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THE HORMONAL PATHWAY TO COGNITIVE IMPAIRMENT IN OLDER MEN

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Abstract: In older men there is a multiple hormonal dysregulation with a relative prevalence of catabolic hormones such as thyroid hormones and cortisol and a decline in anabolic hormones such as dehydroepiandrosterone sulphate, testosterone and insulin like growth factor 1 levels. Many studies suggest that this catabolic milieu is an important predictor of frailty and mortality in older persons. There is a close relationship between frailty and cognitive impairment with studies suggesting that development of frailty is consequence of cognitive impairment and others pointing out that physical frailty is a determinant of cognitive decline. Decline in cognitive function, typically memory, is a major symptom of dementia. The "preclinical phase" of cognitive impairment occurs many years before the onset of dementia. The identification of relevant modifiable factors, including the hormonal dysregulation, may lead to therapeutic strategies for preventing the cognitive dysfunction. There are several mechanisms by which anabolic hormones play a role in neuroprotection and neuromodulation. These hormones facilitate recovery after brain injury and attenuate the neuronal loss. In contrast, elevated thyroid hormones may increase oxidative stress and apoptosis, leading to neuronal damage or death. In this mini review we will address the relationship between low levels of anabolic hormones, changes in thyroid hormones and cognitive function in older men. Then, giving the contradictory data of the literature and the multi-factorial origin of dementia, we will introduce the hypothesis of multiple hormonal derangement as a better determinant of cognitive decline in older men.

Key words: Hormonal dysregulation, cognitive impairment, older men.

Introduction

Decline in cognitive function, typically memory, is a major symptom of dementia. The "preclinical phase" of detectable cognitive impairment precedes by many years the appearance of dementia (1, 2).

The decline of cognitive function with age affects different domains including selective attention, processing capacity and speed, verbal fluency, complex visual and spatial skills, and language analysis (3). There is evidence that a preclinical or sub-clinical phase of reduced cognitive function, such as information-processing speed (4-5), precedes the appearance of diagnosed dementia by at least 10 years. The decline in these domains begins as early as the mid-twenties and continues in an almost linear fashion in the last decades of life (6). Many factors including health status, socioeconomic factors, life-style, and genetics contribute to inter-individual differences in the rate and severity of cognitive decline. Identification of relevant modifiable factors may lead to new strategies for preventing the age-related cognitive impairment. The Intervention on Frailty Working Group recognized that both physical and the cognitive problems play an important role in frailty and disability with a close relationship between frailty and dementia (7). The development of frailty may be due to a cognitive impairment (7), whereas recent findings suggest also that frailty could contribute to cognitive decline (8). As already shown in studies testing the role of the hormonal pathway in frailty (9), one of the potential factors both influencing normal and pathological cognitive ageing is the hormonal dysregulation. In older men there is a multiple hormonal dysregulation with a relative prevalence of catabolic hormones such as thyroid hormones and cortisol and a decline in anabolic hormones such as dehydroepiandrosterone sulphate (DHEAS), testosterone (T) and insulin like growth factor 1 (IGF-1). We will underline the role of anabolic deficiency and namely of the decline in anabolic hormones such as testosterone, IGF-1, and DHEAS in older men. The profound interrelationship between these 3 hormones (DHEAS can be converted into testosterone and estradiol and both hormones affect the liver production of IGF-1) may explain the reason to include all these hormones in the present review (Figure 1). To complete the picture, giving the higher prevalence of subclinical dysthyroidism in older patients, we will also address the role of thyroid hormones on cognitive function.

Since literature provides already evidence of a relationship between chronic stress, elevated cortisol levels and risk of cognitive impairment and dementia (10-12), the link between cortisol and cognitive functions will not be examined here. We will focus on the decline in anabolic hormones introducing the new concept of multiple hormonal dysregulation as a potential factor involved in the onset of cognitive decline in the elderly.

DHEAS and cognitive function

Neurobiological actions

Dehydroepiandrosterone (DHEA) and its sulfate derivative DHEAS are the major secretory products of the adrenocortical

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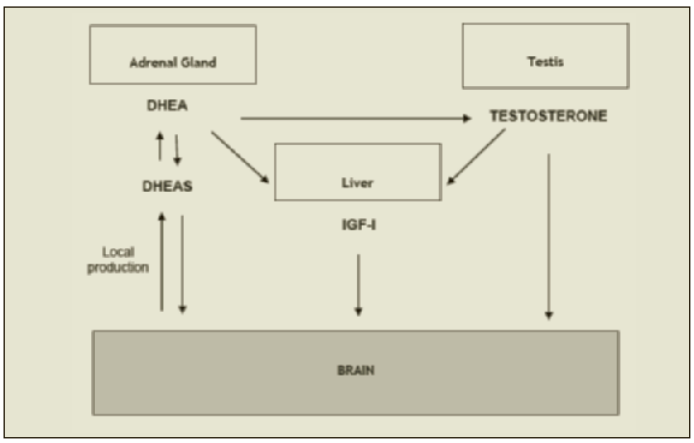
gland, and are produced in larger quantities than any other steroid hormone. The levels of these two hormones decline with age in both sexes. The fall in circulating levels of DHEA/S is concomitant with the onset of many common physiological and functional impairments associated with age (13-15).

Figure 1

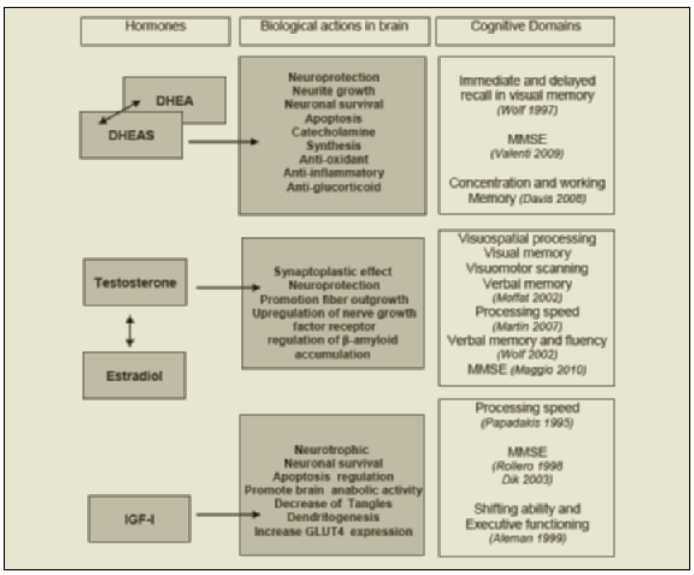


The putative positive effects of DHEA/S in the brain include neuroprotection, neurite growth, neurogenesis and neuronal survival, apoptosis, modulation of catecholamine synthesis and secretion, anti-oxidant, anti-inflammatory and anti-glucocorticoid effects (16) .

