TESTOSTERONE AND THYROID STIMULATING HORMONE LEVELS IN ALZHEIMER'S DISEASE AND THEIR RELATIONSHIP TO COGNITION

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A Thesis

Presented to

The Faculty of the Department

of Psychology

University of Houston

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In Partial Fulfillment

Of the Requirements for the Degree of

Master of Arts

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By

Jennifer N. Travis Seidl

December, 2012

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ABSTRACT

Previous research suggests that low levels of testosterone may be associated with the development of Alzheimer's disease (AD). Furthermore, research indicates that low levels of testosterone may be associated with poorer performance on certain neuropsychological tests, as well as increased risk of depression. Evidence also suggests that low levels of Thyroid Stimulating Hormone (TSH) may be associated with AD and with impairments on neuropsychological tests. Thyroid dysfunction has also been linked to depression. For the testosterone analyses, this study utilized data from 61 healthy older men and 68 men with probable AD. Results of ANCOVA indicated that testosterone levels did not differ between the two groups. Regression analyses revealed that testosterone levels did not significantly predict performance on neuropsychological tests or on a measure of depression among AD men. However, testosterone marginally significantly predicted performance on a test of delayed memory, with higher levels of testosterone associated with a higher score. Among controls, testosterone levels predicted estimated premorbid VIQ as measured by a test of word reading. Testosterone was also found to marginally significantly predict performance on a test of verbal fluency, with higher levels of testosterone associated with better performance. For the TSH analyses, data were utilized from 198 healthy elderly controls and 197 probable AD patients. ANCOVA revealed that the groups' TSH levels did not differ significantly. Regression results indicated that TSH levels did not predict performance on any neuropsychological tests in the AD patients, but within the control group, TSH levels predicted performance on a test of word reading. Additional analyses revealed no association between levels of TSH and testosterone in men. Findings suggest that testosterone and TSH

are not associated meaningfully with most neuropsychological test performances in AD patients.

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Introduction

Overview of Testosterone and Thyroid Stimulating Hormone

Hormone levels often change substantially in the course of normal aging, and may contribute to the risk for developing Alzheimer's disease (AD) and/or impact the neuropsychological functioning of Alzheimer's patients. The present study will examine whether levels of testosterone and thyroid stimulating hormone (TSH) are lower in AD patients than in controls, as well as study the impact of these hormone levels on neuropsychological functioning among AD patients.

Testosterone is the primary sex hormone in males and is a member of the androgen group of steroids. As such, it plays a role in the development of the male brain. However, the brain is sensitive to levels of testosterone even as an adult. Testosterone is often converted to estradiol by an enzyme called aromatase. It can influence the brain either through its actions as testosterone and activation of androgen receptors, or by conversion to estradiol and activation of estrogen receptors. Androgen receptors are located within areas of the brain such as the hippocampus and prefrontal cortex, so lower levels of testosterone are hypothesized to have an impact on cognition, especially memory and visuospatial abilities. Since testosterone levels generally decline as men age, low testosterone levels may impact the cognitive abilities of older men. Further research suggests that low levels of testosterone may lead to an increased risk of developing Alzheimer's Disease (AD), as testosterone may play a protective role against AD neuropathology, such as the neurotoxicity of amyloid beta (Aβ) (Pike, 2001).

There are a number of hormones that are related to thyroid functioning. Thyrotropin Releasing Hormone (TRH) is a hormone that is released from the hypothalamus and

stimulates the secretion of Thyroid Stimulating Hormone (TSH) from the anterior pituitary. When TSH binds to receptors on thyroid cells, Thyroxine (T_4) and tri-iodothyronine (T_3) are released from the thyroid cells. Only small amounts of T_4 and T_3 are free during circulation because most of the hormones are bound to proteins. Even small changes in the amount of free T_4 (fT_4) and free T_3 (fT_3) can lead to changes in the amount of TSH that is secreted. Thyroid dysfunction can cause increased or decreased levels of these thyroid hormones. Generally, hypothyroidism results from lowered levels of T_4, which causes an increase in TSH as a means of compensation. Subclinical hypothyroidism can occur when thyroid hormones levels (T_4 and T_3) are normal, but TSH levels are elevated. Likewise, hyperthyroidism is often caused by increased levels of T_4, accompanied by a decrease in TSH levels, and a subclinical form of hyperthyroidism can result when the TSH levels are below normal levels, but levels of T_4 are within normal limits.

Thyroid dysfunction is relatively common, and becomes increasingly common with older age. Thyroid hormones play a role in brain development, but there is also evidence that thyroid dysfunction in adults may play a role in the development of cognitive and psychiatric problems, most notably depression. Given that older adults may be more susceptible to varying levels of thyroid hormones (Davis et al., 2003), there is also concern that thyroid dysfunction may lead to an increased risk of developing dementia. Thyroid dysfunction has previously been regarded as a reversible cause of dementia, but some research now suggests that thyroid dysfunction may be associated with increased risk of developing the neurofibrillary tangles and plaques that contribute to AD (De Jong et al., 2009).

Testosterone and Normal Aging

For a comprehensive review of the literature, please see Table 1.

Testosterone levels in men decline gradually with age at an average rate of 0.110 nmol/L per year (Harman et al., 2001). Bioavailable testosterone is a form of testosterone that is not bound to sex hormone binding globulin (SHBG) (Raynaud et al., 2008). As men age, the levels of SHBG increase, leading to an even steeper decline in levels of bioavailable testosterone when compared to the total level of testosterone (Harman et al., 2001; Feldman et al., 2002). Bioavailable testosterone in particular may be linked to cognitive performance in men and may be a better predictor of cognitive performance than total testosterone level (Yaffe et al., 2002).

There may be an association in men, particularly older men, between testosterone levels and cognitive performance on certain tasks. Levels of total testosterone have been found to be related to performance on a measure of fluid intelligence (Aleman et al., 2001). One study found an association between MMSE scores and levels of total and bioavailable testosterone in older men (Hyde et al., 2010). However, bioavailable testosterone may be more associated with cognitive performance than total testosterone because of its ability to cross the blood-brain barrier (Yaffe et al., 2002). Higher levels of bioavailable testosterone have also been linked to better performance on tasks of semantic and verbal memory and visuospatial abilities (Thilers et al., 2006). As age increased, levels of testosterone were found to have more influence on cognitive performance in this group of men. Men with higher levels of bioavailable testosterone have also been found to perform better on tests of mental control and long-term verbal memory (Barrett-Connor et al., 1999). Older men with higher bioavailable testosterone performed better on the MMSE, Digit Symbol, and Trailmaking Part B tests than men with lower levels of bioavailable testosterone (Yaffe et al., 2002). However, there may be a negative association between testosterone levels in men and

verbal fluency, such that higher levels of testosterone are associated with lower performance on tests of verbal fluency (Wolf & Kirschbaum, 2002).

A longitudinal study by Moffat et al. (2002) of men over 50 years old found a relationship between levels of bioavailable testosterone and scores on tests of verbal memory, visual memory, visuospatial skills, and visuomotor scanning, such that higher levels of bioavailable testosterone were associated with higher scores on tests of these skills. No relationship was found between levels of bioavailable testosterone and tests of depression or general mental status. Importantly, men in this study who were hypogonadal had an accelerated decline in performance on tests of visual memory, which was found to be predictive of a diagnosis of dementia years later.

Many studies have found a link between testosterone levels and performance on tests of visuospatial abilities and memory specifically (for a review, see Warren et al., 2008). Gouchie and Kimura (1991) suggested that sex hormones such as testosterone and estrogen may play a role in skills that have been found to differ between sexes, such as spatial and verbal abilities. There may be a curvilinear relationship between levels of testosterone and spatial abilities, meaning that levels that are too high or too low result in reduced performance on spatial tasks (Sternbach, 1998). This finding implies that there is a specific range of testosterone levels at which optimal performance on spatial tasks occurs. A study of testosterone supplementation in healthy older men by Janowsky et al. (1994) found an improvement in visuospatial performance following 3 months of supplementation. The authors hypothesized that testosterone influenced performance on these tasks through its inhibitory influence on estrogen levels, as better performance was found in those participants with lower levels of estrogen. Importantly, the authors noted that the amount of

supplementation administered did not raise the levels of testosterone supraphysiologically, or above the normal levels of testosterone, but merely to the levels of healthy young men.

Other studies of testosterone supplementation in healthy older men have produced mixed results (e.g., Cherrier, 1999). The findings of Cherrier et al. (2007) supported a curvilinear relationship between testosterone and cognitive abilities, with men who received large or small increases in testosterone levels exhibiting no change on tasks of verbal and spatial memory. However, men who had moderate increases in testosterone levels experienced an improved performance on these tests. Wolf et al. (2000) also found that raising the levels of testosterone in men to supraphysiological levels has been shown to have no beneficial effects on cognitive tests of spatial or verbal memory, and blocked the practice effect on tests of verbal fluency. However, in another study in which testosterone levels were raised to supraphysiological levels, testosterone treatment was shown to improve verbal fluency and worsen visuospatial abilities (O'Connor et al., 2001). A study of healthy, non-demented older men given different doses of testosterone found that testosterone supplementation resulted in improved visuospatial abilities on a timed test, although this improvement was hypothesized to be the result of increased speed of processing rather than spatial accuracy itself (Gray et al., 2005).

