

Cognitive Function

Literature Review

The Journal of Clinical Endocrinology & Metabolism Vol. 87, No. 11 5001-5007

Longitudinal Assessment of Serum Free Testosterone Concentration Predicts Memory Performance and Cognitive Status in Elderly Men

Scott D. Moffat, Alan B. Zonderman, E. Jeffrey Metter, Marc R. Blackman, S. Mitchell Harman and Susan M. Resnick

Laboratory of Personality and Cognition (S.D.M., A.B.Z., S.M.R.) and Laboratory of Clinical Investigation (E.J.M., S.M.H.), National Institute on Aging, National Institutes of Health, Gerontology Research Center, Baltimore Maryland 21224; and Laboratory of Clinical Investigation, National Center for Complementary and Alternative Medicine, National Institutes of Health (M.R.B.), Bethesda, Maryland 20892

Address all correspondence and requests for reprints to: Susan M. Resnick, Ph.D., National Institute on Aging, Gerontology Research Center, 5600 Nathan Shock Drive, Baltimore, Maryland 21224. E-mail:

resnick@jpc.grc.nia.nih.gov

Abstract

Circulating testosterone (T) levels have behavioral and neurological effects in both human and nonhuman species. Both T concentrations and neuropsychological function decrease substantially with age in men. The purpose of this prospective, longitudinal study was to investigate the relationships between age-associated decreases in endogenous serum T and free T concentrations and declines in neuropsychological performance. Participants were volunteers from the Baltimore Longitudinal Study of Aging, aged 50–91 yr at baseline T assessment. Four hundred seven men were followed for an average of 10 yr, with assessments of multiple cognitive domains and contemporaneous determination of serum total T, SHBG, and a free T index (FTI). We administered neuropsychological tests of verbal and visual memory, mental status, visuomotor scanning and attention, verbal knowledge/language, visuospatial ability, and depressive symptomatology. Higher FTI was associated with better scores on visual and verbal memory, visuospatial functioning, and visuomotor scanning and a reduced rate of longitudinal decline in visual memory. Men classified as hypogonadal had significantly lower scores on measures of memory and visuospatial performance and a faster rate of decline in visual memory. No relations between total T or the FTI and measures of verbal knowledge, mental status, or depressive symptoms were observed. These results suggest a possible beneficial relationship between circulating free T concentrations and specific domains of cognitive performance in older men.

OLDER AGE IS associated with functional declines throughout the body, including some aspects of cognitive performance. Although only some elderly individuals develop dementia, declines in cognitive

functioning impact daily living for many. However, there are individual differences in age-related cognitive changes, and the factors that contribute to this variability have not been well characterized. Recent evidence suggesting that age-related alterations in the endocrine environment may modulate cognitive changes has generated considerable interest.

In women, there is evidence that postmenopausal estrogen replacement therapy (ERT) may exert beneficial effects on specific cognitive functions, most pronounced for verbal memory, and may reduce the incidence and delay the onset of Alzheimer's disease. In men, there is limited information on the effects of testosterone supplementation on cognition despite substantial declines in endogenous testosterone (T) with advancing age. Total T levels decline by as much as 50% from ages 30–80 yr, and as many as 68% of men over 70 yr can be classified as hypogonadal based on their calculated free T concentrations. These observations raise the question of whether the loss of androgens with age (the male andropause) may be associated with age-related declines in selected cognitive functions.

T manipulations both in the neonatal period and later in life have been shown unequivocally to exert behavioral effects in nonhuman species. In humans, studies have focused on those abilities for which reliable sex differences have been reported, such as visuospatial ability. The organizational effects of T on visuo-spatial performance later in life have been suggested by enhanced performance in females exposed prenatally to excess androgens and reduced spatial performance in males with idiopathic hypogonadotropic hypogonadism. The majority of investigations examining the association between circulating T levels and cognition have been small studies in young adult men and women. The results of these studies have been somewhat mixed, with some studies reporting positive linear relationships and others reporting that moderate levels of T (an inverted U) may be associated with higher visuospatial cognitive performance.

