

Improving White Matter Integrity with Thyroid Hormone

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1.0 Project Summary/Abstract

The ability to promote and support remyelination has wide-ranging implications for a number of neuropsychiatric conditions from multiple sclerosis to major depression. Pre-clinical evidence has demonstrated that thyroid hormone treatment, in the form of triiodothyronine (T3) or tetraiodothyronine (T4), can promote and support remyelination by increasing myelin basic protein mRNA and protein, oligodendrocyte proliferation and maturation, and fractional anisotropy (a diffusion imaging measure of white matter integrity). Pilot data from our own studies suggest that baseline thyroid status is correlated with the integrity of white matter tracts associated with major depression. *To date, the impact of thyroid hormone administration on white matter tracts has not been studied in vivo in adult humans.* The purpose of the proposed pilot study is to examine changes in white matter tract integrity using high angular diffusion imaging and multi-component relaxometry in a population of subjects clinically indicated to receive thyroid hormone for hypothyroidism. We will scan patients with hypothyroidism at the initiation of treatment and at three and six months after starting thyroid hormone treatment. We will also administer scales assessing mood and cognition which have been shown to correlate with white matter integrity. We hypothesize that thyroid hormone treatment will be associated with an increase in fractional anisotropy, a decrease in radial diffusivity, and an increase in the myelin water fraction (markers of improved myelination) that will correlate with improvements in cognition and mood ratings. If successful, this will be the first demonstration of improved white matter integrity with thyroid hormone replacement and pave the way for therapies designed to restore structural brain connectivity.

2.0 Background/Scientific Rationale

Thyroid and White Matter: George Bartzokis conceptualized a number of neuropsychiatric conditions according to a “myelin model” of the brain (1). Different disorders from neurodevelopmental (schizophrenia) to neurodegenerative (Alzheimer’s disease) have been associated with disruptions in myelin. Myelin is an essential neural component for maintaining efficient neurotransmission and enhanced processing speed. There is considerable evidence from basic research studies demonstrating that thyroid hormone (TH) plays an important role in myelination, specifically oligodendrocyte proliferation and maturation. For example, it has been shown that tetraiodothyronine (T4) treatment can induce increases in myelin basic protein mRNA and protein as well as oligodendrocyte precursor cells (OPCs) in mice with experimental allergic encephalomyelitis (2). Triiodothyronine (T3) has also been shown to increase myelin basic protein mRNA levels in perinatal rat brain (3). In another study, similar effects have been demonstrated in mice where T3 restored fractional anisotropy (FA) and increased OPC expression after cuprizone-induced demyelination (4). Furthermore, T3 has been shown to promote OPC differentiation and remyelination after cuprizone–induced demyelination in rats (5). According to a recent review (6), it is hypothesized that TH promotes remyelination by binding to thyroid receptor beta in a complex with the retinoid X receptor (RXR). This complex activates a thyroid-responsive element (TRE) which serves as promoter of the Kruppel-like factor 9 (KLF9) gene. KLF-9 then promotes the maturation and differentiation of OPCs through signaling of the chemokine CXCL12 and its receptor CXCR4. Despite the evidence from preclinical studies, there have been very few studies to examine the role of thyroid hormone in myelination in clinical studies. One study in men has shown that thyroid stimulating hormone (TSH) levels significantly correlate with increased “infarct-like vascular lesions” (7). Similarly, white matter hyperintensities have been associated with thyroid gland dysfunction in migraine sufferers (8). To date, the only diffusion tensor imaging (DTI) study examining the effects of thyroid on white matter microstructure was recently conducted in premature infants. While the authors found no difference in DTI parameters for infants who received T4 supplementation compared to placebo, infants in the lowest quartile of plasma free T4 concentrations had reduced white matter integrity in the corpus callosum and right internal capsule (9).

Thyroid and Mood: The relationship between hypothyroidism and major depressive disorder was identified over a century ago (10). There are several symptoms of hypothyroidism that overlap with the clinical presentation of major depression such as psychomotor retardation,

fatigue and apathy. A recent review highlighted that poor mood is commonly reported in patients on TH replacement therapy. Psychological well-being in these patients appears to be related to thyroid function (11). Additionally, studies have shown some improvement in mood symptoms with TH replacement therapy (12-14). Further in support of this notion, in a recent neuroimaging study of patients with Hashimoto's thyroiditis, it was shown that autoimmune markers correlated functional connectivity in affective circuits (15).

