# LATERALIZATION OF MEMORY AND COGNITIVE FUNCTIONS WITH REGARD TO THYROID FUNCTIONING

by

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ABSTRACT

Clinical hypothyroidism has had a long, but conflicted, history as being recognized as a potentially reversible cause of cognitive impairment. One piece of information that recurs throughout the literature concerning the control of thyroid functions data suggests a left-sided dominance. This research aimed to discover which hemisphere controls thyroid functions specific to memory and cognitive functioning. We hypothesized that the left hemisphere controlled thyroid functioning and would show a bias in neuropsychological testing in a clinical population, resulting in individuals with higher TSH levels performing worse on verbal tasks than their lower TSH level counterparts. Twenty-six female participants with either hypothyroidism or Hashimoto's disease were grouped into one of two groups (Low TSH/High TSH) based on their TSH serum levels at the time of neuropsychological testing. The results provided no support, finding no significant differences between the Low TSH and High TSH groups in performance on verbal tasks.

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# CHAPTER I: INTRODUCTION

Several disorders of the thyroid, in particular hypothyroidism, have been found to result in memory and cognitive deficits. The thyroid signaling system is crucial for proper neural formation as low thyroid hormone levels can contribute to impaired cognitive development, altered cognitive processes, metabolism disorders, as well as mental disorders (Leach, Holliday, Kutlu, & Gould, 2015). Hypothyroidism has been associated with a plethora of neurological and psychological deficits, including depression, mania, and dementia-like features, along with the other complimentary symptoms of the disorder (Monzani et al., 1993). In addition to these behavioral and neurological impairments, psychiatric symptoms such as, psychosis, mood instability, mania, and hypersomnia, can also be observed in individuals with hypothyroidism (Noda, 2015). Hypothyroidism is quickly surpassing diabetes mellitus as the most common endocrine disorder in the U.S., and its prevalence may be as high as 18 cases per 1,000 persons in the general population (Hueston, 2001). Since thyroid disorders rival diabetes as the number one endocrine disorder, determining the potential influences on memory and cognitive deficits that result from these thyroid disorders deserves some consideration.

As the link between cognitive functions and thyroid functions is a relatively new topic much is still unknown. A recurring theme throughout the literature suggests left hemisphere dominance in the cerebral control of thyroid functions (Gerendai et al., 1978). Evidence for this left-sided dominance can be seen through research on depression, dementia, and cardiovascular issues, which connect in various ways to thyroid functions. Is there a way to determine which hemisphere of the brain controls the

thyroid? If so, there could be a way to improve memory and cognitive functions in patients with thyroid disorders. Further, if more research is done there could be a way to identify patients with thyroid disorders through neuropsychological screeners, without the necessity of biannual or quarterly blood draws.

Specifically regarding lateralization of thyroid functions with memory and cognitive functions, there has not been any research on this topic. However, much research has been reported regarding general cognitive functions and memory and the relationship with thyroid functions. There is published research on the lateralization of the limbic system, which is related to thyroid function, but most information provided is supportive in nature.

**Thyroid Functioning**

Thyroid hormones affect every organ and cell type in the body, and many areas of the body are implicated when a disruption of hormones occurs, specifically, the cardiovascular system, endocrine system, and the central nervous system. Deficits or excesses of thyroid hormones lead to widespread symptomology throughout the body (Kansagra, McCudden, & Willis, 2010). The thyroid gland produces three main types of hormones: T4 (thyroxine), T3 (triiodothyronine), and calcitonin. The former two hormones are important in regulating body metabolism and are integral to bone growth and the growth and maturation of the brain and nervous system. A lack of these hormones, especially during fetal development, can lead to severe brain underdevelopment, and thus, delays after birth (Wilkinson & Brown, 2015).

**Hypothalamic-Pituitary-Thyroid Axis.** The Hypothalamic-Pituitary-Thyroid Axis (HPT axis) is a collection of influences and feedback interactions that take place between three endocrine glands: the hypothalamus, the pituitary gland, and the thyroid gland. The hypothalamus is located underneath the forebrain, the pituitary gland is located on the hypothalamus at the base of the brain, and the thyroid is a butterfly-shaped gland above the laryngeal prominence, which is commonly referred to as the Adam's apple, in the neck (Wilkinson & Brown, 2015). The HPT axis is regulated by Type II deiodinases in the brain's astrocytes, which are types of glial cells in the central nervous system. Any inactive T4 hormones are converted into T3 hormones by the Type II deiodinases. The hypothalamus releases TRH (thyroid-releasing hormones), which stimulates the pituitary gland in the brain to release TSH (thyroid-stimulating hormone), which then stimulates the thyroid into releasing the T4 and T3 hormones out to the rest of the body. This process works in a biofeedback system; therefore, in a person with hypothyroidism this system is dysfunctional. The hypothalamus recognizes a deficit in T4/T3 hormones, which accounts for the increased presence of TSH in the person's blood; however, the thyroid is unable to adequately produce the T4/T3 hormones on its own. This is where many thyroid medications come into play; they increase levels of T4/T3 hormones circulating in the bloodstream, allowing them to bind with TBG (thyroxine binding globulin), transthyretin, and albumin. This creates an inhibitory effect on the hypothalamus and pituitary glands, which reduces the amounts of TRH and TSH in the blood, and reduces any symptomology felt by the patient (Kansagra et al., 2010).

This process is not changed by the presence of thyroid medications, but rather influenced by them.

**Hypothyroidism.** Hypothyroidism is a disease that is characterized by a deficit of hormone production by the thyroid gland (Hueston, 2001). "In patients with primary hypothyroidism, the TSH (thyroid stimulating hormone) level is elevated indicating that thyroid production is excessive in relation to metabolic demands, and free thyroid hormone levels, T3 and T4, are depressed" (Hueston, 2001, p. 1719). Therefore, increased TSH levels and decreased levels of thyroid hormones are the hallmarks of hypothyroidism. Hashimoto's thyroiditis, the most common cause of hypothyroidism, is an autoimmune thyroid disease caused by the gradual atrophy of the thyroid gland following invasion of lymphocytic cells, follicular atrophy, and hyperemia accompanied oncocytic metaplasia of follicular cells (Pyzik, Grywalska, Matyjaszek-Matuszek, & Roliński, 2015).