Few studies have examined the association between T and cognition in older men. In one such study Barrett-Connor *et al.* measured the association between baseline T and neuropsychological performance in 547 men between the ages of 59 and 89 yr. After controlling for a number of possible confounding variables, they found higher bioavailable T concentrations in men who scored better on a measure of long-term verbal memory. In three small, randomized, placebo-controlled clinical trials, T administration in older men was reported to improve visuospatial performance, verbal memory, and working memory.

In the present study we followed a sample of 407 men with age at baseline T assessment ranging from 50–90 yr for a mean duration of 9.7 yr. We collected multiple serum samples for determination of total T and SHBG and free T concentrations and obtained multiple cognitive measures across a variety of cognitive domains over the same time interval. We report here a prospective longitudinal study assessing the impact of long-term total and free T levels on neurocognitive function in this sample of community-dwelling men.

Menopause and mitochondria: windows into estrogen effects on Alzheimer's disease risk and therapy.

[Prog Brain Res.](#) 2010;182:77-96.

[Henderson VW](#), [Brinton RD](#).

Department of Health Research & Policy (Epidemiology), Stanford University, Stanford, CA, USA.
vhenderson@stanford.edu

Abstract

Metabolic derangements and oxidative stress are early events in Alzheimer's disease pathogenesis. Multi-faceted effects of estrogens include improved cerebral metabolic profile and reduced oxidative stress through actions on mitochondria, suggesting that a woman's endogenous and exogenous estrogen exposures during midlife and in the late post-menopause might favourably influence Alzheimer risk and symptoms. This prediction finds partial support in the clinical literature. As expected, early menopause induced by oophorectomy may increase cognitive vulnerability; however, there is no clear link between age at menopause and Alzheimer risk in other settings, or between natural menopause and memory loss. Further, among older post-menopausal women, initiating estrogen-containing hormone therapy increases dementia risk and probably does not improve Alzheimer's disease symptoms. As suggested by the 'critical window' or 'healthy cell' hypothesis, better outcomes might be expected from earlier estrogen exposures. Some observational results imply that effects of hormone therapy on Alzheimer risk are indeed modified by age at initiation, temporal proximity to menopause, or a woman's health. However, potential methodological biases warrant caution in interpreting observational findings. Anticipated results from large, ongoing clinical trials [Early Versus Late Intervention Trial with Estradiol (ELITE), Kronos Early Estrogen Prevention Study (KEEPS)] will help settle whether midlife estrogen therapy improves midlife cognitive skills but not whether midlife estrogen exposures modify late-life Alzheimer risk. Estrogen effects on mitochondria adumbrate the potential relevance of estrogens to Alzheimer's disease. However, laboratory models are inexact embodiments of Alzheimer pathogenesis and progression, making it difficult to surmise net effects of estrogen exposures. Research needs include better predictors of adverse cognitive outcomes, biomarkers for risks associated with hormone therapy, and tools for monitoring brain function and disease progression.

PMID: 20541661 [PubMed - in process]

Neuropsychiatric aspects of hypothyroidism and treatment reversibility.

[Davis JD, Tremont G.](#)

Department of Psychiatry and Human Behavior, Brown Medical School, Providence, RI 02903, USA.
jdavis3@lifespan.org