Androgen deprivation studies allowed researchers to test the effects of declining levels of testosterone in men. Androgen deprivation is a common treatment for prostate cancer. One study of prostate cancer patients undergoing androgen deprivation treatment found that immediate recall of previously presented information, but not delayed recognition, was impaired when compared to performance on the tasks by controls while undergoing treatment (Bussiere et al., 2005). Patients were found to have a steeper rate of forgetting than

controls. Another study of men undergoing androgen deprivation treatment for prostate cancer found increased levels of plasma beta-amyloid (Aβ) during treatment, in addition to lower levels of testosterone and estradiol (Almeida et al., 2004). This same study found an improvement of scores on tests measuring verbal memory and overall cognitive performance after discontinuing treatment.

There may also be a link between hypogonadism and mood in older men (Hintikka et al., 2009). In Almeida et al.'s (2004) study of androgen deprivation in prostate cancer patients, treatment was associated with increased levels of depression and anxiety. Some of these hypogonadal, depressed older men may experience an improvement of symptoms following androgen treatment (Seidman & Walsh, 1999). However, studies of testosterone replacement in depressed men have produced mixed results (Sternbach, 1998). One review by Shamlian and Cole (2006) suggests that androgen therapy may relieve depressive symptoms in the short term, but that it is not effective as an ongoing treatment in depressed older men.

There are several possible ways that testosterone may exert an effect on cognition. Androgen receptors are located in the hippocampus, amygdala, and prefrontal cortex, suggesting that these areas of the brain may be particularly vulnerable when levels of androgens such as testosterone decline (Bussiere et al., 2005). Higher levels of testosterone in midlife have been associated with larger regional brain volumes in the frontal and parietal lobes at ten to sixteen year follow-up, although the same study found no association between hormone levels and cognitive performance (Lessov-Schlaggar et al., 2005). Another study measured bioavailable testosterone levels at multiple points over a 14 year period and found that levels of bioavailable testosterone predicted a pattern of regional cerebral blood flow in

older men (Moffat & Resnick, 2007). In this study, PET scans showed increased blood flow to the hippocampus, anterior cingulate gyrus, right hippocampal gyrus, and right inferior frontal region in older men with higher levels of testosterone. The authors suggested that higher bioavailable testosterone levels lead to an increase in blood flow to the hippocampus in particular, although it is also possible that activity in the hippocampus and other areas may have an effect on the hypothalamic-pituitary axis and lead to increased levels of testosterone in circulation. The synaptic density of the hippocampus is influenced by testosterone (Janowsky, 2006) and damage in the hippocampus may cause much of the cognitive decline with aging in older adults, leading to impairment in spatial learning (Gallagher & Pelleymounter, 1988).

Table 1: Testosterone and Normal Aging Study Findings

Study	***N***	**Age**	**Findings**
Aleman et al. (2001)	25	65-76	Total T associated with higher scores on visuospatial abilities and processing speed.
Almeida et al. (2004)	40	44-83	Increased scores on BDI during androgen deprivation treatment; increased performance on dementia screening measure after treatment ended.
Barrett-Connor et al. (1999)	547	55-89	Higher total bioavailable T associated with better scores on verbal memory.
Bussiere et al. (2005)	30	50-80	Androgen deprivation treatment leads to impairment on a task of immediate recognition of a previously learned word list.
Cherrier et al. (2007)	57	50-85	Supplementation with moderate increases leads to improvements in verbal and spatial memory.
Emmelot-Vonk et al. (2008)	207	60-80	Testosterone supplementation in men with low T levels did not lead to an improvement in cognition.
Fonda et al. (2005)	981	48-80	No association between T (free or total) and cognition.
Gray et al. (2005)	44	60-75	Testosterone supplementation was not associated with changes on a measure of depression.
Hintikka et al. (2009)	1347	25-65	Higher levels of free T associated with lower scores on measures of depression.
Hyde et al. (2010)	585	>65	Total and free T levels not associated with measures of immediate or delayed verbal recall; but both associated with MMSE.
Janowsky et al. (1994)	56	60-75	Increase in T levels to 150% of baseline levels leads to improvement on visuospatial abilities.
Lessov-Schlaggar et al. (2005)	514	59-70	No association between levels of T and executive function or visual and verbal memory. Higher T levels were associated with larger hemispheric, frontal, and parietal regional brain volumes and smaller L occipital.
Martin et al. (2009)	96	50-70	Free T associated with attentional control.
Moffat et al. (2002)	407	>50	Higher free T levels associated with better scores on visual and verbal memory, visuospatial abilities, visuomotor scanning and attention, and a reduced rate of decline on visual memory longitudinally.
Moffat & Resnick (2007)	40	57.2 ±11.7	Higher free T levels associated with increased blood flow in the bilateral hippocampus.
O'Connor et al. (2001)	30	19-45	Testosterone injections associated with worse performance on tests of visuospatial abilities and improved performance on verbal fluency.

Thilers et al. (2006)	2383	35-90	Higher levels of free T associated with better performance on tests of visuospatial abilities, semantic memory, verbal memory.
Wolf et al. (2000)	30	68.7 ±1.9	Supraphysiological levels of testosterone blocked the practice effect on a test of verbal fluency.
Wolf & Kirschbaum (2002)	68	69 ±1.3	Higher levels of T associated with poorer performance on verbal fluency.
Yaffe et al. (2002)	310	>50	No association between total T and cognition found; but with higher bioavailable T, better performance on MMSE, visuomotor scanning, and processing speed.

Testosterone and Alzheimer's Disease

For a comprehensive review of the literature, please see Table 2.

Several studies have shown a relationship between testosterone in the development of Alzheimer's Disease (AD). Hogervorst et al. (2004) found that low testosterone was an independent predictor of AD in men. In a study of postmortem brain tissue (Rosario et al., 2011), it was found that men between the ages of 60 and 79 with either mild neuropathological changes or AD neuropathology had lower levels of testosterone than did men without these neuropathological changes. However, there was no difference in testosterone levels between the two groups in men over the age of 80. Furthermore, levels of testosterone were inversely related to levels of amyloid beta (Aβ) in men with mild neuropathological changes. Since the decrease in testosterone levels appeared to have occurred before the onset of pathology, the authors concluded that testosterone levels contribute to the development of AD rather than occur as a result of AD. Testosterone bioavailability may be reduced by high levels of sex hormone binding globulin (SHBG). In lean subjects (BMI between 20 and 22) with AD, SHBG was found to be higher than in subjects without AD (Paoletti et al., 2004). However, some studies have not supported an effect of testosterone on the development of AD. For example, Geerlings et al. (2006) found no association between testosterone levels and risk for dementia after adjusting for age. A study by Twist et al. (2000) showed that testosterone levels were unaffected in a sample of brain tissue from AD patients. Additionally, Pennanen et al. (2004) found no support for decreased levels of serum testosterone in AD.

However, many studies of testosterone supplementation in men with AD provide support for the hypothesis that testosterone levels affect cognition. One study of testosterone supplementation in men between the ages of 63 and 85 with AD or MCI demonstrated that

weekly intramuscular injections led to improvement in spatial memory, verbal memory, and visuospatial abilities (Cherrier et al., 2005). A pilot study involving intramuscular injections of testosterone in hypogondal men with AD found that the injections have at least as much of an effect on cognition as acetylcholinesterase inhibitors (Tan & Pu, 2003). Although the effects are temporary, like achetylcholinesterase inhibitors, they may slow the rate of deterioration by up to a year. While Lu et al. (2006) did not find a change in cognition in a group of men with AD following a testosterone gel applied to the skin, caregivers reported significantly improved quality of life following the gel application. There is also support (Kenny et al., 2004) that testosterone supplementation does not lead to increased aggression or a change in behavior in a sample of men with early cognitive decline.

In addition to finding an association between low serum testosterone levels and AD, a study by Hogervorst et al. (2002) found the interaction between testosterone and APOEε4 was also associated with AD. Healthy, non-demented controls who were APOEε4 positive had lower levels of testosterone than controls who were not APOEε4 positive. The authors speculated that APOEε4 positive men may be the only ones who will benefit from testosterone replacement therapy.

Testosterone levels may also be associated with levels of Aβ. A study by Gillet et al. (2003) found an inverse correlation between both testosterone levels and SHBG levels with plasma levels of Aβ. In men with dementia, lower testosterone levels were associated with increased plasma Aβ, leading the authors to conclude that subclinical androgen deficiency enhances the expression of these peptides. However, Verdile et al. (2008) found that serum luteinizing hormone (LH), which is negatively correlated with serum free testosterone levels in older men, correlates with Aβ in these men. Therefore, the authors reached the conclusion that it

is not the lower free testosterone levels that is correlated with increased levels of Aβ, but instead higher levels of serum LH. Testosterone may play a protective role against Aβ neurotoxicity, however, given that cultured hippocampal neurons exposed to AD-related Aβ experience less neurotoxicity in the presence of testosterone (Pike, 2001).

Table 2: Testosterone and AD Study Findings

Study	*N*	Age	Findings
Cherrier et al. (2005)	32	63-85	Men with AD and MCI received T injections, improvements found on spatial memory, visuospatial abilities, and verbal memory.
Chu et al. (2010)	153	>55	Higher levels of bioavailable T in older men predicts lower risk of development of AD.
Geerlings et al. (2006)	2300	71-93	T not associated with risk for dementia or cognitive decline.
Gillett et al. (2003)	28	74.5 ±6.9	Low levels of serum total testosterone are associated with increased levels of plasma Aβ in men with dementia or memory loss.
Hogervorst et al. (2002)	116	39-94	T levels lower in men with APOE4 allele; There is an interaction between low T and APOE4 in AD.
Hogervorst et al. (2004)	210	>46	Low testosterone was an independent predictor of AD.
Kenny et al. (2004)	11	73-87	No changes on any cognitive tests, depression, or ADLs after testosterone supplementation.
Lu et al. (2006)	38	>50	Men with AD who had testosterone treatments had improved quality of life according to caregivers.
Moffat et al. (2004)	574	55-64	Free testosterone levels were lower in men who developed AD, and this occurred before they were diagnosed.
Okun et al. (2004)	118	38-89	Decline in T observed in men with AD.
Paoletti et al. (2004)	200	76.53 ±1.50	Lower free androgenization index in men with AD than men without AD.
Pennanen et al. (2004)	30	73 ±9	No decreased levels of serum T in AD.
Rosario et al. (2011)	44	50-97	Brain levels of testosterone were lower in men 60-79 with mild neuropathology as well as advanced AD pathology; in men over 80, no differences.
Tan & Pu (2003)	36	68-80	Men with AD received T injections; improvements on dementia screening measures.
Verdile (2008)	40	>55	Serum free T levels not associated with development of Aβ.