Typical symptoms exhibited by hypothyroidism patients include: weakness and fatigue, cognitive impairments, dry skin, course hair, loss of hair, cold intolerance and cold extremities, constipation, depression, weight gain, muscle cramps, slow reflexes, and bradycardia (Adlin, 1998; Kansagra et al., 2010). In addition to the list of symptoms that this disease causes, it also inadvertently causes other medical issues, such as fertility issues (Kansagra et al., 2010), predispositions to cardiovascular diseases (Anderson, Olsen, Madsen, Faber, Torp-Pederson, Giaslason, & Selmer, 2015), and some research has suggested a link between hypothyroidism and Alzheimer's disease (Annerbo & Lökk, 2013). According to the American Thyroid Association, TSH levels that are between 0.45

mIU/L to 4.2 mIU/L are indicative of a normally functioning thyroid gland, which is referred to as being euthyroid, while TSH levels that are above 4.3 mIU/L are indicative of hypothyroidism (Garber et al., 2012). Although TSH levels are the primary basis on which a diagnosis of hypothyroidism is made, many physicians will sometimes adjust medication dosages depending on the symptomology of the patient.

**Functional Asymmetries of the Thyroid**

One of the first observations concerning asymmetry of the neuroendocrine system, was completed by Gerendai, Rotsztejn, Marchetti, Kordon, and Scapagnini (1978). They discovered the significant difference in gonadotropic hormone-releasing hormone (GnRH) content between the left and right halves of the hypothalamus of female rats. The results were that the GnRH content was higher in the right half of the hypothalamus than in the left. This led to research in humans, and a study by Ramírez, Prieto, Vives, Gasparo, and Alba (2004) discovered a lateralized difference in TRH in the human brain. There is more abundance of thyrotropin-releasing hormone (TRH) in the left hypothalamus than in the right hypothalamus of the brain. Another study corroborated this in finding a higher concentration of TRH in the left hypothalamic ventromedial, dorsomedial, and paraventricular nuclei (Borzon-Chazot et al., 1986).

Other functional and anatomic asymmetries of the thyroid also exist. For instance, the right lobe of the thyroid gland is usually larger and more vascularized than the left lobe. Further, research has suggested that there are increased levels of serotonin metabolized in the left hippocampus and hypothalamus, the latter of which has important connections with the thyroid. Additionally, thyroid diseases, such as solitary nodules or

other disorders causing diffuse increase in the size of the gland, seem to affect mostly the right side (Gerendai & Halász, 1997).

Additional asymmetries arise from the dual innervation of the thyroid gland from the sympathetic and parasympathetic nervous systems. Parasympathetic supply of the thyroid gland emanates from the vagus nerve, via the nodose ganglion and the thyroid ganglion (Gerendai & Halász, 1997). Studies have found that sympathetic fibers to the thyroid exert an inhibitory action on thyroid growth, especially following hemithyroidectomies. The inhibitory action of sympathetic innvervation suggests that parasympathetic responses play a key role in growth of the thyroid gland (Gerendai & Halász, 1997). Some researchers have posited that the left cerebral hemisphere regulates parasympathetic functioning and the right hemisphere regulates sympathetic functioning (Foster, Drago, Ferguson, & Harrison, 2008; Wittling, 1997). Given the differential roles of the left and right hemispheres in regulating parasympathetic and sympathetic functions, the possibility exists that asymmetries exist in the cerebral control of thyroid functioning. Specifically, there is a possibility that left hemisphere structures may be in control of thyroid functioning. The parasympathetic nervous system provides the 'rest and digest' aspect of functioning and research has indicated that stimulation of the left hemisphere results in bradycardia (Oppenheimer, Gelb, Girvin, & Hachinski, 1992). The bradycardia following left hemisphere stimulation is particularly interesting in the context of one of the hallmarks of hypothyroidism, where these patients exhibit an overall heart rate that is lower compared to healthy patients.

**Memory and Cognitive Functioning in Hypothyroidism**

Clinical hypothyroidism has had a long, albeit conflicted, history as being recognized as a potentially reversible cause of cognitive impairment. Subclinical thyroid diseases such as hypothyroidism, as well as autoimmune thyroiditis (Hashimoto's Disease), have often related to cognitive dysfunction (Nataf, 2017; Monzani et al., 1993). According to Miller et al. (2007), "Cognitive changes have frequently been detected in patients with hypothyroidism, including deficits ranging from minimal to severe in general intelligence, psychomotor speed, visual-spatial skills and memory" (p. 132). They also noted a specific deficit in memory retrieval in hypothyroid patients. Their study concluded that hypothyroid patients had more difficulty retrieving verbal information after a short delay, and this problem persisted when presented with a longer delay, despite being prompted with the information again (Miller et al., 2007). With regards to memory, another study mentions that the cognitive effects felt by hypothyroid patients are specific to retrieval of newly learned information (Burmeister et al., 2001). Considering that this is the issue with many degenerative diseases, this is certainly of importance.

Miller et al. (2006) noted in their discussion that the contrast between the impairment bias against retrieval of information and not encoding or recognition of information suggests that hypothyroidism may have a distinct profile of memory retrieval deficits, which may implicate the prefrontal cortex. The hemispheric encoding/retrieval asymmetry (HERA) model states that the left prefrontal cortex is more involved than the right prefrontal cortex in episodic memory encoding, whereas the right prefrontal cortex is more involved with episodic memory retrieval (Habib, Nyberg, & Tulving, 2003).

