Pros: The role of testosterone replacement therapy for cognitive function

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Cognition

- Definition: Mental processes in gaining knowledge and comprehension
- Associated Activities

  - Attention: focus on a stimulus

  - Language

  - Learning

  - Memory

  - Perception: take information through senses and utilize information

  - Thought: decision making, problem solving

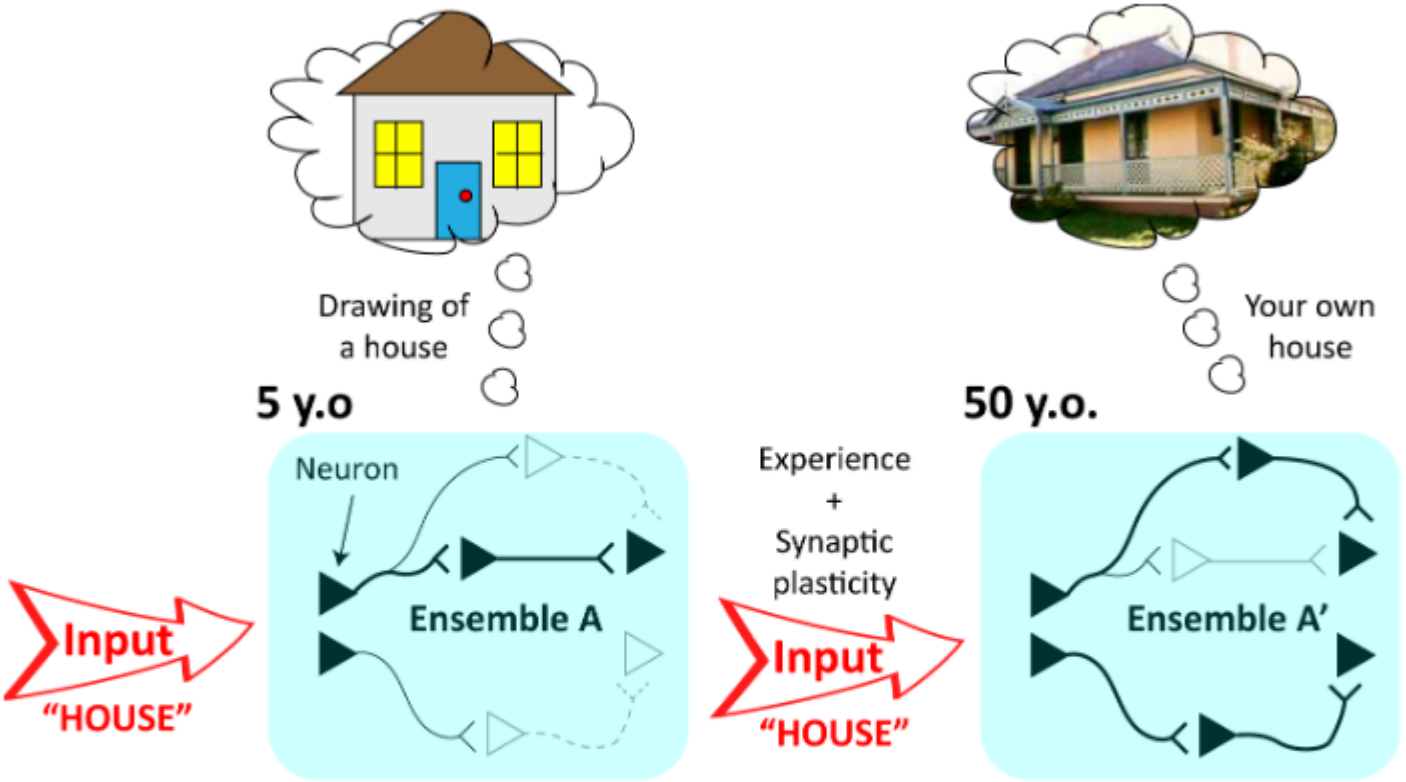
Cognition and molecular biology

★Synaptic plasticity: synapses – repeated activation: to get stronger (long-term potentiation: LTP)/weaker (long-term depression: LTD) of certain pathway by new signals

★Neurogenesis: creation of new neuron or spines of neurons

★Ensembles – memory can be changed.

Neurogenesis, Synaptic plasticity and Ensembles



Memories are stored by changing the connections between neurons. A five-year-old child will activate a certain group of neurons (Ensemble A); whereas adults will activate a different ensemble (Ensemble A') with the same stimulus. Synaptic plasticity driven by repeated experience can change the connection strengths between neurons. This is how there can be the different neuronal responses to the same input. (Image: Alan Woodruff / QBI).

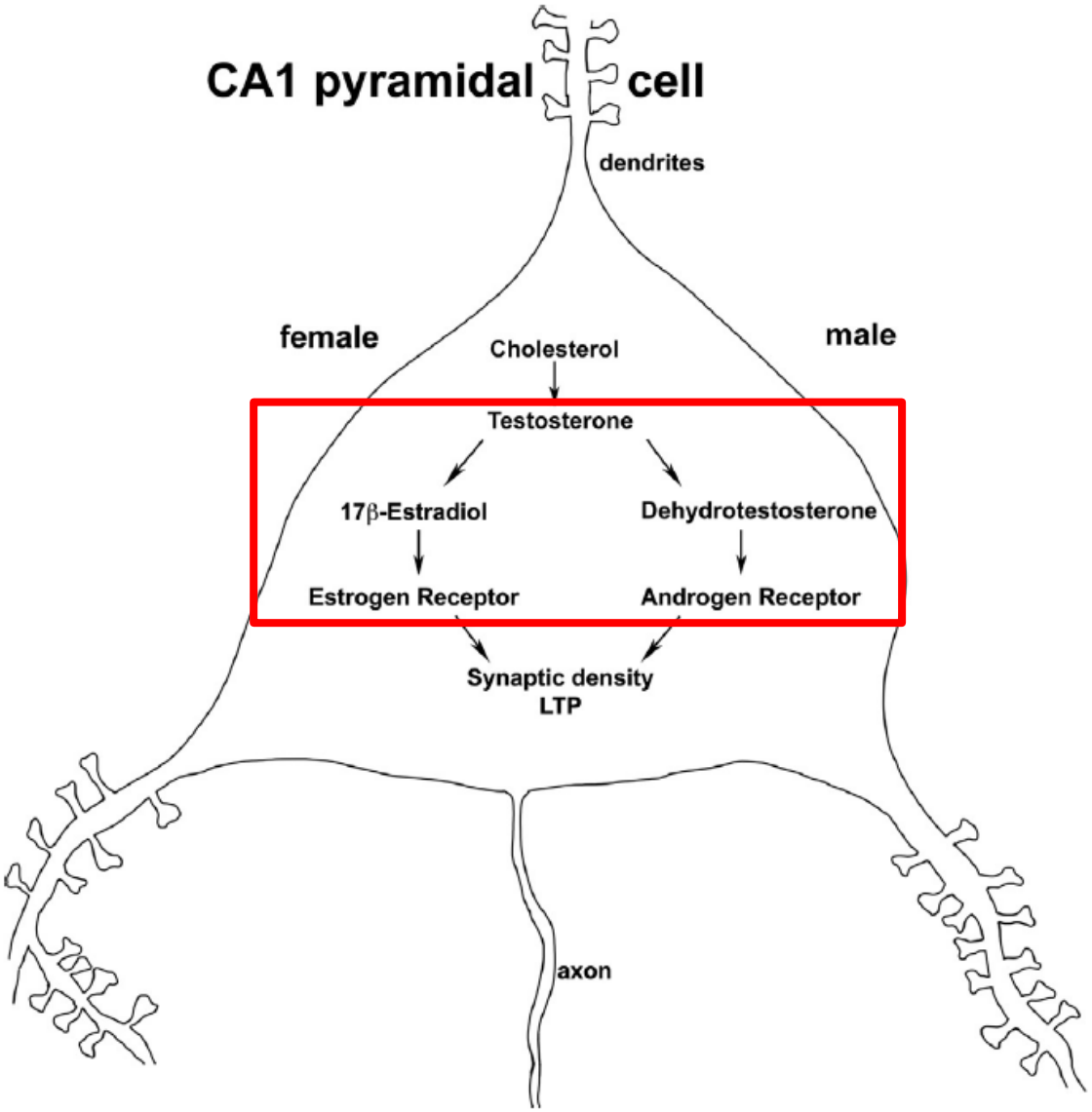
https://qbi.uq.edu.au/brain-basics/memory/how-are-memories-formed

Sex Hormones synthesis in Brain and its role on synaptic plasticity

- In **gonadectomized** animals and in **hippocampal** cultures, **inhibition of estradiol synthesis in female** animals and in cultures from female animals, and **inhibition of dihydrotestosterone synthesis in male** animals and in cultures of male animals, cause **synapse loss and impair LTP in the hippocampus**, but not vice versa.
- It appears that **hippocampal neurons are differentiated in a sex-specific manner**.