Thyroid Hormones and Normal Aging

For a comprehensive review of the literature, please see Table 3.

Dysfunction of the thyroid is relatively common among older adults (Lamberts et al., 1997). However, older adults may be more susceptible to lower levels of thyroid dysfunction than younger adults (Davis et al., 2003). Some studies suggest that thyroid dysfunction can lead to cognitive deficits in older adults, even if the thyroid dysfunction is subclinical. In one study, men and women with subclinical hypothyroidism were found to have lower MMSE scores than those without thyroid dysfunction (Ceresini et al., 2009). Another study of older adults with subclinical hypothyroidism found that those with thyroid dysfunction performed more poorly on the MMSE and on tests of immediate and delayed verbal recall than older adults without thyroid dysfunction. The authors speculated that this association may be due to other disease processes commonly associated with hypothyroidism such as depression, cerebrovascular disease, or the higher anticholinergic burden; however, this was not the case (Cook et al., 2002). Hogervorst et al. (2008) also found lower MMSE scores among older adults with high TSH levels after controlling for age, education, depression levels, and cardiovascular factors. However, there was not an association between high TSH levels and a faster drop in MMSE scores over time (Hogervorst et al., 2008).

Even within the normal range, levels of thyroid hormones may have an impact on memory and other cognitive functions. In a longitudinal study of 75-93 year-olds with TSH levels within the normal range, declining levels of TSH were associated with simultaneously declining verbal fluency and visuospatial abilities. Additionally, there is longitudinal evidence suggesting that declining TSH levels may lead to episodic memory deficits at a 6 year follow-up. Depression, which frequently co-occurs with thyroid dysfunction and may be related to

cognition, was controlled for in this study (Wahlin et al., 2005). Livner, Wahlin, and Backman (2009) studied older adults within the normal range of TSH and thyroxine (T_4) and found a nonlinear association between prospective memory performance and TSH levels above the fourth quartile, such that those with higher TSH performed better on the prospective memory ask. In adults between the ages of 49 and 71, van Boxtel et al. (2004) found that higher levels of TSH were associated with lower levels of verbal memory performance. The effects disappeared when the sample was limited to those participants with TSH levels in the normal range. A strong relationship was also found between depression and lower performance on the memory task. However, not all studies have found an association between thyroid hormone levels and cognitive function. Gussekloo et al. (2004) found no association between levels of thyrotropin and free thyroxin and cognitive performance or depressive symptoms.

Depression frequently co-occurs with thyroid dysfunction (for a review, see Loosen, 1992). Chueire et al. (2006) found that in older adults, subclinical hypothyroidism was found to increase the risk for depression more than four-fold. In fact, it was more frequently observed among those with subclinical hypothyroidism than overt hypothyroidism, possibly because those with overt hypothyroidism are more likely to receive medical attention. Older adults may not even be aware that they are suffering from thyroid dysfunction if it is subclinical.

Table 3: TSH and Normal Aging Study Findings

Study	*N*	Age	Findings
Ceresini et al. (2009)	1343	23-102	Lower MMSE scores in older people with subclinical hyperthyroidism.
Chueire et al. (2007)	323	>60	Depression more likely in subjects with subclinical hypothyroidism than overt hypothyroidism.
Cook et al. (2002)	97	73.6 ±3.4	Those with higher TSH levels performed worse on tests of immediate and delayed verbal recall and MMSE.
Hogervorst et al. (2008)	1047	>65	Those with higher TSH levels had lower MMSE scores.
Livner et al. (2009)	103	>75	Participants with normal but high TSH levels perform better on a task of prospective memory.
van Boxtel et al. (2004)	120	49-71	Participants with higher levels of TSH had lower verbal memory performance.
Wahlin et al. (2005)	45	75-93	Declining TSH levels accompanied by declining performance on verbal fluency and visuospatial abilities.

Thyroid Hormones and Alzheimer's Disease

For a comprehensive review of the literature, please see Table 4.

Ganguli et al. (1996) found an association between subclinical hypothyroidism and cognitive impairment. Individuals with elevated TSH levels were found to have a three-to-four fold increased risk of dementia. Subclinical hyperthyroidism has also been associated with increased risk of developing AD (Kalmijn et al., 2000). De Jong et al., (2009) found that higher levels of fT_4 and T_4 were associated with increased risk for AD. T4 was also associated with increased levels of neurofibrillary tangles and plaques in the cortex. Even within the normal range, low levels of TSH may be a risk factor for the development of AD after controlling for confounding factors (Van Osch et al., 2004). TRH has been found to be protective against apoptosis and synapse loss. One study found a decrease in TRH in the hippocampus of individuals with AD when compared to elderly controls. TRH depletion was also associated with increased tau phosphorylation (Luo et al., 2002). Hogervorst et al. (2004) found that subclinical hyperthyroidism was related to higher levels of SHBG, which in turn was associated with lower levels of free testosterone. These low levels of free testosterone may then have an influence on the development of AD.

Thyroid dysfunction may also be predictive of development of AD in patients with MCI. Annerbo et al. (2006) found that lower TSH levels in older adults with MCI were predictive of conversion to an AD diagnosis. The authors speculated that lower levels of TRH, closely related to levels of TSH, leads to a phosphorylation of tau protein. In another study of older adults with MCI, Quinlan and colleagues (2010) found that total levels of T_3 were associated with neuropsychological features typically found in prodromal AD. In euthyroid older adults who

have already developed AD, lower levels of fT_4 may be associated with fear and fatigue (Stern et al., 2004).

TSH response to TRH can be measured by administering doses of TRH to individuals and measuring the change in TSH following the dose. This procedure can reveal whether there is a blunting of TSH response to TRH. Lampe et al. (1988) found no differences in this TSH response between controls and AD patients. However, Molchan and colleagues (1991) found that AD patients who were more severely demented were more likely to exhibit a blunted TSH response following the TRH dose than those AD patients who were less severely demented. Interestingly, patients with depression may also have a blunted TSH response to the TRH dose. Sunderland et al. (1985) also found a blunted response in AD patients but not in controls. This blunting may be due to lower baseline levels of TSH.

However, not all studies have found an association between thyroid hormones levels and risk of developing AD. Annerbo et al. (2009) found no association between TSH levels and development of AD. However, TSH levels were negatively correlated with homocysteine (tHcy) levels, which were found to be associated with development of AD. Another study found that TSH and thyroid hormones were not associated with risk for AD, and TSH was not related to early MRI markers of AD. However, in the older adults in this study, higher levels of fT4 were found to be associated with increased atrophy of the hippocampus and amygdala (de Jong et al., 2006). Harper & Roe (2010) found that while older adults who were taking a thyroid medication progressed to receiving a diagnosis of AD more rapidly than those who were not, baseline thyroid disease was not associated with time to diagnosis. However, baseline thyroid disease was measured by self-report, which may be problematic since many older adults suffer from undiagnosed thyroid disease (Harper & Roe, 2010).

AD commonly develops among persons with Down Syndrome (DS). In a study of people with DS, an association was found in women, but not in men, between APOE genotype and thyroid status. APOEε2 was found to be negatively associated with hypothyroidism and APOEε4 was positively associated with hypothyroidism. This mirrors the finding that the APOEε2 allele is protective against AD while the APOEε4 allele puts an individual at greater risk for developing AD. The authors speculated that some of the effect of the APOE genotype on AD may be its influence on thyroid hormone status, at least in women (Percy et al., 2003). However, another study of adults with Down Syndrome found no association between thyroid dysfunction and dementia (Prasher, 1995).

Table 4: TSH and AD Study Findings

Study	*N*	Age	Findings
Annerbo et al. (2006)	93	64.7±9.2 (m) 65.4±8.9 (w)	Lower TSH levels associated with lower MMSE.
Annerbo et al. (2009)	200	>75	TSH not associated with AD.
de Jong et al. (2006)	1077	60-90	TSH not related to AD or early MRI markers of AD.
de Jong et al. (2009)	665	71-93	Higher thyroxin levels associated with AD and neuropathology.
Ganguli et al. (1996)	194	>65	Odds ratio of elevated TSH with definite dementia: 3.8.
Harper & Roe (2010)	499	76.9±9.2	Those taking thyroid medication progressed to AD diagnosis faster than those not taking medication, but no difference in time to diagnosis based on thyroid disease itself.
Kalmijn et al. (2000)	1843	>55	Participants with lower levels of TSH have over a three-fold increased risk for dementia and AD.
Lampe et al. (1988)	19	<65	No difference in blunting in AD vs. control.
Luo et al. (2002)	12		TRH concentration lower in AD hippocampus than in hippocampus of controls.
Molchan et al. (1991)	71	64.2±7.8	AD patients had blunted TSH response to TRH stimulation.
Percy et al. (2003)	55		In females only, an association found between APOE allele and thyroid status: E2 negatively associated with and E4 positively associated with hypothyroidism.
Prasher (1995)	201	40-69	No associated found between thyroid dysfunction and dementia in a sample of adults with DS.
Quinlan et al. (2010)	69		In MCI, those with high levels of T3 had impairment in memory, visuospatial abilities, and executive functions.
Sunderland et al. (1985)	25	48-72	Blunted response of TSH to TRH stimulation in AD patients but not controls.
Tsuboyama et al. (1992)	47	52-86	No significant differences in response to TRH stimulation between controls and AD patients.
van Osch et al. (2004)	469	73.2±8.1 74.5±7.8 (AD)	Low TSH within the normal level is a risk factor for AD independent of other risk factors.