Habib et al. (2003) reported that their results provide evidence that both a material-specific and a process-specific asymmetry can coexist in the same area. That is, the authors observed that the left prefrontal cortex site was more active for verbal encoding and retrieval, and the right prefrontal cortex was more active for nonverbal encoding and retrieval (Habib et al., 2003), thus providing more evidence that the verbal retrieval deficit present in hypothyroidism patients could be a result of left hemisphere dysfunction.

As previously mentioned, most agree that there are noticeable cognitive changes in patients with hypothyroidism, most focusing on the decline in the ability to retrieve newly learned information, and general decline in memory. The improvement of memory and cognitive functioning with the addition of thyroid replacement therapies has been noted in the research. A meta-analysis done by Miller et al. (2006) concluded that after a 3-month treatment period on levothyroxine, the hypothyroid group had significant increased verbal memory retrieval compared to the control group. This suggests that some verbal memory deficits associated with hypothyroidism can be reversed with the addition of thyroid replacement therapies. Further, Alzoubi, Gerges, Aleisa, & Alkadhi (2009) reported that in patients with thyroidectomy-induced hypothyroidism their short and long-term memory deficits were abolished with thyroid hormone supplementation.

Annerbo and Lökk (2013) mention that thyroid hormone receptors are prevalent in the hippocampus and the nucleus of the amygdala in the medial temporal lobe, which are both areas in the brain that are involved with memory. The hippocampus, a structure in the limbic system that extends from the lateral neocortex of the medial temporal lobe

toward the midline of the brain, is involved in consolidation and retrieval of information as well as playing an important role in organizing memories of objects in space (Kolb & Whishaw, 2015). Thyroid hormones are crucial for the normal development of the hippocampus, this is evidenced by studies on adolescences with congenital hypothyroidism (those who had low levels of thyroid hormones in late gestation/early life) which showed that these individuals demonstrate weak verbal recall abilities, reduced hippocampal volumes, and abnormal hippocampal functioning (Leach et al., 2015; Wheeler, McLelland, Sheard, McAndrews, & Rovet, 2015). Lee, Brady, & Koenig (2003) found that changes in thyroid status affects hippocampal NR1 and NR2b gene expression. Some studies have found that thyroid hormones can directly affect cognitive performance in a variety of tasks that are hippocampus dependent and hippocampus independent (Leach et al., 2015; Smith, Evans, Costall, & Smythe, 2002; Sui, Wang, Liu, & Wang, 2006), suggesting that thyroid hormones play a large role in hippocampal functioning and development. The left hippocampus has been associated with verbal tasks, such as the learning of prose and retrieval of word lists. Similarly, the encoding of verbal materials into episodic memory is associated with the left medial temporal lobe (Iglói, Doeller, Berthoz, Rondi-Reig, &Burgess, 2010). Given these associations, there could be some lateralization bias regarding thyroid function and memory and cognitive functioning.

**Left Cerebral Hemisphere Regulation of Thyroid Functioning**

It is unclear whether the presence of a thyroid disorder contributes to or results from the presence of Alzheimer's disease (AD). However, it is known that there is a

decrease of TSH concentration levels in the brain as age increases. Furthermore, aging modifies brain asymmetry, and imbalances in asymmetry can cause further neurological and psychological disorders (Ramirez, Prieto, Vives, Gasparo, & Alba, 2004). With both an increase in age, and a decrease in TSH levels, there are both negative memory and cognitive functioning outcomes. There are also other mitigating factors that can bridge the link between thyroid disorders and the presence of AD. Annerbo and Lökk (2013) stated "Subclinical as well as clinical thyroid diseases are shown to relate to cardiovascular disease and vascular risk factors with accumulating epidemiologic evidence that vascular risks factors increase the risk of AD, indicating a connection between thyroid function and AD." As previously mentioned, studies have shown retrieval deficits of newly learned information in hypothyroidism patients. This is also one of the hallmark features of AD, which further suggests a relationship between TSH levels and the impact on cognitive decline. "The hippocampus and nucleus of amygdala in the medial temporal lobe have a high density of thyroid hormone receptors, and patients with mild AD have more atrophy in those areas of the brain than compared to healthy elderly" (Annerbo & Lökk, 2013). These findings seem to demonstrate a clear, but indirect, connection relating thyroid hormones to the memory centers in the brain.

There are two major studies that lay the foundation to suggest that there is a link between the development of Alzheimer's disease and the presence of thyroid dysfunction. The first is The Framingham Study, in which 3330 participants were evaluated over their lifespan. This study started in 1948 and continued until 1975. They concluded that both low and high levels of thyrotropin levels (thyroid releasing hormone, also referred to as

TRH) were associated with an increased incidence of AD in women. 12.8% of women in the study sample developed AD after the mean follow-up time of 12.7 years (Tan et al., 2008). The Honolulu-Asia Aging Study is the second study that looked at thyroid functioning and the risk of dementia. It consisted of 665 men. They found that higher total thyroxine levels were associated with higher number of neocortical plaques and neurofibrillary tangles, which is one of the hallmarks of Alzheimer's disease. They suggested that higher thyroxine levels are present with Alzheimer clinical disease and neuropathology (Jan de Jong et al., 2009).

Studies by Thompson and colleagues have reported that in regard to cortical changes in Alzheimer's disease, there was a pervasive left-sided hemisphere reduction in grey matter, suggesting that the left hemisphere is more affected than the right in the early stages of the disease (Thompson et al., 2001; Thompson et al., 2003). Most left hemisphere regions demonstrated greater than 15% deficit relative to healthy controls (Thompson et al., 2003). Further, they also found that the temporal and tempo-parietal cortex exhibited severe reductions in grey matter, from 10 to 30 % (Thompson et al., 2001). Again in 2003, Thompson et al., found that significant grey matter loss was observed specifically in the bilateral temporal and parietal cortices, where deficits exceeded 15 % (Thompson et al., 2003). In this study, Thompson et al. found that the link between grey matter losses and lower cognitive scores were highly significant (Thompson et al., 2003). The piece of information that was most directly related to the connection between thyroid functioning and Alzheimer's disease- in the left hemisphere, the temporal/entorhinal regions and parietal lobes were the most impaired, and the

cingulate and paralimbic belts being significantly impaired (Thompson et al., 2003). These specific areas have heavy connections within the limbic system and with thyroid hormones: the paralimbic cortex is located on the medical surface of the temporal lobe (where the abundance of thyroid hormone receptors are), and the cingulate cortex is just above the corpus callosum, where there are inputs from the thalamus, amygdala, and hippocampus (Kolb & Whishaw, 2015).

