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Thyroid hormones and cognitive functioning in healthy, euthyroid women: A correlational study

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Abstract

Thyroid hormones (THs) play a critical role in differentiation, growth, and metabolism of animal and human organ systems, including the brain. Although associations between normal levels of THs and cognitive functions in healthy elderly individuals have been reported, the findings are inconsistent, possibly due to differences in study designs. Because thyroid disease occurs more frequently in women, the goal of the present study was to examine the relationship between levels of THs and performance on neuropsychological tests in 122 healthy, euthyroid women whose mean age was 51 years. Higher levels of free T3 were positively associated with longer completion times (slower performance) on Trail Making Test — Part A (p=0.006) and Part B (p=0.032) and on the Tower of London test (p=0.002). Higher levels of thyroglobulin antibodies (TgAb) were positively correlated with more errors on the Trail Making Test Part B (p=0.000), on the Word Fluency test (p=0.023), and on the Design Fluency test (p=0.045). No significant correlations between TH levels and scores on mood, verbal memory, or working memory measures were observed. The findings point to a possible link between THs and cognitive processes that are mediated primarily by frontal cortex, areas associated with executive function tasks, and suggest that elevations in levels of free T3 and TgAB within the normal range may negatively influence executive functions.

Keywords

Thyroid hormones; Thyroid antibodies; Women; Cognition; Executive functions; Euthyroid

Introduction

Thyroid hormones (THs) play a critical role in differentiation, growth, and metabolism of animal and human organ systems, including the brain. Thyrotropin releasing hormone (TRH), secreted by the hypothalamus, stimulates the release of thyroid stimulating hormone (TSH) by the anterior pituitary gland which, in turn, causes the release of thyroxine (T4) and triiodothyronine (T3), tyrosine-based hormones by the thyroid gland. T4 is converted to the active T3 which is three to four times more potent than T4. Approximately 99.97% of T4 and 99.7% of T3 are bound to plasma proteins (Braverman et al., 1970) and only the free or unbound portion of T4 and T3 can exert biologic activity at the cellular level. In healthy

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individuals, neuroendocrine feedback mechanisms ensure that T3 and T4 are maintained within normal limits. Levels of THs within the normal range are crucial for the maintenance of various physiological and cognitive functions such as attention, memory, and mood (for review see Boelaert and Franklyn, 2005; Smith et al., 2002).

Clinical (or overt) hypothyroidism is characterized by high levels of TSH and low levels of T4 and T3. Hypothyroid patients demonstrate deficits in cognitive abilities such as attention, visual perception, memory, language, executive functions as well as depression (Bernal, 2002; Zhu et al., 2006; Davis and Tremont, 2007). Severe hypothyroidism can cause symptoms similar to Alzheimer's disease (AD) such as memory loss, confusion, slowness, paranoid depression and, in extreme stages, hallucinations (Whybrow et al, 1969). Even mild, or subclinical hypothyroidism (defined as elevated levels of TSH and normal levels of free T4) has been associated with cognitive and mood disturbances (Osterweil et al., 1992; Haggerty et al., 1993; Baldini et al., 1997; Kalmijn et al., 2000; Zhu et al., 2006;). For example, in an fMRI study that examined blood oxygen level-dependent (BOLD) responses to performance on various cognitive tasks, Zhu et al. (2006) found that working memory deficits and executive dysfunctions in subclinical hypothyroid patients were reversed after 6 months of treatment with exogenous T4 (or L-thyroxine, LT4). Others have reported that treatment with LT4 significantly reduced cognitive and mood symptoms in both clinically hypothyroid elderly individuals (Osterweil et al., 1992) and in younger, subclinically hypothyroid individuals (Nystrom et al., 1988; Monzani, et al, 1993).

On the other hand, excess production of THs due to a hyperactive thyroid gland causes hyperthyroidism or thyrotoxicosis (Grave's disease). Clinical hyperthyroidism is characterized by low levels of TSH and high levels of T4 and T3 (Werner et al., 1996) and can cause symptoms of depression, anxiety, irritability, and emotional liability (Elberling et al, 2003). While some cross-sectional imaging studies have found increased cerebral metabolism in brain areas commonly associated with memory and executive functions in hyperthyroid patients (Burmeister et al., 2001), others have failed to find any differences compared to euthyroid individuals (Elberling et al., 2003).

