morbid side-effect of dementia, rather than a specific causative factor, cannot be eliminated.

An interesting possibility is that relations between testosterone and cognitive function and dementia could be mediated in part by age-related alterations in levels of gonadotropins. In response to lower testosterone with age in men, the pituitary gland may increase secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) to increase androgen levels.[28] One hypothesis argues that high levels of gonadotropins may have direct and deleterious effects on brain function.[39] Levels of gonadotropins were found to be increased in men with AD compared with age-matched controls.[40] These authors further reported a significant increase in LH in pyramidal neurons and neurofibrillary tangles of AD brains compared to age-matched control brains.[40] These data could be interpreted to suggest that high levels of gonadotropins, rather than low levels of testosterone *per se*, may be implicated in

pathological aging processes. Of course, hypotheses regarding the role of testosterone and gonadotropins in human aging need not be mutually exclusive. Low levels of testosterone may prove to be a risk factor for brain health by virtue of depriving the brain of an important neuroprotective agent, and high levels of gonadotropins could represent a concomitant risk factor. This research is still in the preliminary stages and future studies may be able to determine relative contributions of androgens and gonadotropins to cognitive and brain aging.

To overcome the drawbacks that are inherent in associational studies, it is essential to perform randomized intervention studies to more conclusively investigate the possible cognitive effects of testosterone. A few studies have adopted such an approach in evaluating this issue. In a double-blind placebo-controlled study,[41] cognitive performance was investigated in a community sample of older men to whom testosterone was administered via scrotal patch (15 mg/day) for 3 months to treat androgen deficiency. Men who received testosterone had selectively enhanced Block Design scores compared to men receiving a placebo, demonstrating that testosterone may improve spatial-constructional abilities in elderly men. In a more recent placebo-controlled trial,[42] 150 mg of testosterone enanthate or placebo was administered once per week by intramuscular injection to a sample of older men averaging 67 years of age. These investigators found that men who received testosterone supplementation showed a reduction in working memory errors compared to placebo-treated men. In a recent testosterone intervention study conducted in elderly men, Cherrier *et al*. found improved verbal memory, improved spatial ability, and improved route recall in men who received 6 weeks of testosterone enanthate (100 mg/week, intramuscular injection).[43] In a recent study examining the efficacy of testosterone intervention in men with AD and mild cognitive impairment (a possible prodromal phase of AD), men were administered 100 mg per week of testosterone enanthate by weekly injection for 13 weeks.[44] Men in the study showed selective enhancement of spatial memory, constructional skills, and verbal memory. This may be the first study to demonstrate some enhancement of cognitive function in AD by androgen intervention therapy.

However, not all studies of testosterone intervention have reported improvements in cognition. One such study[45] found that one year of testosterone supplementation did not improve memory or verbal fluency scores. Whether a battery that included more sensitive measures of spatial memory and spatial cognition may have resulted in positive findings could not be evaluated in this study. A second study[46] found no effect of a single injection of testosterone on cognitive testing one week later. This single testosterone injection and 1-week duration of exposure may have been insufficient to detect cognitive effects.

The results of observational studies, taken together with recent small-scale testosterone intervention trials in elderly men, suggest that the progressive

physiological decline in testosterone secretion with aging contributes to selective losses in cognitive function. Preliminary data from well-designed placebo-controlled testosterone intervention studies suggests that these deficits may be reversed, at least in part, by short-term testosterone supplementation. However, we are far from concluding unequivocally that testosterone may enhance brain and cognitive function. The reasons for this are two-fold. First, epidemiologic studies suffer from lack of control of some extraneous variables that are inherent in all studies of this design, and controlling for these factors after the fact in advanced statistical models does not substitute for random assignment. Even when considering the extant placebo-controlled trials, present findings that are less than conclusive. The studies provide important converging data but they tend to based on small samples of men and investigate testosterone interventions that are relatively short in duration. Moreover, because of their short duration and limited scope, they have not adequately evaluated the safety of testosterone intervention on other body systems. What is needed in this field are large, well-controlled intervention studies assessing the effects of testosterone on multiple body systems. Indeed, the Institute of Medicine (IOM) of the National Academy of Sciences recently recommended that clinical trials be conducted in men 65 years of age and over with testosterone concentrations below the physiologic levels of young adult men. This report specifically identified cognitive function as one of four target areas in need of clinical investigation. Currently there is some cause for optimism that testosterone may aid the treatment of cognitive and neural dysfunction in some aging men. However it would be premature to advocate testosterone intervention to prevent or ameliorate cognitive decline unless and until research clearly bears out both the efficacy and safety of so doing.