Another point to consider with regards to the connection between cognitive decline and thyroid functioning is the neurotransmitter acetylcholine. Acetylcholine is a neurotransmitter that inhibits a response and plays a role in normal waking behaviors and is thought to function with attention and memory. Individuals with Alzheimer's disease are often found to have a depletion of cholinergic neurons, therefore their role in this disease is crucial, but unexplained (Kolb & Whishaw, 2015). Supplemental thyroid hormones have been shown to reverse amyloid plaque pathology in mice models of Alzheimer's disease (Fu, Zhou, & Chen, 2010). Supplemental thyroid hormones have been noted to reverse the effects of scopolamine-induced deficits in rats when completing the Morris water maze (Smith et al., 2002), which is important given that scopolamine has anticholinergic effects. Smith et al. (2002) demonstrated that there was an increase in cholinergic activity in the hippocampus and the frontal cortex of rats that were administered levothyroxine. These studies suggest that there is an interaction between acetylcholine and thyroid hormone signaling. The distribution of acetylcholine is asymmetrical, with greater concentration found in the left hemisphere (Glick, Ross, &

Hough, 1982; Kononenko, 1981), which may then suggest greater left hemisphere control of thyroid functioning.

Additional evidence for left hemisphere control of thyroid functioning is demonstrated by the relationship between thyroid functioning and depression. An association between hypothyroidism and depression has been accepted and taught in medicine for many years, although the nature of this relationship is still unclear. Many of the symptoms between hypothyroidism and depression overlap, thus differentiating the two diagnoses is very difficult (Dayan & Panicker, 2013). The Hypothalamic-Pituitary-Adrenal Axis has been implicated in major depression and suicidal behaviors (Gerendai & Halász, 1997). Depression is known to be associated with left frontal lobe dysfunction (Gainotti, 1972; Starkstein et al., 1989). These associations support the possibility that thyroid functioning is related to left hemisphere functioning.

**Summary and Purpose of Current Study**

Based on the aforementioned literature, I hypothesized that individuals with higher TSH levels would perform worse on tests of memory and cognitive functioning that measured left hemispheric functions, (i.e., more verbal tasks), than on tests of memory and cognitive functioning that measured right hemisphere functions, (i.e., more visuospatial or nonverbal tasks). Specifically, I hypothesized that individuals with higher TSH levels would perform worse on measures of verbal memory (Hopkins Verbal Learning Test-Revised), verbal attention/working memory (Digit Span), and verbal fluency (Controlled Oral Word Association Test) than individuals with lower TSH levels. I also hypothesized both individuals with high TSH levels and low TSH levels would

perform similarly on tests of nonverbal/visuospatial memory (Brief Visuospatial Memory Test-Revised), nonverbal/visuospatial attention/working memory (Spatial Span), and nonverbal/visuospatial fluency (Ruff Figural Fluency Test).

# CHAPTER II: METHODS

## Participants

The participant population was recruited from the Endocrinology office of Dr. Rone at Murfreesboro Medical Clinic in Murfreesboro. The patient population consisted of individuals who had a diagnosis of either hypothyroidism or Hashimoto's thyroiditis. This study included 26 female participants between the ages of 24 and 54 ($M_{age}$ = 42.31, *SD* = 7.79) resulting in 13 participants per group (Low TSH: "0.01 mIU/L to 0.53 mIU/L"; High TSH: "0.68 mIU/L to 7.81 mIU/L"). All participants possessed a 12$^{th}$ grade education or GED, but the population otherwise varied in years of post-secondary education (*M* = 14.65, *SD* = 2.74). Refer to Appendix A, Table 1 for Group Demographics. Of the 26 participants, 20 (77% of the population) were right handed and the remaining were left handed. Of the 26 participants, five (19%) reported a past history of a head injury resulting in a loss of consciousness. Seven (27%) participants reported a history of psychological illness. Nine participants (35%) revealed that they were currently taking psychotropic medications, which included anti-anxiety medications, antidepressants, antipsychotics and stimulants. Four participants (15%) indicated they had severe depressive symptoms, which was determined by a total score of 29 or greater on the BDI-II. One participant (4%) indicated moderate depressive symptoms, which is reflective of a score between 20-28 on the BDI-II. Seven participants fell within the 14-19 score range, indicating mild depression. The only exclusionary criterion was the presence of any central neurological disorders, such as Multiple Sclerosis, Strokes,

Epilepsy, or Dementia. None of the participants in this study had any presence of central neurological disorders.

## Apparatus

**Beck Depression Inventory-II (**BDI-II). The Beck Depression Inventory-II (Beck, Steer, & Brown, 1996) is a 21-item self-report questionnaire used for measuring the severity of depression. The items of the BDI-II address problems related to numerous psychological, cognitive, and physiological symptoms. Each item is endorsed by the patient on a scale of 0 to 3, with a range of possible scores from 0 to 63. A total score of 14-19 is recognized as mild symptomology, while a score from 20-28 is considered moderate symptomology, and a score that falls within the 29-63 range is recognized as severe symptomology. Among university samples, internal reliability coefficients for the BDI-II have ranged from .84 to .93 (Al-Musawi, 2001). Among medical or psychiatric samples, internal reliability has still been found to be high, greater than .88. Over short intervals (1 day to 2 weeks), test-retest correlations are adequate ($r$ = .74 to .75) (Al-Musawi, 2001) to high ($r$ = .93 to .96) (Beck, Steer, & Brown, 1996). The BDI-II highly correlates with other depression-related instruments, suggesting strong convergent validity (Strauss, Sherman & Spreen, 2006). The dependent variable in the BDI-II the symptom score.

