Review

Stress hormones, sleep deprivation and cognition in older adults

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\textbf{A B S T R A C T}

Cognition can be deteriorated in older persons because of several potential mechanisms including the hormonal changes occurring with age. Stress events cause modification in hormonal balance with acute and chronic changes such as increase in cortisol and thyroid hormones, and simultaneous alterations in dehydroepiandrosterone sulphate, testosterone and insulin like growth factor-1 levels. The ability to cope with stress and regain previous healthy status, also called resiliency, is particularly impaired in older persons Thus, stressful conditions and hormonal dysregulation might concur to the onset of cognitive impairment in this population.

In this review we address the relationship between stress hormones and cognitive function in older persons focusing on the role of one of the main stress factors, such as sleep deprivation (SD).

We extracted and cross-checked data from 2000 to 2013 March and selected 112 full-text articles assessed for eligibility. In particular we considered 68 studies regarding the contribution of hormonal pathway to cognition in older adults, and 44 regarding hormones and SD both in rats and humans.

We investigated how the activation of a stress-pattern response, like the one evoked from SD, can influence cognitive development and worsen cognitive status in the elderly.

We will show the limited number of studies targeting the effects of SD and the consequent changes in stress hormones on cognitive function in this age group.

We conclude that the current literature is not strong enough to give definitive answers on the role of stress hormonal pathway to the development of cognitive impairment in older individuals.

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1. Introduction

1.1. Hormonal changes with aging and after stressful conditions

Aging is marked by subtle incremental changes in all biological systems, including endocrine ensembles.

In older people generally there is a prevalence of catabolic hormones such as thyroid hormones, thyroxine (T4) and triiodothyronine (T3), and cortisol. These hormones known as “stress hormones”, are involved in the genesis of stress-related conditions implying the activation of adrenergic axis.

The autonomic sympathetic-adrenal system and the hypothalamic–pituitary–adrenal (HPA) axis are considered to be the main neuroendocrine systems involved in the integrated stress response. The activation of the body’s stress systems and the release of stress hormones allows us to adapt and survive in a continuously changing and challenging environment. These stress hormones not only support metabolic processes and physical activity under acute stress but also affect brain function, cognition and mood [1].

A challenge provokes the activation of several mechanisms related to stress response, with the increase of epinephrine and norepinephrine, cortisol, and thyroid hormones. The age-related changes in stress hormones are paralleled by the profound decline of anabolic hormones dehydroepiandrosterone and its sulfate derivative (DHEA and DHEAS), testosterone, estradiol, growth hormone (GH) and insulin growth factor-1 (IGF-1) concentrations resulting in a net increase of catabolic/anabolic ratio.

After a challenge there is a recovery phase with a return to a basal condition of the genesis of a new level of balance. The age-related changes in the pattern of HPA response to challenge influence the individual’s resiliency in the on-going homeostatic regulatory processes of the body [2]. Aging has been more often associated with an hyper-activation of HPA axis in response to a stimulus. Interestingly, the ability of HPA axis to recover from a challenge (resiliency), is more affected than the rate of the initial response or the magnitude of the response [3,4]. The changes of the HPA function occurring with age show a heterogeneous pattern, with some individuals maintaining a pattern similar to those of younger subjects and others experiencing substantial changes with aging. Despite this heterogeneity, the response of HPA axis to stress with age becomes less resilient and less sensitive to the negative feed-back signals of glucocorticoids (GC). As consequence, the altered HPA axis as part of multiple hormonal dysregulation occurring with age, may exert an important role of the development of cognitive impairment in the elderly. If age seems to be the most relevant pathogenic factor for the altered HPA sensitivity toward the steroid inhibition, the occurrence of neurodegenerative cognitive impairment could play an additional role leading to a vicious cycle “HPA axis hyper activation-cognitive impairment”.

The mechanism by which aging influences pituitary function is complex. Comorbidities and adaptations that accompany aging strongly modify the pituitary secretion. In particular, the effects of age on endocrine axes depend on hormone type, inhibitor or stimulus tested, concomitant morbidities, such as obesity, diabetes mellitus, reduced nutritional status, medication use, underlying stress, body composition and gender [5].

Aging-related changes in the HPA axis are more prominent in women than in men, and in patients with Alzheimer disease or major depression.

When homeostatic mechanisms maintaining neuronal function are overwhelmed, the reactive processes must be set in motion.

Moreover, there are changes of the adrenocortical steroidogenetic pattern occurring during aging, with a relative constancy or even a trend toward an increase of cortisol secretion and a progressive age-related decline of the androgen secretion. Both cortisol and DHEA affect metabolism, and the balance between these two hormones has been considered as a marker of catabolic/anabolic status, relating to frailty [6]. The adrenocortical secretory pattern undergoes qualitative and quantitative changes with aging. In particular, beside a relatively steady level of cortisol secretion, there is a trend toward higher plasma levels during evening- and night-time [7].

DHEA and DHEAS production dramatically decrease with aging, and during the eighth decade is only 10–20% of the maximal value usually recorded at 30 years. The imbalance between glucocorticoid and androgen secretions may be caused by the age-related selective impairment of the “zona reticularis” of the adrenal cortex, the sole source of DHEA and DHEAS (Fig. 1).

In fact, the complex vascular supply of the adrenal gland, characterized by communications between the cortex and medulla with reciprocal functional influences, is the anatomical basis for the peculiar susceptibility of the zona reticularis to microhemorrhagic events and vascular necrotic damage, which in turn is responsible for the age-related decline in androgen secretion [8].

As consequence, an imbalance between GC and androgens occurs in the elderly. It is well known that cortisol and DHEAS have opposite activities both at peripheral and central levels.

Aging is accompanied by a decrease in pulsatile GH secretion, IGF-1 levels and an increase in IGFBP-1 and IGFBP-3.
The age-related decrement in pulsatile GH secretion, and thereby IGF-1 production, is due to smaller GH pulses, which reflects diminished secretory-burst mass with no change in pulse frequency.

TSH levels tend to rise with age; however, there are confounding issues in elderly adults that might inhibit or potentiate TSH secretion. Typically, serum T4 levels are preserved in healthy aging adults, while reduced serum T3 concentrations occur in aging individuals of both sexes.

Many observational studies in healthy older individuals, which took into account common confounders, have revealed also an age-dependent decline in serum TSH and FT3 and an age-dependent increase in rT3 with maintenance of stable serum FT4 levels. The mechanisms responsible for this age-related decline in serum TSH have not been fully examined. One hypothesis suggests an age-related reduction in the secretion of pituitary TSH and/or hypothalamic TRH, due to increased pituitary sensitivity to peripheral T3/T4 negative feedback. Therefore, the reduced degradation and clearance of T4 and T3 may lead to reduced activity of thyroid axis.

Although data from heterogeneous populations suggest that T3 levels decline with age, studies of selected healthy people indicate that T3 levels are unaffected by aging. TSH may increase or decrease with age in relation to the iodine intake; however, the very elderly (octogenarians and beyond), may have a mild TSH decrease.

In a study conducted in 59 subjects (7 males and 52 females) aged 100–107 years, aimed at evaluating the neuroendocrine features of centenarian subjects, the authors found that both physiological aging and extreme longevity do not significantly affect thyroid function. Only peripheral changes of thyroxine metabolism occur, leading to an increased rT3 production which might be considered a saving energy response.

1.2. Potential mechanisms by which hormonal dysregulation affects cognitive function

Stress hormones are regarded as factors that can interfere with cognitive function, including memory [11]. Chronic elevation of stress hormones, mainly cortisol, affects cognitive function through various mechanisms including neuronal damage (degeneration and death) in the hippocampus area [12].

The neurotoxic effects of cortisol are counterbalanced by DHEAS, which has anti-gluocorticoid activity and plays a protective role in the neuronal structure and function. Therefore, the impaired DHEAS secretion, together with the relative increase of cortisol, results in an enhanced exposure of the central nervous system to the neurotoxic effects of GC.

Healthy elderly subjects and demented patients, particularly those with AD, had significantly higher cortisol levels at night time, i.e. at the moment of the maximal sensitivity of HPA axis to stimulatory or inhibitory inputs than younger individuals. In these individuals there is also an age- and disease-dependent reduction of DHEAS secretion. Thus the cortisol to DHEAS molar ratio is significantly higher in healthy old subjects, and even more in demented patients, when compared to young controls. This ratio has been significantly linked to both age-related phenomena including cognitive impairment. Finally, the quantitative and qualitative changes of the adrenal secretory pattern were significantly correlated with the decline of hippocampal volumes, measured by magnetic resonance imaging. In conclusion, several lines of evidence suggest a pathogenic role of stress hormones in the occurrence and progression of cognitive disorders in elderly subjects. The consequent hippocampal neuronal impairment may in turn be responsible for the continuous activation of HPA axis and the increased hypothalamic expression of vasopressin and corticotropin releasing hormone [20].

The increase of thyroid hormones is another important component of stress response. The mechanisms by which clinical or subclinical hyperthyroidism negatively affects cognition remain uncertain. Elevated thyroid hormones may increase oxidative stress and apoptosis, leading to neuronal damage or death. 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 and signaling damage due to impairment of acetylcholine release [13].

Stress is also accompanied by changes in anabolic hormones. DHEA and DHEAS are the major secretory products of the adrenocortical gland, and are produced in larger quantities than any other steroid hormone. While the immediate effects of DHEA and DHEAS have not yet been attributed to a specific receptor, some of its protective effects may result from its conversion to sex steroids.

Thus, an 80% decline in DHEA from the adenals may be greatly enhancing cognitive deficits due to the decline in sex steroid production from the gonads.

Injection of DHEAS into the brains of mice improved long term memory [14]. DHEAS may act directly on the hippocampus where has been shown to enhance the magnitude of hippocampal primed burst [15] and induce long term potentiation [16]. Low DHEA and DHEAS levels in older adults may make these subjects more vulnerable to the damaging effects of cortisol [17]. There is increasing evidence that sex hormones, such as estradiol and testosterone, can exhibit protective properties in the brain [18] especially in those regions altered during Alzheimer disease (AD). These areas of brain include the hippocampus and cortical regions with high density of androgen receptors and thus particularly sensitive to testosterone. Testosterone may modulate neuronal damage caused by oxidative stress and may reduce neuronal apoptosis or self programmed
2. Methods

As a basis for this review, we performed a systematic search using MEDLINE via PubMed, the journal article database for the International Library of Medicine, using keywords and limiting the output to studies performed on humans and written in English.

We have extracted and cross-checked data from 2000 to 2013 March for the specified outcomes in order to analyze the relation between these stress hormones and cognitive impairment, and a particular case of stressor which is widespread in older people: sleep loss.

Any discrepancies were discussed and resolved.

We selected from 871 records 112 full-text articles assessed for eligibility based on these keywords: sleep deprivation, stress hormones, cognition, older adults/elderly man by searching in the electronic database Pubmed and Medline. Our first selection was based on the review of title and abstract. We considered 68 studies regarding hormones pathway and cognition in older adults, and 44 regarding hormones and sleep deprivation both in rats and in humans.

Keywords: sleep deprivation, stress hormones, cognition, older adults/elderly men

Electronic database: Pubmed-Medline

Period: since 2000 to 2013

3. Cortisol and cognitive function in elderly

HPA axis hyperactivity, characterized by increased cortisol levels, is a common phenomenon observed during stressful conditions and has been related with aging related phenomena [31]. In Table 1 we tried to summarize the observational and intervention studies that have tested the relationship between cortisol levels and cognitive function (Table 1).

3.1. Observational studies

Few studies have examined the relationship between cortisol levels and greater cognitive impairment in older persons. In particular, Lupien and coauthors [32] collected data from a population of 51 older individuals (range 60–90 years), followed over a period of 3–6 years for yearly 24-h cortisol assessment (The Douglas Hospital Longitudinal Study of Normal and Pathological Aging). Chronic exposure to elevated levels of GC was related to both memory impairments and a smaller volume of the hippocampus.