Purpose of the Current Study

Testosterone levels decrease naturally as men age, but in some men these levels are especially low. Low testosterone levels have been linked to lower performance on cognitive tests, especially memory and spatial test. Testosterone may be a protective factor against Aβ neurotoxicity, and low testosterone levels may be a risk factor for the development of AD. Similarly, low levels of TSH may lead to lowered performance on memory and verbal fluency tests. Abnormally low or high levels of TSH have also been linked to an increased risk in developing AD. Advantages of the current study are that it uses a large (n =395), well-characterized and carefully diagnosed sample. Another advantage is that the effects of both testosterone and TSH levels, as well as their interaction, will be examined within this study. The purpose of the current study is to examine whether abnormal levels of testosterone and TSH are more prevalent among patients with AD than controls, whether abnormal levels of testosterone and TSH are linked to worse performance on neuropsychological tests and more depressive symptoms, and whether testosterone and TSH levels interact with APOE allele status in predicting severity of cognitive dysfunction in AD. Finally, the present study will also examine whether testosterone and TSH interact with one another, such that low levels of one are associated with low levels of the other. The proposed study will use a larger sample of controls than most previous research and examine the potential interaction between levels of testosterone and levels of TSH.

Hypotheses

1. Significantly lower testosterone levels are expected in men with AD when compared to controls.

2. Among AD patients and among normal controls, men with lower testosterone levels will exhibit poorer performances than men with normal levels of testosterone on some tests of neuropsychological functioning, particularly the Mini Mental State Exam (MMSE; among AD patients only), Boston Naming Test, the Wechsler Memory Scale-R (WMS-R) Logical Memory I and II, and the Wechsler Memory Scale-R Visual Reproduction I and II. These measures assess areas that have been well-supported as domains of decline in men with lower testosterone levels. Men with lower testosterone levels will also exhibit more depressive symptoms than men with higher of testosterone. Other measures will also be examined to determine if there is a relationship between performance and testosterone levels.
3. An interaction is expected between subject group (AD vs. normal controls) and APOE status, such that men with AD who are APOEε4 positive will have lower levels of testosterone than men with AD who do not have an APOEε4 allele. An interaction is also predicted between subject group (AD vs. normal controls) and APOE status, such that AD participants who are APOEε4 positive will have lower levels of TSH than AD participants who do not have an APOEε4 allele.
4. It is expected that TSH levels will be lower in men and women with AD than in controls.
5. Among both AD patients and normal controls, participants with lower TSH levels will display worse performance on neuropsychological testing, particularly on the MMSE, WMS-R Logical Memory I and II, WMS-R Visual Reproduction I and II, and the Multilingual Aphasia Examination's Controlled Oral Word Association Test (COWAT). Those with TSH levels outside of the normal range will also display more depressive symptoms than participants with normal levels of TSH.

6. An association between TSH and testosterone levels is expected in men (among both AD patients and normal controls), such that lower levels of TSH will be associated with lower levels of testosterone.

Method

Participants

Participants were 197 probable AD patients and 198 controls enrolled in the Texas Alzheimer's Research and Care Consortium (TARCC). Within the AD group, there were 68 men and 129 women (65% women) and within the NC group, there were 61 men and 137 women (69% women). TARCC institutions include Baylor College of Medicine in Houston (BCM), Texas Tech University Health Sciences Center in Lubbock (TTUHSC), University of North Texas Health Science Center in Fort Worth (UNTHSC), University of Texas Southwestern Medical Center in Dallas (UTSW), and University of Texas Health Science Center at San Antonio (UTHSCSA). Participants were at least 55 years old and based on a clinical examination and the criteria set forth by the National Institute of Neurological and Communicative Disorders and Stroke- Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984) were given a diagnosis of probable AD or judged to be cognitively healthy. A Clinical Dementia Rating (CDR) score was obtained from each participant. Controls obtained a CDR score of 0, performed within normal limits on neuropsychological testing, and had no impairments due to cognition in their activities of daily living. CDR scores were used to rate dementia severity among those who were given a diagnosis of probable AD. Neuropsychological test data was used from the date at which biomarker

testing took place. Participants were excluded if biomarker data was not available from a date at which neuropsychological testing took place.

Measures

Mini Mental State Examination (MMSE) (Folstein, Folstein & McHugh, 1975): The MMSE is a brief measure that screens for cognitive impairment. A maximum of 30 points total can be earned over the areas of orientation, attention and calculations, immediate and delayed recall, repetition, naming, following commands, reading, visual construction, and writing.

Clinical Dementia Rating (CDR) scale (Berg, 1988): The CDR is a scale of severity of dementia. Possible scores are 0 to indicate no symptoms of dementia, 0.5 to indicate very mild symptoms of dementia or MCI, 1 to indicate mild dementia, 2 to indicate moderate dementia, and 3 to indicate severe dementia. Scores are assigned on the basis of performance in the areas of memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.

Multilingual Aphasia Examination's (MAE) Controlled Oral Word Association Test (COWAT) (Benton & Hamsher, 1976): The COWAT is a test of phonemic fluency in which the participant names as many words as he or she can think of that starts with the letters F, A, and S.

Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983): The Boston Naming Test is a test of naming to confrontation. Drawings of objects or animals are viewed and must be named by the participant.

American National Adult Reading Test (AMNART) (Grober & Sliwinski, 1991): The AMNART is a test of single-word reading ability that is often used to estimate premorbid intelligence levels.

Trailmaking Test A and B (Reitan & Wolfson, 1985; Originally part of the Army Individual Test of General Ability, 1944): Trailmaking Test part A is a measure of cognitive speed, as it requires the participant to connect a series of numbered dots as quickly as possible in ascending order. Trailmaking Test part B is a measure of executive functioning, as the participant must now connect the dots by alternating between numbers and letters in ascending order.

Wechsler Memory Scale-Revised (WMS-R): Logical Memory I and II, Visual Reproduction I and II, and Digit Span subtests (Wechsler, 1987): Logical Memory is a measure of verbal memory. Logical Memory I measures the ability to recall a story immediately after it is read, and Logical Memory II measures the ability to recall those stories after a 30 minute delay. Visual Reproduction is a measure of visual construction and visual memory. During Visual Reproduction I, participants are presented with four line drawings, one at a time, for ten seconds each. The line drawings must then be reproduced after the drawing is removed. Visual Reproduction II requires the participant to reproduce all four drawings after a 30 minute delay. Digit Span is a measure of attention and working memory (Digits Backward). In the forward condition, a sequence of numbers is read aloud to the participant, who must then repeat the sequence exactly as it was read. In the backwards condition, a sequence of numbers is read aloud to the participant, who must then repeat the sequence in reverse.

Geriatric Depression Scale (GDS) (Yesavage, et al. 1983): The GDS is a 30 question self-report measure that assesses symptoms of depression among older adults. There are five categories of questions that are answered “yes” or “no”.

In addition to neuropsychological measures, measures of testosterone and TSH levels were obtained as part of biomarker testing. Non-fasting blood samples were requested at each

visit and were collected in early to mid-morning as part of the clinical evaluation. For 30 minutes, samples were allowed to clot at room temperature before being centrifuged, aliquoted, and then stored in plastic vials at a temperature of -80 degrees Celsius. Following this, the blood samples were frozen and shipped to Rules Based Medicine (RBM, www.rulesbasedmedicine.com, Austin, TX) where they underwent thawing and genetic and biomarker analyses. These analyses were performed using multiplexed immunoassay human Multi-Analyte Profile (human MAP). The biomarkers that are of interest in the present study are testosterone (ng/mL) and TSH (uIU/mL).

Results

Testosterone Analyses. Participants were 129 males (68 AD patients and 61 non-demented controls). As shown in Table 5, the AD and NC men did not differ significantly in age, but the AD men had significantly fewer years of education than the NC men.

Table 5. Demographic Characteristics and Testosterone Levels

	AD Men (n = 68)		NC Men (n = 61)	
	Mean	SD	Mean	SD
Age	75.56	8.25	72.66	8.62
Education	14.29**	3.50	16.49	2.92
Testosterone (ng/mL)	2.29	1.01	2.56	0.99

**differed from NC men at p<.001

Hypothesis 1—Testosterone levels in AD versus NC men

Testosterone values were normally distributed, so raw values were utilized. ANCOVA, with age as the covariate, revealed that the AD and NC men did not differ significantly in testosterone levels $F(1, 126) = .59$, $p = .44$ (see Table 5). Age was significantly associated with

testosterone levels, $p < .001$. Within the AD group, age was significantly associated with testosterone levels, r (68) = -.32, p <.001. Within the NC group, age was also significantly associated with testosterone levels, r (61) = -.50, p <.001.

Hypothesis 2—Role of testosterone in predicting neuropsychological performances and depression in AD men

Neuropsychological test performances of the AD men are shown in Table 6.