## REFERENCES

1. BEATTY, W.W. 1992. Gonadal hormones and sex differences in nonreproductive behaviors. *In* Handbook of Behavioral Neurology Volume II: Sexual Differentiation. A.A. Gerall, H. Moltz & I.L. Ward IL, Eds.: 85–128. Plenum Press. New York.
2. BECKER, J.B., S.M. BREEDLOVE & D. CREWS. 1992. Behavioral Endocrinology. MIT Press. Cambridge, MA.
3. GOY, R.W. & B.S. MCEWEN. 1980. Sexual Differentiation of the Brain. MIT Press. Cambridge, MA.
4. KERR, J.E., R.J. ALLORE, S.G. BECK & R.J. HANDA. 1995. Distribution and hormonal regulation of androgen receptor (AR) and AR messenger ribonucleic acid in the rat hippocampus. Endocrinology **136:** 3213–3221.
5. ROOF, R.L. & M.D. HAVENS. 1992. Testosterone improves maze performance and induces development of a male hippocampus in females. Brain Res. **572:** 310–313.

6. STEWART, J., A. SKVARENINA & J. POTTIER. 1975. Effects of neonatal androgens on open-field behavior and maze learning in the prepubescent and adult rat. Physiol. Behav. **14:** 291–295.
7. WILLIAMS, C.L. & W.H. MECK. 1991. The organizational effects of gonadal steroids on sexually dimorphic spatial ability. Psychoneuroendocrinology **16:** 155–176.
8. WILLIAMS, C.L., A.M. BARNETT & W.H. MECK. 1990. Organizational effects of early gonadal secretions on sexual differentiation in spatial memory. Behav. Neurosci. **104:** 84–97.
9. JACOBSON, C.D., V.J. CSERNUS, J.E. SHRYNE & R.A. GORSKI. 1981. The influence of gonadectomy, androgen exposure, or a gonadal graft in the neonatal rat on the volume of the sexually dimorphic nucleus of the preoptic area. J. Neurosci. **1:** 1142–1147.
10. DIAMOND, M.C. 1991. Hormonal effects on the development or cerebral lateralization. Psychoneuroendocrinology **16:** 121–129.
11. FLOOD, J.F., S.A. FARR, F.E. KAISER, *et al.* 1995. Age-related decrease of plasma testosterone in SAMP8 mice: replacement improves age-related impairment of learning and memory. Physiol Behav. **57:** 669–673.
12. POULIOT, W.A., R.J. HANDA & S.G. BECK. 1996. Androgen modulates N-methyl-D-aspartate-mediated depolarization in CA1 hippocampal pyramidal cells. Synapse **23:** 10–19.
13. MORSE, J.K., S.T. DEKOSKY & S.W. SCHEFF. 1992. Neurotrophic effects of steroids on lesion-induced growth in the hippocampus. II. Hormone replacement. Exp. Neurol. **118:** 47–52.
14. TIRASSA, P., I. THIBLIN, G. AGREN, *et al.* 1997. High-dose anabolic androgenic steroids modulate concentrations of nerve growth factor and expression of its low affinity receptor (p75-NGFr) in male rat brain. J. Neurosci. Res. **47:** 198–207.
15. GOURAS, G.K., H. XU, R.S. GROSS, *et al.* 2000. Testosterone reduces neuronal secretion of Alzheimer's beta-amyloid peptides. Proc. Natl. Acad. Sci. USA **97:** 1202–1205.
16. PIKE, C.J. 2001. Testosterone attenuates beta-amyloid toxicity in cultured hippocampal neurons. Brain Res. **919:** 160–165.
17. GANDY, S., O.P. ALMEIDA, J. FONTE, *et al.* 2001. Chemical andropause and amyloid-beta peptide. JAMA **285:** 2195–2196.
18. HAMMOND, J., Q. LE, C. GOODYER, *et al.* 2001. Testosterone-mediated neuroprotection through the androgen receptor in human primary neurons. J. Neurochem. **77:** 1319–1326.
19. RESNICK, S.M., S.A. BERENBAUM, I.I. GOTTESMAN & T.J. BOUCHARD. 1986. Early hormonal influences on cognitive functioning in congenital adrenal hyperplasia. Dev. Psychol. **22:** 191–198.
20. HAMPSON, E., J.F. ROVET & D. ALTMANN. 1998. Spatial reasoning in children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Developmental Neuropsychology **14:** 299–320.
21. HIER, D. & W. CROWLEY. 1982. Spatial abilities in androgen deficient men. N. Engl. J. Med. **302:** 1202–1205.
22. MOFFAT, S.D. & E. HAMPSON. 1996. A curvilinear relationship between testosterone and spatial cognition in humans: possible influence of hand preference. Psychoneuroendocrinology **21:** 323–337.