In another study, Geoffroy obtained two morning salivary cortisol sample (45 min after waking and 3 h later) from numerous men and women with mean age of 45 years, and administered standardized tests assessing immediate and delayed verbal memory, verbal fluency and speed of processing at 50 years. Higher cortisol levels in late morning at 45 years were associated with poorer verbal memory and fluency at 50 years, with a contribution from childhood cognition to these associations [33].

Karlamangla et al. investigated in a sample of 538 older men and women the association between overnight urinary cortisol excretion, a measure of resting basal cortisol levels, and the risk, over 7-year follow up, of decline in cognitive performance. The authors found that urinary cortisol excretion at the start of the study was positively and independently associated with the risk of incident cognitive impairment over the following 7 years (OR 2.34, 95% CI 1.07–5.14) [34]. However, as reported by Fenske in a letter to the Editor, this study was affected by some limitations including the not precise urine collection and the lack of sufficient data about urine volume and control of fluid intake [35].

3.2. Intervention studies

Among the intervention studies shown in Table 1, the only great study is by Lupien et al. who found that in older persons with moderate circulating levels of cortisol, memory performance can be acutely modulated by pharmacological manipulations of GCs [36]. In this within-subject double-blind experimental model, the authors first induced a chemical reduction of GCs by administration of metyrapone, and then restored baseline circulating GC levels after infusion of hydrocortisone. Memory performance of participants under each of these conditions was compared to that measured on placebo day. Individuals with mean hourly levels above 8.5 g/dl were included in the increasing/high cortisol group, and individuals with levels lower than 8.5 g/dl were included in the increasing/moderate group. The results confirmed the chronic exposure hypothesis of memory impairments in the increasing/high cortisol group. Metyrapone treatment did not have any effect on memory performance in this group. However, replacement of baseline GC levels by subsequent infusion of hydrocortisone negatively and significantly affected memory. Surprisingly, in another group of subjects, that can be defined increased/moderate cortisol group, the inhibition of cortisol...
production was significantly associated with impaired memory, and this deficit was completely reversed by hydrocortisone therapy.

Despite the potential strong link between stress activation, HPA hyperactivity and cognitive function, only few longitudinal studies have tested the role of higher cortisol levels in the development of cognitive impairment in older individuals [32,33].

Although some authors suggest a predictive role for rising serum cortisol and urinary cortisol excretion in cognitive alterations [34], no definitive conclusions can be drawn based on these data [35]. Pharmacological treatments aimed at preventing GC-induced cognitive impairments, could potentially positively affect cognition and memory in elderly. Nevertheless, there are not enough intervention studies to support this hypothesis. Lupien et al. [36] demonstrates that the chronic exposure to high cortisol levels causes memory impairments, and acute manipulation of GC is less important in these subjects than treatment of the increasing/moderate cortisol group. Thus, a chronic exposure to elevated levels of GC seems to be related to both memory impairments and a smaller volume of the hippocampus, and this condition should be avoided.

4. DHEAS and cognitive function in the elderly

Several human studies have investigated the relationship between DHEA-DHEAS and the age-related cognitive impairment (Table 2).

4.1. Observational studies

No significant association between DHEAS and cognition has been reported in men in two large prospective cohort studies: the Baltimore Longitudinal Study of Aging and the Massachusetts Male Aging Study (MMAS).

The first study did not support the hypothesis that decline in endogenous DHEAS concentration contributes to cognitive decline in elderly community-dwelling men, and although both DHEAS concentrations and neuropsychological performance clearly decrease with age, these phenomena appear to be independent of each other [37]. In the second study, higher DHEA and DHEAS were initially predictors of better cognitive function including MMAS participants, but the effect is not independent of age and other covariates [38].

Another cross-sectional study in 2001 conducting in 370 male and female nursing home residents demonstrated that among males, higher sex hormone levels are associated with better ADL performance, and lower levels of these hormones are significantly associated with greater dependency. On the contrary, in women higher levels of estrone and DHEAS were directly associated with ADL dependency suggesting a gender effect in the relationship between DHEAS and functional independence [39].

Plasma DHEA and DHEAS levels were independently related to higher basic ADL in older women aged 70–93 years with functional decline [40].

In spite of these results, other studies show that in older men and women endogenous DHEAS levels are associated with better cognitive ability.

Susan R. Davis by using a cross-sectional design tested whether women with higher circulating levels of DHEAS exhibit better performance in terms of executive function, concentration, and working memory [41].

In another study based on the INCHIANTI Study, Valenti et al. investigated whether DHEAS levels are associated with presence and development of lower cognitive function. The authors showed a significant and positive association between DHEAS and cognitive function, assessed by MMSE test, independently of age and other potential confounders. Moreover, low DHEAS levels predict accelerated decline in MMSE score during the 3-year follow-up period [42].

More recently, Forti and coauthors investigated the association of serum DHEAS with frailty in 416 men and 504 women aged ≥65 years from an Italian prospective population-based cohort study. Lower DHEAS levels were associated with incident frailty in older men and with fatal and nonfatal frailty-related adverse outcomes in older women [43].

4.2. Intervention studies

The encouraging data coming from observational studies led in the recent years to testing the fascinating hypothesis that DHEA supplementation may improve memory function and other cognitive domains in older individuals [44].

However, most of the clinical studies with DHEA supplementation failed to provide convincing evidence in support of this hypothesis [45]. In healthy elderly populations, neither acute administration nor chronic (up to 12 months) DHEA supplementation, has shown significant clinical benefit in memory after treatment [46–48], and some studies have even observed a negative effect on this specific cognitive domain [49]. Longer-term DHEA supplementation was evaluated by Nair in 2006 with
Table 2
Observational and intervention studies investigating the effects of DHEAS on cognitive function.

<table>
<thead>
<tr>
<th>Author reference</th>
<th>Year</th>
<th>Design</th>
<th>Population</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observational</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moffat et al. [37]</td>
<td>2000</td>
<td>Longitudinal</td>
<td>883m 22–91y</td>
<td>31y</td>
<td>DHEAS decline with age independently</td>
</tr>
<tr>
<td>Fonda et al. [38]</td>
<td>2005</td>
<td>Cross sectional</td>
<td>981m 48–80y</td>
<td>–</td>
<td>The effects of DHEAS on cognition are not significant</td>
</tr>
<tr>
<td>Breuer et al. [39]</td>
<td>2001</td>
<td>Cross sectional</td>
<td>64m 306w</td>
<td>–</td>
<td>Higher DHEAS are associated with better ADL performance in male, the opposite is in females</td>
</tr>
<tr>
<td>Fukuai et al. [40]</td>
<td>2009</td>
<td>Cross sectional</td>
<td>108m 100w 70–95y</td>
<td>–</td>
<td>Sex hormones, included DHEA, have sex-specific associations with physical and neuropsychiatric functions</td>
</tr>
<tr>
<td>Davis et al. [41]</td>
<td>2008</td>
<td>Cross sectional</td>
<td>295w 21–77y</td>
<td>–</td>
<td>DHEAS levels are associated with executive function, concentration, and working memory</td>
</tr>
<tr>
<td>Valenti et al. [42]</td>
<td>2009</td>
<td>Cross sec/longitudinal</td>
<td>410m 345w &gt;65y</td>
<td>3y</td>
<td>Association between DHEAS and cognitive function, assessed by MMSE test</td>
</tr>
<tr>
<td>Forti et al. [43]</td>
<td>2012</td>
<td>Longitudinal</td>
<td>416m 504w &gt;60y</td>
<td>8y</td>
<td>DHEAS is associated with incident frailty in older men and women</td>
</tr>
<tr>
<td>Intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Legrain et al. [45]</td>
<td>2003</td>
<td>Double blind RCT</td>
<td>280m and w &gt;60y</td>
<td>DHEA 50–100 mg/day</td>
<td>No benefit after DHEA treatment in healthy men</td>
</tr>
<tr>
<td>Arlt et al. [46]</td>
<td>2001</td>
<td>Double blind RCT</td>
<td>22m 50–69y</td>
<td>DHEA 50 mg/day</td>
<td>No benefits of DHEA supplementation for memory and well-being</td>
</tr>
<tr>
<td>van Niekerk et al. [52]</td>
<td>2001</td>
<td>Double blind RCT</td>
<td>46m 60–80y</td>
<td>DHEA 50 mg/day</td>
<td>DHEA supplementation was associated with no significant changes in physical or mental components</td>
</tr>
<tr>
<td>Nair et al. [47]</td>
<td>2006</td>
<td>Double blind RCT</td>
<td>87m 57w &gt;60y</td>
<td>DHEA 75–50 mg/day</td>
<td>No differences between DHEA treatment and placebo in cognitive function</td>
</tr>
<tr>
<td>Kritz-Silverstein et al. [48]</td>
<td>2008</td>
<td>Double blind RCT</td>
<td>110m 115w 55–85y</td>
<td>DHEA 50 mg/day</td>
<td>DHEA does not significantly improve cognitive performance</td>
</tr>
<tr>
<td>Wolkowitz et al. [51]</td>
<td>2003</td>
<td>Double blind RCT</td>
<td>58m and w 55–85y</td>
<td>DHEA 50 mg/day</td>
<td>DHEA supplementation may have beneficial effects on cognitive function and ADL</td>
</tr>
<tr>
<td>Yamada et al. [53]</td>
<td>2010</td>
<td>No RCT</td>
<td>27w 65–90y</td>
<td>DHEA 25 mg/day</td>
<td>DHEA administration produces no beneficial effects on cognitive performance</td>
</tr>
<tr>
<td>Merritt et al. [54]</td>
<td>2012</td>
<td>Double blind RCT</td>
<td>48w 55–80y</td>
<td>DHEA 50 mg/day</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

m = men; w = women; RCT = randomized controlled trials; DHEA-S = Dehydroepiandrosterone-sulphate; ADL = activities of daily living; MMSE = Mini Mental State Examination.
administration of two doses (50 mg/day in women and 75 mg/day in men) over 2 years, [47] and by Kritz-Silverstein in 2007 with one dose (50 mg/day) for 1 year [48].

While one of the entry criteria for Nair’s study was low baseline DHEA levels, this criterion was not applied by Kritz-Silverstein et al. in order to enroll a more generally representative sample of older people. There was no evidence that either dosage of DHEA (50 mg/day, 75 mg/day) improved cognitive function or quality of life, physical or mental function [50].

DHEA supplementation has not also shown any benefit in the treatment of Alzheimer’s disease. A randomized, double-blind, placebo-controlled study regarding DHEA treatment of Alzheimer’s disease concluded that DHEA did not significantly improve cognitive performance or overall ratings of change in disease severity [51].

The study of van Niekerk did not provide support for beneficial effects of short term DHEA supplementation on cognition or well-being in normal older men [52].

As result of the study of Yamada et al., 25 mg daily administration of DHEA for 6 months in elderly women with mild to moderate cognitive impairment improved cognitive function and maintained basic ADL, compared to the control group; among the cognitive domains, DHEA significantly improved verbal fluency [53].

In the recent study of Merritt, DHEA administration produced no beneficial effects on cognitive performance in DHEA group, but surprisingly a strong positive correlation between DHEA levels and performance on digit span forward/backward and verbal span forward only in the placebo group [54]. Low DHEAS levels seem to be more robustly associated with incident frailty and frailty-related adverse outcomes [43]. Only Yamada’s one [53] concluded that DHEA supplementation may have beneficial effects on cognitive function and ADL, while others have opposite results showing no benefit with DHEA treatment [41,45,47,48,51,52,54].

Correlations between endogenous DHEA concentrations and cognitive ability have yet to be convincingly demonstrated during normal aging. Other studies are needed to be performed to understand the relative efficacy or inefficacy of DHEA replacement therapy in humans, especially in elderly.

In conclusion, human data are not consistent enough to support a role of DHEA and DHEAS decline in the age-related cognitive impairment. Further studies are needed to fully understand the benefits of DHEA supplementation on cognitive function.

5. Testosterone and cognitive function in the elderly

Table 3 shows the studies that have investigated the effects of endogenous and exogenous sex hormones, like testosterone, in older people, to improve the cognitive function or to counteract the age-related cognitive decline.