The mechanisms by which DHEA/S operates in brain are not fully understood.

In animal models DHEA/S could operate its neurobiological functions through genomic and non-genomic mechanisms (Figure 2).

Figure 2



At genomic level DHEA/S may decrease neuronal death, enhance astrocitic differentiation (17), induce cortico-thalamic dendritic projection growth (18), and facilitate transcription of genes that lead to the synthesis of enzymes and structural proteins (19).

At non-genomic level, the actions of DHEA/S include allosteric antagonism of γ-Aminobutyric acid (GABA) receptor (20), activation of N-Methyl-D-aspartic acid (NMDA) receptors (21), interference with muscarinic acetylcholine receptors (22), dopamine and serotonine agonistic effects (23), attenuation of oxidative stress and neurotoxic effects of certain aminoacids (24-25), stimulation in the production of IGF-I, vascular endothelial growth factor (VEGF), transforming growth factor (TGF) beta 1 (26) and antagonism of glucocorticoid exposure (27).

DHEA/S may mediate some of its actions through conversion into sex steroids and activation of androgen and estrogen receptors at tissue level.

Morley et al showed that the rate of decline in bioavailable testosterone levels is paralleled by decline in its precursor DHEAS, suggesting that decreased synthesis of DHEA can contribute to the reduction in testosterone levels (28).

Moreover, in mice, estrogens may potentiate the effects of DHEA on brain. In this animal model DHEAS injection into the hippocampus improved memory retention in a dose dependent manner (29).

In addition, DHEA/S may also have effects through its more immediate metabolites, such as 7 -hydroxy-DHEA. Although no DHEA or DHEAS nuclear steroids receptor has been found, DHEA and DHEAS show affinity for some binding sites.

DHEA and DHEAS have different effects on neural survival, suggesting that the balance between these two neurosteroids may play a critical role in nervous system development and maintenance (16).

Observational studies

Several human studies have investigated the relationship between the age-related DHEA/S decline and cognitive impairment. No significant association between DHEAS and cognition has been found in two large prospective cohort studies in men: 1) men and women of Rancho Bernardo Study (30); and 2) men in the Baltimore Longitudinal Study of Aging (31).

Moreover in the large older male cohort of Massachusetts Male Aging Study no significant correlation was found between DHEA/S and cognition (32).

These data were not confirmed in a second large population study of older women showing a positive relationship between DHEAS levels and some cognitive domains (simple concentration and working memory) (33) (Table 1).

A trend toward an inverse association between DHEA and rate of cognitive decline was detected in a French community-based cohort study (34) and in a small sample of healthy older subjects of the population-based Rotterdam study (30).

Valenti et al recently reported the association between DHEAS and cognitive function over time, by analyzing data from the population-based sample of the InCHIANTI Study.

Table 1
DHEA-S and cognitive function

Author/Reference	Type of survey	Population	Follow up	Results
		Observational studies		
Kalmijn S. et al 29	Longitudinal	189 healthy participants from the populationbased Rotterdam Study, aged 55–80 yr	1,9 yr	Inverse non significant, association between DHEAS and cognitive impairment and decline.
Moffat S.D. et al. 30	Longitudinal	883 men from a community-dwelling volunteer sample in the Baltimore Longitudinal Study of Aging. aged 22 to 91years	Up to 31 yr (mean, 11.55 yr)	Neither the decline in DHEA-S nor DHEA-S concentrations within individuals were related to cognitive status or cognitive cognitive decline. A comparison between the highest and lowest DHEA-S quartiles revealed no cognitive differences, in healthy aging men.
Fonda S.J. et al 31	Cross sectional	981 subjects from Massachusetts Male Aging Study	--	DHEA and DHEAS did not mediate the relationship between age and cognitive function
Davis S.R. et al 32	Cross sectional	295 women aged 21-77 yr median age 5 yr	--	Higher endogenous DHEAS levels are independently and favorably associated with executive function, concentration and working memory.
Valenti G. et al. 34	Cross sectional Longitudinal	755 subjects (410 men, 345 women) aged > or = 65 yr of the InCHIANTI Study	3 yr	Significant and positive association between DHEAS and cognitive function, assessed by MMSE test. Low DHEAS levels predict accelerated decline in MMSE score during the 3 yr follow up period.
		Intervention studies		
Wolf O.T. et al. 38	RCT	40 healthy elderly men and women (mean age, 69 yr)	6 weeks 50 mg/day	No beneficial effects of DHEAsubstitution could be observed in any of the tests of the neuropsychological test battery in either sex.
Wolf O.T. et al. 39	RCT	17 elderly men (mean age 71,1±1,7 yr, range 59-81)	2 weeks DHEA 50 mg/day	DHEA replacement in elderly men results in changes in electrophysiological indices of SNC stimulus processing. This effects do not appear to be strong enough to improve memory or mood.
Barnhart K.T. et al 42	RCT	60 perimenopausal women aged 45-55 yr	3 months	DHEA 50 mg/ day per os DHEA supplementation does not improve perimenopausal symptoms or well-being compared to placebo.
Van Niekerk J.K. et al. 41	RCT	46 men aged 62–76	13 weeks 50 mg DHEA/day	Higher morning DHEA was associated with lower confusion, while higher evening DHEA was associated with lower anxiety, and lower current negative mood. No significant effects of supplementation were observed on any of the trial outcomes.
Wolkowitz O.M. et al 43	RCT	58 patients with Alzheimer disease 28 cases 30 controls	7 months DHEA 50 mg per os twice a day or placebo	DHEA did not significantly improve cognitive performance. A transient effect on cognitive performance may have been seen at month 3, but narrowly missed significance

They showed that at enrolment, DHEAS was significantly and positively associated with Mini Mental State Examination (MMSE) score, independently of age and other potential confounders. Then, low baseline DHEAS levels were predictive of larger decline of MMSE and this relationship was significant after adjusting for covariates ($\beta \pm SE$ -0.004 ± 0.002, $p<0.03$) (35).