Abstract

Thyroid hormone has important actions in the adult brain, and it is well accepted that hypothyroidism is associated with neuropsychiatric complaints and symptoms. Neuropsychiatric symptoms refer to a spectrum of emotional and cognitive problems that are directly related to changes in the brain secondary to multiple factors, including the direct effects of thyroid disease, as well as hormone deprivation in brain tissue. Hypothyroidism impacts aspects of cognitive functioning and mood. More severe hypothyroidism can mimic melancholic depression and dementia. Neuropsychiatric symptoms tend to improve with treatment and normalization to a euthyroid state, though the pattern is inconsistent and complete recovery is uncertain. The degree to which mild hypothyroidism, or subclinical hypothyroidism (SCH), impacts mood and cognitive functions and whether these symptoms respond to treatment, remains controversial. Most studies support a relationship between thyroid state and cognition, particularly slowed information processing speed, reduced efficiency in executive functions, and poor learning. Furthermore, hypo-thyroidism is associated with an increased susceptibility to depression and reductions in health-related quality of life. Controlled studies suggest that cognitive and mood symptoms improve with treatment, though the data are equivocal and limited by diverse methodologies. Functional neuroimaging data provide support for the mood and cognitive findings and treatment reversibility for both overt and SCH. These findings are not, however, without controversy. Recent investigations into the impact of SCH on cognition and mood, coupled epidemiological studies investigating the normal spectrum of thyroid stimulating hormone, have fueled significant debate regarding the appropriate, healthy range for TSH levels. This has led to concern over whether patients with overt hypothyroidism may be undertreated and whether SCH patients are truly out of the range of normal thyroid functioning and should be treated. The following is a review of the extant literature on the impact of hypothyroidism on cognition and mood, reversibility of symptoms, and treatment approaches. The spectrum of thyroid disease is reviewed, but mild, or subclinical, hypothyroidism is emphasized. The potential role of autoimmunity in neuropsychiatric symptoms and treatment resistance is addressed. Limitations of the current literature and future directions are discussed.

PMID: 17353866 [PubMed - indexed for MEDLINE]

The stress system in the human brain in depression and neurodegeneration.

[Swaab DF](#), [Bao AM](#), [Lucassen PJ](#).

Netherlands Institute for Brain Research, Meibergdreef 33, 1105 AZ Amsterdam, The Netherlands.
d.f.swaab@nih.knaw.nl

Abstract

Corticotropin-releasing hormone (CRH) plays a central role in the regulation of the hypothalamic-pituitary-adrenal (HPA)-axis, i.e., the final common pathway in the stress response. The action of CRH on ACTH release is strongly potentiated by vasopressin, that is co-produced in increasing amounts when the hypothalamic paraventricular neurons are chronically activated. Whereas vasopressin stimulates ACTH release in humans, oxytocin inhibits it. ACTH release results in the release of corticosteroids from the adrenal that, subsequently, through mineralocorticoid and glucocorticoid receptors, exert negative feedback on, among other things, the hippocampus, the pituitary and the hypothalamus. The most important glucocorticoid in humans is cortisol, present in higher levels in women than in men. During aging, the activation of the CRH neurons is modest compared to the extra activation observed in Alzheimer's disease (AD) and the even stronger increase in major depression. The HPA-axis is hyperactive in depression, due to genetic factors or due to aversive stimuli that may occur during early development or adult life. At least five interacting hypothalamic peptidergic systems are involved in the symptoms of major depression. Increased production of vasopressin in depression does not only occur in neurons that colocalize CRH, but also in neurons of the supraoptic nucleus (SON), which may lead to increased plasma levels of vasopressin, that have been related to an enhanced suicide risk. The increased activity of oxytocin neurons in the paraventricular nucleus (PVN) may be related to the eating disorders in depression. The suprachiasmatic nucleus (SCN), i.e., the biological clock of the brain, shows lower vasopressin production and a smaller circadian amplitude in depression, which may explain the sleeping problems in this disorder and may contribute to the strong CRH activation. The hypothalamo-pituitary thyroid (HPT)-axis is inhibited in depression. These hypothalamic peptidergic systems, i.e., the HPA-axis, the SCN, the SON and the HPT-axis, have many interactions with aminergic systems that are also implicated in depression. CRH neurons are strongly activated in depressed patients, and so is their HPA-axis, at all levels, but the individual variability is large. It is hypothesized that particularly a subgroup of CRH neurons that projects into the brain is activated in depression and induces the symptoms of this disorder. On the other hand, there is also a lot of evidence for a direct involvement of glucocorticoids in the etiology and symptoms of depression. Although there is a close association between cerebrospinal fluid (CSF) levels of CRH and alterations in the HPA-axis in depression, much of the CRH in CSF is likely