5.1. Observational studies

Lower free testosterone concentration could lead to a faster decline in cognitive function in elderly Japanese men who already show cognitive impairment [55].

Matousek et al. reported curvilinear associations between both free and bioavailable testosterone levels and working memory function in a population of 54 men ranging from 61 to 77 years of age. No other relationships were evident between either estradiol or testosterone levels and any of the other cognitive functions evaluated [56].

In a more numerous population of community-dwelling older men, Yap found that serum concentration of free testosterone contributes to the modulation of cognitive function in older men, independently of age, mood and physical comorbidity. The relationship between androgen status and cognitive performance is determined either by circulating free testosterone or by an interaction between testosterone and SHBG, but not by either total testosterone or SHBG in isolation [57].

Yaffe and coworkers found in white and black older women and men a significant association between bioavailable estradiol and cognitive decline which was stronger in women than men, but did not differ between whites and blacks [58].

However, the excess of testosterone is also linked to adverse cognitive outcomes, as demonstrated in the study of Ryan et al. a population of 148 women, where a relative androgen excess in midlife was negatively associated with performance on tasks of semantic and verbal episodic memory [59].

On the contrast, LeBlanc in 1602 men of Osteoporotic Fractures in Men Study (MrOS) where sex steroid levels were measured by Mass Spectrometry (MS) at baseline and 2623 MrOS participants with sex steroids measured by RIA, found that free-testosterone and free-estradiol levels did not predict cognitive function 4.5 years later or cognitive performance change over that time period [60]. Similarly Muller et al. failed to find any significant association between testosterone levels and the decline in MMSE in a population mainly composed of hypogonadal men [61].

5.2. Intervention studies

Cherrier et al. completed a number of double blind placebo-controlled randomized clinical trials examining testosterone supplementation and cognition in elderly eugonadal men.

Participants were randomized to receive weekly IM injections of definite doses of testosterone enanthate or placebo for 6 weeks. These studies showed significantly improved memory [62,64] and visuo-spatial function [62,63] in testosterone compared to placebo groups.

Moreover, Cherrier et al. have investigated the effects of testosterone 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 testosterone enanthate (N = 19) or placebo (N = 13). Testosterone supplementation improved spatial memory, spatial or constructional ability and verbal memory also in these patients [65]. In another double-blind, randomized, placebo-controlled trial of 237 healthy men aged 60 and 80 years with a baseline testosterone level lower than 13.7 nmol/L, supplementation with 80 mg of T undecanoate orally twice daily for 6 months resulted in increased lean body mass and decreased fat mass. No significant difference was observed in verbal memory, executive function or visuo-spatial performance [66].

However, there was a remarkable number of flaws in the methodology of this paper. Testosterone concentration did not significantly increase in the supplementation group, but did in the placebo group [67].

In contrast with the findings in eugonadal men, studies giving testosterone to hypogonadal men produced overall no effect on cognition. Thus, it seems that hypogonadal men are less likely to benefit from testosterone treatment in terms of improvement in cognitive function [68].

One pilot study without placebo was performed by Cherrier et al. in 2003 to assess possible changes in cognition in hypogonadal men receiving testosterone gel for 180 days (n = 12) or older hypogonadal men under dehydrotestosterone (DHT) gel for 90 days (n = 9). The testosterone supplementation group showed improved verbal memory and those in the DHT gel study better spatial memory. However the small sample size and the absence of control group were significant limitations in this study [69].

In a better powered randomized controlled trial involving 67 hypogonadal men receiving transdermal testosterone patches daily for 12 months, Kenny and collaborators found no
Table 3
Observational and intervention studies investigating the effects of Testosterone on cognitive function.

<table>
<thead>
<tr>
<th>Author reference</th>
<th>Year</th>
<th>Design</th>
<th>Population</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matousek et al.</td>
<td>2010</td>
<td>Cross sectional</td>
<td>54m, 61–77y</td>
<td>–</td>
<td>A suggestion of optimal T level on tasks of executive/frontal lobe functioning</td>
</tr>
<tr>
<td>Yeap et al.</td>
<td>2008</td>
<td>Cross sectional</td>
<td>2932m, 70–89y</td>
<td>–</td>
<td>Positive but weak association between FT and TT and global cognition</td>
</tr>
<tr>
<td>Ryan et al.</td>
<td>2012</td>
<td>Cross sec/longit</td>
<td>148w, 56–67y</td>
<td>2y</td>
<td>E and T are associated with memory abilities</td>
</tr>
<tr>
<td>Nagai et al.</td>
<td>2012</td>
<td>Longitudinal</td>
<td>52m, 65–87y</td>
<td>3y</td>
<td>T concentration is an independent predictor of decrease in MMSE score</td>
</tr>
<tr>
<td>LeBlanc et al.</td>
<td>2010</td>
<td>Longitudinal</td>
<td>1602MS, 2633RIA, &gt;65y</td>
<td>4.5y</td>
<td>No association between cognition and T or E</td>
</tr>
<tr>
<td>Muller et al.</td>
<td>2009</td>
<td>Longitudinal</td>
<td>242m, 73–91y</td>
<td>4y</td>
<td>No protective effect of T against cognitive decline</td>
</tr>
<tr>
<td>Yaffe et al.</td>
<td>2006</td>
<td>Longitudinal</td>
<td>435mn, 357w, 70–79y</td>
<td>2y</td>
<td>Endogenous sex hormones may play an important role in the maintenance of cognitive function</td>
</tr>
</tbody>
</table>

Intervention

<table>
<thead>
<tr>
<th>Author reference</th>
<th>Year</th>
<th>Design</th>
<th>Population</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cherrier et al.</td>
<td>2001</td>
<td>Double blind RCT</td>
<td>25m, 50–80y</td>
<td>100 mg TE, 6 weeks</td>
<td>Short-term T administration enhances cognitive function</td>
</tr>
<tr>
<td>Cherrier et al.</td>
<td>2004</td>
<td>Double blind RCT</td>
<td>25m, 50–80y</td>
<td>100 mg TE, 6 weeks</td>
<td>Improves spatial ability, spatial and verbal memory, verbal fluency and attention</td>
</tr>
<tr>
<td>Cherrier et al.</td>
<td>2007</td>
<td>Double blind RCT</td>
<td>57m, 50–90y</td>
<td>50–100–300 mg TE, 6 weeks</td>
<td>Moderate increases in serum T determine improvements in verbal and spatial memory</td>
</tr>
<tr>
<td>Cherrier et al.</td>
<td>2005</td>
<td>Double blind RCT</td>
<td>15m AD 17m MCI, 63–85y</td>
<td>100 mg TE, 6 weeks</td>
<td>Improves spatial memory, spatial or constructional ability and verbal memory</td>
</tr>
<tr>
<td>Emmelot-Vonk et al.</td>
<td>2008</td>
<td>Double blind RCT</td>
<td>237m, 60–80y</td>
<td>80 mg T, undecanoate, 6 months</td>
<td>T supplementation does not affect functional status or cognition</td>
</tr>
<tr>
<td>Cherrier et al.</td>
<td>2003</td>
<td>Pilot study</td>
<td>21m hypogonadal</td>
<td>T gel 180 days, DHT gel, 90 days</td>
<td>Beneficial changes in cognition can occur using T</td>
</tr>
<tr>
<td>Kenny et al.</td>
<td>2002</td>
<td>Double blind RCT</td>
<td>67m, 65–87y hypogonadal</td>
<td>T 2–2.5 mg patches/day, 12 months</td>
<td>T may improve cognitive function</td>
</tr>
<tr>
<td>Kenny et al.</td>
<td>2004</td>
<td>Pilot study</td>
<td>11m, 73–87y hypogonadal</td>
<td>200 mg im T, 12 weeks</td>
<td>No significant changes in cognitive performance after T replacement</td>
</tr>
<tr>
<td>Vaughan et al.</td>
<td>2007</td>
<td>Double blind RCT</td>
<td>69m, 65–83y hypogonadal</td>
<td>200 mg T, T + finasteride, 36 months</td>
<td>T has no clinically significant effect on tests of cognitive function</td>
</tr>
</tbody>
</table>

m = men; w = women; RCT = randomized controlled trials; T = testosterone; FT = free testosterone; TT = total testosterone; E = estradiol; MS = Mass Spectrometry; RIA = radioimmunoassay; TE = testosterone enanthate; AD = Alzheimer disease; MCI = mild cognitive impairment; DHT = dehydrotestosterone.
significant improvement in the treatment group compared to placebo regarding attention, processing speed or executive function [70]. Another later much smaller and shorter 12 week study by the same group of investigators using 200 mg intramuscular testosterone in hypogonadal men also found no effect on verbal fluency, attention, visuo-spatial or executive function, as well as on behavior and depression [71].

Vaughan, by using parenteral testosterone supplementation with 5 mg of finasteride daily, did not detect any significant effect in a large array of cognitive functions, indicating that hormonal replacement, whether given alone or in combination with finasteride, in older men without cognitive impairment at baseline had no clinically significant effect on cognitive function [72].

The literature shows numerous studies that have examined the association between testosterone levels in men and performance on various cognitive tests. However, the observations are far to be conclusive, suffering from significant disparity in terms of results and methodologies. Moreover, the studies detailing testosterone supplementation in older men have had similarly varying results. There is growing evidence to support the potential protective effects of testosterone against age-related decline and dementia [73]. There is evidence from a consistent number of studies of an optimal level for testosterone which, if surpassed, offers no further benefit or may hinder a possible improvement in cognition and even have negative effects.

The correlation of testosterone levels with cognitive function may not necessarily be linear. Several studies have reported a curvilinear, U-shaped relationship between androgen levels and tests of cognitive function [74], whereby higher and lower levels of testosterone were associated with low scores and intermediate levels with better performance. These data suggest that a mid-range of serum testosterone levels may correspond with optimal cognitive performance [75].

Although some studies have shown that T supplementation might have positive effects on cognitive function [62–65], caution is need in the elderly before starting a treatment. This not aggressive approach is also motivated by other available data in the literature showing that hypogonadal men seem to have less benefit from testosterone treatment in terms of improvement in cognitive performance than eugonadal men [68,70–72].

6. GH and IGF-1 and cognitive function in the elderly

The decline of serum IGF-1 might contribute to age-related cognitive decline in elderly people. In more developed species, serum levels of IGF-1 are modulated by different physiological (sleep, hormones, exercise, etc.) and pathological (illness, stress, etc.) processes that influence the cognitive status [76].

The effects of GH and IGF-1 on cognition were widely evaluated in different studies (Table 4).

6.1. Observational studies

Studies focusing on the possible relationship between the hormones of the somatotropic axis and cognition can be divided in those who have assessed cognitive function in patients with GH deficiency (both childhood- and adulthood-onset) and those who have evaluated correlations between circulating IGF-1 and cognitive performance in normal physiology, in particular during the aging process [77]. There is a positive correlation between IGF-1 and cognitive performance in various domains, data confirmed in a 2005 meta-analysis integrating findings from several studies [78].

A study in 1318 elderly people aged 65–88 years was performed by Dik et al. who collected information on the association of IGF-1 with processing speed, memory, fluid intelligence and MMSE [79]. The analysis in quintiles of IGF-1 revealed a threshold effect of low IGF-1 on information processing speed, with lower speed in subjects in the lowest quintile of IGF-1 (< 71.7 ng/ml) versus those in the other four quintiles. Thus, according to this data, IGF-1 levels below 71.7 ng/ml are negatively associated with decline of information processing speed, but not with memory or fluid intelligence. The apparent threshold suggests that intervention may be primarily directed to elderly with IGF-1 deficiency, and that therapy would be less efficient in individuals with IGF-1 levels above this threshold.

In the study of Aleman et al. [80], IGF-1 levels were correlated with other tests sensitive to aging, such as visuconstructive ability and verbal long-term memory, speed of information processing. The same association was not observed for vocabulary, basic visual perception and reading ability.