The three principle thyroid antibodies involved in autoimmune thyroid disease (AITD) are thyroperoxidase, thyroglobulin (TgAB), and the TSH receptor antibodies; however, the pathologic role of TgAB is still unclear (Weetman and McGregor, 1984). Thyroid antibodies can bind to the enzymes essential for T4 and T3 synthesis and either enhance their actions leading to overproduction of T4 and T3 as in Graves's disease (Burman and Baker, 1985) or block their function, as in Hashimoto's thyroiditis, an autoimmune disease that results in hypothyroidism (Bogner et al., 1984).

While autoimmune thyroid disease (AITD) affects 5 to 15% of the general population, its prevalence is especially high in elderly women (Bastenie et al., 1980).

Although a considerable amount of information is available on the effects of thyroid diseases on cognition, it is not clear whether these effects are primary (i.e., direct effects on the brain) or whether they occur secondary to their influence on other systems vital to cognitive functioning. Several mechanisms of action of THs in the brain and their resultant effects on

cognition have been examined. For example, T3 modulates serotonin levels, a neurotransmitter integral to moods and behavior (Cleare et al, 1996). Furthermore, T3 binds to nuclear α and β receptors, triggers protein synthesis in mitochondria and influences gene transportation (Wrutniak-Cabello et al., 2001). THs also stimulate nerve growth factor synthesis in the brain of mature rats (Walker et al., 1979) and changes in TH levels have been directly associated with changes in cerebral metabolism in animals (Chapa et al., 1995) and humans (Smith and Ain, 1995). Decreases in T4 levels have been linked to a reduction in neuronal actin polymerization in cultured astrocytes, and replacement with exogenous T4 normalizes the process (Siegrist-Kaiser et al., 1990). Finally, in both clinical and preclinical studies, exogenous T3 diminished the memory impairment associated with electroconvulsive therapy (Stern et al., 1991, 1995) and T4 significantly improved cognitive performance in patients taking lithium (Prohaska et al., 1996). It is therefore likely that THs have direct effects on the brain and, subsequently, on cognition.

Although associations between normal levels of THs and cognitive functions and mood in healthy elderly individuals have been reported, the findings of these studies are inconsistent. For example, Wahlin et al. (1998) found a significant positive association between TSH, but not T4, and scores on a verbal learning and memory test in individuals whose average age was 83 years. In physically impaired, but cognitively healthy 65 year old euthyroid women, lower but normal levels of total T4 were associated with a greater risk of cognitive decline over a three year period (Volpato et al., 2002). In contrast, Prinz et al. (1999) found a positive correlation between total T4 levels and performance of 72-year old men on several cognitive tests, suggesting that middle to high normal levels of THs might be optimal for maintaining cognitive functions. When 558 individuals aged, on average, 85 years were followed for over three years, thyroid function was not a risk factor for cognitive impairment or for depressive symptoms (Gussekloo et al., 2004). Age of the participants, differences in sample populations, variability in cognitive test batteries, and study designs most likely explain the diversity reported in these studies.

Women are more susceptible to a variety of autoimmune diseases including systemic lupus erythematosus, multiple sclerosis primary biliary cirrhosis, rheumatoid arthritis and Hashimoto’s thyroiditis (for review see Beeson, 1994; Voskuhl, 2011). Thyroid disease occurs more frequently in women than it does in men (Hollowell et al, 2002) possibly due to an interaction between estrogen and THs. Estrogen blocks the efficiency of THs causing the thyroid gland to produce more TH in women than in men and probably contributing to larger thyroid gland in women (Tahboub and Arafah, 2009).

The goal of the present study was to examine the relationship between levels of THs and performance on tests of executive functions, working memory, verbal learning and memory, attention, and vigilance in euthyroid women. It was hypothesized that levels of free T4 and free T3 would correlate positively with performance on neuropsychological tests. An inverse relationship was expected between levels of TgAB and test scores such that women with higher levels of TgAB would have worse scores on the neuropsychological tests.