Table 6. Descriptive Statistics for Neuropsychological Measures in AD Men

Measure	N	Mean	SD
MMSE	66	19.29	7.44
CDR Global	66	1.23	0.80
AMNART VIQ	60	107.63	10.40
COWAT	56	7.38	3.08
BNT	60	7.22	3.93
Digit Span	64	7.86	3.02
Trails A	51	6.55	3.05
Trails B	44	5.05	3.41
LM I	47	3.83	2.25
LM II	47	3.64	1.98
VR I	54	4.91	2.49
VR II	54	4.93	2.11
GDS	58	5.69	5.24

To test whether testosterone levels and APOE ε4 status predicted AD men's performance on neuropsychological tests, multiple hierarchical regression analyses was conducted. The alpha level was set at .01 for all analyses. Results that were greater than .01 but less than .05 were designated as marginally significant.

Global Measures

The regression model including age and education did not predict MMSE score, F(2, 63) = .38, p = .69 (see Table 7). The addition of testosterone and APOE ε4 status did not significantly enhance prediction of performance on the MMSE, R^2 change = .05, p = .39. The regression model including age and education did not predict CDR global scores, F(2, 63) = .50,

p = .61. The addition of testosterone and APOE ε4 status to the model did not significantly improve prediction of CDR global scores, R^2 change = .01, p = .83. Estimated premorbid VIQ score (AMNART) was significantly predicted by the regression model including age and education, $F(2, 57) = 26.11$, $p < .001$. Education was the significant predictor of VIQ, $p < .001$, such that higher levels of education were associated with higher estimated premorbid VIQ. The addition of testosterone and APOE ε4 status to the model did not significantly enhance prediction of estimated premorbid VIQ, R^2 change = .02, $p < .001$.

Table 7. Prediction of Global Functioning in AD Men

	MMSE (n=66)		CDR global (n=66)		AMNART VIQ (n=60)	
	n=66		n=66		n=60	
	Beta (β)	t	Beta (β)	t	Beta (β)	t
Age	.02	.18	.12	.88	-.11	-1.08
Education	-.10	-.78	-.03	-.19	.66**	6.71
Testosterone	-.08	-.61	.08	.59	.04	.42
APOE ε4	-.20	-1.61	.04	.28	-.17	-1.79
APOE ε4 X Testosterone	-.26	-.47	.55	.99	.40	.99

*p<.05, **p<.01

Language

Performance on COWAT was not significantly predicted by the regression model including age and education, $F(2, 53) = 1.11$, p = .34 (see Table 8). Adding testosterone and APOE ε4 status to the model did not significantly improve prediction of COWAT scores, R^2

change = .01, p = .65. The regression model including age and education did not significantly predict score on the BNT, $F(2, 57) = .82$, p = .45. The addition of testosterone and APOE ε4 status did not significantly improve prediction of performance on the BNT, R^2 change = .07, p = .20.

Attention and Executive Function

The regression model including age and education marginally significantly predicted performance on Digit Span, $F(2, 61) = 3.48$, p = .04. Age was a marginally significant predictor of performance, p = .01. Adding testosterone and APOE ε4 status did not significantly enhance prediction of performance, R^2 change = .04, p = .06. The regression model including age and education did not significantly predict performance on Trails A, $F(2, 48) = 1.50$, p = .24, and the addition of testosterone and APOE ε4 status did not significantly improve prediction of performance, R^2 change = .03, p = .35. Performance on Trails B was not significantly predicted by the regression model including age and education, $F(2, 41) = 1.91$, p = .16. The addition of testosterone and APOE ε4 status also did not significantly improve prediction of performance on Trails B, R^2 change = .03, p = .30.

Table 8. Prediction of Language and Attention/Executive Functioning in AD Men

	COWAT (*n*=56)		BNT (*n*=60)		Digit Span (*n*=64)		Trails A (*n*=51)		Trails B (*n*=44)	
	Beta (β)	t	Beta (β)	t	Beta (β)	t	Beta (β)	t	Beta (β)	t
Age	.16	1.17	.17	1.27	.33*	2.63	-.04	-.25	-.26	-1.72
Education	.15	1.11	.05	.40	.05	.43	.23	1.66	-.17	-1.11
Testosterone	.07	.51	-.22	-1.58	.11	.89	.16	1.04	.01	.04
APOE ε4	-.04	-.31	-.15	-1.12	-.17	-1.42	-.14	-.93	.17	1.09
APOE ε4 X Testosterone	-.23	-.39	.27	.48	-.71	-1.39	-.39	-.62	1.54	2.28

*p<.05, **p<.01

Memory

Performance on Logical Memory I was not significantly predicted by the regression model including age and education, $F(2, 44) = 1.78$, $p = .18$ (see Table 9). The addition of testosterone and APOE ε4 status to the model did not significantly enhance prediction of performance, R^2 change = .06, p =.20. The regression model including age and education marginally significantly predicted performance on Logical Memory II, $F(2, 44) = 4.21$, $p = .02$. The addition of testosterone and APOE ε4 status also marginally significantly improved prediction of performance on Logical Memory II, $F(5, 41) = 3.19$, R^2 change = .08, $p = .02$. In this regression model, age significantly predicted performance, $p < .01$, with increasing age associated with higher scores on LM II, and testosterone marginally significantly predicted performance, $p = .04$. Higher levels of testosterone were associated with a higher score on LM

II. Performance on Visual Reproduction I was marginally significantly predicted by the regression model including age and education, $F(2, 51) = 3.55$, $p = .04$. Age was a marginally significant predictor, $p = .01$. The addition of testosterone and APOE ε4 status did not significantly improve prediction of performance, R^2 change = .03, $p = .09$. The regression model including age and education significantly predicted performance on Visual Reproduction II, $F(2, 51) = 10.07$, $p < .001$. Age was a significant predictor, $p < .001$, with older age associated with higher scores. The addition of testosterone and APOE ε4 status did not significantly enhance prediction of performance, R^2 change = .05, $p < .001$.

Table 9. Prediction of Memory Performances in AD Men

	LM I (*n*=47)		LM II (*n*=47)		VR I (*n*=54)		VR II (*n*=54)	
	Beta (β)	T	Beta (β)	t	Beta (β)	t	Beta (β)	t
Age	.26	1.77	.36**	2.54	.36*	2.65	.46**	3.83
Education	.13	.91	-.14	-1.03	.03	.23	-.18	-1.49
Testosterone	.23	1.50	.28*	1.93	.05	.36	.20	1.59
APOE ε4	-.15	-.98	-.18	-1.27	-.16	-1.20	-.15	-1.26
APOE ε4 X Testosterone	-1.29	-2.06	-.90	-1.51	.58	.98	-.30	-.57

*p<.05, **p<.01

Depression

The regression model including age and education did significantly predict score on the GDS, $F(2, 55) = 6.53$, $p < .01$ (see Table 10). Education was the significant predictor of GDS score, $p < .01$. Higher education was associated with a lower GDS score (i.e., fewer symptoms

of depression). The addition of testosterone and APOE ε4 status to the model did not significantly improve prediction of GDS score, R^2 change = .02, p = .01.

Table 10. Predicting Depressive Symptoms in AD

	GDS (n=58)	
	Beta (β)	t
Age	-.31	-2.47
Education	-.38**	-3.06
Testosterone	.10	.78
APOE ε4	.07	.56
APOE ε4 X Testosterone	.53	1.02

*p<.05, **p<.01

Follow-up Analyses

Follow-up analyses were conducted for each neuropsychological measure among the AD men. Additional ANCOVAs were conducted in which the neuropsychological performances of AD participants with testosterone levels one standard deviation or more below the NC mean (n = 13) were compared to the performances of those AD participants with testosterone levels higher than the NC mean (n = 28). Results also did not differ from the above analyses.

Hypothesis 2—Role of testosterone in predicting neuropsychological performances and depression in NC men

Neuropsychological test performances of the NC men are shown in Table 11.

Table 11. Descriptive Statistics for Neuropsychological Measures in NC Men

Measure	N	Mean	SD
AMNART VIQ	59	118.23	9.52
COWAT	60	11.82	3.14
BNT	61	12.97	3.19
Digit Span	61	12.21	3.24
Trails A	55	10.65	2.91
Trails B	54	10.96	2.39
LM I	58	13.22	3.04
LM II	58	13.72	3.01
VR I	61	12.74	3.42
VR II	61	13.72	2.98
GDS	61	2.64	2.27

Global Measures

Estimated VIQ was significantly predicted by the regression model including age and education, $F(2, 55) = 34.62$, $p < .001$ (see Table 12). Education was a significant predictor, $p < .001$, such that higher levels of education were associated with a higher estimated VIQ. The addition of testosterone and APOE ε4 status significantly improved prediction of estimated VIQ, $F(4, 53) = 24.22$, R^2 change = .09, $p < .001$. In this model, testosterone was a significant predictor, $p < .01$. Higher levels of testosterone were associated with a higher estimated VIQ.

Table 12. Prediction of Global Functioning in NC Men

	VIQ (*n*=59)	
	Beta (β)	t
Age	.03	.30
Education	.75**	8.28
Testosterone	.33**	3.52
APOE ε4	.09	1.10
APOE ε4 X Testosterone	-.13	-.309

*p<.05, **p<.01

Language

Performance on COWAT was not significantly predicted by the regression model including age and education, $F(2, 56) = 2.98$, $p = .06$ (see Table 13). The addition of testosterone and APOE ε4 status to the model did significantly enhance prediction of performance on the COWAT, $F(4, 54) = 3.73$, R^2 change = .12, $p < .01$. Testosterone was a marginally significant predictor, $p = .03$, and higher testosterone levels were associated with higher COWAT scores. The regression model including age and education only marginally significantly predicted BNT score $F(2, 57) = 4.50$, $p = .02$, but the addition of testosterone and APOE ε4 status did significantly improve prediction of performance, $F(4, 55) = 3.99$, R^2 change = .09, $p < .01$. Education was a significant predictor, $p < .01$, and APOE ε4 status was a marginally significant predictor, $p = .02$. Higher levels of education were associated with higher BNT scores, and the presence of the APOE ε4 allele was associated with poorer performance.