In contrast to these findings, Marx et al found that in patients with Alzheimer's disease DHEA levels were elevated in postmortem prefrontal and temporal cortex (36, 37). The cerebrospinal fluid DHEA levels were correlated with temporal cortex brain levels of this neurosteroid, suggesting that high level of DHEA in cerebrospinal fluid may be an indicator of Alzheimer disease (38).

Intervention Studies

The effect of DHEA treatment on cognitive performance in men has been tested in four randomized controlled clinical trials (39-42) with a significant improvement in the attention after stress (Table 1).

Wolf OT et al (39) in a crossover trial of 2 weeks DHEA or placebo treatment, found a significant improvement in both immediate recall and delayed recall of a visual memory test in women receiving DHEA treatment. However, verbal memory or other cognitive tests were not affected by treatment.

Wolf OT et al (40) found a deterioration in selective attention following psychosocial stressor in placebo group but not in DHEA group, after two weeks of treatment. However, DHEA produced a significant impairment of visual memory following the stressor compared to placebo. These effects were not found when DHEA was co administered with stressor.

Barnhart KT et al (43), in a randomized double-blind placebo-controlled trial examined the effects of 3-month DHEA supplementation in 60 perimenopausal women. They found no significant effect on cognitive symptoms and well-being. Wolkowitz et al have detected a transient positive effect of DHEA supplementation on cognitive performance in patients with Alzheimer's disease (44).

Huppert FA et al (45) in a systematic review limited to studies performed in older people did not show any significant improvement in memory or other cognitive domains after DHEA treatment.

In conclusion, the relationship between DHEA/S and cognitive function is stronger in animals than humans where data are not consistent enough to support a role of DHEA/S decline in the age-related cognitive impairment (46-49). Further studies are needed to fully understand the benefits of DHEA supplementation on cognitive function.

Since DHEAS may also affect cognition after conversion into sex steroids (testosterone and estradiol) and peripheral activation of androgen and estrogen receptors, the attention should also focus on these hormones.

Testosterone and cognitive function

Mechanisms of neuroprotection

The brain is a highly androgen responsive tissue where androgens induce several beneficial actions (Figure 2). It has been hypothesized that the age-related decline in testosterone in men is associated with the decline in cognitive function and mild cognitive impairment (50).

In vitro and in vivo studies support the biological plausibility of a protective effect of T on cognitive function (51-52) (Table 2).

Previous data have demonstrated that the integrity of the male hippocampus requires normal levels of male sex hormones. T has a synaptoplastic effect on the hippocampus of gonadectomized male rats (53). In addition, it is well known that most of neurons in the monkey hippocampus, similarly to the rat hippocampus (54, 55), has androgen receptors (56-58). In the rat hippocampus, androgen receptors are primarily located in pyramidal neurons (52, 59).

In primates, the androgens in the prenatal or postnatal period affect learning abilities as well as maturation of the cortical regions sub serving these abilities (60, 61). In adult animals, androgen receptors are at high concentration in hippocampal pyramidal cells (52). Androgens may reduce Aβ levels in culture by an AR dependent mechanism involving the increased expression of the Aβ-degrading enzyme neprilysin and the inhibition of tau hyperphosphorilation (62).

Androgen treatment may prevent N-methyl-daspartate excitotoxicity in hippocampal CA1 neurons (63) and may facilitate recovery after injury by promoting fiber outgrowth and sprouting in hippocampal neurons (64). T administration increases nerve growth factor levels in the hippocampus, septum, and neocortex and induces an up-regulation of nerve growth factor receptors in the forebrain (65).

T treatment accelerates the rate of nerve regeneration and attenuates neuron loss. These effects are true not only for T but also for its potent androgenic metabolite dihydrotestosterone (DHT) (66).

Studies conducted in participants with prostate cancer undergoing antiandrogen therapy provide evidence to the notion that T has beneficial effects on cognitive function. In these patients the anti-androgen flutamide attenuated the neuroprotective effects of T on motor neurons (67).

The mechanism behind these neuroprotective actions include the regulation of trophic factors, the promotion of neuron survival in brain regions vulnerable to neurodegenerative diseases and the modulation of GABA-A receptors. GABA activation reduces excitatory signaling, which in turn attenuates seizure activity thereby minimizing lesion severity (66).

Androgens may also protect the brain from Alzheimer's disease by regulating accumulation of β-amyloid. Gandy et al showed in a small group of subjects affected by prostatic cancer and on androgen deprivation therapy that plasma -amyloid levels increased together with the decrease of steroid hormones concentrations (67).

Furthermore, the protective effect of testosterone was partially blocked by an aromatase inhibitor, suggesting that T aromatization into estradiol (E2) within the brain may explain some of beneficial effects of testosterone on the central nervous system.

Thus, the effects of circulating T levels could be mediated either via actions of the steroid on androgen receptors or conversion to E2. Morphological studies suggest that androgens and estrogens both modulate hippocampus structure in males.

It is also known that the biological activity of T is down-regulated in neurodegenerative disease. The activation of androgen receptors (ARs) has been found to be markedly reduced in mice that express the ε4 allele (68), suggesting that APOE genotype may regulate the androgen receptors (69). Indeed, having an ε4 allele combined with low levels of T has been found significant predictors of Alzheimer disease (70). A recent study demonstrated an interaction effect between testosterone and the APOE 4 allele on hippocampal volume in middle-aged men.

Participants with at least one copy of the ε4 allele and low T had the smallest left hippocampal volumes, whereas subjects who had low T levels and no ε4 allele had significantly larger left hippocampal volumes relative. These findings suggest a potential interactions between APOE gene and either androgen receptor polymorphisms or genes associated with T (71).

Recent and growing interest has been developed for the role of polymorphisms of androgen receptors in the development of cognitive impairment.

Lehmann et al found that glutamine (CAG) repeat polymorphisms of androgen receptor in men is associated with Alzheimer's disease, especially when coexisting with low T levels (72).

Polyglycine (GGN) repeat polymorphism was associated with immediate logical memory only in females (73). Nevertheless, the association between cognition and androgen receptor CAG repeat length remain controversal: Lee et al found no association between CAG repeat length and fluid cognition in a large community-based, cross-sectional study of 3369 men aged 40-79 years from European Male Ageing Study (74).