**Subject History and Demographics Form**. The Subject History and Demographics Form requires the participant to give general demographic information including age, handedness, education level, as well as information regarding past and present medical history. The participant was asked to note if they had a history of head

injury, any neurological and psychological illness. They also listed any current psychotropic medications that they were taking (i.e., names and dosages).

**Left Hemisphere Measures**

**Controlled Oral Word Association Test** (COWAT). The COWAT is a test that requires the participant to produce orally as many words as possible beginning with a specified letter (F, A, or S) in one minute. All words are permissible with the exception of proper nouns, repeated words, wrong words and words that include a repeated stem (such as 'begin' and 'beginning'; only one would be included). This test is a measure of verbal fluency. The total number correct is the sum of all admissible words given during the three trials. Coefficient alpha was found to be high ($r$ = .83) when computing all three letters (F, A, & S, and C, F, & L) as separate items (Tombaugh et al., 1999). Test-retest correlations tend to be high, typically above .70 for letter fluency with short and long intervals (Basso, Bornstein, & Lang, 1999). Correlations among phonetic fluency tasks are high; for letters FAS and BHR the correlation is .83 and for FAS and PRW the correlation is .82 (Strauss, Sherman & Spreen, 2006). The dependent variable in the COWAT is verbal phonemic fluency, (i.e., the number of total correct words given).

**Digit Span** (DS). Digit Span is a subtest on the WAIS-IV (Wechsler, 2009), and it requires the participant to repeat various number sequences in same order presented, and in the reverse order from presented. The total number of correct sequences are totaled to get a total forward score and a total backward score, which are then transferred into a scaled score (1-19). This test, specifically DS backwards, can be used as a way to determine the difference between working memory deficits and attentional control

(Rosenthal, Riccio, Gsanger & Jarratt, 2006). Internal consistency was found to be very high for this subtest, .90+. Test-retest reliability for the Digit Span subtest was also high, ($r$ = .80-.89) (Strauss, Sherman & Spreen, 2006). The dependent variable that is associated with Digit Span in the current study is the raw total recall score.

**Hopkins Verbal Learning Test-Revised** (HVLT-R). The Hopkins Verbal Learning Test-Revised (Brandt & Benedict, 2001) requires the participant to recall a list of 12 words that all fall into one of three semantic categories (four-legged animals, precious gems, and dwellings), under different time conditions (Strauss, Sherman & Spreen, 2006). The HVLT-R contains three learning trials and a delay trial that takes place 20-25 minutes after the first trial is given. The last trial consists of a list of 24 words, 12 of which are targets and 12 are distractors, 6 of which are taken from the same semantic categories used in the trials. The participant is asked to identify the correct words from the list. For each trial, the number of correct responses is totaled. Percentage retained after the delay (percentage retention) is calculated by dividing Trial 4 by either Trial 2 or 3, and then multiplying by 100. The recognition discrimination index is the number of true positives minus the number of false positives gathered from the last trial given. Test-retest reliability coefficients for the four primary HVLT-R variables were .74 for Total Recall, .66 for Delayed Recall, .39% for Retention and .40 for the Recognition Discrimination Index (Benedict et al., 1998). Learning curves and retention rates were quite similar between the HVLT and the CVLT (Strauss, Sherman & Spreen, 2006). The dependent variables in the HVLT-R consist of total learning and delayed recall of verbal learning and memory.

**Right Hemisphere Measures**

**Brief Visuospatial Memory Test- Revised** (BVMT-R). The Brief Visuospatial Memory Test-Revised (Benedict, 1997) requires participants to reproduce a series of designs from memory, reproducing them in the same matrix location they were shown on the display, with three learning trials. The participant is presented an 8.5 x 11 sheet that contains six geometric designs in a 2x3 matrix for 10 seconds. The BVMT-R does have a delay task 25 minutes after the first. Each item is given two points if the design is correctly drawn in the correct placement, and one point is awarded if the design is correctly drawn but in the incorrect place. When the score is combined across all six test forms, reliability coefficients are marginal to high, ranging from .60 for Trial 1 to .84 for Trial 3. The reliability coefficient for the total recall score is .80 (Benedict, 1997). The indices of learning and delayed recall correlated most strongly with other tests of explicit memory, such as the Hopkins Verbal Learning Test, the Visual Reproduction subtest on the WMS-R, and Rey Figure recall ($r$ = .65 to .80) (Strauss, Sherman & Spreen, 2006). The dependent variables in the BVMT-R consist of total learning and total learning delayed recall of visual learning and memory.

**Ruff Figural Fluency Test** (RFFT). The Ruff Figural Fluency Test (Ruff, 1998) requires the participant to produce spontaneous written figures under different conditions. There are five pages of matrices, all arranged in seven rows and five columns on an 8.5 x 11 piece of paper. Each page consists of a different stimulus pattern: symmetrical dot pattern, dots and diamonds, dots with lines, and two with asymmetrical dot patterns. The participant is to draw as many different designs as possible in one minute. Any repeated

design count as a perseveration, thus counts as an error. The total number of unique designs across all 5 pages, as well as the number of perseverative errors across all 5 pages are used in the scoring process. Test-retest reliability for total number of unique designs are high ranging from three weeks to 12 months ($r$ = .71-.88), but low for the number of perseverative errors ($r$ = .36-.48) (Ross et al., 2003). Test-retest reliability for production strategies (i.e., the strategies a test taker uses to produce designs) was adequate ($r$ = .70+). (Ross et al., 2003) "The perseveration and error ratio scores are highly correlated ($r$ = .89), but the number of unique designs only shows small correlations ($r$ = .24) with the error ratio score and the number of perseverative designs" (Ross et al., 2003). Scores on the RFFT are moderately correlated with those of other figural fluency tasks, and with measures of general cognitive status, such as the Performance IQ on the WAIS-R (Strauss, Sherman & Spreen, 2006). The dependent variables in the RFFT are the total number of unique designs and perseverative errors from figural fluency. These were used to obtain an error ratio score, which is derived from the amount of perseverative errors divided by the total of unique designs made by each participant.