In another cross-sectional study of Aleman [81], serum IGF-1 levels were correlated with both fluid intelligence and crystallized intelligence, respectively modifiable and not modifiable by aging.

The relationship between GH-IGF-1 axis and cognition was tested in elderly normal subjects performing a working memory task during PET scanning. The authors found that memory processing is faster in subjects with higher IGF-1 levels, but only for a small memory load, and they are able to recruit prefrontal areas to a greater extent than low IGF-1 subjects [82].

Landi et al. measured free IGF-1 and its binding protein-3 in 353 elderly persons >85 years. They did not find any significant association between IGF-1 levels and cognition across the entire sample. However, a small group of subjects with specific cognitive impairments had lower free IGF-1 levels than those with normal cognition [83]. Recent data have indicated a positive association between serum IGF-1, working memory, selective attention and executive control in healthy fit older adults [84].

A cross-sectional analysis [85] found a significant association between IGF-1 levels and cognitive functioning in a large sample from the Rancho Bernardo study (median age 74) of men (N = 636), but not in women (N = 899). IGF-1 was independently and positively related to MMSE and verbal fluency in men, and IGFBP-1 was inversely associated with MMSE in men.

6.2. Prospective studies

Some studies have investigated whether low levels of IGF-1 are predictive of consequent cognitive decline.

Kalmijn, based on a sample of 186 healthy participants from the Rotterdam Study, reported an association between higher serum total IGF-1 levels and higher total IGF-1/IGFBP-3 ratios, but not higher free IGF-1 levels with less cognitive decline over the following 2 years [86].

Okereke et al. conducted a secondary analysis from the Physician’s Health Study II, a prospective cohort of U.S. male physicians [87]. Free IGF-1 levels were measured in midlife blood samples from 1982 to 1984, whereas cognitive function was measured in 376 participants nearly 20 years later. Cognitive function was assessed by telephone with an adaptation of the MMSE (the Telephone Interview of Cognitive Status, TICS) and with measures of verbal memory and category fluency (in which participants were asked to name as many different animals as they could in 1 min). Each increment in free IGF-1 was associated with an increase in the global cognition score (average of all cognitive tests). The conclusion was that higher midlife free IGF-1 might be associated with better late-life cognition.

In another study in 2007 based on only female sample, Okereke et al. used the same cognitive tests but now on average 10 years later than the measurement of plasma IGF-1 levels. They found that IGF-1 was related to general cognitive function in these older women; in detail, a significant association of IGF-1 levels and
<table>
<thead>
<tr>
<th>Author reference</th>
<th>Year</th>
<th>Design</th>
<th>Population</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observational</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dik et al. [79]</td>
<td>2003</td>
<td>Cross sectional</td>
<td>1318m and w 65–88y</td>
<td>–</td>
<td>IGF-1 levels below 9.4 nmol/l are negatively associated with information processing speed</td>
</tr>
<tr>
<td>Aleman et al. [80]</td>
<td>2000</td>
<td>Cross sectional</td>
<td>17m 66–76y</td>
<td>–</td>
<td>IGF-1 is positively associated with mental process and perceptual motor speed</td>
</tr>
<tr>
<td>Aleman et al. [81]</td>
<td>2001</td>
<td>Cross sectional</td>
<td>25m 65–76y</td>
<td>–</td>
<td>IGF-1 is positively associated with fluid/crystallized intelligence</td>
</tr>
<tr>
<td>Arwert et al. [82]</td>
<td>2005</td>
<td>Cross sectional</td>
<td>14m 10w 75–85y</td>
<td>–</td>
<td>Memory processing is faster in subjects with higher IGF-1 levels</td>
</tr>
<tr>
<td>Landi et al. [83]</td>
<td>2007</td>
<td>Cross sectional</td>
<td>353m and w &gt;80y</td>
<td>–</td>
<td>Lower levels of IGF-1 and IGFBP-3 are associated with higher IGF-1 levels</td>
</tr>
<tr>
<td>Bellar et al. [84]</td>
<td>2011</td>
<td>Cross sectional</td>
<td>28m and w 48–85y</td>
<td>–</td>
<td>Positive association between IGF-1, working memory, selective attention and executive control</td>
</tr>
<tr>
<td>Al-Delaimy et al. [85]</td>
<td>2009</td>
<td>Cross sectional</td>
<td>636m 899w 30–79y</td>
<td>–</td>
<td>Association of IGF-1 levels with cognitive function in older men, but not in women</td>
</tr>
<tr>
<td>Kalmijn et al. [86]</td>
<td>2010</td>
<td>Longitudinal</td>
<td>93m 93w 55–80y 2y</td>
<td>Higher Total IGF-1 levels and total IGF-1/IGFBP-3 ratio are associated with lower cognitive performance</td>
<td></td>
</tr>
<tr>
<td>Okereke et al. [87]</td>
<td>2006</td>
<td>Longitudinal</td>
<td>376m midlife 20y</td>
<td>Higher midlife free IGF-1 may be associated with better late-life cognition</td>
<td></td>
</tr>
<tr>
<td>Okereke et al. [88]</td>
<td>2007</td>
<td>Longitudinal</td>
<td>590w 60–68y 10y</td>
<td>Higher IGF-1 levels may be associated with better general cognition</td>
<td></td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friedlander et al. [89]</td>
<td>2001</td>
<td>Double blind RCT</td>
<td>16w &gt;60y</td>
<td>IGF-1 15 μg/kg twice daily 1 year</td>
<td>IGF-1 replacement do not alter body composition, bone density, or psychological status</td>
</tr>
<tr>
<td>Vitiello et al. [90]</td>
<td>2006</td>
<td>Double blind RCT</td>
<td>89m and w 60–85y</td>
<td>GHGH 14 μg/kg 6 months</td>
<td>GHRH treatment improves the cognitive function</td>
</tr>
<tr>
<td>Sathiavageswaran et al. [91]</td>
<td>2007</td>
<td>Double blind RCT</td>
<td>34GHD 60–77y</td>
<td>GH 0.1 mg/day 52 weeks</td>
<td>Discrete beneficial effects on cognition with GH therapy</td>
</tr>
<tr>
<td>Cherrier et al. [63]</td>
<td>2004</td>
<td>Double blind RCT</td>
<td>23m 50–80y</td>
<td>100 mg TE 6 weeks</td>
<td>After testosterone administration, there is an association between IGF-1 and IGF-2 levels and spatial reasoning and memory and verbal fluency</td>
</tr>
</tbody>
</table>

m = men; w = women; RCT = randomized controlled trials; IGF-1 = insulin like growth factor 1; IGF-2 = insulin like growth factor 2; IGFBP-3 = insulin like growth factor binding protein 3; GHRH = growth hormone releasing hormone; GH = growth hormone; GHD = childhood-onset GH deficiency; TE = testosterone enanthate.
performance on the TICS was observed, the association with the global cognition score was nearly significant, but no association was found with memory performance [88]. Thus, although there is some (unexplained) heterogeneity in cognitive tests that show an association with serum IGF-1 levels, the findings converge on a positive relationship, i.e., higher levels at baseline predict better performance later on. Together, these observations suggest that IGF-1 may be an important factor associated with salutary brain aging and circulating IGF-1 levels may have predictive value with regard to cognitive functioning later in life [76].

6.3. Intervention studies

The study of Friedlander et al. included 16 healthy post-menopausal women (mean age 70.6 years), randomly assigned to either the self-injection IGF-1 (15 μg/kg twice daily) or placebo group. One year of IGF-1 treatment did not improve memory functioning (name face and word list recall), and did not affect bone density, body composition, or psychological measures in older women [89].

In contrast, Vitiello et al. reported beneficial effects of 6 months of growth hormone-releasing hormone (GHRH) treatment versus placebo in a group of 89 healthy older (>60 years) adults. IGF-1 levels increased by 35% in the treatment group and only 1% in the placebo group. With regard to cognitive functions, the GHRH induced improvement was particularly evident for tests involving problem solving, psychomotor processing speed and working memory, areas of cognitive function showing stronger age-related deficits; treatment showed no changes in over-learned verbal knowledge, often called “crystallized intelligence”, that is, relatively well preserved with age [90]. A strength of this study is the use of GHRH rather than GH to ameliorate the somatotropic axis. The GH release induced by GHRH more closely resembles the physiological pulsatile GH secretion, in contrast to the prolonged rise in GH levels as seen with GH supplementation. Finally, the authors suggest that supplementation of the GH/IGF-1 neuro-hormonal axis may partially ameliorate cognitive declines in healthy normal older adults and potentially in individuals with impaired cognitive function associated with aging or neurodegenerative disease.

A controlled study was based on the effects of GH on cognition in elderly patients with childhood-onset GH deficiency (GHD). A significant improvement was observed for memory as compared to placebo, supporting the beneficial effects of GH therapy on cognition [91].

Cherrier et al. [63] reported an association between IGF-1 and IGF-2 levels and spatial reasoning and memory and verbal fluency, after 6-week testosterone administration in 25 healthy older men (ranging from 50 to 80 years). The association between IGF-1 and cognition was independent of testosterone.

Several findings converge on a positive relationship between higher plasma levels of IGF-1 and better cognitive performance [79–81,84–88]. Together these studies suggest that in older men circulating IGF-1 levels have a more predictive value with regard to specific cognitive domains than other stress hormones.

However, the results of cross-sectional and longitudinal studies do not allow definitive conclusions about the relationship between IGF-1 levels and cognitive function.

Moreover, just some small interventional studies have shown improvements in cognitive function deriving by administration of GH [90], or GHRH [91]. It is difficult to draw definitive conclusions about the influence of somatotropic axis and cognitive performance in older people.

7. Thyroid hormones and cognitive function in elderly

Variations in hypothalamic–pituitary–thyroid axis causing altered hormonal concentrations can determine cognitive effects, which were studied with different results (Table 5).

7.1. Observational studies

Subclinical hyperthyroidism (SH) is defined as a serum TSH concentration below the reference range, with normal free T4 (FT4) and free T3 (FT3) levels, and attenuated thyroid stimulating hormone (TSH) response to thyrotropin releasing hormone (TRH) stimulation. Several studies have reported an association between subclinical hyperthyroidism and dementia.

In the InCHIANTI study, a population-based study of 916 Italians aged 65 years and older, the relationship between SH and impaired cognitive function measured by MMSE was investigated. SH was significantly associated with low MMSE independent of chronic heart failure, smoking, and physical activity [13]. Similarly, data from the Sao Paulo Aging and Health Study, a large cross-sectional study comprising 1119 community-dwelling participants aged 65 years and over, showed an independent association between subclinical hyperthyroidism and dementia [92].

The Rotterdam study was the first longitudinal study to examine the relationship between SH and dementia in 1843 participants aged >55 years. After 2 years, an increased risk of dementia and Alzheimer’s disease was found among those with a low baseline TSH level [93]. This study was limited by the small number of the SH group with dementia (n = 25) and a short follow-up period. Nevertheless, the positive findings in this study are supported by other well-conducted, large population-based studies with a longer follow-up period.

Volpato found an association between lower FT4 concentrations within the reference range and cognitive impairment over a 3-year period [94]. In a small 6-year prospective follow-up study on MCI patients, Annerbo et al. found a significant correlation between reduced TSH levels and progression in AD, whereby 34% of patients converted in AD within 6 years [95]. Hogervorst et al. conducted a large prospective study involving 1047 community-dwelling patients aged 65–94 years. Higher serum FT4 concentrations within the reference range were associated with lower global cognitive function (as measured with the MMSE) at baseline, and with accelerated cognitive decline after 2 years [96].

Vadiveloo et al., analyzing data from a cohort of 12,115 participants carefully selected found that those affected by SH had an increased risk of dementia, as well as cardiovascular disease and dysrythmia [97]. Interestingly, when patients were divided into two groups according to the TSH level (0.1–0.4 mU/L vs. <0.1 mU/L), no relationship was detected between suppressed TSH (<0.1 mU/L) and dementia, but a significant association remained for the group having TSH levels at 0.1–0.4 mU/L [98].