Attention and Executive Function

Performance on Digit Span was not significantly predicted by the regression model including age and education, $F(2, 57) = .40$, $p = .68$. The addition of other variables to the model did not significantly enhance prediction of performance, R^2 change = .05, $p = .44$. The regression model including age and education did not significantly predict performance on Trails A, $F(2, 52) = .46$, $p = .64$. The addition of testosterone and APOE ε4 status to the model did not improve prediction, R^2 change = .04, $p = .54$. Performance on Trails B was not significantly predicted by the regression model including age and education, $F(2, 51) = .54$, $p = .59$, and the addition of other variables to the model did not significantly improve prediction of performance, R^2 change = .05, $p = .45$.

Table 13. Prediction of Language and Attention/Executive Functioning in NC Men

	COWAT (*n*=60)		BNT (*n*=61)		Digit Span (*n*=61)		Trails A (*n*=55)		Trails B (*n*=54)	
	Beta (β)	t	Beta (β)	T	Beta (β)	t	Beta (β)	t	Beta (β)	t
Age	-.20	-1.56	.11	.92	.09	.68	.05	.33	-.02	-.13
Education	.21	1.62	.37**	2.96	.09	.66	.13	.93	.14	1.01
Testosterone	.31*	2.21	.09	.64	.09	.61	.12	.72	.22	1.34
APOE ε4	.23	1.83	-.29*	-2.42	.22	1.63	.18	1.31	.14	.96
APOE ε4 X Testosterone	-.65	-1.00	-.49	-.77	-.61	-.87	.23	.31	.43	.60

*p<.05, **p<.01

Memory

The regression model including age and education did not significantly predict performance on Logical Memory I, $F(2, 54) = .34$, $p = .72$ (see Table 14). The addition of testosterone and APOE ε4 status did not significantly enhance prediction of performance, R^2 change = .03, $p = .68$. Performance on Logical Memory II was not significantly predicted by the regression model including age and education, $F(2, 54) = .28$, $p = .76$. Adding testosterone and APOE ε4 status to the model did not significantly enhance prediction of performance, R^2 change = .07, $p = .39$. Performance on Visual Reproduction I was not significantly predicted by the regression model including age and education, $F(2, 57) = 1.79$, $p = .18$. The addition of other variables to the model also did not significantly improve prediction of performance, R^2 change = .04, $p = .25$. The regression model including age and education did not significantly predict

performance on Visual Reproduction II, $F(2, 57) = 1.79$, $p = .18$. The addition of testosterone and APOE ε4 status to the model did not significantly improve prediction of performance on Visual Reproduction II, R^2 change < .01, $p = .48$.

Table 14. Prediction of Memory Performances in NC Men

	LM I (*n*=58)		LM II (*n*=58)		VR I (*n*=61)		VR II (*n*=61)	
	Beta (β)	t	Beta (β)	t	Beta (β)	t	Beta (β)	t
Age	-.11	-.82	-.10	-.73	-.18	-1.42	-.24	-1.82
Education	-.01	-.04	-.04	-.27	.14	1.04	.03	.24
Testosterone	.20	1.27	.29	1.89	-.20	-1.32	.02	.13
APOE ε4	-.001	-.01	.04	.31	-.07	-.52	-.04	-.30
APOE ε4 X Testosterone	.36	.51	1.00	1.46	.62	.89	-.10	-.14

*p<.05, **p<.01

Depression

The regression model including age and education did not significantly predict GDS score, $F(2, 57) = .23$, $p = .79$ (see Table 15). The addition of testosterone and APOE ε4 status also did not significantly improve prediction of GDS score, R^2 change = .02, $p = .85$.

Table 15. Predicting Depressive Symptoms in NC Men

	GDS (n=61)	
	Beta (β)	t
Age	-.07	-.49
Education	-.07	-.55
Testosterone	.08	.49
APOE ε4	.11	.80
APOE ε4 X Testosterone	-.39	-.54

*p<.05, **p<.01

Follow-up Analyses

Follow-up analyses were conducted for each neuropsychological measure among the control participants. Additional ANCOVAs were conducted in which the neuropsychological performances of NC participants with testosterone levels one standard deviation or more below the NC mean (n = 11) were compared to the performances of those NC participants with testosterone levels higher than the NC mean (n = 34). Results also did not differ from the above analyses.

Hypothesis 3—Relationship between APOE status and testosterone and TSH levels

A 2 (Group--AD versus NC) X 2 (APOE e4 present versus absent) factorial ANOVA with testosterone as the dependent variable revealed that there were not significant main effects for Group (p = .12) or APOE status (p = .37), and that (contrary to hypothesis 3) there was not a significant Group X APOE status interaction (p =.50). A similar analysis was conducted to determine if TSH levels differed by participant type, gender, and APOE ε4 status. In this

analysis and all of the following, a log transformation of TSH data was conducted as the data were positively skewed. Inspection of scatterplots suggested it was reasonable to assume a linear relationship between TSH levels and cognition. A 2 (Group--AD versus NC) X 2 (Gender) X 2 (APOE e4 present versus absent) factorial ANOVA with log-transformed TSH as the dependent variable revealed no significant main effects for Group (p= .35), gender (p= .05), or APOE status (p= .94). There was not a significant Group X Gender interaction (p= .73), Group X APOE status interaction (p= .54), or Gender X APOE status interaction (p= .67). The Group X Gender X APOE status interaction was also not significant (p=.82).

Hypothesis 4—TSH levels in AD versus NC participants

An ANCOVA, with age as the covariate, showed that the AD and NC groups' TSH levels did not differ, $F(1, 391) = .92$, $p = .34$ (see Table 16). AD and NC participants differed significantly by age, as AD participants were significantly older than NC participants ($p < .001$). AD and NC participants also differed significantly by education, with AD participants having significantly lower levels of education than NC participants ($p < .001$). Within the AD group, age was not significantly associated with TSH levels, r (197) = .01, p = .90. Within the NC group, age was also not significantly associated with testosterone levels, r (198) = -.04, p = .58.

Table 16. Demographic Characteristics and Log-transformed TSH Levels in AD and NC Participants

	AD (*n* = 197)		NC (*n* = 198)	
	Mean	SD	Mean	SD
Age	77.41**	8.29	70.42	8.89
Education	14.09**	3.31	15.48	2.64
TSH (uIU/mL)	2.10	2.01	2.13	1.80

**differed from NC participants at $p<.001$

Hypothesis 5—Role of TSH in predicting neuropsychological performances and depression in AD patients

Neuropsychological test performances for the overall total sample of AD patients (both men and women) is shown in Table 17.

Table 17. Descriptive Statistics for Neuropsychological Measures in the Total AD Sample

Measure	N	Mean	SD
MMSE	194	19.21	6.22
CDR global	194	1.32	0.75
AMNART VIQ	176	108.90	10.05
COWAT	170	7.14	3.13
BNT	179	6.30	3.81
Digit Span	187	8.27	2.97
Trails A	155	6.07	3.07
Trails B	117	4.81	3.27
LM I	150	4.00	2.42
LM II	148	3.57	1.84
VR I	162	4.61	2.92
VR II	160	4.73	2.35
GDS	170	5.06	4.75

Global Measures

Performance on the MMSE was not significantly predicted by the regression model including age and education, $F(2, 191) = .67$, $p = .51$ (see Table 18). The addition of other

variables to the model also did not significantly improve prediction of MMSE score, R^2 change < .01, p = .76. CDR global score was not significantly predicted by the regression model including age and education, $F(2, 191) = 2.56$, p = .08. The addition of TSH and APOE ε4 status did not significantly improve prediction of CDR global score, R^2 change < .01, p = .27. Estimated premorbid VIQ (AMNART) was significantly predicted by the regression model including age and education, $F(2, 173) = 68.03$, $p < .001$. Education was the significant predictor in this model, $p < .001$. Higher levels of education were associated with higher estimated VIQ. Prediction of performance was not improved with the addition of TSH and APOE ε4 status to the model, R^2 change < .01, $p < .001$.

Table 18. Prediction of Global Functioning in AD

	MMSE (*n*=194)		CDR global (*n*=194)		AMNART VIQ (*n*=176)	
	Beta (β)	t	Beta (β)	t	Beta (β)	t
Age	.06	.84	.14	1.97	-.03	-.52
Education	.07	.93	-.06	-.75	.66**	11.39
TSH	-.02	-.32	.03	.37	.01	.15
APOE ε4	-.05	-.62	.00	.04	.03	.50
APOE ε4 X Testosterone	-.02	-.10	-.28	-1.28	-.07	-.37

*p<.05, **p<.01

Language

The regression model including age and education significantly predicted performance on COWAT, $F(2, 167) = 5.74$, $p < .01$ (see Table 19). Education was the significant predictor, $p <$

.01. Higher levels of education were associated with higher scores on the COWAT. Prediction of performance was not significantly enhanced by the addition of TSH and APOE ε4 status to the model, R^2 change < .01, p = .02. Performance on the BNT was not significantly predicted by the regression model including age and education, $F(2, 176) = 2.64$, p = .07. The addition of TSH and APOE ε4 status also did not significantly enhance prediction of performance on BNT, R^2 change < .01, p = .21.