Table 2
Testosterone and cognitive function

Author/Reference	Type of survey	Population	Follow up	Results
		Observational studies		
Morley J.E. et al. 27	Cross-sectional	56 healthy men aged 20-84 years	--	Positive association between bioavailable testosterone levels and the cognitive measurements.
Barrett-Connor E et al 101	Cross-sectional Longitudinal	547 community-dwelling men 59–89 yr of age	7 yr	Low estradiol levels were associated with better performance on two standard cognitive function tests, whereas high TT or BioT levels predicted better performance on tests of verbal memory and mental control.
Moffat SD, et al 77	Longitudinal	407 volunteers from the Baltimore Longitudinal Study of Aging, aged 50–91 yr	10 yr	Higher FTI was associated with better scores on visual and verbal memory, visuospatial functioning, and visuomotor scanning and a reduced rate of longitudinal decline in visual memory.
Yaffe K, et al 76	Longitudinal	310 men mean age 73.0±7.1	6,5 yr	BioT but not TT level was positively associated with cognitive scores in older men. Testosterone improves cognitive function in older men and this association is not an indirect effect via aromatization to estradiol.
Wolf OT, & Kirschbaum C. 86	Cross-sectional	38 older women (mean age 68 years) and 30 older men (mean age 69 years).	--	In men no positive association between sex steroids and cognition could be detected. Only higher testosterone (TT and FT) levels were negatively associated with verbal fluency.
Muller M, et al. 75	Cross-sectional	400 men ages 40 and 80	--	Higher T levels are associated with better cognitive performance in the oldest age category. Men with lower T levels performed significantly worse than men with higher T levels.
Lessov-Schlaggar CN et al. 87	Longitudinal	514 pairs of twins selected by the National Heart Lung and Blood Institute (the NHLBI Twin Study)	10- to 16-yr	No significant associations between sex hormone or SHBG levels and performance on a series of cognitive tasks measuring global and executive function, visual and verbal learning and memory.
Yonkers J.E. et al. 88	Cross-sectional	450 healthy men aged 35-80 years, stratified to testosterone levels	--	Participants with low free T performed at a superior level on both the block design task and draw-a-figure task as compared to participants with high free T.
Martin DM, et al . 78	Cross-sectional	1046 community-dwelling men aged 35–80 years	--	Higher TT and FT levels were associated with better performance on a measure of processing speed and poorer performance on measures of both learning and memory and executive function.
Chu L. et al. 80	Cross-sectional	203 Chinese older men, aged 55-93 yr 48 with mild) cognitive impairment (aMCI 66 with Alzheimer disease (AD) 89 with normal cognition	--	Bioavailable T levels, but not Total T, were significantly lower in the aMCI and AD groups than in the normal controls with no significant difference between the aMCI and AD groups.
Yeap B.B. et al. 81	Cross-sectional	2932 men aged 70-89 yr	--	There is a positive association between serum free testosterone levels and cognitive function assessed by MMSE.
Chu L, et al. 79	Longitudinal	153 ambulatory healthy Chinese men, aged 55 yr or over	1 yr	The baseline serum bioavailable testosterone level predicted a reduced risk of Alzheimer's disease in older men
Maggio M et al. 82	Cross-sectional	455 men aged > 65 1) severely hypogonadal (T<230 ng /dl); 2) moderately hypogonadal (230< T<350 ng/dL), 3) eugonadal (T > 350 ng/dL)	--	In the age and BMI adjusted analysis, a significant difference in MMSE score, was observed among the three groups, with severely hypogonadal men having lower values of MMSE. However, in a fully-adjusted analysis MMSE did not remain significantly associated with testosterone levels.
		Intervention studies		
Janowsky, J.S., et al 89	No RCT	56 subjects aged > 65 years 26 case (testosterone) 29 control (placebo)	Dose 3 months	Testosterone use was associated with enhanced spatial abilities, as measured by the block design test, but had no effect on delayed recall or visual reproduction abilities at 3 months.
Wolf, O.T., et al 91	RCT	Thirty men age: 68.7 ± 1.9 yr 17 case, 13 controls	5 days single testosterone (250 mg testosterone enanthate) or placebo injection	A single testosterone injection resulting in supraphysiologic hormone levels had no beneficial effects on the five cognitive tests used in this study.
Cherrier, M.M., et al, 92	No RCT	25 community-dwelling s, volunteer aged 50 to 80 year	6 weeks intramuscular	Improvement of spatial memory spatial ability, and verbal memory in testosterone group compared to baseline and the

			injections of either 100 mg testosterone enanthate or placebo	placebo group
Cherrier, M.M., et al. 93	No RCT	32 healthy young men between the ages of 21 and 46 yr	8 weeks 1) im T enanthate ; 100 mg/wk + daily oral placebo 2) im placebo/wk + 125 g daily oral levonorgestrel (LNG); 3) im T enanthate 100mg/ wk + 125 g daily oral LNG; 4) im placebo/wk + daily oral placebo	Decline in serum T levels adversely affects verbal memory in normal young men. Increased T and/or E2 levels maintain verbal memory and significantly improve attention. No significant changes on measures of spatial memory
Cherrier M.M., et al. 94	No RCT	32 partecipants aged 63-85 years with AD; 19 cases 13 controls	6 weeks intramuscular injection of 100 mg testosterone enantate or placebo	Improvements in spatial memory, constructional abilities and verbal memory were evident in the T group.
Haren M.T. et al. 96	No RCT	76 healthy men aged 60-86 years; 39 cases 34 controls	12 months oral supplementation testosterone undecanoate (TU) (80 mg twice daily) or placeb	Supplementation with oral TU does not affect scores on visuospatial tests in older men with low-normal gonadal status.
Lu P.H. et al. 100	RCT	38 subjects 16 male patients with AD and 22 healthy male control subjects	24 weeks Testosterone or placebo, in the form of hydroalcoholic gel (75 mg), applied daily to the skin	No significant treatment group differences were detected in the cognitive function, although less decline on measures of visuospatial functions was demonstrated with testosterone treatment compared with placebo.
Vaughan C. et al. 97	RCT	69 healthy men aged 65-83 years; 24 testosterone group (T-only), 22 testosterone + finasteride group (T+F), 23 placebo group	36 months 1) T-only group, T enanthate (200 mg im every 2 weeks + orally placebo daily; 2) T+F group, TE 200 mg im every 2 weeks + finasteride (5 mg/d orally) 3) placebo group, sesame oil injections, 1 mL im every 2 weeks + placebo pill daily.	T replacement, whether given alone or in combination with finasteride, in healthy older men without cognitive impairment at baseline has no clinically significant effect on cognitive function.
Maki P.M. et al. 99	RCT	15 cognitively normal men, aged 66-86 yr	9 months testosterone enanthate 200 mg im every other week (for 90 d) or placebo im	T treatment leads to a significant decrease in short-delay verbal memory and a nonsignificant decrease on a composite verbal memory measure.
Emmelot-Vonk M.H. et al. 98	RCT	237 healthy men aged 60- 80 yr with testosterone lower than 13.7 nmol/L	6 months 80 mg of testosterone undecenoate or a matching placebo twice daily	Testosterone supplementation in older men with a low normal testosterone concentration did not affect cognition.
Fukai S et al. 95	No RCT	11 men with cognitive impairment, and 13 controls aged 81±6	6 months oral testosterone undecanoate 40 mg daily	At 3 months subjects on testosterone treatment showed no significant increase in MMSE and HDS-R, whereas at 6 months, cognitive scores were significantly greater than the baseline.