Brandt et al. Vitamins and Hormones. 2020;114:125-143

Sex dependent Hr synthesis



Brandt et al. Vitamins and Hormones. 2020;114:125-143

Sex dependent Hr synthesis

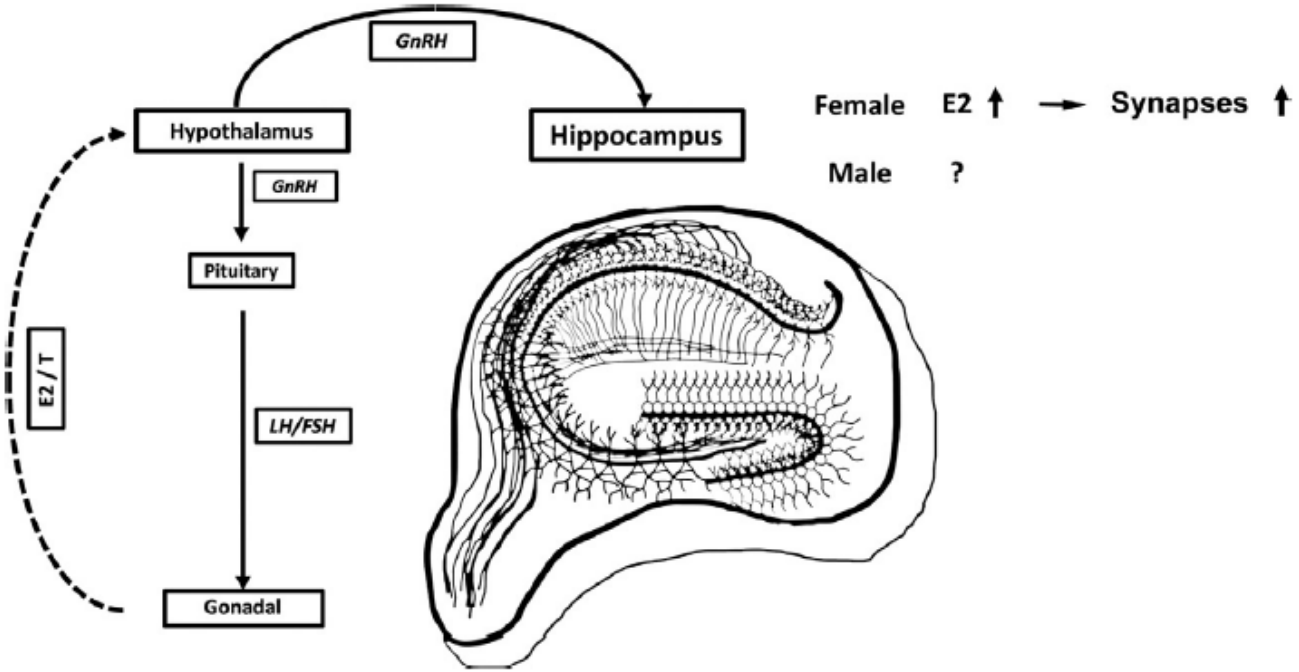


Fig. 3 GnRH from the hypothalamus is likely to maintain the sex dependent action of neurosteroids on synaptic plasticity in the hippocampus, where GnRH receptors are abundantly expressed. GnRH was shown to increase synapse density *via* stimulation estradiol synthesis in the hippocampus.

Brandt et al. Vitamins and Hormones. 2020;114:125-143

Sex Hormones and neurogenesis

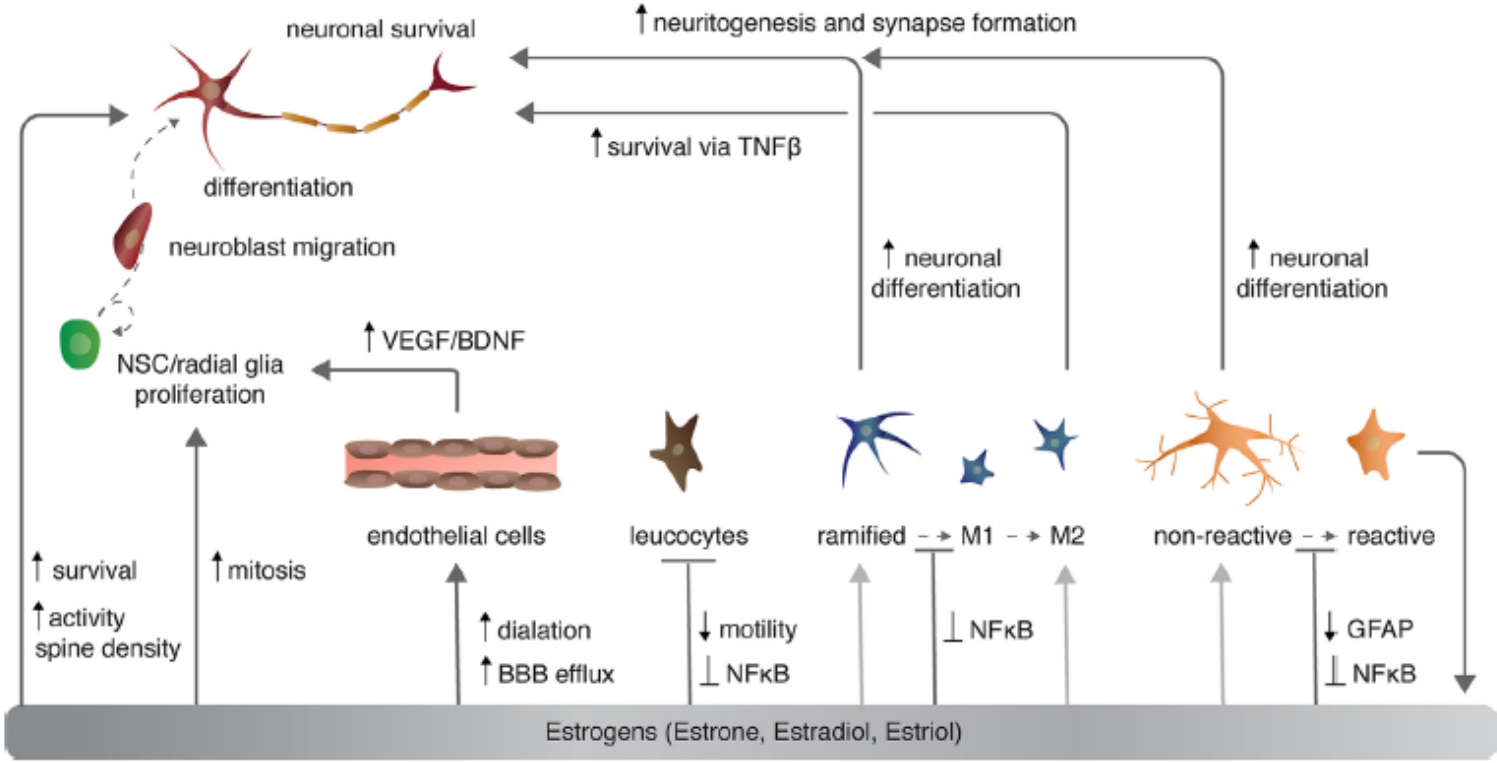


FIGURE 2 | The effects of estrogen on various cell types in the central nervous system. Light gray arrows indicate that estrogens have an effect on neurons via the given cell type to which the arrow points.