Four thousand two hundred and forty-nine community-dwelling men aged 70–89 years participated in the prospective longitudinal study of Yeap et al. The conclusion of this study was that higher FT4 levels predict new-onset dementia in older men, independently of conventional risk factors for cognitive decline. Despite the inverse log-linear relationship between TSH and FT4 levels, no association was found between TSH level and incidence of dementia [99].

Using the NHANES III sample (National Health and Nutrition Examination Survey III), Beydoun found that higher levels of thyroxine and TSH were associated with improved cognitive performance on a math test and a story recall test in the 60–90 years age group (n = 5989 and 5878, respectively) [108].

In contrast, the largest cross-sectional population-based study, involving 5868 participants, showed no association between
## Table 5
Observational and intervention studies investigating the effects of thyroid hormones on cognitive function.

<table>
<thead>
<tr>
<th>Author reference</th>
<th>Year</th>
<th>Type of survey</th>
<th>Population</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observational</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceresini et al. [13]</td>
<td>2009</td>
<td>Cross sectional</td>
<td>403m 513w &gt;65y</td>
<td>–</td>
<td>Subclinical hyperthyroidism is associated with cognitive impairment</td>
</tr>
<tr>
<td>Bensenor et al. [92]</td>
<td>2010</td>
<td>Cross sectional</td>
<td>1119m and w &gt;65y</td>
<td>–</td>
<td>Consistent association exist among people with subclinical hyperthyroidism and dementia</td>
</tr>
<tr>
<td>Roberts et al. [100]</td>
<td>2006</td>
<td>Cross sectional</td>
<td>5868m and w 65–98y</td>
<td>–</td>
<td>No clinically relevant association exists between thyroid function and cognitive function</td>
</tr>
<tr>
<td>De Jongh et al. [101]</td>
<td>2011</td>
<td>Cross sectional</td>
<td>1219m and w &gt;65y</td>
<td>–</td>
<td>Subclinical thyroid disorders have not disadvantageous effects on physical or cognitive function</td>
</tr>
<tr>
<td>van der Cammen et al. [102]</td>
<td>2003</td>
<td>Cross sectional</td>
<td>268m 561w 60–98y</td>
<td>–</td>
<td>No difference in TSH levels between AD and control patients</td>
</tr>
<tr>
<td>Patterson et al. [103]</td>
<td>2010</td>
<td>Cross sectional</td>
<td>119m 290w 52–94y</td>
<td>–</td>
<td>Neither T4 nor TSH significantly influence cognitive performance in AD patients</td>
</tr>
<tr>
<td>Quinlan et al. [104]</td>
<td>2010</td>
<td>Cross sectional</td>
<td>69m and w &gt;60y</td>
<td>–</td>
<td>Total T3 levels are inversely associated with cognitive performance</td>
</tr>
<tr>
<td>Beydoun et al. [108]</td>
<td>2012</td>
<td>Cross sectional</td>
<td>5989–5878m and w 60–90y</td>
<td>–</td>
<td>TSH is associated with better performance on cognitive tests</td>
</tr>
<tr>
<td>Kalmijn et al. [93]</td>
<td>2000</td>
<td>Longitudinal</td>
<td>1843m and w 54–94y</td>
<td>2–4y</td>
<td>Subclinical hyperthyroidism in the elderly increases the risk of dementia and AD</td>
</tr>
<tr>
<td>Volpato et al. [94]</td>
<td>2002</td>
<td>Longitudinal</td>
<td>464w &gt;65y</td>
<td>3y</td>
<td>Low T4 levels are associated with a greater risk of cognitive decline</td>
</tr>
<tr>
<td>Annerbo et al. [95]</td>
<td>2006</td>
<td>Longitudinal</td>
<td>45m 48w &gt;65y</td>
<td>6y</td>
<td>Significant correlation between reduced TSH levels and AD conversion</td>
</tr>
<tr>
<td>Hogervorst et al. [96]</td>
<td>2008</td>
<td>Longitudinal</td>
<td>1047m and w 65–94y</td>
<td>2y</td>
<td>Higher serum T4 concentrations are associated with accelerated cognitive decline</td>
</tr>
<tr>
<td>Vadiveloo et al. [97]</td>
<td>2011</td>
<td>Longitudinal</td>
<td>12,115m and w 66.5 ± 15.9</td>
<td>7y</td>
<td>Association between subclinical hyperthyroidism and increased risk of dementia</td>
</tr>
<tr>
<td>Yeap et al. [99]</td>
<td>2012</td>
<td>Longitudinal</td>
<td>4249m 70–89y</td>
<td>8y</td>
<td>Higher T4 levels predict new-onset dementia in older men</td>
</tr>
<tr>
<td>Gussekloo et al. [105]</td>
<td>2004</td>
<td>Longitudinal</td>
<td>558m and w 20–75y</td>
<td>3.7y</td>
<td>No consistent association between thyroid status and ADL, depressive symptoms, and cognitive performance</td>
</tr>
<tr>
<td>De Jong et al. [106]</td>
<td>2006</td>
<td>Longitudinal</td>
<td>1077m and w 60–90y</td>
<td>5.5y</td>
<td>No relationship between thyroid function and the risk of dementia or AD</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parle et al. [110]</td>
<td>2010</td>
<td>RCT</td>
<td>37m 57w &gt;65y SH</td>
<td>T4 25 g/day 1 year</td>
<td>T4 replacement therapy in elderly does not improve cognitive function</td>
</tr>
<tr>
<td>Jorde et al. [111]</td>
<td>2006</td>
<td>RCT</td>
<td>69m and w 5H 29–75y</td>
<td>T4 25–50–100 μg 1 year</td>
<td>Patients with no treated subclinical hypothyroidism have no cognitive deficits</td>
</tr>
<tr>
<td>Correia et al. [112]</td>
<td>2009</td>
<td>No RCT</td>
<td>57m and w 18–65 21Hypo 17SH</td>
<td>T4 50 μg/day 6 months</td>
<td>After T4 replacement, there are no differences from control</td>
</tr>
<tr>
<td>Samuels et al. [107]</td>
<td>2007</td>
<td>RCT</td>
<td>19w Hypo 20–75y</td>
<td>T4 steady or lower 12 weeks</td>
<td>The group of T4-treated subjects has decrements in working memory</td>
</tr>
</tbody>
</table>

m = men; w = women; RCT = randomized controlled trials; TSH = thyroid stimulating hormone; T4 = thyroxine; T3 = triiodothyronine; AD = Alzheimer disease; ADL = activities of daily living; Hypo = hypothyroidism; SH = subclinical hypothyroidism.
thyroid function and cognition after controlling for several con-
founders [100]. However, participants were invited by mail with a
response rate of 38%. Although the responders were representative
of the regional population with respect to demographic charac-
teristics, the average MMSE score was above 27 in all subgroups,
suggesting that the responder population was skewed toward a
cognitively intact group [98].

In a cross-sectional study involving 1219 community-dwelling
participants endogenous subclinical thyroid dysfunction was not
associated with impaired physical or cognitive function, or depres-
sion [101].

Other cross sectional studies in AD patients failed to demon-
strate any association between cognition and low serum TSH or
high serum FT4 level.

Among these, an observational study, involving 829 consecutive
unselected referrals to a hospital geriatric clinic, did not demon-
strate any statistically significant differences in TSH levels between
the AD patients and the cohort without any form of dementia [102].
However, comorbidities and medication use were not described,
so the results may be confounded by nonthyroidal illness, thyroid
medication, or overt thyroid dysfunction. The study of Patterson
et al. involved 409 euthyroid patients aged 52–94 years diagnosed
with probable AD according to NINCDS-ADRDA criteria. No associ-
ation was found between serum TSH or FT4 and dementia [103].
In a smaller study of Quinlan et al., involving 69 hospital based
participants, among those with MCI, total T3 levels were inversely
associated with cognitive performance in domains of memory,
visuo-spatial and executive functions [104].

Prospective follow-up of 558 individuals aged 85 living in Leiden,
in the Netherlands, demonstrated no consistent associations
between thyroid status and ADLs, depressive symptoms, and cog-
nitive performance. Nevertheless, this study had a small sample size
and a 41.5% loss of follow-up due to death or refusal to continue
participation [105].

The Rotterdam Scan study, another prospective community-
based study involving 1077 subjects aged 60–90 years with a mean
follow-up interval of 5.5 years, showed no association between
dementia and serum TSH or thyroid hormone levels. In contrast,
the investigators found a positive association between a higher FT4
and rT3 and greater atrophy at the hippocampus and amygdala on
magnetic resonance imaging [106]. Although the Rotterdam Scan
study had greater power than the original Rotterdam study [93],
due to a larger-sized dementia cohort (n = 60 vs. 25) and a longer
follow-up period, this study was limited by single measurements
of thyroid function and a small number of dementia cases with low
TSH (n = 7).

7.2. Intervention studies

The association between dementia and increased thyroid hor-
mones is less well documented than hypothyroidism-related
dementia. Therapeutic response of hyperthyroid dementia has not
been elucidated.

However, the return of euthyroid status has been associated
with an improved cognitive function. So we analyzed the con-
dition of hypothyroidism in which a supplementation of thyroid
hormones, with the return to normal thyroid hormone levels,
improved cognitive outcomes.

In the study of Samuels, subjects with L-T4-treated hypo-
thyroidism were randomized to continue their usual L-T4 dose or to
receive a lower dose to induce subclinical hypothyroidism. The
authors found decrements in working (short-term) memory at the
end of the subclinical hypothyroid arm, suggesting that subcli-
ncal hypothyroidism induces specific deficits in brain areas which
control working memory [107].

In another study, hypothyroid patients who underwent 3-
month thyroxin treatment increased their performance on verbal
memory [109].

In contrast, several studies demonstrated that in hypo-
thyroid demened, supplementation treatment is not sufficient
to determine an improvement in cognitive function. The largest
double-blind randomized controlled trial of Parle et al. considered
94 subjects aged 65 years and over with subclinical hypothyroidism
receiving 25 g T4 per day for 1 year. The Authors found lack of effect
of T4 treatment on cognitive function, suggesting that l-thyroxin
replacement therapy should not be recommended to improve cog-
nitive status in these patients [110]. In another study by Jorde et al.,
subjects with subclinical hypothyroidism underwent detailed cog-
nitive testing of multiple domains at baseline and after treatment
with placebo or L-T4 for 12 months. There were no baseline differ-
ences between subclinical hypothyroid subjects and controls [111].

In a smaller intervention study, Correia et al. assessed cognitive
function in 21 overt hypothyroid and 17 subclinical hypothyroid
patients and in 19 controls. They 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, reporting that subjects with subclinical hypothyroidism had
impaired spatial, associative and verbal memory on detailed cog-
nitive testing. This impairment was resolved after 6-month L-T4
therapy. The authors also concluded that hypothyroidism causes
the cognitive deficits by disruption of normal hippocampal func-
tion [112]. However, this was an open-label, nonrandomized study
where all subjects were treated; besides, the study was more
focused on memory and included patients younger than other stud-
ies.

Although an association between SH and cognitive impairment
has been frequently observed, there is no clear mechanistic expla-
nation for this link and no strong evidence to support the use of
antithyroid measures for preventing or improving cognitive decline
in this patient group. Larger and more detailed prospective lon-
titudinal or randomized controlled trials are required to answer to
these important questions.

There is a strong body of evidence to support the association
between subclinical hyperthyroidism and cognitive impairment
[13,92–99].

However, a similar number of examined studies did not show
any influence of subclinical hyperthyroidism on cognitive status
[100–106].

There is no clear mechanistic explanation for these associations,
but the results don't allow considering thyroid hormones as pre-
dictors of cognitive dysfunction.

We have not found articles addressing the relationship between
return of euthyroid condition in hyperthyroid older men and
cognitive function. On the other hand, therapeutic response of
hypothyroid dementia has been exposed in a small number of inter-
ventional studies [107–112].