Table 3
GH-IGF-I axis and cognitive function. Observational Studies

Author/Reference	Type of survey	Population	Follow up	Results
Paolisso G et al. 121	Cross sectional	Three groups of subjects: 1) 30 adults (50 yr), 2) 30 aged men (75–99 yr), 3) 19 centenarians (100 yr).	--	In centenarians, the plasma IGF-I/IGFBP-3 molar ratio correlated with Mini Mental State Examination (r 0.53; P<0.0.03).
Aleman A, et al. 122	Cross sectional	Twenty five healthy older men with well-preserved functional ability aged 65–76 yr	--	Subjects with higher IGF-I levels performed better on these tests
Rollero A et al. 123	Cross sectional	22 subjects (7 females, 15 males) aged 65-86 yr.	--	IGF-I levels were directly correlated with MMSE scores, being lowered in patients with more advanced cognitive deterioration.
Deijen JB et al. 126	Cross sectional	89 subjects 31 men with multiple pituitary hormone deficiencies MPDH 17 men with isolated growth hormone deficiency (IGHD). 41 controls (healthy). aged 19-37 yr	--	IGHD patients only showed subnormal memory performance. Cognitive impairment in both MPHD and IGHD was related to GH deficiency.
Kalmijn S et al. 127	Longitudinal	186 healthy participants from the population based Rotterdam Study, aged 55–80 yr.	4 yr	In elderly subjects, total IGF-I and the total IGF-I to IGFBP-3 ratio were both inversely related to cognitive decline in the next 2 yr. These results were independent of differences in age, sex, insulin levels, body mass index, or other major confounders. No association between free IGF-I and cognitive decline.

Experimental human studies conducted in young men suggest that sex hormones may specifically affect verbal and spatial skills (75). However there are little and scant data on the possible relationships between hormonal changes and selective cognitive function, such as memory and processing speed in older men.

Observational Studies

Some studies show a positive association between free and bioavailable T levels and cognitive performance (Table 2).

Muller M et al (76) assessed cognitive performance in 400 independently living men aged between 40 and 80. They observed a curvilinear association between sex hormones and some cognitive functions suggesting an optimal hormone level for certain cognitive tasks. The positive linear associations between T and cognitive performance observed in the oldest age subjects accounted for the curvilinear associations between T and cognitive functioning across the full age range. The authors hypothesized that because of increasing vulnerability in aging men, decreased T levels in elderly men lead to an imbalance of cognitive functioning, while in younger men, the balance is preserved by other factors.

In line with other studies, the positive association between bioavailable T and cognition is stronger than that observed for total T (77, 78), probably because bioavailable T crosses the blood–brain barrier more readily than total T, which is largely bound by sex hormone binding globulin (SHBG) (77).

Moffat et al (78) have investigated the relationships between age-associated decreases in endogenous serum total T (TT) and free T (FT) concentrations and decline in neuropsychological performance in 407 men from the Baltimore Longitudinal Study of Aging, aged 50–91 yr, and followed for an average of 10 years. These authors showed that higher FT levels, within the normal range, were associated with better performance on measures of visuospatial processing, visual memory, visuomotor scanning, and multiple measures of verbal memory. No significant relationship was found between TT or FT concentrations and measures of mental status, verbal knowledge, or depressive status. Moreover, when men were classified as hypogonadal or eugonadal, hypogonadal men had lower visual and verbal memory, visuomotor scanning, and visuospatial rotation.

In a cross-sectional study, Yaffe et al (77) found that bioavailable T but not TT level was positively associated with cognitive scores in older men. They also found that SHBG level and total but not bioavailable E2 levels were negatively associated with cognitive function. These findings support the hypothesis that T may improve cognitive function in older men directly and not via aromatization to E2.

At variance with previous studies, Martin et al (79) analyzed 1046 community-dwelling male participants (aged 35–80 years) of the Florey Adelaide Male Ageing Study (FAMAS). In this population higher TT and FT levels were associated with better performance on a measure of processing speed and poorer performance on measures of both learning and memory and executive function even after adjustment for age, and salient health and lifestyle variables.

Chu et al (80) have recently investigated the effect of serum TT, bioavailable T and SHBG levels on the subsequent risk of Alzheimer disease in 153 non-demented Chinese older men

(aged 55 years or over), in a one-year prospective cohort study. They found that the serum levels of bioavailable T levels in late life span are predictors of lower risk of Alzheimer disease in older men.

More recently, Chu et al have examined the association between amnestic mild cognitive impairment and bioavailable T and TT in 203 Chinese older men. In this population bioavailable T but not TT was positively associated with amnestic mild cognitive impairment (81).

A cross-sectional study conducted by Yeap et al on 2932 men aged 70-89 years evaluated the relationship between testosterone levels (TT and FT) with cognitive function assessed by MMSE, showing that FT levels higher then 210 pmol/L were associated with a better cognitive performance (82).

Finally, using data from the InCHIANTI study, a population based study in two municipalities of Tuscany, Maggio et al evaluated 410 >65 year old men with complete data on T levels and MMSE. According to baseline serum levels of TT, three different groups of older men were created: 1) severely hypogonadal (N= 20) with serum TT levels <230 ng /dl; 2) moderately hypogonadal (N=75) (TT >230 and <350 ng/dL), and 3) eugonadal (N=297) with serum TT levels > 350 ng/dL. In the age and BMI adjusted analysis, a significant difference in MMSE score (p for trend<0.001) was found among the three groups, with severely hypogonadal men having lower values of MMSE (83).