Materials and method

Participants

One hundred and twenty two healthy women between the ages of 25 and 75 years agreed to participate in this study. All women were recruited from advertizing in local newspapers. Inclusion criteria required that participants had no current or past history of neurological or psychiatric illness and were not taking any medications. Exclusion criteria were a history of head injury, presence of an acute or chronic illness, such as diabetes or heart disease, or untreated, known thyroid disease, smoking more than 20 cigarettes per day for over 20 years and alcohol consumption of greater than 14 or more 5 oz drinks per week.

Materials

Mood measures

Profile of Mood States-Bi-Polar Form (POMS-BI; Lorr et al., 1982): This measure yields scores on six bi-directional dimensions of mood: elated-depressed, clearheaded-confused, energetic-tired, composed-anxious, confident-unsure, and agreeable-hostile. Each mood appears on a bipolar scale, with negative numbers representing the negative affect pole and positive numbers representing the positive affect pole.

Beck Depression Inventory, Second Edition (BDI-II), (Beck et al., 1996): This questionnaire consists of several groups of statements related to various aspects of mood and emotional states. The participant is asked to indicate one statement from each group that best describes their mood during the past two weeks including the day of testing.

Neuropsychological tests

General intelligence

Vocabulary subtest (Wechsler Adult Intelligence Scale — Third Edition; WAIS-III) (Wechsler, 1997): This subscale provides a measure of general intelligence.

Verbal learning and memory

California Verbal Learning Test — II (CVLT-II) (Delis et al., 2000): The CVLT is a verbal learning and memory test that also provides an assessment of the strategies involved in the process or learning and memorizing of new verbal information. The following variables were analyzed:

1. Trial 1: number of recalled words after the first reading of the list.
2. Total Words (T1-T5): all words learned across the five trials.
3. Short Delayed Free Recall: words recalled immediately following an interference trial;
4. Long Delayed Free Recall, or words recalled following a 20-minute long delay;
5. Learning Slope (T1-5) provides a global index of learning ability that reflects both auditory attention and verbal learning skills.

6. Total Repetitions across all recall trials;
7. Total Intrusions across all recall trials;
8. Recognition Discriminability: examines the ability to distinguish targets from the distractor words and reflects performance on hits, misses, false-positive and false-negative responses, as well as correct rejections. This index is the single best measure of overall recognition performance because it takes into account an examinee's hit rate relative to false positive rate.

Executive function tests

Trail Making Test (Form A and Form B) (Partington and Leiter, 1949): This test measures attention, sequencing skills, mental flexibility.

Chicago Word Fluency test (University of Chicago): This test assesses ability to generate verbal information. Part A requires that participants write as many words as they can that start with the letter "S" in 5 min, whereas in Part B, participants need to write as many 4-letter words that start with the letter "C" in 4 min..

Jones-Gotman Design Fluency test (Jones-Gotman and Milner, 1977): This test is a non-verbal analog to the Word-Fluency Test. Instead of words, participants have to generate abstract designs (Part A) or abstract designs that are composed of 4 lines only (Part B).

Tower of London-DX (Culbertson and Zillmer, 2000): This is a problem solving test that requires planning and execution of moves under rule-controlled conditions.

Sequential tapping test (Leonard et al., 1988): This is a test of motor speed, hand coordination, and sequencing.

Stroop test–Victoria modification (Regard, 1981): This test measures inhibitory processes and the ease with which a person can shift his or her perceptual set to conform to changing demands and suppress a habitual response.

Working memory tests

Modified N-Back test (Grigorova and Sherwin, 2006; Cohen et al., 1997 for original NBack task): This test measures visual working memory skills. Full description can be found in Grigorova and Sherwin (2006).

Letter–number sequencing subtest, (WAIS-III): The test measures auditory working memory skills. For this test, a mixture of numbers and letters is read to the participant who is required to reorganize the stimuli so that the numbers are reported first (in order form smallest to largest) followed by the letters (in alphabetical order). The test is terminated when three consecutive trials are failed.