Larson TA. Front. Endocrinol. 2018;9:205
(doi: 10.3389/fendo.2018.00205)

Sex Hormones and neurogenesis

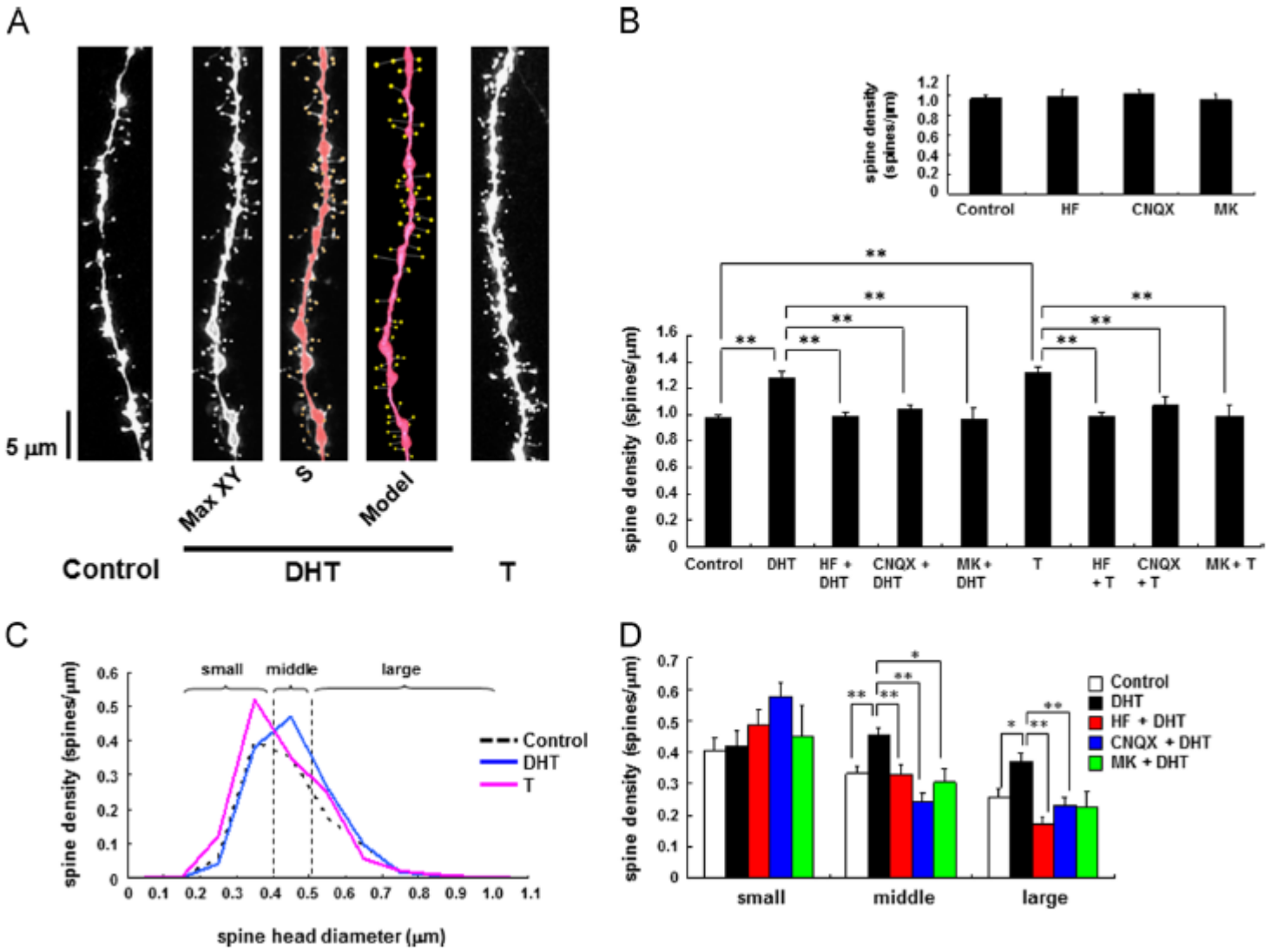
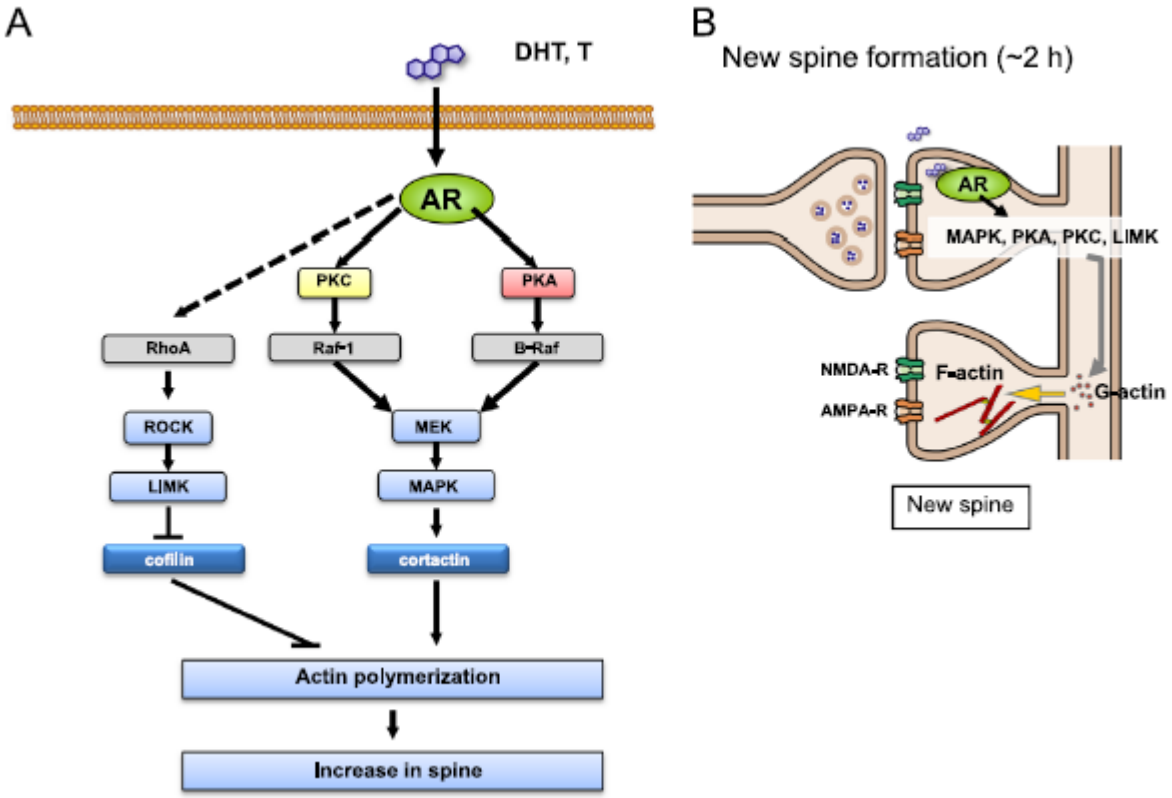


Fig. 1 – Changes in the density and morphology of spines by androgen and blockers in hippocampal slices. (A) Spines were

Hatanaka et al. Brain Research 2015;1621:121-32.

Sex Hormones and neurogenesis



Hatanaka et al. Brain Research 2015;1621:121-32.

SEXUAL MEDICINE REVIEWS

Is Testosterone a Food for the Brain?

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ABSTRACT

Introduction: Testosterone is fundamental for psychological, sexological, cognitive, and reproductive aspects, and its lack or reduction largely impacts the quality of life in males and females.

Aim: Therefore, the aim of this review is to describe the role of testosterone in the neurophysiology of the brain and related aspects regarding the quality of general and sexual life.

Methods: We listed and discussed the principal studies on the role of testosterone in the brain regarding sexual health, psychopathological conditions, and the elderly. The search strategies were composed by the insertion of specific terms in PubMed regarding the main studies from January 2000 to June 2015.

Main outcome measures: Using a psychoneuroendocrinologic perspective, we considered 4 main sections: brain and testosterone, sexuality and testosterone, psychopathology and testosterone, and cognitive impairment and testosterone.

Results: Much evidence on the neuroendocrinology of testosterone regarding brain activity, sexual function, psychological health, and senescence was found. In any case, it is known that testosterone deficiency negatively impacts quality of life, first, but not exclusively, through a central effect. Moreover, testosterone and androgen receptors are differently expressed according to age and gender. This aspect contributes to gender differences and to the dimorphic physiological role of this hormone.

Conclusion: A universal role for testosterone can be recognized: low levels of testosterone are associated with mental disorders, sexual dysfunction, and cognitive impairment in both sexes. Hence, physicians should carefully assess testosterone levels, not only in the management of sexual dysfunctions but also when seeking to help patients with severe mental or organic diseases.

Sex Med Rev 2016;4:15–25.