Data from oservational studies are supported by studies conducted in androgen deprivation therapy (ADT). Beer et al have analyzed long term memory, working memory and profile of mood state in 18 patients with androgen independent prostate cancer beginning second line hormonal therapy with transdermal estradiol (0.6 mg/24 hours), in a control groups of 18 patients with prostate cancer undergoing androgen deprivation therapy and 17 healthy men. Verbal memory, immediated or delayed resulted significantly worse and processing speed slower in patients with prostatic cancer on ADT whereas subjects with prostatic cancer did not differ significantly from healthy controls (84). Nelson et al have recently reviewed studies testing the relation between ADT in men with prostate cancer and its cognitive effects. All these data support a strong relationship between the decline in T levels and the alterations in multiple cognitive domains during ADT (85).

By contrast Alibhai et al, in a prospective matched cohort study comparing men affected by prostate cancer in ADT, subjects with prostate cancer and healthy men, found a weak association between bioavailable T and verbal learning, memory and measures of cognitive flexibility. However, these associations were not independent of multiple confouders (86).

Others studies failed to find any association between FT and cognitive performance.

Wolf et al (87) tested the association between endogenous sex steroids (E2 and T) and cognition in 38 healthy older women (mean age 68 years) and 30 healthy older men (mean age 69 years). Five cognitive tests assessing verbal memory, spatial memory, verbal fluency, mental rotation, and susceptibility to interference were administered. The authors found that women having higher E2 and T levels were associated with better verbal memory. In men the only significant association was a negative correlation between T and verbal fluency (r 0.38, $P < 0.05$). The associations observed in this small study suggest that E2 is protecting verbal memory and possibly also frontal lobe mediated functions in older women. The positive findings on endogenous sex steroids and cognitive function in women were not replicated in older men.

Lessov-Schlaggar et al (88) examined the relationship between sex hormone concentrations and cognitive function in a longitudinal sample of World War II veteran twin men aged 52-70 years old. In this study no significant and independent association was found between midlife plasma T, E2, estrone, or SHBG concentrations and cognitive task measures during 10- to 16-year follow-up period.

On the contrary, higher T levels (in analyses including T and T adjusted for SHBG) were associated with larger hemispheric, frontal, and parietal regional lobe volumes and with smaller left occipital lobe volume. Additionally, higher concentration bioavailable T was associated with larger total cranial volume independent of SHBG.

Finally, Jonker et al have examined the relationship between FT levels and visuospatial ability in a sample of 450 healthy men aged 35-80 years: partecipants with lower FT levels performed worse as compared to partecipants with higher levels (89).

Intervention Studies

Few and controversial results come from intervention studies (Table 2).

T supplementation improved certain aspects of cognitive function in both young and older adults (90-95).

Janowsky et al (90) randomized 56 older men to testosterone (n = 27) or placebo (n = 29). Three months of T treatment was associated with enhanced spatial abilities, assessed by the block design test, without obvious effect on delayed recall or visual reproduction abilities.

Wolf et al (92) investigated the effects of a single testosterone depot injection on cognition in thirty healthy older men. Five days after injection, T and E2 levels were still in the supraphysiologic range. In the verbal fluency task, the placebo group, but not the T group, showed a practice effect. Therefore, the T group performed significantly worse than the placebo group. No effects of T were observed in the other verbal and spatial tasks. However, beneficial effects on spatial cognition or memory might need more time to be detected or might only occur when a less pronounced T increase is induced.

Cherrier et al (93) explored the relationship between T administration and spatial and verbal memory in a healthy older men population by using a moderate replacement dose of T. A

randomized, placebo-controlled, double-blind design was used, with 6 weeks of T treatment followed by 6 weeks of washout. Participants were healthy men aged between 50 and 80 years. An improvement in spatial memory (recall of a walking route), spatial ability (block construction), and verbal memory (recall of a short story) was observed in T group in comparison with baseline and with placebo group.

Moreover, in another study, Cherrier et al (94) examined the effects of exogenous T treatment on cognitive functioning in a group of healthy young men. Thirty-two men were randomized to receive 8 week of treatment including: 1) im T enanthate 100 mg/wk plus daily oral placebo (T); 2) im placebo/wk plus 125 g daily oral levonorgestrel (LNG); 3) im T enanthate 100 mg/wk plus 125 g daily oral LNG (T LNG); 4) im placebo/wk plus daily oral placebo. Cognitive functions were assessed at baseline and during treatment. They showed that decreased serum T levels induced by LNG and the direct effects of the progestin, adversely affects verbal memory in normal young men.

More recently, Cherrier et al have investigated the effects of T supplementation on cognition in men with Alzheimer's disease or mild cognitive impairment. 32 patients were randomized to receive weekly intramuscular injection of 100 mg T enantate (N=19) or placebo (N=13). A battery of neuropsychological tests were conducted at baseline, week 3, and week 6 of treatment and again after 6 weeks of washout. T supplementation improved spatial memory, spatial or constructional ability and verbal memory in patients with Alzheimer's disease or with mild cognitive impairment (95).

Recently, a pilot study investigated the effect of 6-month oral T supplementation in Japanese older men with mild to moderate cognitive decline. Eleven men with mean age of 81 ± 6, were assigned to take oral T undecanoate 40 mg daily for 6 month and the control group was of 13 subjects. Cognitive function was evaluated using MMSE and Hasegawa Dementia Scale, Revised (HDS-R) at baseline, and at 3 and 6 months. At 3 months, subjects who received T treatment showed a nonsignificant increase in MMSE and HDS-R scores, whereas at 6 months, cognitive scores were significantly greater than at baseline (96).

Other studies that tested the effects of T supplementation on cognition in healthy subjects without significant cognitive decline, failed to find any significant association (97-101).

In the context of relationship between multiple hormonal dysregulation and cognition it is not possible to neglect the role of estrogens, particularly E2, even in men.

Estradiol and cognitive function

The positive effects of T on cognitive parameters are at least partially explained by its aromatization into E2. E2 levels have been positively associated with cognitive tests score in healthy older women. Significant improvements in verbal recall have been reported in patients with AD after estrogen replacement treatment (102, 103). In men, exogenous estrogens improve verbal memory for a paired associate learning task, a task generally favoring women (104).

However, the studies testing the relationship between E2 and cognitive function do not only show positive results. Some studies suggest that higher E2 levels may preserve brain function (76, 105-107) while more recent studies showed no or detrimental effects of endogenous and exogenous estrogens on brain function in both women (107, 108) and men (109).