**Spatial Span** (SS). Spatial Span (Wechsler, 1997) is a subtest on the WMS-III that requires the participant to repeat back sequences of block tapping that were presented by the examiner, going in the same order and in the reverse order presented. The total number of correct sequences are summed to get a total forward score and a total backward score, which are then transformed into an age-adjusted scaled score. Internal consistency for Spatial Span was found to be adequate, ($r$ = .70-.79). Test-retest reliability for Spatial Span was found to be adequate, ($r$ = .70-.79) (Strauss, Sherman &

Spreen, 2006). The dependent variable that is associated with Spatial Span in the current study is the raw total recall score.

**Procedure**

This study was approved by the Institutional Review Board of Middle Tennessee State University (see Appendix A). After being treated by Dr. Rone or Melissa Fulghum, NP, all patients that met criteria were given an opportunity to participate in this study. All testing was conducted in an office at Murfreesboro Medical Center. The participants provided informed consent (see Appendix B) and completed a battery of neurological assessments, as listed above. The participants were given the two memory tests (HVLT-R & BVMT-R) first, which were counterbalanced. Afterwards, the counterbalanced attention/working memory tests (DS & SS) and fluency tests (COWAT & RFFT) were administered. Lastly, the delay portion of the two memory tests were administered. The examinee then completed a brief questionnaire regarding general demographic information, current or past medication usage, neurological and psychological history (Subject History and Demographic Form), and their self-reported level of depression in the last two weeks (BDI-II). The entire length of testing ranged from approximately forty-five minutes to one hour, depending on the participant. The TSH levels of the patients who chose to participate were then gathered from their most recent laboratory panel, the majority were taken within 2 weeks of the day of testing. The lab results and test scores were kept confidential until all testing had been completed. All patients were treated in accordance with the ethical principles set forth by the American Psychological Association.

## CHAPTER III: RESULTS

Before SPSS statistical analyses were performed, all individual scores for each test variable were ranked. Based on a median split of the gathered TSH levels, two groups of 13 participants were created. The Low TSH group had a median rank of 0.21, with a range of 0.01 mIU/L to 0.53 mIU/L, and the High TSH group had a median rank of 1.59 with a range of 0.68 mIU/L to 7.81 mIU/L. The Mann-Whitney U-Test was chosen for SPSS analyses due to the violation of normality from the small sample size. A Mann-Whitney U-Test was conducted to examine the group differences between the Low TSH and the High TSH groups. The results from a Mann-Whitney U-Test ($U = 0$, $p < .001$) indicated that the median rank of the Low TSH group was significantly different from the median rank of the High TSH group.

Initial analyses were conducted to determine group equivalency with regard to age, education, and depression. The results of a Mann-Whitney U-Tests indicated that no statistical differences were found. Refer to Appendix A, Table 2 for the Mann-Whitney U-Test Statistics.

Primary analyses were conducted in order to evaluate both of the hypotheses. The first hypothesis stated that individuals in the High TSH group would perform significantly worse than individuals in the Low TSH group on measures of left hemisphere functioning. The results of a Mann-Whitney U-Test indicated that the median rank of the Low TSH group did not significantly differ from the median rank of the High TSH group on tests of left hemisphere function. Refer to Table 3 of Appendix A for

specific results and median ranks for these analyses. The second hypothesis stated that individuals in the Low TSH group would perform similarly to those individuals in the High TSH group on measures of right hemisphere functioning. The results of a Mann-Whitney U-Test indicated that the median rank of the Low TSH group did not significantly differ from the median rank of the High TSH group on tests of right hemisphere function. Refer to Table 3 of Appendix A for specific results and median ranks for these analyses.

# CHAPTER IV: DISCUSSION

Based on all the SPSS analyses, the findings did not support the first hypothesis on significant differences between the High and Low TSH groups on measures of left hemisphere functioning. The results of a Mann-Whitney U-Test indicated that the median rank of the Low TSH group was not significantly different from the median rank of the High TSH group on tests of left hemisphere function, indicating that there are no significant differences in performance between the two groups. Participants with higher TSH levels did not perform worse on tests of memory and cognitive functioning that measured left hemispheric functions, including measures of verbal recall, verbal fluency, and verbal attention/working memory. As predicted, there were no significant differences between the High and Low TSH groups in performance on measures of right hemispheric functions, including visuospatial recall, nonverbal fluency, and visuospatial attention/working memory. However, the current investigation was more interested in examining purported differences between the two groups in regard to left hemisphere functioning. There were several methodological limitations that might have impacted the results of the current study, thus resulting in no significant differences between the two groups on measures of left hemisphere functioning.

First and foremost, the sample size of the population was insufficiently small, thus violating the normality assumption and leaving the resultant data skewed and difficult to interpret reliably. In addition, there were quite a few participants that were included in the statistical analyses that ideally should have been excluded due to certain circumstances

that could affect the reliability of the data, such as the presence of depression or a history of psychological illness or head injury. These individuals were ultimately kept due to the small sample size. As is well documented in the supporting literature, the heavy overlap between depression, memory functioning, age, and TSH levels made it difficult to surmise any crucial information from the data.

Secondly, a large portion of the TSH values that were used to create the two individual groups fell within a close subset of the range, which presents an issue when the primary goal was identifying differences between the two groups. According to the American Thyroid Association, the euthyroid range for TSH levels is between 0.45 mIU/L and 4.2 mIU/L. In this sample, 20 of the 26 participants had TSH levels that fell below 2.3 mIU/L, (which is roughly half of the estimated acceptable range), therefore 77% of the participants had TSH levels that were on the low-end of normal. In addition to this, 12 participants had TSH levels that were below 0.45 mIU/L, which is indicative of an overactive thyroid gland. In comparison, only 2 participants had TSH levels that were above 4.2 mIU/L, which is indicative of uncontrolled hypothyroidism. Therefore, the sample was potentially biased in that there was limited variability within the participant population.