Key Words: Testosterone; Testosterone Replacement Therapy; Brain; Sexuality; Psychopathology; Elderly

Nunez JL, et al (2003)[2]	Animal models	n = 10 (Sprague-Dawley rats)	Androgen receptors may directly influence the cerebral cortex
Kritzer M (2004)[3]	Animal models	n = 10 (Sprague-Dawley rats)	Pyramidal neurons and androgen receptors play a role in cortical information processing
Schattmann L, Sherwin BB (2007)[22]	Case-control	n = 51	↑T in women, may be associated with poorer performance on cognitive tasks
Barry JA, et al (2013)[23]	Cross-sectional	n = 110	↑T in polycystic ovarian syndrome increases visual spatial skills
Davis SR, et al (2014)[25]	Open-label study	n = 9	Testosterone therapy facilitates preservation of cognitive function
Nguyen TV (2010)[26]	Cell cultures	N. A.	Androgens have a neuroprotective action
Marazziti D, Canale D (2004)[47]	Longitudinal	n = 48	During the process of falling in love, testosterone increases in female and decreases in male
Meydan S, et al (2010)[27]	Animal models	Wistar rats	Testosterone suppresses orchiectomy-induced oxidative damage and morphological changes in the hippocampal tissue
Redoute J, et al (2005)[29]	Case-control	n = 17	↑T increases activation in right insula, claustrum and orbital frontal cortex
Wainwright SR (2011)[63]	Animal models	Adult male Sprague-Dawley rats	Testosterone confers resiliency to chronic stress in males toward affective disorders
Sexual medicine and gender issues			
Hamann S (2004)[4]	Neuroimaging of human neurophysiology	n = 28	The amygdala and hypothalamus are both testosterone-dependent, with significant gender difference
Corona G (2013)[7]	Retrospective	n = 3714	↓T is a clear risk factor for secondary reduced libido
Corona G (2013)[28]	Longitudinal/ Cross-sectional	n = 1687	Sexual activity appears to be a protective factor against cardiovascular events
Corona G (2010)[44]	Cross-sectional	n = 2652	Testosterone is involved in ejaculatory control, and cases of premature or delayed ejaculation also are moderated from testosterone levels
Bramen JE, et al (2011)[17]	Cross-sectional	n = 80	Testosterone facilitates a different development in the male and female hippocampus, amygdala, and cortical gray matter
Bramen JE, et al (2012)[18]	Cross-sectional	n = 85	Testosterone impacts on cortical thickness according to gender
Aydogan U, et al (2012)[62]	Longitudinal	n = 79	Testosterone replacement treatment improves psychological and sexological health
Burkhardt MS, et al (2006)[20]	Cross-sectional	n = 45	↑T was not associated with better cognitive function in men at increased risk for Alzheimer's disease
Psychopathology and epidemiology			
Akhondzadeh S, et al (2006)[52]	Cross-sectional	n = 79	↑T decreases severity of negative symptoms
Vercammen A, et al (2013)[53]	Case-control	n = 40	↑T may be of cognitive benefit to men with schizophrenia

Baron-Cohen S, et al (2015)[60]	Retrospective	n = 128	↑T during the fetal period, characterizes males who later receive a diagnosis of autism
Wu F, et al (2010)[10]	Randomized	n = 3.369	↓T is correlated and specified also by a lack of sexual desire and erectile dysfunction
Morsink LF, et al (2007)[65]	Retrospective	n = 2.855	↓T is associated with high rate of depression in elderly
Travison TG (2007)[11]	Prospective cohort	n = 1.532	↓T is not associated to specific lifestyles, such as smoking or obesity
Rausch J (2015)[56]	Case-control	n = 102	↑T is associated with borderline personality disorder, above all in males
Roepke S (2010)[57]	Case-control	n =61	↑T in women with polycystic ovaries is associated with borderline personality disorder
Peters S (2015)[58]	Cross-sectional	n = 173	↑T in boys is associated with reduced amygdala-orbitofrontal cortex connectivity, which in turn is associated with increased alcohol intake
Ramanathan S (2015)[54]	Retrospective	n = 58	↓T in the late onset of puberty, is associated with negative symptoms of schizophrenia
Beyazyuz M (2014)[55]	Case-control	n = 84	↑T is negatively associated with positive symptoms in first episode psychosis
Senescence			
Moffat SD, et al (2002)[13]	Longitudinal	n = 407	↑T was associated with better scores on specific domains of cognitive performance in older men
Brant LJ, et al (2005)[76]	Longitudinal	n = 1.236	↓T was considered a predictor of dementia and negatively impacts cognitive performance
Salminen EK, et al (2005)[78]	Longitudinal	n = 23	↓T due to androgen ablation therapy, is responsible for a deterioration in cognitive functioning
Bussiere JR, et al (2005)[79]	Case-control	N.A.	↓ plays a role in hippocampus-mediated memory processes
Beer TM, et al (2006)[80]	Longitudinal	n = 36	↓T has negative effects on specific cognitive processes in older men
Verdile G, et al (2014)[82]	Prospective cohort	n = 427	Testosterone and luteinizing hormone are involved in the early preclinical stages of Alzheimer's disease
Feldman HA, et al (2002)[83]	Longitudinal	n = 1.079	Testosterone levels are not related to cognition
Hall JR, et al (2015)[84]	Longitudinal	n = 87	The subjects with AD, having borderline or normal testosterone levels, are more subject to development of neuropsychiatric symptoms

Study	Participant	Age	Outcome	Comments
Yeap *et al.* 2008 [80]	n=2932 (elderly men)	Aged 76-80 years	An increase in testosterone level was associated with better cognitive performance.	Longitudinal follow-up is required to determine whether men with reduced free testosterone exhibit greater incidence of cognitive decline over time.
Muller *et al.* 2005 [81]	n=400 (elderly men)	aged 40- 80 years	Higher testosterone levels were associated with better cognitive performance.	Controlled trials will be necessary to determine definitely whether sex hormone therapy can prevent or delay loss of cognitive function in men.
Yaffe *et al.* 2002 [70]	n=300 (elderly men)	aged > 50 years	Higher testosterone levels were associated with better cognitive function.	Randomized trials should be directed toward the investigation of testosterone and cognition in older men.
Wolf *et al.* 2002 [82]	n=38 women, n=30 men	mean age 68 years (women) mean age 69 years (men)	Endogenous sex steroids were not associated with cognition in older men.	Estradiol replacement might be a promising venue for future intervention studies in older women.
Hogervorst *et al.* 2004 [83]	n= 66 (elderly women) n=79 (elderly men)	aged 61-91 years	Testosterone and estradiol showed positive relationship with verbal recall, information processing speed and spatial span performance.	More studies are needed to determine why men show poorer cognitive performance with increased age than women.
Boss *et al.* 2015 [84]	n=71 (elderly men mean)	aged 86.4 years	Sex hormones were not significantly associated with cognitive function.	Future studies should adjust for comorbidity and psychosocial factors that might influence cognitive function.
Hogervorst *et al.* 2001 [85]	n=83 dementia or Alzheimer disease n= 103 control group	mean age 75 years	Low levels of testosterone were associated with the dementia of Alzheimer disease.	Prospective longitudinal studies should investigate whether low total testosterone levels precede or follow the onset of dementia of the Alzheimer's type.
Lee *et al.* 2010 [86]	n=3369 (healthy, community-dwelling men)	aged 40-79 years	Endogenous sex hormones were not associated with a vision-based measure of fluid cognition.	Future studies should determine whether high levels of dehydroepiandrosterone sulfate (DHEAS) have detrimental effects on a broad range of neuropsychological tests.
Seidl *et al.* 2015 [87]	n=68 patients with AD n=61 non-demented controls,	aged > 55 years	Testosterone was not associated with most neuropsychological test performances in patients with AD.	Older adults with higher IQs are more likely to engage in healthy and active lifestyles, which may have an impact on hormone levels.
Zhao *et al.* 2016 [88]	n=4212 (elderly men)	aged > 50 years	Testosterone did not exert protective effects on cognitive function.	Need more studies to provide minimal support for a protective effect of endogenous testosterone.

Cross sectional Studies

Associated

Not associated

Mohamad et al. Current Drug Targets 2018;19:898-906.