Procedure

Women who answered the advertisement completed a telephone interview prior to recruitment to verify that the selection criteria were met. Those who met these criteria and who agreed to participate reported to the Psychoendocrine Laboratory at McGill University. After they signed a consent form approved by the Research Ethics Board, Faculty of Medicine, McGill University, a blood sample was obtained. The neuropsychological battery was administered during a single 3-hour test session. A 15-minute break was given half way through testing. Participants were compensated 40 dollars for their transportation expenses.

Hormone assays

10 ml of blood was drawn by venipuncture into heparinized Vacutainer tubes. The blood was centrifuged immediately and the plasma was separated and stored at −50 °C. All serum samples were assayed at the Endocrine Laboratory, Royal Victoria Hospital, McGill University Health Center, Montreal, Canada. Serum TSH was measured by an immunoassay with direct chemiluminescence detection (Advia-Centaur, Bayer Diagnostics, Tarrytown, NY 10591, USA). Free thyroxine (T4) and free triiodothyronine (T3) were analyzed by a competitive immunoassay with direct chemiluminescence detection (Advia-Centaur, Bayer Diagnostics, Tarrytown, NY 10591, USA). TgAB were analyzed by an enzyme-linked immunosorbent assay (ELISA; Vita Diagnostics, Freiburg, Germany). All endocrine analyses were done at the conclusion of the study in order to minimize interassay variability.

Results

Statistical analyses were conducted using the PAWS statistical package software (SPSS version18.0). Because of the wide age range of the women who participated in this study and the independent effect that age can have on performance on neuropsychological tests, partial correlations using age as a control factor were performed to examine the relationship between levels of free T4, free T3, TSH, and TgAB and outcome variables on the neuropsychological tests.

Demographic characteristics

One hundred and twenty two healthy women between the ages of 25 to 75 years participated in this study. The average age of the participants was 51 years (SD=15.2) and the average years of education was 15.8 (SD=3.15) (Table 1).

Thyroid hormones status

Levels of free T4, free T3, TSH, and TgAB were within the normal range for all participants (Table 2).

Mood tests

The women were euthymic (BDI-II mean score=6.32, SD=6.37) and described themselves as composed, agreeable, energetic, clearheaded, confident and appropriately elated.

There were no significant correlations between any of the thyroid hormone levels and the mean mood scores.

Neuropsychological tests

Verbal learning and memory

No significant correlations between levels of THs and scores on the verbal memory tests were observed.

Executive function tests

Significant positive correlations were found between free T3 levels and processing speed as well as between TgAB levels and error rates on the executive function tests (see Table 3). More specifically, higher levels of free T3 were positively associated with longer completion times (or slower performance) on Trail Making Test — Part A (r=0.380;p=0.006) and Part B (r=0.268; p=0.032). Higher levels of free T3 were also associated with slower completion times on the Tower of London test (r=0.377; p=0.002). Furthermore, higher levels of TgAB were positively correlated with more errors on the Trail Making Test Part B (r=0.470; p=0.000), on the Word Fluency test (r=0.284; p=0.023), and on the Design Fluency (r=0.28, p=0.045) test.

Due to the skewed distribution of TgAB values, possible differences between the women with high vs. low TgAB status with regard to their performance on the neuropsychological tests were examined further by performing two-tailed, independent sample t-tests. The demographic, mood, and neuropsychological test data of all participants with TgAB levels lower than 20 mU/L were collapsed into a low (<20 mU/L) TgAB group (n=96) and compared to that of the women whose TgAB levels were >20 mU/L (high TgAB group; n=29). There were no significant differences between the groups on any of the demographic or mood scores. However, the women in the high TgAB group made significantly more perseverative errors on the Design Fluency test (p=.003) compared to women in the low TgAB group. This difference remained significant even after correcting for the inequality of variance that resulted due to the differences in group sizes (p=0.034) (Table 4).

Working memory tests

There were no significant correlations between any of the thyroid hormone levels and mean scores on any of the working memory tests.

Discussion

This study investigated the relationship between TH levels and neuropsychological test performance in healthy, euthyroid women whose average age was 51 years. Our hypothesis that women with higher, but still normal, levels of THs would perform better on the neuropsychological test battery was not supported. Overall, there was a significant inverse relationship between higher levels of freeT3 within the normal range and slower processing speed on the Trial Making Test and the Tower of London tests of executive function. This suggests that high T3 levels within the normal range are associated with poorer performance on tests of processing speed and executive functions which are thought to be prefrontal cortical functions.