The results after L-T4 treatment are conflicting, having a consis-
tent number of methodological differences in age range, types of
cognitive tests used, as well as different assays to measure hor-
mones, and do not permit definitive conclusions on the role of
thyroid dysfunction in the cognitive status.

8. Sleep deprivation (SD) as a stress condition causing
cognitive impairment

8.1. Characteristics of physiological sleep

Sleep is a complex behavioral state that occupies one-third of
the human lifespan.
Until recently, sleep was believed to be important primarily for restoring brain function. However, increasing evidence suggests that sleep also modulates the metabolic, endocrine and cardiovascular systems.

The lighter stages of NREM (non rapid-eye-movement) sleep, also called stages 1 and 2 come first and often alternate with brief waking episodes before stages 3 and 4, which are considered the deeper stages of NREM sleep and occur predominantly early in the night. In contrast, REM (rapid-eye-movement) sleep appears at intervals of approximately every 90 min. Usually 4–6 of these sleep cycles occur each night, with REM sleep episodes becoming longer and NREM sleep episodes becoming shorter and lighter over the course of the night.

Deep NREM sleep is characterized by ‘slow waves’ in the electroencephalogram (EEG), so the intensity of NREM sleep is quantified by slow wave activity (SWA; EEG spectral power in the 0.5–4 Hz frequency range). Because SWA decreases in the course of the sleep period, is higher after SD and lower when the waking period has been interrupted by a long nap, SWA is considered as the major marker of homeostatic sleep pressure.

In fact, sleep is regulated by a homeostatic factor, which increases sleep propensity after prolonged wakefulness, and by a circadian factor, which facilitates falling asleep in the evening [113]. Circadian rhythmicity is an endogenous oscillation with a near 24-h period generated in the suprachiasmatic nucleus of the hypothalamus. Interaction between sleep and this endogenous timing system regulate hormonal control including melatonin, the HPA axis with cortisol, the hypothalamic–pituitary–thyroid axis, and epinephrine [114].

Melatonin (N-acetyl-5-methoxy-tryptamine) plays a crucial role in the regulation of circadian and seasonal changes in various aspects of physiology and neuroendocrine functions.

This hormone, produced predominantly by the pineal gland, is released into the circulation, and because it is not stored in the pineal gland, the profile of its plasma levels reflects pineal activity. In humans, melatonin levels gradually rise after the time of lights off, reaching a peak around the middle of the night, and then decline slowly during the second half of the night to reach low day-time values near the time of lights on.

Light is the dominant factor that controls biosynthesis of melatonin. In this way, melatonin serves as a signal of darkness in the organism, affecting the brain structures associated with the circadian cycles [115]. Melatonin receptors (MT1 and MT2) have been detected in the suprachiasmatic nucleus of the hypothalamus and are believed to be involved in the regulation of the sleep–wake cycle [116].

Core temperature is reduced by increased melatonin levels and this is associated with sleep propensity. Accordingly, sleep is impaired and the core temperature rhythm amplitude is blunted in the absence of melatonin at night compared to when it is present [117].

Furthermore, there is evidence for an influence of melatonin on immune system, and melatonin supplementation has been advocated as potential strategy to prevent or delay the functional age-associated deterioration in the immune system. Finally, melatonin is a powerful antioxidant and prevents tissue damage associated with oxidative stress [118].

Several studies have demonstrated a progressive decline with age in the amplitude of melatonin rhythm in the elderly, and some have tried to find a relation between this decline and sleep disruption typical of older age.

One study indicated that low melatonin production may not be an important factor in insomnia among the elderly [119]. Another suggested that it is not the absolute level of endogenous melatonin, but rather the timing of the circadian rhythm in evening melatonin secretion that might be related to disturbances in the sleep–wake cycle in older people [120].

The use of melatonin for sleep disorder in elderly subjects has been well studied. From a pharmacological point of view, two synthesized ligands of melatonin receptors have a therapeutic importance: agomelatine and ramelteon.

Agomelatine is a potent agonist of melatonin MT1 and MT2 receptors and an antagonist of the serotonin 5-HT2C receptor subtype, and is endowed with antidepressant properties.

Ramelteon has a very high affinity for human MT1 and MT2 receptors. Ramelteon does not significantly alter sleep architecture [121]. By contrast to commonly used hypnotic drugs, ramelteon does not impair motor and cognitive function [122]. Besides, in older adults with chronic insomnia and particularly susceptible to falls, ramelteon does not impair balance, mobility or memory in the middle of the night [123].

For these reasons, the efficacy and safety of ramelteon is acceptable for the chronic insomnia patients, as a recent meta-analysis demonstrated [124].

A prolonged-release formulation of melatonin (2 mg), mimicking the nocturnal melatonin profile, has been found to significantly facilitate sleep onset and improve subjective sleep quality and morning alertness in insomnia patients aged 55 years and older [125].

Short- or long-term treatment with the prolonged-release formulation was not associated with dependence, tolerance, rebound insomnia or withdrawal symptoms [126]. Despite the sleep promoting effects, this formulation did not impair postural stability during the night [127].

Finally, sun-downing (the appearance or exacerbation of behavioral disturbances associated with the afternoon and/or evening hours) improves with melatonin treatment in patients with dementia, and it is likely that melatonin could also have the same positive effects in patients with delirium [128].

The selective reduction of nocturnal melatonin secretion, evident in physiological aging and even more in senile dementia, mirrors the impairment of the central noradrenergic mechanisms regulating the pineal secretion [129].

In both diurnal species like humans and nocturnal species such as the rat, plasma levels of catecholamines are higher during the circadian waking phase. Epinephrine in particular shows a pronounced daily rhythm, which is partly a consequence of the rhythm in sleep and wakefulness and partly due to an endogenous oscillator or biological clock independent of the sleep–wake behavior. The daily norepinephrine rhythm is weaker and mainly a direct result of the daily rhythm in sleep and wakefulness [130]. Accordingly, under normal conditions sleep onset is associated with a rapid decline in circulating catecholamines and various reports have shown lower levels of these hormones during sleep compared to wakefulness [131].

8.2. Characteristics of pathological sleep

Normal aging is accompanied by changes in the sleep quantity and quality: in older adults sleep tends to become shorter (decreased total sleep time), shallower (increased stages 1 and 2 and decreased slow-wave sleep), and more disrupted (declined REM sleep, decreased sleep efficiency and prolonged wake after sleep onset).

Possible mechanisms related to these changes in sleep include age-related changes in circadian modulation, homeostatic factors and endocrine function [132].

A number of studies confirmed that healthy, postmenopausal women sleep worse than young controls, when measured at baseline or after SD; in particular sleep tends to be more impaired during
the peri and postmenopausal years [133]. Furthermore, measuring subjective sleep quality in the morning, the young women had somewhat better sleep state perception than the older women [134].

Sleep onset is associated with an increase in circulating levels of IL-6. These data suggest an important role for sleep in the nocturnal regulation of IL-6 secretion. Alternatively, cytokines such as IL-6 are hypothesized to have a regulatory influence on sleep. Thus, loss of sleep during part of the night may be one of the factors exacerbating the immunological alterations. In addition, given the association between increases in IL-6 and REM sleep, disturbances of sleep architecture may lead to abnormalities in the sleep-related secretion of IL-6, with implications for inflammatory status and increased risk of cardiovascular disease [135].

In general, inadequate sleep duration and poor sleep quality have been found to be associated with numerous adverse health outcomes, including total mortality, cardiovascular and gastrointestinal disease, and metabolic disorders, such as insulin resistance, type 2 diabetes mellitus, and obesity [136,137]. This impaired ability to initiate and maintain sleep is associated with increased morbidity and mortality in the elderly.

Several studies focused on the effects of sleep restriction in animal models and in humans.

SD results in an acute effect due to an acute total sleep loss (prolonged wakefulness for 24, 48 or even 72 h) and in a chronic effect due to a partial sleep restriction for a variable number of days.

SD is a condition often associated with mild, temporary increases in the activity of the major neuroendocrine stress systems, i.e. the autonomic sympathetic-adrenal system and the HPA axis.

Sleep appears to have suppressive effects on the stress systems and, consequently, SD maintains the activity of these systems at the higher level that occurs during wakefulness. An open question is whether activation of stress systems during SD is a consequence of sleep loss per se or is due to the stressful nature of the SD procedure [1].

In the long run, SD may affect the reactivity of these systems to other stressors and challenges. In fact, experimental studies in rodents show that chronic SD may gradually alter neuroendocrine stress responses as well as the central mechanisms involved in the regulation of these responses. Instead, few controlled studies in humans have focused on this topic.

SD does not alter only stress hormones, but also other hormones determining an imbalance in catabolic/anabolic ratio, as shown in Fig. 2.

In this review, we paid attention to sleep as a potential confounding factor, although it was not matter of investigation in all studies. Besides, subjects with potential sleep disorders were excluded.

8.3. SD in animal models

Characteristic findings have emerged from studies in laboratory animals.

SD induces increased HPA axis activity, with a facilitated HPA axis response to a subsequent mild stressor in sleep-deprived animals [138]. SD represents an energetic challenge sufficient to prompt demand for available energy substrates centrally and peripherally. For this reason, the elevation of GC [i.e. corticosterone in rats] caused by SD promotes brain glycolysis, and in the absence of a GC surge (prevented by adrenalectomy), glycogen stores in all brain regions are spared while glucose levels are significantly decreased [139].

Enhanced secretion of a catabolic hormone like corticosterone, caused by SD, influences the balance between protein synthesis and protein degradation, causing loss of muscle mass [140].

Finally, sleep appears to be essential to ameliorate physiological responses to stress, as the corticosterone level returns to normal after the sleep recovery period.

The results of experiments testing the capacity of SD to cause cognitive impairment were controversial.

It has been accepted that gentle handling and other methods used for SD (treadmill, disk-over water and small platform) reduced significantly cell proliferation and/or maturation in the adult rodent hippocampus [141–143].

On the contrary, Mirescu et al. found that SD reduces cell proliferation and adult neurogenesis in the hippocampus by elevations in GC [144]. This study examined the effects of acute (24-h) or prolonged (72-h) sleep loss; although 24 h of SD affected neither cell proliferation nor cortisol levels, 72 h of SD substantially lowered cell proliferation and increased stress hormone levels. These findings are consistent with previous studies demonstrating that stressful nature of SD exerts negative effects on the hippocampus: SD or sleep disruption may not only have a negative impact on neuronal cell proliferation but, perhaps more relevant, also on subsequent survival, maturation and differentiation of these cells.

Moreover, a number of experiments have shown that cell proliferation or maturation in the adult rodent hippocampus is not inhibited by SD procedures lasting 24 h or less, but is significantly suppressed by SD or fragmentation procedures lasting 3 days or more. The study of Grassi Zucconi was one of these [145]. The relationship between acute SD and cortisol levels has been tested in several studies.

In rats, it is common to use an experimental model called paradoxical sleep deprivation (PSD) which corresponds to the REM stage in humans. This model is based on a platform technique and involves numerous awakenings that predominantly affect the paradoxical stage of sleep. Thus, the PSD model mimics REM sleep fragmentation due to repeated awakenings.

Instead, according to various authors [141,143,146,147], SD was not responsible for memory impairments induced by PSD. Thus, the acute or chronic inhibition of corticosterone release immediately after or during PSD, respectively, did not prevent the impairment of memory induced by this adverse situation [148].

The alterations in GH-IGF-1 axis during SD have been also a matter of investigation. In these studies, the role of hypothalamic GH releasing hormone (GHRH) was also considered.

GHRH promotes NREM stages after various routes of administration in rats, rabbits, mouse and humans.

Promotion of NREM stages by GHRH is given by a hypothalamic action mediated by GABAergic neurons in the anterior
hypothalamus/medial pre-optic region in rats, while GH and IGF-1 are not involved in the NREM sleep promoting activity of GHRH.

GHRH may also stimulate REM sleep but this effect is indirect and requires the presence of GH.