Muller M et al (109), in a population-based prospective study of 242 independently living elderly men showed that high serum levels of total and free E2 and estrone are associated with an increased risk of cognitive decline, independent of age, cardiovascular risk factors and ApoE- 4.

In the Rancho Bernardo Study, Laughlin et al in a cohort of 304 community-dwelling postmenopausal women, found that higher levels of endogenous estrone and bioavailable E2 were predictors of a greater decline in verbal fluency, cognitive flexibility and executive function. No association was found between estrogens and MMSE (110).

Other studies failed to find any association between E2 levels and cognitive performance (77, 87, 111). Le Blanc et al, in 1602 men from The Osteoporotic Fractures in Men Study (MrOS) during 4,5 years follow-up period found no association between E2 levels and cognition (111).

Despite these data, it is unclear whether T depletion or changes in E2 levels can contribute to Alzheimer's disease.

In a recent study, Rosario et al analyzed T and E2 levels in brain samples from the mid-frontal gyrus of 45 men during autopsy. They observed that men with AD exhibit significantly lower levels of T, but not of E2 in the brain. This finding suggests that T depletion, more than estrogens modifications, may contribute to the development of AD (112).

Both T and E2 are capable to stimulate the IGF-I secretion in the liver, another anabolic hormone with potential beneficial effects in the brain.

GH/IGF-I and cognitive decline

Mechanisms of neuroprotection

The activity of the Growth Hormone (GH)/IGF-I axis declines significantly with aging (113). Reduction in GH/IGF-1 activity is associated with reduced lean body mass, reduced protein synthesis, increased adiposity, and decreased bone mass. Hoffman et al (114) termed this syndrome in older individuals as the somatopause. Several investigators studied the effects of GH replacement on body composition in healthy older adults.

These studies showed increased lean body mass and decreased adipose tissue mass after GH administration (115-117). GH may also affect cognitive and emotional functioning (118). Animal and in vitro studies showed that IGF-I enhances neuronal survival and inhibits apoptosis. It exerts neurotrophic activities in the hippocampus, area involved in learning and memory processes. Finally, IGF-I may induce a reduction of

tangles, one of the hallmarks of Alzheimer's disease (119) (Figure 2).

The homologous insulin and IGF receptors are both expressed in the brain, in overlapping but distinct neuroanatomical patterns. Irrespective of insulin, IGF-I is also highly expressed within the brain and is essential for the normal brain development.

IGF-I promotes brain anabolic activity resulting in increased neuronal survival, process growth and synaptogenesis during early postnatal development. IGF-I also promotes neuronal growth and dendritogenesis by 'insulin-like' anabolic effects on glucose utilization and protein synthesis, ensuring the biosynthetic needs of the growth.

IGF-I induces GLUT4 expression and surface membrane localization in growing projection neurons. IGF-I inhibits glycogen synthase kinase 3h (GSK3h), thereby augmenting glycogen and protein synthesis in IGF-I-expressing neurons. Inhibition of GSK3h may also mediate IGF-I's neuroprotective role, since GSK3h has pro-apoptotic effects on neurons (120).

All these observations suggest that serum IGF-I necessary for building experience-dependent functional plasticity. Therefore, the decline in serum IGF-I associated with aging may contribute to cognitive loss found in aged individuals due to diminished neurogenetic rate and synaptic plasticity abilities (121).

The IGF-I influences higher brain functions through two types of processes. A first set encompasses neuroprotective mechanisms while a second type relates to cognition-specific processes. IGF-I may influence the balance in brain activity of the two main neurotransmitter systems: the inhibitory GABA and excitatory glutamate. In particular, the ratio of excitation to inhibition in the hippocampus is lower when serum IGF-I is low. This under-excitation reduce synaptic plasticity in the hippocampus in an IGF-I-dependent mechanism, and IGF-I administration is able to restore this deficit (122). These results suggest that serum IGF-I modulates glutamatergic transmission and signalling (123). Other neurotransmitters are modulated by IGF-I. These include acetylcholine, which is a major determinant of cognition, GABA and glycine. IGF-I is an important modifier of neuronal excitability, modulating the size of the receptive field of target neurons. Its effects on numerous types of membrane channels and neurotransmitter receptors likely explain these actions. A more radical action on synaptic plasticity by IGF-I is through maintenance of synapse number (124).

Observational studies

Few cross-sectional epidemiological studies tested the relationship between IGF-I levels and cognitive function (Table 3). In childhood GH deficiency, a state characterized by low total IGF-I levels, there is an higher prevalence of cognitive impairment (127-132). Healthy centenarians with a higher serum total IGF-I and total IGF-I over IGF-binding protein-3 (IGFBP-3) ratio, an index of IGF-I bioactivity, had less cognitive impairment (125). In two other small studies of older subjects, high serum total IGF-I levels were associated with better cognitive performance (126, 127).

Significant cognitive deficits have been reported in GH-deficient (GHD) children (128, 129). Furthermore, impaired psychosocial functioning and personality development have been documented in GHD children.

These findings have been replicated in GHD adults (118, 130-132).

The first study reporting on IGF-I levels and cognitive functioning in healthy elderly people was performed in 1995 (133). The authors studied the association between IGF-I and tests of mental processing speed and executive functioning in 104 men with a mean age of 75 years. They found no significant association between IGF-I levels and cognition after correcting for age. However, closer examination of their results reveals a significant association between IGF-I levels and a measure of mental processing speed (the Digit Symbol Substitution Test) and no significant association with executive functioning assessed by the Trail making test B.

Deijen et al (130) demonstrated subnormal memory performance in GHD adults. Zelissen et al (132) conducted a profile analysis on the results of a number of neuropsychological tests administered to GHD adults. They report deficits in memory retrieval of verbal information, compared with the normal range.

Two other studies found similar associations between IGF-I and cognitive function, either using a coarse screening test of general cognitive ability, the MMSE (127) or a detailed neuropsychological assessment (126). More specifically, Aleman et al (126) found strong associations between IGF-levels and performance on the Concept Shifting Task, a test of set shifting ability, which is an aspect of executive functioning. However, both studies included small samples. By contrast Dik et al (134) collected information on processing speed, memory, fluid intelligence and MMSE, IGF-I in 1318 elderly people aged 65–88 years. Although correlations across the whole sample were not significant, IGF-I levels below 9.4 nmol/l were negatively associated with both the level and decline of information processing speed.