Study	Participant	Treatment	Study Duration	Outcome	Comments
Wahjoepramono *et al.* 2016 [89]	n=44 (low testosterone level men, aged ≥ 50 years)	Testosterone, transdermal (50 mg/ daily)	24 weeks	Testosterone caused a modest improvement on global cognition.	Larger long term studies are needed to investigate the efficacy of testosterone treatment on cognitive and clinical measures with the inclusion of blood and brain imaging markers.
Lašaitė *et al.* 2016 [90]	n= 19 (hypogonadotropic hypogonadal men, aged 18-56 years)	Testosterone, intramascular ($1{,}000\ mg^{-4}$ ml every 10–14 weeks)	2 years	Testosterone improved attention, visual canning ability, executive function and psychomotor speed.	Larger sample size is needed to validate this study.
Borst *et al.* 2014 [91]	n=60 (hypogonadal men, aged > 60 years)	Testosterone-enanthate, intramascular (125 mg/week)	1 year	Testosterone caused small decrease in depressive symptoms and moderate increase in visuospatial memory.	Future research should investigate the potential benefits of testosterone on the areas of drive, motivation, and other untested cognitive domains
Tan *et al.* 2003 [92]	n=36 (new diagnosis of men with Alzheimer's disease, aged 34-70 years)	Testosterone, intramuscular (200 mg/2week,)	12 months	Testosterone caused improvement in ADAScog, MMSE and CDT assessment.	More studies are required to confirm this pilot study.
Cherrier *et al.* 2001 [22]	n=25 (healthy older men, aged 50-80 years)	Testosterone enanthate, intramuscular (100 mg/weekly)	6 weeks	Testosterone enhanced cognitive function.	More studies are required to examine the relative contribution of testosterone *vs* estradiol on cognition in men.
Janowsky *et al.* 2000 [29]	n=19 (healthy older men, 61–75 years)	Testosterone, injection (150 mg/week)	1 month	Testosterone significantly increased working memory.	Additional results are required to better confirm and clarify the effects of testosterone administration on cognition.
Huang *et al.* 2016 [93]	n= 308 (older men with low testosterone level, aged > 60 years)	1% Testosterone gel (7.5 g/daily)	3 years	Testosterone did not improve cognitive function.	Long-term trials are required to investigate the efficacy of testosterone replacement in Alzheimer's disease patients.
Emmelot-Vonk *et al.* 2008 [94]	n=237 (healthy older men, aged 60-80 years)	Testosterone undecenoate (8 mg/daily twice)	6 months	Testosterone did not affect functional status or cognition.	The largest study of testosterone supplementation with the most end points and a randomized, double-blind design. Adherence was high and the dropout rate was low.
Maki *et al.* 2007 [95]	n=15 (healthy older men, aged 66-86 years)	Testosterone enanthate, intramuscular (200 mg/week)	90 days	Decreased verbal memory and altered relative activity in medial temporal and prefrontal regions.	The study does not address the impact of physiological testosterone upon cognition and cannot be used to definitively exclude a neuroprotective impact of testosterone upon central nervous system functioning in elderly men.
Lu *et al.* 2006 [25]	n=16, older men with Alzheimer's disease (aged > 50 years) n=22, healthy controls (aged > 50 years)	Testosterone, gel (75 mg/daily)	24 weeks	Testosterone had no effects in cognitive scores after treatment.	Larger sample size is required before clinical decisions.
Kenny *et al.* 2004 [96]	n=11 (older men with early cognitive decline and low testosterone level, aged 73-87 years)	Testosterone, intramuscular (200 mg/week)	12 weeks	No significant effect on cognitive performance after treatment.	Larger trials of testosterone replacement are required to address the effect of testosterone on depression and cognition.
Wolf *et al.* 2000 [97]	n=30 (elderly men, mean age 67.1-68.7 years)	Testosterone enanthate, intramuscular (250 mg/ single injection)	5 days	Testosterone did not improve the verbal and spatial tasks.	Long-term testosterone treatment is required as beneficial effects on spatial cognition or memory might need more time to develop.

Observational Studies or RCT

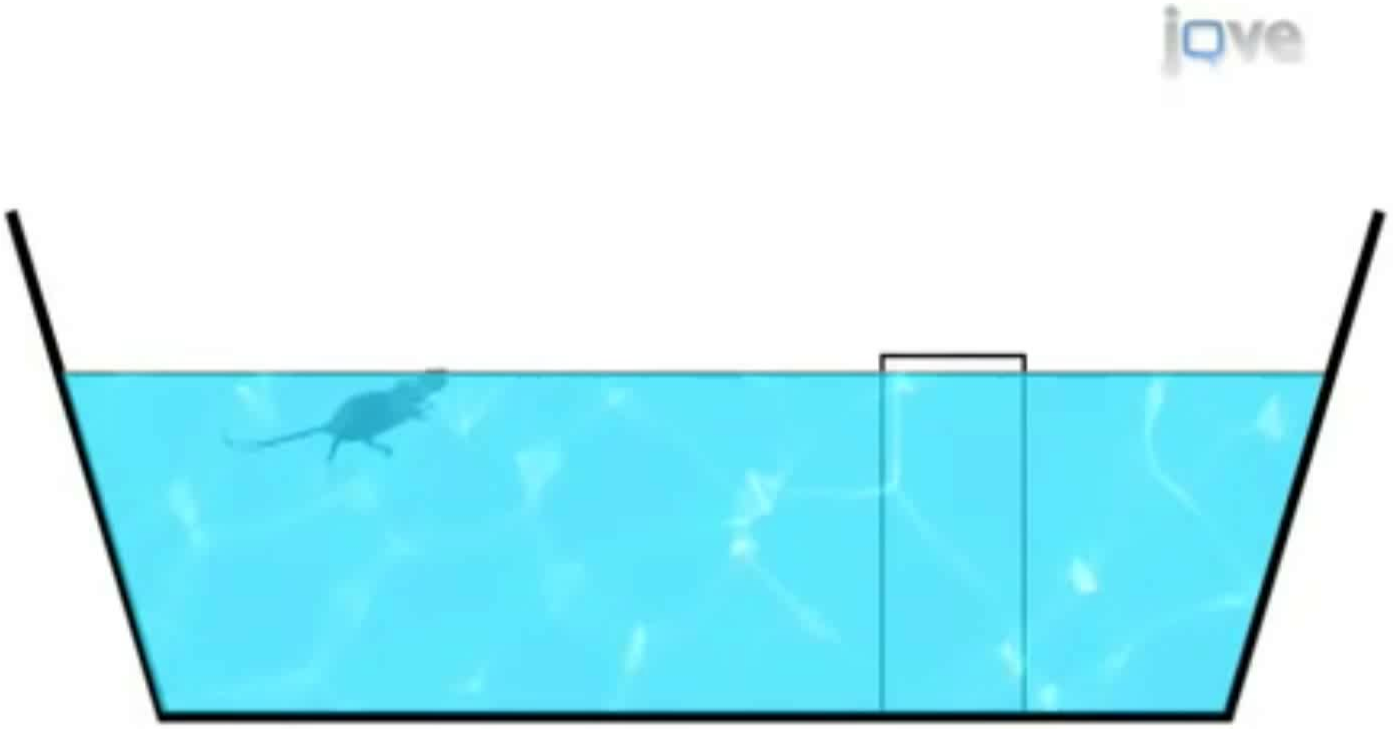
Associated

Not associated

Mohamad et al. Current Drug Targets 2018;19:898-906.

Animal behavior test for cognition
“Morris water maze test”