Ohal and coworkers chose the lit/lit mice to study the role of GHRH in sleep regulation [149]. The lit/lit mouse beard a point mutation in the GHRH-R gene, resulting in a loss of receptor function. The lack of NREM sleep in these animals was consistent with the proposed importance of GHRH in the regulation of NREM stages. The results suggested that somatostatin and ghrelin may modulate NREM stages via GHRH.

The promotion of NREM sleep and stimulation of GH are parallel outputs of hypothalamic GHRH through which anabolic activities in the body are synchronized to periods of sleep [150]. As occurs with GH levels, EEG slow wave activity during NREM sleep and hippocampal cell proliferation also decline with age suggesting that perhaps these changes could be related.

During SD, GH release is significantly diminished, but during sleep recovery, it strongly rebounds.

In addition, GH replacement during SD is known to protect the hippocampal function and its structural integrity. In the hippocampus, N-methyl-D-aspartate (NMDA) receptors play critical roles in memory formation and induction of long-term potentiation (LTP), a widely used synaptic model of learning and memory [151].

In an intervention study, adult rats were injected with a low dose of recombinant human GH (rhGH 5 ng/kg) for seven days and then the animals were sleep deprived for 48 consecutive hours [152].

Daily administrations of rhGH completely blocked the inhibitory effect of SD on hippocampal cell proliferation and rhGH improved hippocampal cell survival. Many GH effects are mediated by IGF-1 produced by liver and target tissues. Reduced GH release leads to a decrease in plasma IGF-1. Effects of GH hippocampal synaptic function or NMDA receptor expression could be mediated by IGF-1.

However, a growth hormone treatment of sleep-deprived animals did not restore circulating IGF-1 levels. Several factors could explain this lack of effect. First, GH is not the only hormone affected by SD: circulating thyroid hormone, insulin, corticosterone, leptin, and ghrelin are all altered by this condition. Second, although IGF-1 expression is regulated by GH, circulating IGF-1 concentration is dependent on the presence of IGF-binding proteins (IGF-BPs).

SD has various effects on metabolic functions and hormone levels, which in turn may alter production of IGF-1, IGF-BPs, or decouple IGF-1 production from GH. Restoration of GH alone may not be sufficient to restore IGF-1 levels [151].

A series of studies has demonstrated the drastic effects that PSD has on androgen levels in rats.

Decreased concentrations of testosterone in sleep-deprived male rats have consistently been observed [153–155].

The mechanisms by which SD affects serum testosterone and how age may modify the process are still unclear. The observed reduction in serum testosterone levels after total SD or sleep restriction may result from a reduced sensitivity of gonadal Leydig cells to the stimulating effects of luteinizing hormone (LH). Also corticosterone, whose levels increase in SD, has been shown to reduce testosterone production and to induce apoptosis in Leydig cells [156]. Wu et al. [155] suggested that testosterone production may be decreased due to a combination of serotonin-related inhibition and decreased STAR expression in SD rats.

Furthermore, selective sleep loss induced decreased levels of estrone and increased levels of progesterone, prolactin, corticosterone, and catecholamines after 4 days of SD in male rats [157]. An experimental study in inbred mice investigated whether androgen replacement in males and estrogen replacement in females alters sleep pattern and sleep rebound after SD [158]. During baseline recording estradiol-treated females exhibited a reduction in NREM sleep amount. Conversely, testosterone-treated males exhibited an increase in NREM sleep amount. After 6 h of SD, hormone-treated males and females exhibited similar amounts of recovery sleep, however both groups exhibited slightly more sleep than placebo-treated controls. The results of these experiments demonstrated that the androgens and estrogens are primarily responsible for sex differences in baseline sleep–wake amount but do not have substantial effects on homeostatic sleep rebound after extended wakefulness.

A recent study was performed to assess serum testosterone alterations induced by PSD and during sleep recovery in rats of different ages [159]. The older group showed a significantly lower level of testosterone compared with the younger group after PSD. Besides, the testosterone level continued to rise for 5 days after sleep recovery in the younger group, whereas testosterone concentrations failed to recover into same days in the older group. It seems to be reasonable that PSD caused a more detrimental effect on serum testosterone in the older group compared to the younger group, and that the effects of sleep recovery may be age-dependent.

Concerning the hypothalamic–pituitary–thyroid axis, a Chinese study concluded that PSD could remarkably change energy metabolism and consequently serum thyroxine (T4) and triiodothyronine (T3) levels [160].

In 3-wk survival period in sleep-deprived rats, despite a resemblance to hyperthyroidism (peripheral hypercatabolism, increased food intake and weight loss), the study of Everson et al. revealed a panel of central hypothyroidism [161]. In fact, SD in rats resulted in progressive decline in circulating concentrations of both total and free T4 and T3. T4 showed a greater decline than T3. The increased T3–to–T4 ratio likely involved local T3 production by brown adipose tissue (BAT), a major T4-to-T3 conversion pathway in the rat. Indeed, the T4-to-T3 conversion enzyme, type II 5′-deiodinase, in BAT was increased in sleep-deprived rats.

Moreover, there was no change, or only slight increases, in plasma thyroid stimulating hormone (TSH) at the end of the deprivation period. This blunted TSH response in sleep deprived animals, therefore, was inappropriate, given both the duration of hypothyroxinemia and the demonstrated increase in thyrotropin-releasing hormone (TRH) transcripts; in fact, prepro-TRH mRNA levels increased during prolonged SD as an apparently appropriate response to decreased circulating thyroid hormone concentration, but expected TSH responses to peripheral hypothyroxinemia and to increased TRH transcript levels did not occur.

The thyroid hormone profile of the sleep deprived rat is consistent with central hypothyroidism in humans and resembles TRH deficiency in paraventricular nucleus (PVN)-lesioned rats.

Administration of TRH resulted in appropriate increases in plasma TSH, free T4, and free T3 across experimental days, suggesting deficient endogenous TRH production and/or release. The locus of abnormal thyroid hormone regulation lies after prepro-TRH transcription.

8.4. SD in humans

Like in rats, similar hormonal alterations were also found in humans subjected to SD or reduced sleep time. However, in human subjects, it is more important to distinguish between acute loss of sleep and chronic SD, because the impact on the hormonal pathway is different.

Sleep onset is associated with a short-term inhibition of cortisol secretion that may not be detectable when sleep is initiated in the morning, i.e. at the peak of corticotropic activity. Awakenings (final as well as during the sleep period) consistently induce a pulse in cortisol secretion.

Short-term SD (3 h sleep/night for 4 consecutive days), in young adults, seems to be related with a significant decrease in morning serum cortisol levels [162]. This hormone decreases more after four
nights of sleep loss in the earlier-night sleep restriction group (sleep from 00:00 to 03:00) than in the later-night group (sleep from 03:00 to 06:00). Data in this study suggested that SD, especially in the later night, differentially initiates the activation of HPA-axis and reduces cortisol secretion, pointing out the importance of sleep at the 03:00 to 06:00 period, during the circadian nadir, in protecting normal physiological rhythms and function of the HPA-axis.

On the contrary, chronic SD is associated with an elevation in evening cortisol levels that may reflect decreased efficacy of the negative feedback regulation of the HPA axis. This elevation may result in a significant glucocorticoid overload [4].

Few investigators have tried to correlate cortisol secretion with sleep impairment in the elderly. Prinz and colleagues measured the 24-h urine-free cortisol levels in 88 healthy, old, non-obese men and women (mean age of 70.6 years) and observed that subjects with higher cortisol levels had more impaired sleep (lower sleep efficiency, fewer minutes of stages 2, 3, and 4 sleep, and more EEG beta activity during NREM sleep) [163].

Evaluating the sleeping and waking brain electrophysiology, the SD-related changes in cortisol release are significantly associated with the changes in frontal waking EEG alpha activity (increased daytime waking EEG power in the delta, theta and gamma frequency bands of the frontal cerebral area) [164]. In terms of age-related changes of the EEG responses to SD, Münch and colleagues submitted healthy young (20–31-year-old) and older (57–74-year-old) subjects to a 40-h SD protocol, and noted that the frontal predominance of delta activity after sleep loss decreased with aging [165].

With the exception of studies by Prinz and Münch [163,165], we did not find other studies evaluating cortisol levels and specific protocols of SD in the elderly.

It is well-documented that GH is a hormone essentially controlled by sleep–wake homeostasis. Indeed, in men, the most reproducible pulse of GH occurs shortly after sleep onset, during slow wave sleep (SWS, referring to stages 3 and 4 of sleep).

In both young and older men, there is a ‘dose–response’ relationship between SWS and nocturnal GH release. When the sleep period is displaced, the major GH pulse is also shifted, so that nocturnal GH release during SD is minimal or frankly absent. This impact of sleep pressure on GH is particularly clear in men but can also be detected in women [166]. Several studies analyzed the effects of SD on overall 24 h growth-hormone secretion, but the greater part regarded only young people.

One of these concluded that SD tends to make GH secretory profile less regular [167].

On the contrary, the acute SD does not induce deficiency of GH release in 24 h [168].

In the state of sleep debt resulting from 1 wk of sleep curtailment achieved by delaying bedtime by 2 h and advancing wake time by 2 h, nocturnal GH secretion followed a biphasic pattern, with a first pulse (presleep onset GH pulse) occurring during wakefulness around the usual time of sleep onset and a second pulse (post-sleep onset GH pulse) after the onset of sleep [169]. The GH profiles during acute SD achieved by delaying bedtimes show that the secretory profile that has consistently emerged was characterized by absent or minimal secretion when the waking state was enforced during the usual sleep period, followed by a rebound of secretion during recovery sleep. On the basis of such evidence, one would predict chronic sleep curtailment to be associated with minimal GH secretion during prolonged wakefulness and a large secretory pulse associated with high levels of SWA after the initiation of recovery sleep. As demonstrated by Spiegel, neither the pattern of GH secretion nor the distribution of SWA conformed to these expectations, indicating that adaptation mechanisms that are not apparent during acute SD are operative during chronic partial sleep loss. The amount of SWA in the first sleep cycle was also not increased during chronic partial SD. This discrepancy with the predictions of current models of SWA homeostasis could also reflect inhibitory effects of presleep onset GH secretion on growth hormone-releasing hormone (GHRH)-dependent mechanisms involved in the generation of SWS. Thus, although the initial response to the first night of sleep restriction most likely involved an increase in SWA and GH release in early sleep, it appears that in the course of adaptation to chronic sleep loss, increasing amounts of presleep onset GH secretion may have inhibited central GHRH activity, limiting both SWA and GH release in early sleep.

The finding of a highly significant negative correlation between pre-sleep onset and post-sleep onset GH secretion strongly suggest that, during chronic sleep curtailment involving a delay of bedtimes, pre-sleep onset GH secretion partly inhibited post-sleep onset GH release.

In older adults and depressed patients, a pre-sleep onset GH pulse was more commonly observed than in young healthy subjects. Both aging and depression are associated with marked decreases of total sleep duration due to increased sleep fragmentation and advanced morning awakening. The findings of this study suggested that the alterations in temporal distribution of GH secretion in these conditions could partly reflect the impact of chronic sleep loss.

GH secretion is dependent on age and decreases greatly in older people [170]. Van Cauter and colleagues [171] noted a biphasic decline in GH secretion: early adulthood to midlife is accompanied by a major decline in GH secretion followed by a slower decline from mid- to late-life. This biphasic decline in GH secretion correlated with a parallel decline in slow-wave sleep. They also detected an age threshold of 50 years of age, after which evening cortisol levels rose together with worsening sleep fragmentation and decline in REM sleep.

It was well established that GHRH promotes spontaneous NREM sleep in human subjects and in rabbits, rats, and mice. Furthermore, various studies pointed to a key role of GHRH in sleep promotion after SD.

The study of Schüssler et al. suggested that, during the recovery night after SD, exogenous GHRH was capable of enhancing the effects of endogenous NREM sleep promoting factors, including probably endogenous GHRH. This observation supported the view that GHRH promotes NREM sleep, particularly in conditions of high sleep propensity [172]. The same study concluded that the administration of corticotropin-releasing hormone (CRH) increased the NREM sleep promoting effect of SD. Surprisingly, after CRH there was a positive correlation between the increase of slow-wave sleep SWS and age.