Thyroid function and Cognitive Impairment

Changes in thyroid function participate in the overall readjustment of the hormonal milieu occurring during aging (50). The prevalence of overt and subclinical hypothyroidism in older populations is about 20% (135). Subclinical hyperthyroidism also increases with aging, with a prevalence of 1-2 % in iodine-sufficient areas (136, 137) and 7-8 % in iodine-deficient areas (137). Whether subclinical thyroid dysfunction affects health and functional status in older persons is still unclear (138, 139).

Neurobiological actions

The thyroid hormone (T3) is essential for the development and maturation of central nervous system (CNS). T3 regulates the axonal and dendritic growth, synapse formation, myelination, cell migration, and proliferation of specific glial and neuronal populations (140).

T3 treatment protects astrocytes from glutamate toxicity (141). Astrocytes have a crucial role in glutamate clearance and T3 promotes up-regulation of the astrocytic glutamate transporters GLAST and GLT-1, resulting in increased glutamate uptake and therefore increased astrocytic and neuronal viability against glutamate toxicity. Moreover, thyroid hormone induces cerebellar astrocyte secretion of growth factors, such as basic fibroblast growth factor (bFGF) and epidermal growth factor (EGF), which promote in situ astrocyte proliferation, adhesion, and extracellular matrix (ECM) production and organization. The growth factors secreted by astrocytes may also induce neuronal growth with paracrine pathway (140).

Neverthless, studies suggest that not only hypothyroidism, but also hyperthyroidism may cause cognitive impairment in older subjects. The mechanism by which clinical or subclinical hyperthyroidism negatively affects cognition remains uncertain.

Elevated thyroid hormones may increase oxidative stress and apoptosis, leading to neuronal damage or death. In addition, TRH has been shown to increase local acetylcholine synthesis and release. Therefore, the decline in TRH secretion induced by hyperthyroidism, may lead to an impairment of brain acetylcholine metabolism. High thyroid hormone levels may have a two-fold negative effect on neuronal cells, namely a direct metabolic damage and a signalling damage due to impairment of acetylcholine release (142).

Epidemiological studies that have investigated the relationship between subclinical hypothyroidism (143, 144) or subclinical hyperthyroidism (135, 145) and impaired cognition have reported inconsistent findings. The lack of consistency between studies may depend on different assay methods, different diagnostic criteria for thyroid dysfunction, and different assessments of cognition. Moreover, many of these studies were clinical case series that may not be representative of the general population.

Subclinical Hyperthyroidism

As recently summarized by Etgen T et al, the relevance of subclinical thyroid dysfunction in the development of mild cognitive impairment or dementia is controversial (146).

Subclinical hyperthyroidism consists of a subnormal basal TSH level, peripheral thyroid hormones (T3 and T4) within normal range and attenuated TSH response to thyrotropin-releasing hormone (TRH) stimulation.

In the Rotterdam Study, a population-based prospective trial involving 1843 participants aged >55 years, participants with subclinical hyperthyroidism at baseline had increased risk of dementia (RR: 3.5, 95% CI: 1.2–10.0) after 2 years (145). In the Birmingham Elderly Thyroid Study which included 127 participants with subclinical hyperthyroidism no association between subclinical hyperthyroidism and cognition was detected after controlling for several confounders (147).

In the InCHIANTI study was investigated the relationship between subclinical hyperthyroidism and impaired cognitive function measured by MMSE. Subclinical hyperthyroidism was significantly associated with low MMSE independent of chronic heart failure, smoking, and physical activity (148). In another recent study, Quinlan et al analyzed 43 cases with mild cognitive impairment (MCI) and 26 healthy controls. Among those with MCI, total T3 levels were inversely associated with cognitive performance in domains of memory, visuospatial and executive functions (149).

Subclinical Hypothyroidism

Hypothyroidism has been considered cause of reversible cognitive impairment. Subclinical hypothyroidism is defined as an elevated serum TSH concentration in the presence of a normal serum free T4 and T3 levels. The association between cognitive impairment and thyroid dysfunction has been reviewed in recent meta-analysis without any definitive conclusion (150).

The effect of thyroxine replacement in elderly subjects with subclinical hypothyroidism was recently tested in a clinical trial conducted in 94 subjects (57 females, 37 males). In this study Parle et al (151) did not show any significant change in measures of cognitive function (assessed by MMSE, SCOLP and trail making test) over time (12 months) and no difference between T4 supplementation group and placebo group. However, MMSE at baseline was such normal (28.2 ± 2.0) in both placebo and active group.

By contrast, Jaeschke et al in a randomized controlled trial of 37 subjects (9 men and 28 women) over 55 years of age with subclinical hypothyroidism reported an improvement in composite memory score after T4 treatment (152). Moreover, Jorde et al in 69 subjects (37 men, 32 women) affected by subclinical hypothyroidism (SHT), defined as serum TSH of 3.5–10.0 mIU/liter, found a negative association between serum TSH levels and Trial-Making test A and a positive association between free T4 concentration and word association test. In these subjects T4 substitution for 1 year had no effect on any of the fourteen tests of cognitive function (144).

According to the available data no definitive conclusions on the role of thyroid dysfunction in the cognitive impairment can be extrapolated. The effect of thyroid replacement on cognitive function should be investigated in future clinical trials.

Multiple hormonal dysregulation and Cognition: a "theoretical hypothesis"

We summarized the current literature available on the relationship between the single hormonal derangement, namely

anabolic hormones and thyroid dysfunction, and the impairment in specific cognitive domains in older men. The results are conflicting and consistent with the other studies that have tested the impact of the single hormonal change on frailty and mortality (139, 153).

Since cognitive impairment and dementia, similarly to physical frailty, are the results of multiple factors, such as health status, socioeconomic factors, life-style, and genetic factors, this is not surprising. According to the multifactorial origin of dementia, multiple hormonal dysregulation rather than a single hormonal derangement, is more likely to be associated with the development of cognitive impairment in the elderly.

Therefore we underline the need to consider the parallel changes in multiple hormonal axes (PADAM, somatopause, adrenopause, thyroid dysfunction) to better address the role of hormonal dysfunction in the development of cognitive impairment in men.

This paradigm could also be further expanded to include additional networks outside the endocrine system, most notably inflammation, which can affect and be affected by multiple hormones. Despite the unclear therapeutic implications of the paradigm of multiple hormonal dysregulation, these findings suggest to move beyond the "one deficiency, one replacement" model into an integrated approach to multiple hormonal dysregulation.

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