https://www.youtube.com/watch?v=leHLL4vcbCc



Animal cognition test

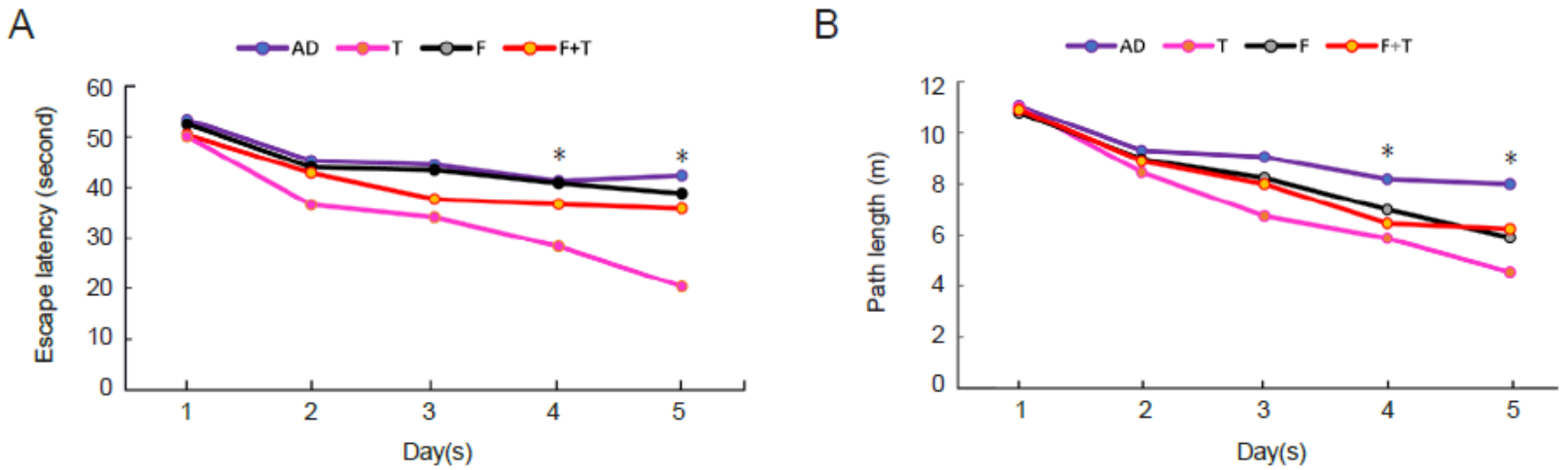


Figure 1 Effects of testosterone on cognitive functions of AD rat models in positioning navigation of the Morris water maze test.
(A) Escape latency is given in seconds and (B) path length in meters. Data are expressed as the mean (n = 10; one-way analysis of variance followed by the least significant difference *post hoc* test). $*P < 0.05$, *vs.* AD group. AD: AD group; T: testosterone group; F: flutamide group; F + T: flutamide + testosterone group. AD: Alzheimer's disease.

Yan et al. Neural Regen Res. 2019;14(4):649-657.

Baltimore Longitudinal Study of Aging (BLSA)

- Each visit starting in 1963 and stored at –70 C
- 50 yr or older and who had androgen measures (n=407)
- Duration of follow-up averaged 9.7 yr
- For each subject, samples selected for assay were those from the visits closest to 10, 15, and 20 yr before the most recent visit.

MOFFAT et al. J Clin Endocrinol Metab 87: 5001–5007, 2002

Results after regression

TABLE 3. Performance on cognitive measures as a function of gonadal status

Cognitive tests	Cognitive outcome (no. hypogonadal/ no. eugonadal)	Hypogonadal	Eugonadal
Memory			
BVRT ®	Status (134/188)	0.182 (1.05)	−0.134 (0.92)[c]
	Change (63/49)	0.377 (0.66)	0.130 (0.40)[b]
CVLT-A	Status (80/113)	−0.258 (1.09)	0.178 (0.89)[b]
CVLT-D	Status (80/113)	−0.181 (1.01)	0.113 (0.97)[a]
CVLT-R	Status (79/113)	−0.132 (0.96)	−0.082 (1.02)
Spatial ability			
ROT	Status (78/112)	−0.289 (0.88)	0.207 (1.03)[b]
Visuomotor scanning and attention			
TRAILSA ®	Status (111/143)	0.139 (1.05)	−0.124 (0.92)[a]
	Change (52/33)	0.403 (3.25)	0.547 (4.28)
TRAILSB ®	Status (111/143)	0.139 (1.11)	−0.119 (0.88)[b]
	Change (50/32)	1.77 (7.25)	3.21 (6.49)
DIGFOR	Status (87/119)	0.017 (1.03)	0.024 (0.96)
DIGBAC	Status (87/119)	0.120 (0.97)	−0.075 (1.01)
Verbal knowledge/language			
Vocabulary	Status (79/113)	0.086 (0.93)	−0.064 (1.04)
FLUCAT	Status (112/144)	−0.014 (0.95)	0.022 (0.97)
	Change (56/41)	−0.340 (0.58)	−0.500 (0.52)
FLULET	Status (112/144)	−0.020 (1.00)	0.002 (1.05)
	Change (56/41)	−0.234 (0.62)	−0.332 (0.74)
Mental status			
MMSE	Status (112/144)	−0.031 (0.95)	0.024 (1.05)
	Change (55/33)	−0.085 (0.73)	−0.118 (0.43)
Depressive symptoms			
CES-D	Status (115/163)	0.092 (0.99)	−0.045 (1.00)
	Change (54/46)	−0.099 (1.14)	0.159 (1.54)

Data represent mean (SD). ® Reversed scoring scale, higher scores represent poorer performance; Status, within-individual mean performance across repeated test administrations; Change, within-individual slopes calculated to assess the annualized rates of change.

[a] $P < 0.05$.
[b] $P < 0.01$.
[c] $P < 0.001$.

Human study (RCT)

Table 1. Cognitive scores and serum testosterone, DHT and estradiol for men that were administered Testosterone then Placebo (Group A, n=22, Mean±SD).

	Baseline (Week 0)	Testosterone (Week 24)	Wash Out	Placebo (Week 52)
MMSE[1]	27.3±1.7	28.3±1.5*	28.0±1.2*	28.2±1.3*
RAVLT[2]				
Immediate Recall[3]	44.3±6.9	46.9±7.8	47.9±7.9	47.0±10.1
Delayed Recall	8.4±2.2	8.9±1.9	9.5±2.5	9.6±2.6
GDS[4]	7.1±5.5	4.5±3.3*#	3.5±3.1*	3.2±2.8*
Testosterone (nmol/L)	16.5±4.4	26.7±12.1*#	17.3±4.4	15.3±4.1
DHT (nmol/L)	1.84±0.9	9.1±4.9*#	1.8±1.7	1.7±0.8
Estradiol (pmol/L)	81.2±22.7	85.6±33.8	83.1±7.9	92.4±18.6
LH (U/L)	4.2±2.8	2.1±1.2*#	4.2±2.4	4.8±3.3

[1]Mini Mental State Examination; [2]Rey Auditory Verbal Learning Test; [3]RAVLT Learning Trial 1-5 total score; [4]Geriatric Depression Scale. *p<0.05, values significantly different compared to baseline; #p<0.05, values significantly different compared to placebo.

Table 2. Cognitive scores and serum testosterone, DHT and estradiol for men that were administered Placebo then Testosterone (Group B, n=22, Mean±SD).

	Baseline (Week 0)	Placebo (Week 24)	Wash Out	Testosterone (Week 52)
MMSE[1]	27.05±1.64	27.82±1.3	27.77±1.5	28.14±1.8*
RAVLT[2]				
Immediate Recall[3]	42.4±9	44.1±8.2	47.4±8.6	46.7±10.2
Delayed Recall	8.5±3	8.1±3.2	9.8±2.8	9.7±3.5
GDS[4]	6.4±5.6	4.9±3.9	4.9±4.5	4.5±4*
Testosterone (nmol/L)	17.9±6.3	16.6±4.6	16.8±5.9	24.5±13.8*#
DHT (nmol/L)	2.8±0.8	1.7±0.9	1.7±1.6	8.4±5.7*#
Estradiol (pmol/L)	85.8±26.4	88.4±29.6	84.8±29.3	91.3±40.1
LH (U/L)	4.7±2.6	5.6±3.4	4.6±1.9	3.1±2.6* #

[1]Mini Mental State Examination; [2]Rey Auditory Verbal Learning Test; [3]RAVLT Learning Trial 1-5 total score; [4]Geriatric Depression Scale. *p<0.05, values significantly different from baseline; #p<0.05, values significantly different from placebo.

CNS & Neurological Disorders - Drug Targets, 2016, 15, 337-343

Human study (RCT)

Men were randomized to receive 12 months of treatment with either transdermal testosterone supplementation (5 mg/d)

Table 1. Baseline Characteristics of 44 Men Selected for Low Testosterone Levels Completing 1 Year of Testosterone or Placebo Supplementation

Variable	Testosterone $n = 24$	Placebo $n = 20$
Age (years)	76 ± 4	75 ± 5
Testosterone (nmol/l)	13.5 + 6.1	13.5 + 3.6
BioT (nmol/l)	3.23 ± 1.28	3.47 ± 0.80
Estradiol (pmol/l)	70 ± 26	58 ± 21
Estrone (pmol/l)	28 + 8	27 + 7
Calcium intake (mg/d)	805 ± 322	876 ± 333
Strength (Newtons)	735 ± 223	755 ± 220
Power (Watts)	368 + 114	380 + 140
Marital status (*n* married)	21 (87%)	17 (85%)
Education (% with college degree or higher)	12 (50%)	15 (75%)
History of depression	0	1
History of heart disease	12	15
History of hypertension	12	15
Antihypertensive treatment	8	4
Cholesterol-lowering agent	3	4
Antidepressant therapy	0	1

Notes: Values are mean and standard deviation. Comparison made either by analysis of variance for continuous variables or chi-square analysis for dichotomous variables. BioT = bioavailable testosterone.