Attention and Executive Function

Performance on Digit Span was significantly predicted by the regression model including age and education, $F(2, 184) = 9.24$, $p < .001$. Education was again the significant predictor in this model, $p < .001$. Higher levels of education were associated with higher scores on Digit Span. The addition of other variables to the model did not significantly improve prediction of scores, R^2 change < .01, $p < .01$. The regression model including age and education did not significantly predict performance on Trails A, $F(2, 152) = 1.74$, p = .18. Adding TSH and APOE ε4 status to the model did not significantly enhance prediction of performance, R^2 change = .02, p = .22. Performance on Trails B was not significantly predicted by the regression model including age and education, $F(2, 114) = .71$, p = .50. The addition of TSH and APOE ε4 status did not significantly improve prediction of performance on Trails B, R^2 change = .02, p = .42.

Table 19. Prediction of Language and Attention/Executive Functioning in AD

	COWAT (*n*=170)		BNT (*n*=179)		Digit Span (*n*=187)		Trails A (*n*=155)		Trails B (*n*=117)	
	Beta (β)	t	Beta (β)	t	Beta (β)	F	Beta (β)	F	Beta (β)	F
Age	.07	.88	.11	1.48	.30	4.16	-.02	-.24	-.10	-1.01
Education	.25**	3.34	.15	1.95	.12**	1.73	.15	1.83	.05	.48
TSH	-.02	-.20	.04	.54	-.02	-.27	-.01	-.10	.02	.21
APOE ε4	.03	.38	.05	.60	.02	.30	-.12	-1.52	.15	1.56
APOE ε4 X TSH	-.05	-.21	-.11	-.46	-.22	-.99	.29	1.12	.12	.42

*p<.05, **p<.01

Memory

The regression model including age and education significantly predicted performance on Logical Memory I, $F(2, 147) = 6.34$, $p < .01$ (see Table 20). Age was a significant predictor, $p = .004$, and education was marginally significant predictor, $p = .03$. Older age and higher levels of education were associated with higher scores. Other variables did not significantly improve prediction of performance, R^2 change < .01, $p = .02$. Performance on Logical Memory II was significantly predicted by the regression model including age and education, $F(2, 145) = 19.86$, $p < .001$. Age was the significant predictor, $p < .001$. Older age was associated with better performance on LM II. The addition of other variables to the model did not enhance prediction of performance, R^2 change = .01, $p < .001$. Performance on Visual Reproduction I was significantly predicted by the regression model including age and education, $F(2, 159) = 5.40$, p

< .01. Age was a significant predictor, $p < .01$, such that older age was associated with higher scores. No other variables significantly improved prediction of performance, R^2 change = .01, $p = .02$. The regression model including age and education significantly predicted performance on Visual Reproduction II, $F(2, 157) = 20.65$, $p < .001$. Age was the significant predictor in this model, $p < .001$. Older age was associated with better performance on VR II. The addition of TSH and APOE ε4 status to the model did not significantly enhance prediction of score, R^2 change = .01, $p < .001$.

Table 20. Prediction of Memory Functioning in AD Patients

	LM I (*n*=150)		LM II (*n*=148)		VR I (*n*=162)		VR II (*n*=160)	
	Beta (β)	t	Beta (β)	t	Beta (β)	t	Beta (β)	t
Age	.23**	2.94	.45**	6.14	.25**	3.27	.44**	6.12
Education	.18*	2.25	-.07	-.93	.05	.67	-.09	-1.28
TSH	.02	.27	.05	.67	.05	.68	.05	.64
APOE ε4	.04	.46	-.10	-1.37	-.05	-.63	-.10	-1.33
APOE ε4 X TSH	.08	.33	-.28	-1.24	-.26	-1.04	-.15	-.64

*p<.05,**p<.01

Depression

GDS score was not significantly predicted by the regression model including age and education, $F(2, 167) = 2.84$, $p = .06$ (see Table 21). Adding TSH and APOE ε4 status did not significantly enhance prediction of GDS score, R^2 change < .01, $p = .23$.

Table 21. Predicting Depressive Symptoms in AD

	GDS (*n*=170)	
	Beta (β)	T
Age	-.02	-.31
Education	-.18	-2.38
TSH	.00	.06
APOE ε4	-.02	-.27
APOE ε4 X TSH	-.07	-.30

*p<.05, **p<.01

Follow-up Analyses

Follow-up analyses were conducted for each neuropsychological measure among the AD participants. Additional ANCOVAs were conducted in which the neuropsychological performances of AD participants with TSH levels one standard deviation or more below the NC mean (n = 25) were compared to the performances of those AD participants with TSH levels higher than the NC mean (n = 94). Age, education, and gender were included as covariates in these analyses. Results did not differ from the above analyses.

Hypothesis 5—Role of TSH in predicting neuropsychological performances and depression in NC participants

Neuropsychological test performances of the total NC sample (both men and women) is presented in Table 22.

Table 22. Descriptive Statistics for Neuropsychological Measures in the Total NC Sample

Measure	N	Mean	SD
AMNART VIQ	187	117.34	8.54
COWAT	197	11.64	2.74
BNT	198	11.92	3.03
Digit Span	198	11.69	2.78
Trails A	189	10.34	2.69
Trails B	187	10.98	2.53
LM I	182	13.58	2.75
LM II	182	13.99	2.63
VR I	198	12.37	3.20
VR II	198	13.56	3.13
GDS	198	2.75	2.60

Global Measures

Estimated VIQ was significantly predicted by the regression model including age and education, $F(2, 183) = 77.59$, $p < .001$ (see Table 23). Prediction of estimated VIQ was significantly improved by the addition of TSH and APOE ε4 status to the regression model, $F(4, 181) = 43.79$, R^2 change = .03, $p < .001$. Education was a significant predictor, $p < .001$, as was TSH, $p < .01$, with higher TSH levels being associated with lower estimated VIQ scores.

Table 23. Prediction of Global Functioning in NC Participants

	AMNART VIQ (*n*=187)	
	Beta (β)	T
Age	-.04	-.81
Education	.68**	12.43
TSH	-.18**	-3.34
APOE ε4	.04	.80
APOE ε4 X TSH	.03	.16

*p<.05,**p<.01

Language

Performance on the COWAT was significantly predicted by the regression model including age and education, $F(2, 193) = 12.86$, $p < .001$ (see Table 24). Education was the only significant predictor, $p < .001$. Higher education was associated with higher scores on the COWAT. The addition of TSH and APOE ε4 status did not significantly enhance prediction of performance, R^2 change < .01, $p < .01$. The regression model including age and education significantly predicted performance on the BNT, $F(2, 194) = 25.22$, $p < .001$. The addition of TSH and APOE ε4 status to the model significantly improved prediction of performance on the BNT, $F(4, 192) = 14.94$, R^2 change = .03, $p < .001$. Age was a significant predictor, $p < .01$, as was education, $p < .001$. Older age and a higher level of education were associated with better performance on BNT. APOE ε4 status was a marginally significant predictor, $p = .01$. The presence of the APOE ε4 allele was associated with poorer performance on the BNT.

Attention and Executive Function

Performance on Digit Span was marginally significantly predicted by the regression model including age and education, $F(2, 194) = 4.27$, $p = .02$. Education marginally significantly predicted performance, $p = .02$, such that higher levels of education were associated with better Digit Span performance. Prediction of performance was not significantly improved by the addition of TSH and APOE ε4 status to the regression model, R^2 change < .01, $p = .03$. Performance on Trails A was not significantly predicted by the regression model including age and education, $F(2, 186) = 2.20$, $p = .11$, nor was prediction significantly improved by the addition of other variables to the model, R^2 change < .01, $p = .30$. Performance on Trails B was also not significantly predicted by the regression model including age and education, $F(2, 184) =$

2.98, $p = .05$. The addition of TSH and APOE ε4 status to the model did not significantly enhance prediction of performance on Trails B, R^2 change = .01, $p = .11$.

Table 24. Prediction of Language and Attention/Executive Functioning in NC Participants

	COWAT (*n*=197)		BNT (*n*=198)		Digit Span (*n*=198)		Trails A (*n*=189)		Trails B (*n*=187)	
	Beta (β)	t	Beta (β)	t	Beta (β)	t	Beta (β)	t	Beta (β)	t
Age	-.13	-1.94	.19**	2.90	.13	1.83	.05	.74	.05	.72
Education	.32**	4.66	.42**	6.50	.16*	2.29	.14	1.97	.17	2.34
TSH	-.06	-.86	-.08	-1.28	-.10	-1.41	-.003	-.04	-.06	-.88
APOE ε4	.02	.25	-.16*	-2.51	.02	.32	.06	.77	.07	.91
APOE ε4 X TSH	.23	1.08	.02	.09	.21	.96	-.20	-.90	.16	.71

*p<.05, **p<.01

Memory

The regression model including age and education did not significantly predict performance on Logical Memory I, $F(2, 178) = .58$, $p = .56$ (see Table 25). The addition of other variables to the model did not significantly enhance prediction of performance, R^2 change = .01, $p = .56$. Performance on Logical Memory II was not significantly predicted by the regression model including age and education, $F(2, 178) = .34$, $p = .71$. The addition of TSH and APOE ε4 status to the model did not significantly improve prediction of performance, R^2 change = .03, $p = .28$. The regression model including age and education marginally significantly predicted performance on Visual Reproduction I, $F(2, 194) = 3.16$, $p = .05$. Education was a marginally

significant predictor, p=.02, such that higher levels of education were associated with better performance on VR I. The addition of TSH and APOE ε4 status to the model did not significantly improve prediction of performance, R^2 change < .01, p =.14. Performance on Visual Reproduction II was not significantly predicted by the regression model including age and education, $F(2, 194) = 2.10$, p = .13. The addition of TSH and APOE ε4 status to the model did not significantly enhance prediction of performance, R^2 change = .01, p = .25.