Third, the framework of this study that was detailed in the methods section needs to be adjusted in order to form two discriminative groups based on TSH levels. For example, if the ideal number of participants is 40, instead of dividing 40 participants into two groups by the lowest 20 and the highest 20, each participant that is tested needs to be placed into one of the two groups based on their TSH levels at the time of testing (i.e. 20

in the 0.45 mIU/L- 4.2 mIU/L group and 20 in the 4.3+ mIU/L group), even if that results in some participants not being included in the study. Being more discriminative in participant inclusion is one way to ensure that the two groups are distinct and not too similar.

Future research should focus on expounding upon the foundation that this study has provided, since there was not any previous research specifically regarding this topic. Gaining access to and recruiting participants is one of the best ways to ensure that all limitations that were mentioned above are overcome. If enough time is available to the researcher, gathering an appropriate number of participants with more varied thyroid functioning, as well as ensuring that participants meet all inclusionary criteria, would be the most helpful in future endeavors. Specifically, there are three observations with this patient population that might make any future data collection easier. First, contacting potential participants before their scheduled appointment time, and informing them of the study might increase the likelihood of participation if they are able to plan ahead. Second, cutting out a few of the tests would decrease the amount of time the participant needs to spare, and therefore might make them more willing to participate. Last, take into consideration and plan for any special circumstances that might affect data collection. For example, this study took place during late Spring and early Summer. Once summer break started in the county, most women were unable to participate because they either had their children with them during their appointment or had no childcare resources in order to come back in for testing.

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# APPENDICES

# APPENDIX A: TABLES

Table 1

*Low TSH and High TSH Group Demographics*

| | Education | | | Handedness | | |
|---|---|---|---|---|---|---|
| Group | 12 | 13-16 | 17+ | Left | Right | Hx LOC |
| Low TSH | 6 | 4 | 3 | 3 | 10 | 2 |
| High TSH | 3 | 8 | 2 | 3 | 10 | 3 |

| | BDI-II | | | |
|---|---|---|---|---|
| | 14-19 | 20-28 | >29 | Hx Illness | Hx Med |
| Low TSH | 2 | 0 | 3 | 6 | 8 |
| High TSH | 4 | 1 | 1 | 1 | 2 |

**APPENDIX A: TABLES** (continued)

Table 2.

*Median Ranks and Statistical Results for Group Comparisons of Age, Education, and Depression*

| Variable | Low TSH | High TSH | Mann-Whitney *U* |
|---|---|---|---|
| Age | 16.50 | 10.00 | $U = 63.50$, $p = .28$ |
| Education | 13.50 | 13.50 | $U = 77.00$, $p = .69$ |
| BDI-II | 12.50 | 14.00 | $U = 78.00$, $p = .74$ |

**APPENDIX A: TABLES** (continued)

Table 3.

*Median Ranks and Statistical Results for Group Comparisons of Primary Variables of Interest*

| Variable | Low TSH | High TSH | Mann-Whitney U |
|---|---|---|---|
| Left Hemisphere | | | |
| COWAT | 12.00 | 16.00 | $U = 66.5$, $p = .36$ |
| DS | 13.00 | 9.50 | $U = 70.5$, $p = .47$ |
| HVLT-TR | 13.50 | 13.50 | $U = 70.0$, $p = .45$ |
| HVLT-DR | 18.00 | 10.50 | $U = 76.0$, $p = .65$ |
| Right Hemisphere | | | |
| RFFT | 10.00 | 16.50 | $U = 56.0$, $p = .14$ |
| SS | 12.50 | 15.50 | $U = 72.0$, $p = .52$ |
| BVMT-TR | 10.00 | 16.00 | $U = 58.5$, $p = .18$ |
| BVMT-DR | 13.00 | 13.00 | $U = 54.0$, $p = .10$ |

# APPENDIX B: IRB APPROVAL FORM

# IRB

**INSTITUTIONAL REVIEW BOARD**
Office of Research
Compliance, 010A Sam
Ingram Building, 2269
Middle Tennessee Blvd
Murfreesboro, TN 37129

## IRBN001 - EXPEDITED PROTOCOL APPROVAL NOTICE

Monday, February 12, 2018

| | |
|---|---|
| Principal Investigator | **Leslie Meranda Qualls-Lambert** (Student) |
| Faculty Advisor | Paul Foster |
| Co-Investigators | NONE |
| Investigator Email(s) | *lmg2c@mtmail.mtsu.edu; paul.foster@mtsu.edu* |
| Department | Psychology |
| Protocol Title | ***Lateralization of memory and cognitive functions with regard to thyroid functioning*** |
| Protocol ID | **18-2131** |

Dear Investigator(s),

The above identified research proposal has been reviewed by the MTSU Institutional Review Board (IRB) through the **EXPEDITED** mechanism under 45 CFR 46.110 and 21 CFR 56.110 within the category *(7) Research on individual or group characteristics or behavior* A summary of the IRB action and other particulars in regard to this protocol application is tabulated below:

| | |
|---|---|
| IRB Action | APPROVED for one year from the date of this notification |
| Date of expiration | **2/28/2019** |
| Participant Size | 40 (FORTY) |
| Participant Pool | **General female adults (18 to 55 years old) with no history of traumatic brain injury, stroke or dimentia.** |
| Exceptions | NONE |
| Restrictions | **1. Mandatory signed informed consent; The participants must be clearly notified that enrollment is voluntary with ability to withdraw at anytime without retribution**<br>**2. Identifiable information must be destroyed after data processing.** |

| | |
|---|---|
| Comments | NONE |

This protocol can be continued for up to THREE years (**2/28/2021**) by obtaining a continuation approval prior to **2/28/2019**. Refer to the following schedule to plan your annual project reports and be aware that you may not receive a separate reminder to complete your continuing reviews. Failure in obtaining an approval for continuation will automatically result in cancellation of this protocol. Moreover, the completion of this study MUST be notified to the Office of Compliance by filing a final report in order to close-out the protocol.