$p < .05$.

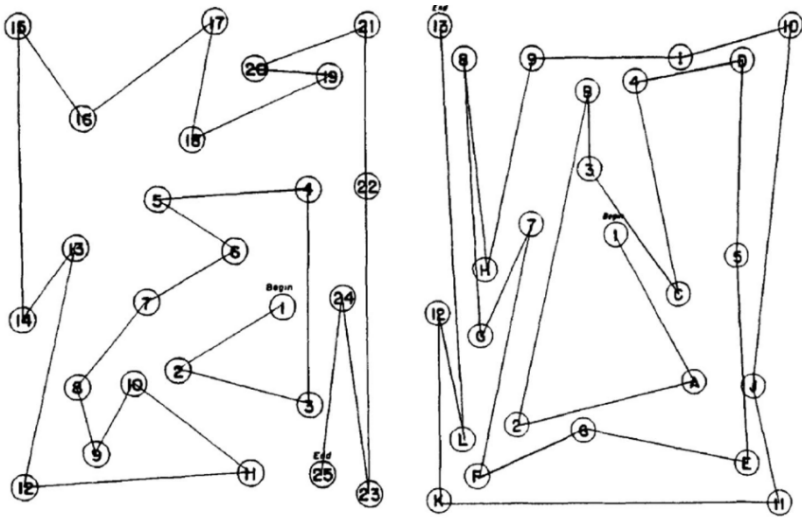


Table 2. Comparison of Cognitive Test Scores Prior to and Following 12 Months of Testosterone or Placebo Treatment

	Testosterone		Placebo	
Test	Baseline	12 mo	Baseline	12 mo
Digit Span	11.4 ± 2.6	11.5 ± 2.5	11.8 ± 1.8	12.4 ± 1.9
Digit Symbol	42 ± 8	46 ± 9*	43 ± 8	47 ± 7**
Trailmaking A (sec)	42 ± 14	38 ± 8	39 ± 16	38 ± 17
Trailmaking B (sec)	104 ± 39	87 ± 29*	95 ± 30	90 ± 38

Notes: Values are mean and *SD*. No differences between groups by analysis of variance.

*$p \leq .01$ compared to baseline; **$p \leq .05$ compared to baseline.

Kenny et al. Journal of Gerontology 2002;57A:321-325
Zeng et al. International Journal of Crowd Science 2017:1:83-99

Observational study

TABLE 1 Baseline anthropometric and hormonal characteristics of young and middle-aged hypogonadal men

	Minimum	Maximum	Mean ± *SD*
Age, years	18.0	56.0	30.5 ± 12.7
Body mass index, kg m^{-2}	17.5	45.9	26.3 ± 7.1
Height, cm	158.0	189.9	173.8 ± 7.7
Weight, kg	51.5	136.0	79.7 ± 22.4
Testosterone, nmol L^{-1}	0.2	46.0	13.8 ± 10.9
SHBG, nmol L^{-1}	0.08	7.5	2.4 ± 16.6

Lašaitė et al. Andrologia. 2017;49:e12633.

TABLE 2 Differences of cognitive functions at baseline and after 2 years of testosterone replacement therapy in young and middle-aged hypogonadal men

		Mean ± *SD*	Minimum-maximum values	Median (25–75 percentile)	*p*
Trail Making Test—A[a]	Baseline	42.9 ± 22.3	20.0–110.0	40 (27.2–56.2)	.050
	After 2 years	36.2 ± 22.5	15.0–110.0	30 (20.0–42.0)	
Trail Making Test—B[a]	Baseline	90.6 ± 55.3	35.0–240.0	70 (56.2–107.5)	.025
	After 2 years	65.6 ± 21.4	35.0–115.0	59 (50.0–84.2)	
Digit Span Test, forwards score[b]	Baseline	5.4 ± 2.0	2.0–9.0	5.5 (4.5–6.2)	.046
	After 2 years	6.1 ± 2.6	2.0–12.0	6.0 (4.0–7.2)	
Digit Span Test, backwards score[b]	Baseline	4.8 ± 2.3	0.0–8.0	5.0 (2.7–7.0)	.218
	After 2 years	4.4 ± 1.6	1.0–7.0	4.0 (3.0–6.0)	

Meta-analysis: TRT on cognition

Title and Abstracts Screened
N= 512

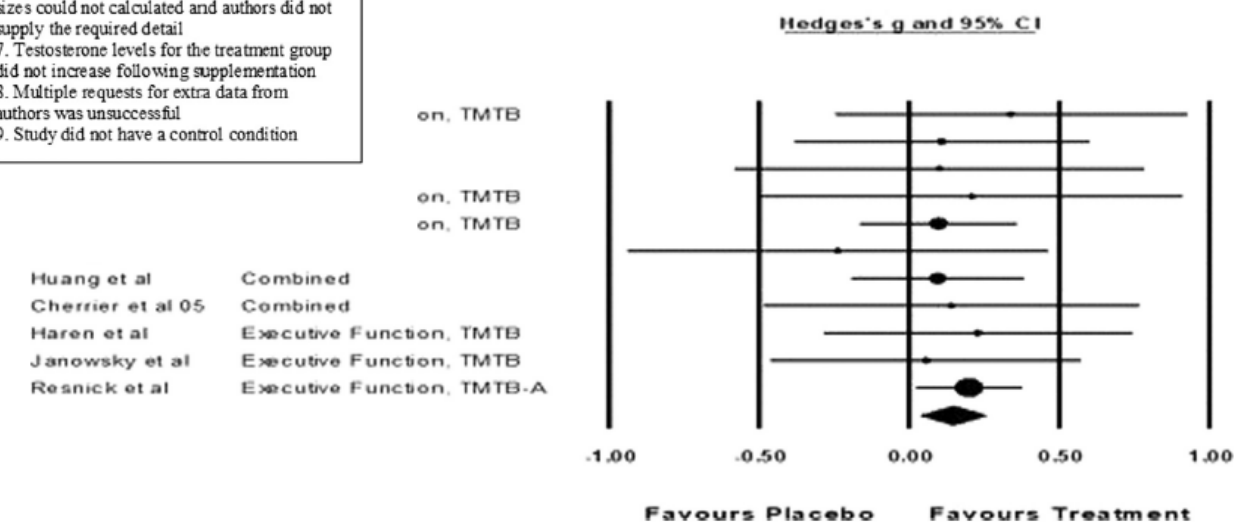
Abstracts excluded (N= 454)
Reasons:
1. Paper was not relevant to the topic
2. Paper was not in an appropriate format (e.g. observational studies, review articles)
3. Participants had pre-existing medical conditions.

Full text copies retrieved for evaluation
N = 58

Studies excluded (N= 35)
Reasons:
1. Study was not a RCT
2. Testosterone was not included as a supplement
3. Participants were below the pre-determined age range
4. Testosterone supplementation was not given routinely
5. Cognitive function was not an outcome measure; cognitive scores were not reported.
6. Data were presented in a way that effect sizes could not calculated and authors did not supply the required detail
7. Testosterone levels for the treatment group did not increase following supplementation
8. Multiple requests for extra data from authors was unsuccessful
9. Study did not have a control condition