The hypothesis that higher levels of TgAB would be associated with worse performance on all of the neuropsychological tests was only partially supported. Indeed, higher levels of TgAB were associated with more errors on the Trails Making Test — Part B, the Design Fluency and the Word Fluency tests. These findings suggest that higher levels of TgAB antibodies are related to poorer performance on tasks of executive functions. On the other hand, there were no significant correlations between the thyroid hormone levels or TgAb levels and any of the verbal learning and memory tests.

The few studies that had investigated the relationship between normal levels of THs and cognitive performance in healthy individuals found inconsistent results (Wahlin et al., 1998; Prinz et al., 1999; Volpato et al., 2002; Gussekloo et al., 2004). For example, in older, euthyroid women lower total serum T4 (TT4) levels were associated with a greater risk of cognitive decline over a 3-year period (Volpato et al., 2002). In contrast, a positive relationship between TT4 and FT4 and cognitive functions occurred in healthy, euthyroid men (Prinz et al., 1999) such that, after controlling for age and education, TT4 accounted for 8% to 12% of the variance in the performance and verbal score of the WAIS intelligence test. Others failed to find a relationship between thyroid status and cognitive performance (Gussekloo et al., 2004). Methodological differences between these studies, including dissimilar population samples and study designs, do not allow for direct comparison and may explain the discrepancies in their findings.

Our findings suggest that the relationship between THs and cognition is powerful in that even differences in TH levels within the normal range are associated with differences in cognitive function. We found that in a sample of 122 healthy, euthyroid women with mean age of 51 years, higher levels of fT3 and TgAB levels within the normal range were correlated with slower performance and more errors on tests of executive function. It has been previously reported that mild hypothyroidism can cause significant worsening of information processing speed, reduced efficiency in executive functions, and poorer learning (Osterweil et al., 1992; Haggerty et al., 1993; Baldini et al., 1997; Kalmijn et al., 2000; Zhu et al., 2006). Our results therefore demonstrate a similar relationship between higher levels of fT3 and TgAB within the normal range and tests of executive functions in healthy euthyroid women.

Although it is unclear why fT3 and fT4 were not associated with performance on neuropsychological tests, it is likely that this depends on in the neural pathways activated when performing these tests and on the distribution of TH receptors in the brain. It is generally accepted that effects of thyroid hormones are mediated by an interaction with specific thyroid nuclear receptors. T4 and T3 are secreted by the thyroid gland and transported to the target cells by different serum proteins. In the adult rat brain, it has been estimated that more than 80% of T3 is produced from the local deiodination of T4 by a 5′II deiodinase (Giordano et al., 1992). Thus, in the target cell, T3 is the active form of the hormone. As such, it is more likely that fT3 and not fT4 would be responsible for changes in cognitive functions as we found. Our failure to replicate studies that found relationships between THs and cognition may have been due to the fact that others measured total T4 (TT4) and total T3 (TT3) (Volpato et al., 2002; Wahlin et al., 1998; Prinz et al., 1999).

It is also unclear why levels of TgAB correlated positively with the error rates on two of the executive function tests but not with performance on the verbal learning and memory, attention, or working memory tests. In healthy elderly adults, elevated levels of TgAB are a risk factor for AD (Ewins, et al., 1991; Genovesi et al., 1996). Imaging studies on patients with brain lesions demonstrate that both design fluency and word fluency are dependent on frontal lobe processes (Benton, 1968; Bornstein, 1986; Milner, 1964; Jones-Gotman and Milner, 1977; Ruff et al., 1994; Baldo and Shimamura, 1998) and scores on these same tests were positively correlated with TgAB levels in the present study. Indeed, design fluency is negatively affected by right frontal cortical lesions whereas word fluency is impaired in patients with left frontal cortical lesions (Jones-Gotman and Milner, 1977; Baldo et al., 2001). Performance on both word fluency and design fluency tasks is also impaired in people with dementia (Bigler et al., 1988). Patients with AD were deficient in generating novel designs, and when designs were generated, often significant perseveration errors were made (Bigler et al., 1988). Word fluency is also impaired in AD patients. In fact, impaired performance on word fluency was one of the most sensitive psychometrically discriminating measures between AD patients and normal controls (Storandt et al., 1984). In the present study, errors on both the Design Fluency and Word Fluency tests were positively correlated with higher TgAB levels within the normal range.