to be derived from sources other than the PVN. Furthermore, a close interaction between the HPA-axis and the hypothalamic-pituitary-gonadal (HPG)-axis exists. Organizing effects during fetal life as well as activating effects of sex hormones on the HPA-axis have been reported. Such mechanisms may be a basis for the higher prevalence of mood disorders in women as compared to men. In addition, the stress system is affected by changing levels of sex hormones, as found, e.g., in the premenstrual period, ante- and postpartum, during the transition phase to the menopause and during the use of oral contraceptives. In depressed women, plasma levels of estrogen are usually lower and plasma levels of androgens are increased, while testosterone levels are decreased in depressed men. This is explained by the fact that both in depressed males and females the HPA-axis is increased in activity, parallel to a diminished HPG-axis, while the major source of androgens in women is the adrenal, whereas in men it is the testes. It is speculated, however, that in the etiology of depression the relative levels of sex hormones play a more important role than their absolute levels. Sex hormone replacement therapy indeed seems to improve mood in elderly people and AD patients. Studies of rats have shown that high levels of cumulative corticosteroid exposure and rather extreme chronic stress induce neuronal damage that selectively affects hippocampal structure. Studies performed under less extreme circumstances have so far provided conflicting data. The corticosteroid neurotoxicity hypothesis that evolved as a result of these initial observations is, however, not supported by clinical and experimental observations. In a few recent postmortem studies in patients treated with corticosteroids and patients who had been seriously and chronically depressed no indications for AD neuropathology, massive cell loss, or loss of plasticity could be found, while the incidence of apoptosis was extremely rare and only seen outside regions expected to be at risk for steroid overexposure. In addition, various recent experimental studies using good stereological methods failed to find massive cell loss in the hippocampus following exposure to stress or steroids, but rather showed adaptive and reversible changes in structural parameters after stress. Thus, the HPA-axis in AD is only moderately activated, possibly due to the initial (primary) hippocampal degeneration in this condition. There are no convincing arguments to presume a causal, primary role for cortisol in the pathogenesis of AD. Although cortisol and CRH may well be causally involved in the signs and symptoms of depression, there is so far no evidence for any major irreversible damage in the human hippocampus in this disorder.

PMID: 15996533 [PubMed - indexed for MEDLINE]

[Neurology](#). 2009 Nov 24;73(21):1729-37.

Characteristics of hormone therapy, cognitive function, and dementia: the prospective 3C Study.

[Ryan J](#), [Carrière I](#), [Scali J](#), [Dartigues JF](#), [Tzourio C](#), [Poncet M](#), [Ritchie K](#), [Ancelin ML](#).

INSERM U888, Nervous System Pathologies: Epidemiological and Clinical Research, Hôpital La Colombière, BP 34493, 34093 Montpellier Cedex 5, France. joanne.ryan@inserm.fr

Abstract

OBJECTIVES: To examine the association between hormone therapy (HT) and cognitive performance or dementia, focusing on the duration and type of treatment used, as well as the timing of initiation of HT in relation to the menopause.

METHODS: Women 65 years and older were recruited in France as part of the Three City Study. At baseline and 2- and 4-year follow-up, women were administered a short cognitive test battery and a clinical diagnosis of dementia was made. Detailed information was also gathered relating to current and past HT use. Analysis was adjusted for a number of sociodemographic, behavioral, physical, and mental health variables, as well as APOE epsilon4.

RESULTS: Among 3,130 naturally postmenopausal women, current HT users performed significantly better than never users on verbal fluency, working memory, and psychomotor speed. These associations varied according to the type of treatment and a longer duration of HT appeared to be more beneficial. However, initiation of HT close to the menopause was not associated with better cognition. HT did not significantly reduce dementia risk over 4 years but current treatment diminished the negative effect associated with APOE epsilon4.

CONCLUSIONS: Current hormone therapy (HT) was associated with better performance in certain cognitive domains but these associations are dependent on the duration and type of treatment used. We found no evidence that HT needs to be initiated close to the menopause to have a beneficial effect on cognitive function in later life. Current HT may decrease the risk of dementia associated with the APOE epsilon4 allele.

PMID: 19933973 [PubMed - indexed for MEDLINE]