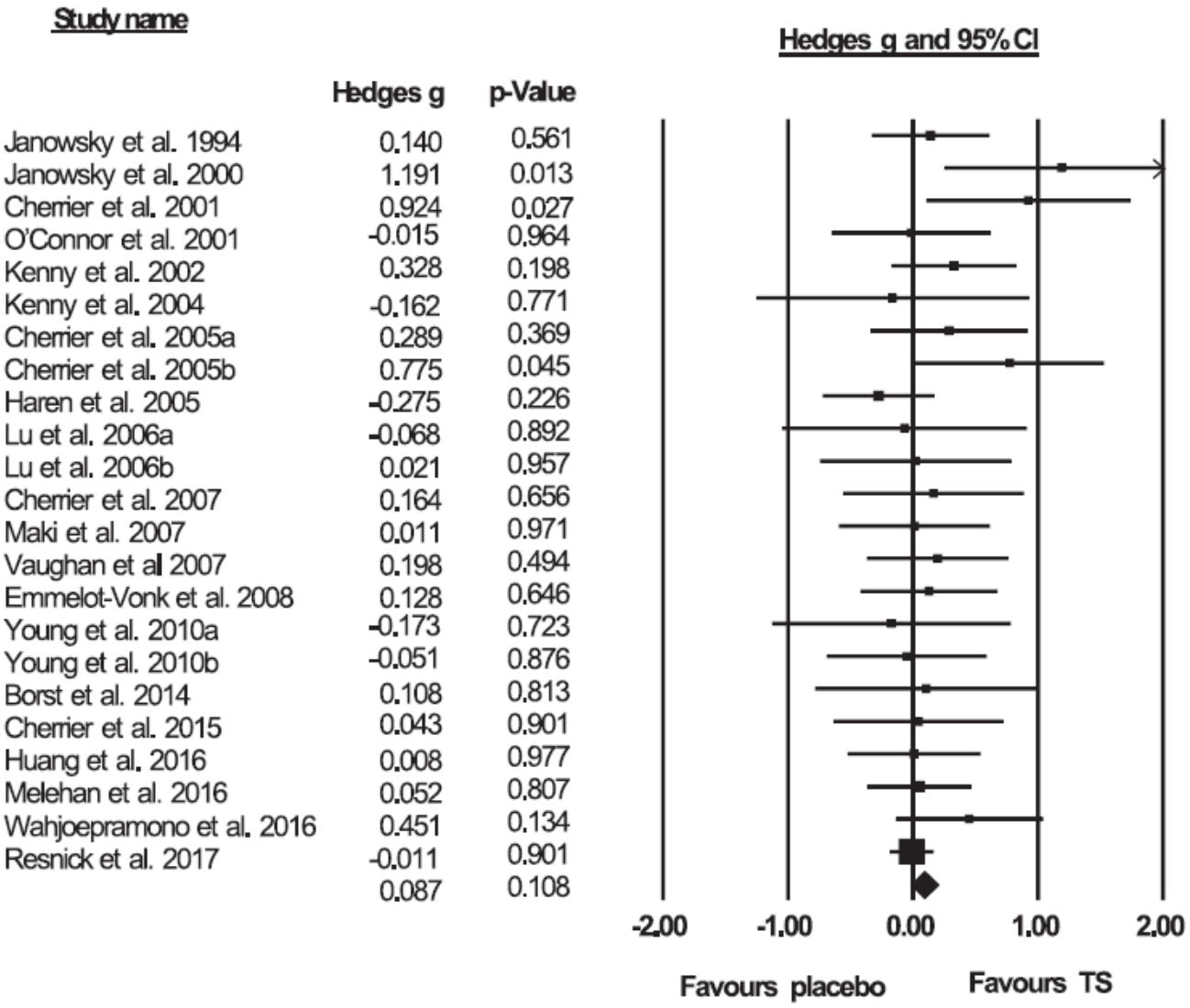
Descriptive Data Extracted
N = 29
Author/s, publication status, year of publication, study design, sample size, participant details, baseline testosterone levels, end of study testosterone levels, testosterone supplementation method, dosage and cognitive tests scores.

Data Analysis
N= 14
Calculated effects sizes
Calculated Statistical Heterogeneity
Publication Bias
Analysis of methodological variables



Tan et al. Am J of Geriatric Psychiatry 27:11 (2019) 1232–1246

Meta-analysis: TRT on cognition



Buskbjerg et al. Journal of the Endocrine Society 2019;3:1465-84.

Table 1. Description of Included Studies (Continued)

Study	Cognitive Outcome	n[a] Pre	n[b] Post	Duration[c]	Type[d]	Doses	Mean Age (Range/SD)[e]	Cognitive Status	Gonadal Status Pre[f]	Gonadal Status Post[f]	TS Effect[g]	T Medium	Assay	Time
Cherrier *et al.* [54]	Verbal memory; visuospatial memory	57	50	6.00	Injection	50, 100, or 300 mg/6 wk	67.00 (56–78)	Normal	Normal 396.3 (160.5) ng/dL	High 1915.5 (1230.8) ng/dL	2.50	Serum	Direct CIA	Random/not fasting
Maki *et al.* [55]	Executive function; verbal memory; verbal learning; visuospatial learning; attention/working memory	15	15	12.90	Injection	200 mg/2 wk	73.90 (66–86)	Normal	Normal 10.2 ± 3.2 pg/mL	High 970.21 (359.1) ng/dL	1.82	Serum	Direct RIA and CIA	NR/NR
Vaughan *et al.* [56]	Executive function; verbal memory; verbal learning; visuospatial learning visuospatial function; attention/working memory	47	32	156.00	Injection	200 mg/2 wk	70.80 (65–83)	Normal	Low–normal 285.3 (46.1) ng/dL	Normal 587.9 (279.5) ng/dL	1.10	Serum	NR	Morning/NR
Emmelot-Vonk *et al.* [57]	Executive function; verbal memory; verbal learning; visuospatial function	257	223	26.00	Pellets	160 mg/d	67.25 (60–80)	Normal	Low–normal 317.0 (54.8) ng/dL	Low–normal "unchanged"	−0.56	Serum	Direct CIA	Morning/fasting
Young *et al.* [44][h]	Executive function; language; verbal memory; verbal learning; visuospatial learning; visuospatial function; attention/working memory	13	13	6.00	Gel	100 mg/d	29.31 (3.3)	Normal	Normal 411 (125.8) pM	Normal 541.9 (310.2) pM	0.23	Serum	Direct RIA	NR/NR
Young *et al.* [44][h]	Executive function; language; verbal memory; verbal learning; visuospatial learning; visuospatial function; attention/working memory	15	15	6.00	Gel	75 mg/d	67.40 (5.5)	Normal	Normal 241 (65.5) pM	Normal 347.6 (155.2) pM	1.06	Serum	Direct RIA	NR/NR
Borst *et al.* [58]	Executive function; visuospatial memory; visuospatial learning; visuospatial function; attention/working memory	30	19	52.00	Injection	125 mg/wk	70.00 (8.9)	Normal	Low–normal 245.0 (73.0) ng/dL	Normal 474.0 (193.5) ng/dL	1.46	Serum	Direct CIA	NR/NR
Cherrier *et al.* [59]	Executive function; language; verbal memory; visuospatial memory; verbal learning; visuospatial learning; visuospatial function; reaction time	22	19	24.00	Derma gel	50–100 mg/d[i]	70.50 (60–88)	Impaired (MCI)	Low–normal 308.2 (92.1) ng/dL	Normal 600.7 (19.7) ng/dL	1.91	Serum	LC-MS/MS	Random/not fasting
Huang *et al.* [60]	Executive function; language; verbal memory; visuospatial memory; verbal learning; visuospatial learning	308	240	156.00	Gel (1%)	7.5 g 1% T gel/d	67.55 (5.10)	Normal	Low–normal 305.5 (63.4)	Normal 567.7 (265.1) ng/dL	1.40	Serum	Direct IA	Morning/fasting
Melehan *et al.* [61]	Executive function; reaction time	67	54	18.00	Injection	1000 mg/6 wk	49.00 (1.6)	Normal	Normal 352.7 (161.4) ng/dL	Normal 539.04 (115.16) ng/dL	1.40	Serum	LC-MS/MS	Morning/NR
Vahjoepramono *et al.* [62]	Cognitive status; verbal memory; verbal learning	50	44	24.00	Cream (5%)	50 mg/d	61.05 (7.7)	Normal	Normal 474.4 (136.8) ng/dL	Normal 769.5 (34.8.7) ng/dL	1.40	Serum	LC-MS/MS	NR/NR
Resnick *et al.* [63]	Cognitive status; executive function; verbal memory; verbal learning; visuospatial learning; reaction time	493	438	52.00	Gel (1%)	5.00 g 1% T gel/d	72.20 (6.0)	Impaired (AAMI)[h]	Low–normal 234.4 (65.2) ng/dL	Normal 490 (86.2) ng/dL	1.80	Serum	LC-MS/MS	NR/NR

Buskbjerg et al. Journal of the Endocrine Society 2019;3:1465-84.

Pitfalls

- Old age (response to questionnaires)
- Strict standardization
- Multiple confounding factors
- Include Impaired cognition status
- Include Hypogonadism
- Lack of imaging or Bio-marker(objective brain metabolism)

Summary

- Recent evidences in neuro-endocrine studies showed roles of sex-hormone
  → Neuronal plasticity, Neurogenesis
- Several longitudinal studies revealed association between T and Cognition.
- A few RCTs describes TRT on impaired cognition in hypogonadism.
- TRT is never harmful to cognitive function but needs well designed randomized control studies.

Thank you for listening

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