Our results demonstrate moderate correlations between fT3 and FT4 and executive functions and suggest that THs may be important for optimal executive functioning. Furthermore, even slightly elevated levels of TgAB within the normal range may be negatively associated with frontal lobe cognitive functions. However, caution is invoked because this is a correlational study which does not allow causal statements with regard to this hormone–behavior relationship to be made. Second, our sample size may not have been large enough to detect smaller effect sizes. Therefore, it is not possible to exclude the possibility that an effect of TgAB levels on the verbal memory or attention tests might have been evident in a larger sample. Third, our study utilized a comprehensive battery of neuropsychological tests, each with multiple outcome variables, thus raising the risk of Type II error. Finally, the results are not necessarily generalizable to men. However, the findings are important because they point to a possible link between THs and cognitive processes that are mediated primarily by the frontal cortex. Therefore, these results underscore the importance of selecting neuropsychological measures that are sensitive to frontal cortex processes in future investigations of thyroid status and cognition.

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Table 1

Demographic characteristics.

Participants N=122	Mean	Standard deviation
Age	51.1	15.2
Education	15.8	3.15
BDI-II	6.82 [a]	6.37
POMS-Bi composed-anxious	55.2 [b]	9.86
POMS-Bi agreeable-hostile	53.20 [b]	11.13
POMS-Bi elated-depressed	53.16 [b]	10.94
POMS-Bi confident-unsure	54.16 [b]	10.51
POMS-Bi energetic-tired	54.63 [b]	9.51
POMS-Bi clearheaded-confused	57.63 [b]	10.44

[a]Beck Depression Inventory-II (BDI-II). BDI score between 0 and 13 is considered minimal, 14–19 is mild, 20–28 is moderate, and 29–63 is severe depression range.

[b]Scaled scores for Profile of Mood States Bi-Polar (POMS-Bi). POMS-Bi scaled scores have a mean of 50 (SD=10) and are calculated on a bipolar scale with numbers below 50 representing the negative affect pole and number above 50 representing the positive affect pole.

Table 2

Thyroid hormones and antibody levels.

Participants=122	free T4	Free T3	TSH	TgAb
Mean (SD)	11.31 (1.66) pmol/L	3.935 (.397) pmol/L	1.84 (1.33) mU/L	31.36 (52.7) mU/L

Picomols per liter (pmol/L); international units per liter mU/L; thyroid stimulating hormone (TSH); thyroxine (T4) and triiodothyronine (T3).

Table 3

Significant correlations between scores on the executive function tests and thyroid hormone levels.

Outcome variable	Free T3	TgAB
Trails A time[a]	r=0.380; p=0.006	
Trails B time[a]	r=0.268; p=0.032	
TOL-II total time[b]	r=0.377; p=0.002	
Trails B errors[a]		r=0.470; p=0.000
Word Fluency (total errors)		r=0.284; p=0.023
Design Fluency (total errors)		r=0.283, p=0.045

[a]Trail Making Test.

[b]Tower Of London Test — Second Edition (TOL-II), total execution time outcome variable.

Table 4

Endocrine characteristics of the High vs. Low TgAB status groups.

Variable	TgAB mU/L mean/SD	Free T3 pmol/L mean/SD	Free T4 pmol/L mean/SD	TSH pmol/L mean/SD	Age mean/SD	Design fluency perseverative errors mean/SD
High TgAB group	105.1(121.67)	3.93 (.48)	11.62 (1.55)	1.77 (2.9)	51 (15.91)	15.87 (15.87)
Low TgAB group	<20 (.00)	3.97 (0.38)	11.39 (2.23)	2.43 (1.3)	56 (12.76)	6.61 (10.25)