Table 25. Prediction of Memory Performances in NC Participants

	LM I (n=182)		LM II (n=182)		VR I (n=198)		VR II (n=198)	
	Beta (β)	t	Beta (β)	t	Beta (β)	t	Beta (β)	t
Age	.03	.37	.04	.54	.07	1.00	.07	.93
Education	.08	1.01	.05	.63	.16*	2.31	.13	1.83
TSH	-.10	-1.27	-.15	-2.04	-.02	-.26	-.04	-.52
APOE ε4	.04	.49	.04	.57	-.06	-.82	-.07	-1.01
APOE ε4 X TSH	-.08	-.36	.08	.32	.32	1.46	.19	.86

*p<.05, **p<.01

Depression

GDS score was not significantly predicted by the regression model including age, gender, and education, $F(2, 194) = .39$, p = .68 (see Table 26). The addition of TSH and APOE ε4 status to the model did not significantly enhance prediction of GDS score, R^2 change = .01, p = .73.

Table 26. Prediction of Depressive Symptoms in Controls

	GDS (*n*=198)	
	Beta (β)	t
Age	-.06	-.85
Education	.02	.24
TSH	-.06	-.86
APOE ε4	.05	.71
APOE ε4 X TSH	-.09	-.39

*p<.05, **p<.01

Follow-up Analyses

Follow-up analyses were conducted for each neuropsychological measure among the NC participants. Additional ANCOVAs were conducted in which the neuropsychological performances of NC participants with TSH levels one standard deviation or more below the NC mean (n = 19) were compared to the performances of those NC participants with TSH levels higher than the NC mean (n = 110). Age, education, and gender were included as covariates in these analyses. Results did not differ from the above analyses.

Hypothesis 6—Relationship between TSH and testosterone levels in AD and NC men

A regression was performed to determine if TSH levels predicted testosterone levels (see Table 27) in all male participants. The regression model including age and TSH levels significantly predicted testosterone levels, $F(1, 126) = 14.53$, $p < .001$. Age significantly predicted testosterone scores, as described earlier. TSH levels did not significantly predict testosterone levels.

Table 27. Prediction of Testosterone Levels in AD and NC Men

Testosterone		
	Beta (β)	t
Age	-.42**	-5.23
TSH	-.10	-1.25

*p<.05, **p<.01

Discussion

Hypothesis 1- Testosterone levels in AD versus NC men

ANCOVA results revealed no difference in testosterone levels between AD and NC men, so this hypothesis was not supported. These results are contrary to the findings of Hogervorst, et al. (2004), but support the findings of Geerlings, et al. (2006), who found no association between testosterone levels and risk for dementia. Age was significantly associated with testosterone levels in both the AD and NC groups, a finding which is well supported in the literature (for example, see Harman et al., 2001).

Hypothesis 2- Role of testosterone in predicting neuropsychological performances and depression in AD and NC men

Within AD men, testosterone was only found to be marginally significantly associated with performance on LM II, such that higher levels of testosterone were associated with improved performance. Testosterone levels were not associated with performance on any other neuropsychological tests in the AD men, which did not support this hypothesis. APOE ε4 status was also not associated with performance on any neuropsychological tests in AD men. Neither testosterone levels nor APOE ε4 status was found to be associated with depression levels in AD men, which was also contrary to this hypothesis.

Within NC men, testosterone was significantly associated with estimated premorbid VIQ, such that higher levels of testosterone were associated with higher performance on the AMNART. Testosterone was also marginally significantly associated with performance on COWAT, such that higher levels of testosterone were associated with higher performance on COWAT. This was unexpected, given Wolf and Kirschbaum's (2002) finding that higher levels of testosterone were associated with poorer performance on verbal fluency tasks. However, this finding became non-significant when education was controlled for. Testosterone levels did not predict neuropsychological test performance on any other tests. This is similar to the results from Fonda et al. (2005), who found no association between free or total testosterone levels and cognition. APOE ε4 status was marginally significantly associated with performance on the BNT, such that the presence of the APOE ε4 allele was associated with poorer performance on the BNT. APOE ε4 status was not predictive of performance on any other neuropsychological tests. Neither testosterone levels nor APOE ε4 status were found to be associated with depression levels in NC men. This finding contradicts the results presented by Hintikka et al. (2009).

Hypothesis 3- Relationship between APOE status and testosterone and TSH levels

Factorial ANOVA did not reveal significant main effects for patient type (AD or NC) or APOE ε4 allele status on testosterone levels among male participants. This is in contrast to the results of Hogervorst et al. (2002), who found that the APOE ε4 allele was associated with lower levels of testosterone in men with AD. Main effects for patient type or APOE ε4 allele status on TSH levels were also not found.

Hypothesis 4- TSH levels in AD versus NC participants

ANCOVA results revealed no differences in TSH levels between AD and NC participants, so this hypothesis was not supported. This is consistent with the results of Annerbo et al. (2009), de Jong et al. (2006), and others who did not find differences in TSH levels between AD and NC participants.

Hypothesis 5- Role of TSH in predicting neuropsychological performances and depression in AD and NC participants

In participants with AD, TSH levels did not predict performance on any neuropsychological tests, which did not support this hypothesis. APO ε4 status also did not predict performance on any neuropsychological tests. Neither TSH levels nor APOE ε4 status predicted depression levels among AD participants. This is in contrast to the well-established finding of an association between thyroid functioning and depression (for a review, see Loosen, 1992).

In NC participants, TSH levels were a significant predictor of estimated premorbid VIQ, with higher TSH levels associated with lower estimated VIQ performance. TSH levels did not predict performance on any other neuropsychological tests. APOE ε4 status was marginally significantly associated with performance on the BNT, with the presence on the APOE ε4 allele associated with lower performance on the BNT. Neither TSH levels nor APOE ε4 status predicted depression levels among NC participants.

Hypothesis 6- Relationship between TSH and testosterone levels in AD and NC men

TSH levels were not associated with testosterone levels among the male participants, which was contrary to the hypothesis. Hogervorst et al. (2004) proposed that subclinical hyperthyroidism was associated with lower levels of testosterone, but the present findings did not support this relationship.

Limitations

A possible limitation of the current study is the hormones available for analysis. Research has suggested that bioavailable testosterone may be a better predictor of cognitive function than total testosterone levels (Yaffe et al., 2002). However, bioavailable testosterone levels were not available in this sample, so total testosterone levels were used in the analyses. It is possible that bioavailable testosterone levels would have been a more useful predictor of cognitive performance within the current sample. Likewise, TSH levels were the only measure of thyroid functioning available in the sample for analysis. Use of additional measures of thyroid functioning, such as TRH, T_3, and T_4, could have provided additional information about thyroid dysfunction among the sample. It is possible that some participants had thyroid dysfunction resulting in lower levels of TRH, T_3, or T_4 but had TSH levels within normal limits.

Information about cancer history and treatment within the sample was also not available at the time of analyses. Since androgen deprivation is a common treatment for prostate cancer, it is possible that some participants had undergone this treatment. Information was also not available about the use of thyroid medications within the sample. The use of thyroid medications could have impacted the TSH levels observed in this study. These participants could not be identified and excluded from analyses, and so may have affected the results.

Although inspection of scatterplots indicated that it was reasonable to assume a linear relationship between TSH levels and cognition, the literature suggests that TSH levels at both extremes, those too high as well as too low, may be detrimental to cognition. As this study assumed a linear relationship, perhaps future research could use deviation scores to investigate the impact of both high and low levels of TSH on cognition.

Another limitation of the current study may be that both the AD and NC participants were highly educated. One might expect that more significant relationships may have emerged if the sample had more closely resembled the general population. However, it is not the case that this high level of education was associated with reduced variability on the neuropsychological tests in this study, as the standard deviations were close to the expected values.

Implications

Neither testosterone nor TSH levels were found to differ in AD patients and normal controls. The literature is mixed on whether testosterone or TSH levels are associated with the development of AD; however, no evidence was found in this sample to support an association between testosterone or TSH and AD. Testosterone and TSH levels were also not associated with APOE ε4 allele status. Among the male participants, TSH levels were not associated with testosterone levels. This is contrary to research suggesting that there may be a link between the two (Hogervorst et al., 2004).

Testosterone and TSH levels were also not found to be predictive of neuropsychological test performance among AD participants, although two marginally significant findings emerged. Higher levels of testosterone predicted a higher score on a test of delayed memory among AD participants, as well as a higher score on a test of verbal fluency among controls. It may be that by the time AD develops within an individual, the fluctuations in hormone levels have little to do with test performance because of the overwhelming influence of the AD pathology. As participants in the current AD sample had, on average, mild dementia, it may be that the differences in hormone levels are not yet distinguishable. Additionally, APOE ε4 allele status was not found to be predictive of performance on any neuropsychological tests. Among NC participants, both testosterone and TSH levels were found to be predictive of estimated

premorbid VIQ. Higher testosterone levels were associated with higher performance while higher TSH levels were associated with poorer performance. Further research is needed into this association, as neither testosterone nor TSH has been established in the literature as a predictor of estimated premorbid VIQ. One possibility may be that older adults with higher IQs are more likely to engage in healthy and active lifestyles, which may have an impact on hormone levels. Given these results, testosterone and TSH may not be useful clinically to predict cognitive performance.

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