Another study considered the reciprocal interaction between GHRH and sleep-impairing CRH. Changes in the GHRH-CRH ratio result in changes of sleep–endocrine activity. There was good evidence that the change of this ratio in favor of CRH contributes to aberrances of sleep during aging and depression [173].

The above reported changes in nocturnal growth hormone and cortisol levels correlated significantly with an age-dependent decrease in slow-wave sleep and REM sleep, and may be partially responsible for the reduced restorative neurocognitive and anabolic functions of sleep in the aged [172].

9. Sleep is critical for testosterone regulation

Normally, testosterone concentrations start to rise with sleep onset and then reach a plateau at REM sleep onset approximately 90 min later.

Circulating testosterone concentrations increase after sleep onset reaching a peak at the time of first REM episode and then remain elevated until awakening after which they rapidly decline.
The onset of the first REM episode but not the total amount of REM sleep across a night has been previously shown to determine the increase in circulating testosterone levels during night-time sleep [175].

As it is known, a decline in androgen levels is a normal consequence of the aging process. Indeed, as pointed out by Goh and Tong [176], age is a major determinant of many of the physiological changes in men with regard to sleep, sex steroid hormone levels and sexual activity. Their results showed that men with acute sleep restriction (less than 4 h daily) and those with moderate sleep restriction (4–6 h daily) had significantly lower androgen concentrations than did those who slept over 8 h.

These two studies demonstrate a positive association between sleep duration and androgen concentrations in men, thus confirming that sleep, rather than a circadian rhythm, is critical for testosterone regulation.

Moreover, the synthesis of testosterone is dependent on endocrine and neuronal signals which in turn are influenced by physiological conditions such as stress [177]. SD is a known physiological stressor; hence, it is unsurprising that serum testosterone concentrations were altered in rats and humans following SD.

Referring to sexual hormone binding globulin (SHBG), the most important binding protein of testosterone, the study of Goh and Tong [176] did not provide any evidence that short sleep duration is associated with a reduction in SHBG levels, whereas they clearly indicated an association with reduced total and free testosterone concentrations.

Several human studies reported that SD is associated with decreased testosterone levels. Some of these have considered a sample of young men exposed to SD.

The study of Schmid et al. [178] examined 15 young, healthy men in a condition of sleep time restriction to 4 h during the late part of the night (bedtime, 02:45 to 07:00 h) for two consecutive nights as compared to a control condition of 8 h regular sleep, with wake-up time kept constant across conditions. The authors showed that the diurnal profiles of serum LH, testosterone and prolactin concentrations in young healthy men are not affected by two consecutive nights of sleep restriction to 4 h. In contrast, morning concentrations of testosterone were found to be markedly reduced after total SD for one night and, notably, even after merely one night of mild sleep restriction scheduled during the second half of the night.

Moreover, an earlier study by Leproult and coworkers [179] demonstrated a profound reduction in testosterone concentrations after eight nights with an average sleep duration of 4 h 48 min as compared to 8 h 55 min in the control condition.

Thus, these two studies demonstrate that the duration of sleep restriction rather than the number of sleep restriction nights plays a pivotal role for morning circulating androgens levels.

Concerning sexual hormones, therefore, the difference of the response of hormonal pathway between acute and chronic loss of sleep is less pronounced. In fact, in both cases, these anabolic hormones decrease.

However, a high-dose testosterone treatment didn’t improve the length of sleep time, both NREM and REM stages in older men. [180] At the same time, Barrett-Connor et al. reported that lower testosterone levels were associated with less consolidated sleep (decreased sleep efficiency and increased awakenings) in elderly men [181]. Thus, both high and low circulating testosterone concentrations may be associated with sleep disturbances.

Despite an extensive body of literature that describes the effects of testosterone on sleep in men, only few studies have focused on the effect of testosterone on sleep in women and limited to women with sleep disorders.

As response to SD, young women show a more dramatic increase in SWA after 40 h of total SD than do age-matched men, demonstrating a greater response to sleep loss.

The Seattle Midlife Women’s Health Study reported no association between sleep disruption and testosterone during the menopausal transition and early postmenopause, although a negative trend was observed [182]. Studies describing the effects of testosterone in women are rare and demonstrate inconsistent findings. This is probably because of the complexity to measuring hormonal androgen levels across the menstrual cycle and many other confounding factors, such as the use of birth control pills, normal versus abnormal cycles, and baseline testosterone levels.

Obstructive sleep apnea (OSA) is one of the most common sleep disorders and is characterized by an airflow interruption despite persistent respiratory efforts, causing chronic SD due to frequent awakenings at the termination of apneic episodes. Testosterone may inhibit breathing via several mechanisms, because upper airway patency is determined by many structural and neuromuscular factors controlling pharyngeal airway size and collapsibility.

The well-established male preponderance of OSA leads to the hypothesis that gonadal hormones were involved in the pathological mechanism of this sleep-breathing disorder. Indeed induction of OSA or symptom exacerbation have been described after testosterone supplementation in hypogonadal males [180]. The results showed that testosterone injections shortened sleep, worsened sleep apnea, and increased the duration of hypoxemia. Obesity and aging, in conjunction with hypoxia and sleep fragmentation, have also been indicated as additional contributing factors in the decreased pulsatile testosterone concentrations in OSA subjects. Concerning thyroid hormonal patterns, various studies analyzed the relationship between sleep and TSH, T3 and T4 levels.

TSH has a circadian rhythm, with a maximum in the middle of the biological night and nadir during the biological afternoon. No circadian rhythm are present in total T3 or T4 concentrations.

Nighttime TSH levels are higher in the absence than in the presence of sleep indicating that sleep has an inhibitory influence on TSH secretion and opposes the circadian influence on this hormone.

TSH values are negatively correlated with both SWS and SWA. Moreover, recovery sleep following SD suppresses TSH levels to larger extent than normal sleep does, further suggesting a relationship between NREM sleep intensity and the magnitude of TSH suppression.

On the contrary, a study examined alterations in the 24-h hormonal profiles in the state of sleep debt. The 24-h mean TSH levels were reduced and the nocturnal TSH elevation was markedly dampened, most likely as a result of elevated levels of thyroid hormones [183].

Several studies have revealed the profound effects of acute SD on the secretory activity of the pituitary-thyroid axis in healthy men. Among these, one had different results [184]. The authors used in 11 healthy volunteers (mean age 39.± 5 years) a protocol of recurrent restriction of the overnight time-in-bed of 5.5 or 8.5 h/night. Tests obtained after 2 weeks of this experimental sleep restriction did not show the well-known rise in serum TSH and thyroid hormone concentrations, typical of acute sleep loss. Instead, partial sleep loss was accompanied by modest but statistically significant declines in TSH and free T4, which were seen mainly in female study participants.

The investigators reported various explanation for their findings, but they concluded that other long sleep restriction experiments will be needed to determine whether the observed changes in TSH and free T4 represent a step in the normal process of re-equilibration after a transient shift due to acute sleep loss, or the result of central changes in the hypothalamic–pituitary–thyroid axis similar to those seen in sleep deprived rodents [161]. We found many studies which aimed to estimate the functional role
of nocturnal sleep in the regulation of human-energy metabolism, or sleep-disordered breathing in association with hypothyroidism and metabolic risk factors. Because of the young samples usually considered, we left out these articles. No study was based on older people.

However, in special condition such as thyroid cancer, SD has been associated with elevated TSH concentration as suggested by a recent study conducted in postmenopausal women [185]. This large, prospective study considered women 50–79 years selected from the Women’s Health Initiative and followed over an average of 11-year period. Subjects with higher insomnia scores had a significantly higher risk of thyroid cancer. This observation was confined in non-obese women. In the same study, was not observed any significant association between sleep duration and risk of thyroid cancer.

In conclusion, chronic sleep loss seems to increase the levels of TSH and thyroid hormones, and it is conceivable that in older people, lacking the homeostatic mechanisms due to the plasticity of hormonal system present in young people, the net effect is the promotion of a catabolic status.

10. Conclusions and perspectives

We summarized the current literature available on the relationship between stress hormones and different domains of cognitive function in older people including attention, concentration, language, memory, psychomotor and executive function. These domains can be deteriorated in elderly, and one of the potential causes is the altered hormonal pathway.

Alterations in hormone profile that occur during the aging process are implicated in the development of cognitive impairment, through a variety of mechanisms involving the adaption to stressful conditions. In fact, stress causes increased levels of stress hormones with elderly people less resilient to return to a basal condition of homeostasis.

We believe that it is essential to consider the parallel changes in multiple hormonal axes in older men (PADAM, somatopause, adrenopause, thyroid dysfunction) to better address the role of multiple hormonal dysregulation in the development of cognitive impairment [186].

Further studies are needed to fully understand the links between hormones and cognitive functioning, as well as the benefits of hormonal supplementation in protecting against cognitive decline and/or dementia.

Cognitive impairment and dementia are the results of multiple factors, such as genetic factors, socioeconomic factors, life-style and health status. Into this multifactorial origin of dementia, multiple hormonal dysregulation rather than a single hormonal derangement has more likely a role in the development of cognitive impairment. Because of the association between stress hormones and cognitive disruptions, stress has great importance in determining of cognition in the elderly.

In our review, we have chosen to examine a particular stressor, such as SD.

Distinguishing physiologic age-related changes in sleep from pathologic sleep can be problematic, because of the close association in the elderly between sleep disorders and a higher prevalence of comorbid conditions that disrupt sleep.

We have focused on cognitive effects caused by not only acute, but especially chronic sleep loss. In fact, it is imaginable that sleep disruptions in older men are more similar to a condition of chronic SD.

Nevertheless, the most controlled studies in humans applied acute SD protocols, while little is known about the consequences of chronic sleep restriction and disruption as they often occur in real life.

On the basis of the scientific evidence, it is possible to state that good sleep quality has a direct effect on the neuroendocrine activity, allowing the optimal regulation of the hormonal homeostasis.

SD alters these hormonal profiles, causing increase in GC and TSH levels, decrease in testosterone concentrations and alteration in GHRH and GH release.

Animal studies suggest that SD has effects on hippocampal structure and function that are not explained by elevated adrenal GC. These results raise the possibility that in humans chronic sleep disruptions associated with lifestyle, adverse life events, aging, sleep disorders, neurodegenerative diseases, or other conditions may attenuate the production of new hippocampal neurons, thereby compromising hippocampal adaptive plasticity and associated memory or other functions.

Apart from sleep loss, also a chronic insomnia influences the diurnal hormonal pattern [187,188]. In addition, there is growing evidence that short sleep duration is associated with a high risk of hypertension [189] and normotensive subjects with chronic insomnia have higher nighttime blood pressure (BP) and a blunted day-to-night BP reduction compared to age-matched good sleepers [190].

Because of the lack of studies considering SD as a confounding factor, we propose the need to conduct further investigations which may pay attention to the role of sleep disorders in elderly.

Moreover, the full constellation of consequences caused by prolonged sleep restriction, which is well-documented in rats and young people, remains to be demonstrated in older people.

Further research is needed to understand the role of hormones in aging associated sleep alterations, and to clarify how SD affects various hormonal systems. Such research will enable the development of appropriate hormonal strategies to prevent or attenuate bad consequences of sleep loss.

Contributors

Maggio and Ceda contributed in study concept and design. Colizzi, Fischella and Valenti contributed in acquisition of data. Dall’Aglio, Ruffini, Laurentini, Parrino and Maggio contributed in analysis and interpretation of data. Maggio, Colizzi, Fischella and Parrino contributed in drafting of the manuscript. Maggio, Valenti, Parrino and Ceda contributed in critical revision of the manuscript for important intellectual content. Maggio, Parrino and Ceda contributed in study supervision.

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References


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Richardson NG, Duan KE, Billiot J, Bazan NG, Laporte CJ. Eliminating the adverse stress response does not affect sleep deprivation-induced acquisition deficits in the water maze. Life Science 2006;78(24):2833–8.