23. SHUTE, V.J., J.W. PELLEGRINO, L. HUBERT & R.W. REYNOLDS. 1983. The relationship between androgen levels and human spatial ability. Bull. Psychonom. Soc. **21:** 465–468.
24. GOUCHIE, C. & D. KIMURA. 1991. The relationship between testosterone levels and cognitive ability patterns. Psychoneuroendocrinology **16:** 323–334.
25. NEAVE, N., M. MENAGED & D.R. WEIGHTMAN. 1999. Sex differences in cognition: the role of testosterone and sexual orientation. Brain Cogn. **41:** 245–262.
26. CHRISTIANSEN, K. & R. KNUSSMANN. 1987. Sex hormones and cognitive functioning in men. Neuropsychobiology **18:** 27–36.
27. SILVERMAN, I., D. KASTUK, J. CHOI & K. PHILLIPS. 1999. Testosterone levels and spatial ability in men. Psychoneuroendocrinology **24:** 813–822.
28. LAMBERTS, S.W., A.W. VAN DEN BELD & A.J. VAN DER LELY 1997. The endocrinology of aging. Science **278:** 419–424.
29. HARMAN, S.M., E.J. METTER, J.D. TOBIN, *et al.* 2001. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J. Clin. Endocrinol. Metab. **86:** 724–731.
30. MORLEY, J.E., F. KAISER, W.J. RAUM, *et al.* 1997. Potentially predictive and manipulable blood serum correlates of aging in the healthy human male: progressive decreases in bioavailable testosterone, dehydroepiandrosterone sulfate, and the ratio of insulin-like growth factor 1 to growth hormone. Proc. Natl. Acad. Sci. USA **94:** 7537–7542.
31. BARRETT-CONNOR, E., D. GOODMAN-GRUEN & B. PATAY. 1999. Endogenous sex hormones and cognitive function in older men. J. Clin. Endocrinol. Metab. **84:** 3681–3685.
32. BARRETT-CONNOR, E. & D. GOODMAN-GRUEN. 1999. Cognitive function and endogenous sex hormones in older women. J. Am. Geriatr. Soc. **47:** 1289–1293.
33. MOFFAT, S.D., A.B. ZONDERMAN, E.J. METTER, *et al.* 2002. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. J. Clin. Endocrinol. Metab. **87:** 5001–5007.
34. HOGERVORST, E., J. WILLIAM, M. BUDGE, *et al.* 2001. Serum total testosterone is lower in men with Alzheimer's disease. Neuroendocrinol. Lett. **22:** 163–168.
35. HOGERVORST, E., S. BANDELOW, M. COMBRINCK & A.D. SMITH. 2004. Low free testosterone is an independent risk factor for Alzheimer's disease. Exp. Gerontol. **39:** 1633–1639.
36. PAOLETTI, A.M., S. CONGIA. S. LELLO, *et al.* 2004. Low androgenization index in elderly women and elderly men with Alzheimer's disease. Neurology **62:** 301–303.
37. WATANABE, T., S. KOBA, M. KAWAMURA, *et al.* 2004. Small dense low-density lipoprotein and carotid atherosclerosis in relation to vascular dementia. Metabolism **53:** 476–482.
38. MOFFAT, S.D., A.B. ZONDERMAN, E.J. METTER, *et al.* 2004. Free testosterone and risk for Alzheimer disease in older men. Neurology **62:** 188–193.
39. MEETHAL, S.V., M.A. SMITH, R.L. BOWEN & C.S. ATWOOD. 2005. The gonadotropin connection in Alzheimer's disease. Endocrine **26:** 317–326.
40. BOWEN, R.L., M.A. SMITH, P.L. HARRIS, *et al.* 2002. Elevated luteinizing hormone expression colocalizes with neurons vulnerable to Alzheimer's disease pathology. J. Neurosci. Res. **70:** 514–518.

41. JANOWSKY, J.S, S.K. OVIATT & E.S. ORWOLL. 1994. Testosterone influences spatial cognition in older men. Behav. Neurosci. **108:** 325–332.
42. JANOWSKY, J.S., B. CHAVEZ & E. ORWOLL. 2000. Sex steroids modify working memory. J. Cogn. Neurosci. **12:** 407–414.
43. CHERRIER, M.M., S. ASTHANA, S. PLYMATE, *et al*. 2001. Testosterone supplementation improves spatial and verbal memory in healthy older men. Neurology. **57:** 80–88.
44. CHERRIER, M.M., A.M. MATSUMOTO, J.K. AMORY, *et al.* 2005. Testosterone improves spatial memory in men with Alzheimer disease and mild cognitive impairment. Neurology **64:** 2063–2068.
45. SIH, R., J.E. MORLEY, F.E. KAISER, *et al.* 1997. Testosterone replacement in older hypogonadal men: a 12–month randomized controlled trial. J. Clin. Endocrinol. Metab. **82:** 1661–1667.
46. WOLF, O.T., R. PREUT, D.H. HELLHAMMER, *et al*. 2000. Testosterone and cognition in elderly men: a single testosterone injection blocks the practice effect in verbal fluency, but has no effect on spatial or verbal memory. Biol. Psychiatry **47:** 650–654.