IRBN001

Institutional Review Board

Continuing Review Schedule:

| Reporting Period | Requisition Deadline | IRB Comments |
|---|---|---|
| First year report | 1/31/2019 | NOT COMPLETED |
| Second year report | 1/31/2020 | NOT COMPLETED |
| Final report | 1/31/2021 | NOT COMPLETED |

Post-approval Protocol Amendments:

| Date | Amendment(s) | IRB Comments |
|---|---|---|
| NONE | NONE. | NONE |

The investigator(s) indicated in this notification should read and abide by all of the post-approval conditions imposed with this approval. Refer to the post-approval guidelines posted in the MTSU IRB's website. Any unanticipated harms to participants or adverse events must be reported to the Office of Compliance at (615) 494-8918 within 48 hours of the incident. Amendments to this protocol must be approved by the IRB. Inclusion of new researchers must also be approved by the Office of Compliance before they begin to work on the project.

All of the research-related records, which include signed consent forms, investigator information and other documents related to the study, must be retained by the PI or the faculty advisor (if the PI is a student) at the secure location mentioned in the protocol application. The data storage must be maintained for at least three (3) years after study completion. Subsequently, the researcher may destroy the data in a manner that maintains confidentiality and anonymity. IRB reserves the right to modify, change or cancel the terms of this letter without prior notice. Be advised that IRB also reserves the right to inspect or audit your records if needed.

Sincerely,

Institutional Review Board
Middle Tennessee State University

# APPENDIX C: INFORMED CONSENT FORM

**INSTRUCTIONS FOR INVESTIGATOR**

**The following is a template for a complete informed consent document. As a guide, it can be partially revised to fit your study. However, the first two (2) paragraphs and all questions need to be included, as required the by the Office of Human Research Protections.**

**If you choose to alter or waive consent for your study, you must provide justification to do so. Fill out the appropriate portion of the Request for Waiver or Alteration of Consent and attach it to your IRB application. The form can be accessed at http://www.mtsu.edu/irb/irbforms.shtml**

**If a question is not applicable to your study, simply insert n/a. You should also eliminate suggested language (in brackets and red type) if not pertinent to your study, to enhance participant comprehension. If used for a parent/legal guardian, alter language to refer to child.**

**Should you have any questions or need additional information, please do not hesitate to contact my office.**

**Compliance Officer**

compliance@mtsu.edu

**Box 134**

**Sam Ingram Building 011B**

**(615) 494-8918**

**Principal Investigator: Leslie Meranda Qualls-Lambert**
**Study Title: Lateralization of Memory and Cognitive Functions with Regard to Thyroid Functioning**
**Institution: Middle Tennessee State University**

Name of participant: _____ Age: _____

The following information is provided to inform you about the research project and your participation in it. Please read this form carefully and feel free to ask any questions you may have about this study and the information given below. You will be given an opportunity to ask questions, and your questions will be answered. Also, you will be given a copy of this consent form.

Your participation in this research study is voluntary. You are also free to withdraw from this study at any time. In the event new information becomes available that may affect the risks or benefits associated with this research study or your willingness to participate in it, you will be notified so that you can make an informed decision whether or not to continue your participation in this study.

For additional information about giving consent or your rights as a participant in this study, please feel free to contact the MTSU Office of Compliance at (615) 494-8918.

1. **Purpose of the study:**
   You are being asked to participate in a research study because we are interested in determining if thyroid functioning is related to verbal and/or visuospatial memory and cognitive functioning.

2. **Description of procedures to be followed and approximate duration of the study:**
   If you agree to participate, a battery of standardized neuropsychological tests assessing memory and cognitive functioning, mood characteristics, and a demographic questionnaire will be administered. The duration of the study will be between 45 minutes to 1 hour.

3. **Expected costs:**
   There are no costs for participation.

4. **Description of the discomforts, inconveniences, and/or risks that can be reasonably expected as a result of participation in this study:**
   It is possible that some of the neuropsychological tests will cause some mental fatigue.

5. **Compensation in case of study-related injury:**
   MTSU will not provide compensation in the case of study related injury.

6. **Anticipated benefits from this study:**
   a) The potential benefits to science and humankind that may result from this study are that we gain further understanding of the effects of how thyroid functioning may impact memory and cognitive functioning.
   b) The potential benefits to you from this study are gaining a better understanding of how research is conducted, as well as contributing to research that is new to this field.

7. **Alternative treatments available:**
   N/A

8. **Compensation for participation:**
   N/A

9. **Circumstances under which the Principal Investigator may withdraw you from study participation:**
   Non-compliance with the study procedures, or failure to follow instructions. Also, you may be withdrawn if you have any history of traumatic head injury, neurological illness, or are taking psychotropic medication.

10. **What happens if you choose to withdraw from study participation:**
    Participation in this study is voluntary and there are no penalties for refusing to participate and there are no consequences from withdrawing from the study. The participants may choose to withdraw from the study at any point.

11. **Contact Information.** If you should have any questions about this research study or possible injury, please feel free to contact Leslie Meranda Qualls-Lambert at (615) 828-8906 or my Faculty Advisor**,** Paul S. Foster at (615) 898-2007.

12. **Confidentiality.** All efforts, within reason, will be made to keep the personal information in your research record private but total privacy cannot be promised. Your information may be shared with MTSU or the government, such as the Middle Tennessee State University Institutional Review Board, Federal Government Office for Human Research Protections, if you or someone else is in danger or if we are required to do so by law.

13. **<u>STATEMENT BY PERSON AGREEING TO PARTICIPATE IN THIS STUDY</u>**
    **I have read this informed consent document and the material contained in it has been explained to me verbally. I understand each part of the document, all my questions have been answered, and I freely and voluntarily choose to participate in this study.**

_____ _____

Date Signature of patient/volunteer

Consent obtained by:

_____ _____

Date Signature

_____

Printed Name and Title