Thyroid and Cognition: Thyroid dysfunction (related to both subclinical and overt hypothyroidism) is associated with a wide array of cognitive impairments (16). A recent review demonstrated that subclinical hypothyroidism is associated with cognitive decline in aging (17). More specific deficits related to the cognitive domains of memory (18, 19), executive function (20), and processing speed (21, 22) have also been reported. Furthermore, there are a few studies demonstrating improvements in executive function and attention with TH replacement therapy (23, 24). There is some controversy regarding the reliability of these findings as there have been several negative studies showing no association between thyroid status and cognitive deficits (16, 25, 26). The literature demonstrating the cognitive benefits from thyroid replacement in adults with frank hypothyroidism is sparse. This is a gap in the literature that the proposed study seeks to address by incorporating neuroimaging data from a population of adult participants with overt hypothyroidism.

3.0 Objectives/Aims

The purpose of this proposed multidisciplinary, translational pilot study is to examine changes in white matter integrity using complementary neuroimaging techniques: high angular diffusion tensor imaging (HARDI) and multi-component relaxometry (MCR), in a population of participants clinically indicated to receive thyroid hormone for hypothyroidism. We will scan patients with hypothyroidism when they initiate treatment to determine baseline levels of white matter integrity and then rescan them three months and six months after starting thyroid hormone treatment to determine changes in white matter integrity. Given our sensitive and specific biomarkers of myelin integrity, we hypothesize that thyroid hormone treatment will be associated with an increase in white matter cohesion, i.e., fractional anisotropy as measured by HARDI, white matter microstructure as measured by HARDI (radial diffusivity), and MCR markers of improved myelination (myelin water fraction). In addition, we hypothesize that increases in white matter integrity will be correlated with improvements in cognition and mood. If successful, this will be

the first demonstration of improved white matter integrity with thyroid hormone replacement and pave the way for reparative therapies designed to restore structural brain connectivity.

Specific Aim 1: To measure white matter integrity at the initiation of thyroid hormone replacement and after euthyroid status using HARDI

Hypothesis 1: Participants diagnosed with hypothyroidism that become euthyroid will show improved white matter integrity measured by increasing fractional anisotropy and decreasing radial diffusivity.

Specific Aim 2: To measure white matter integrity at the initiation of thyroid hormone replacement and after euthyroid status using multicomponent relaxometry

Hypothesis 2: Participants diagnosed with hypothyroidism that become euthyroid will show improved white matter integrity measured by increasing myelin water fraction

Specific Aim 3: To correlate changes in white matter integrity with improvement in cognition and mood

Hypothesis 3: Improvement in white matter integrity will be positively correlated with cognitive function indicated by faster psychomotor processing speeds and improved executive function and with mood measured with lower depression severity ratings

4.0 Eligibility

4.1 Inclusion Criteria

a) Age: 21-60 years of age; b) a diagnosis of primary hypothyroidism from autoimmune thyroiditis (Hashimoto); c) able to give informed consent.

4.2 Exclusion Criteria

Participants with the following will be excluded from the study: (a) major depressive disorder with or without active suicidal ideation; (b) mild or major neurocognitive disorder; (c) presence of contraindications to magnetic resonance imaging (presence of ferrous-containing metals within the body (e.g., aneurysm clips, shrapnel/retained particles); inability to tolerate small, enclosed spaces without anxiety (e.g., claustrophobia); (d) unwilling/unable to sign informed consent document; (d) positive urine drug screen results; (e) pregnancy (positive pregnancy test), trying to become pregnant, or lactation.

5.0 Subject Enrollment

Participants diagnosed with primary hypothyroidism from autoimmune thyroiditis (Hashimoto) will be recruited from clinics at the University of Illinois at Chicago (UIC). Participants may be initially contacted using by mail or through the Patient Portal using the following recruitment script:

“Dear [Participant], you are being asked to be a subject in a research study about the effect of thyroid hormone on the brain structure.

You have been asked to participate in the research because you have been diagnosed with hypothyroidism and have recently been started on thyroid hormone replacement therapy.

Your participation in this research is voluntary. Your decision whether or not to participate will not affect your current or future dealings with the University of Illinois at Chicago. If you decide to participate, you are free to withdraw at any time without affecting that relationship. If you are interested, please reply to this message or contact the Principal Investigator directly, Dr. Olu Ajilore at 312-413-4562 or oajilore@uic.edu”

Since the co-Investigator is also likely to be the subject’s treating physician, it will be made clear through the informed consent process that participation is completely voluntary and has no impact on their treatment. The following language is included on the consent form:

“Your health care provider may be an investigator on this research protocol, and as an investigator, is interested in both your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from a clinician who is not associated with this project. You are not obligated to participate in any research project offered by your clinician. Your participation in this research study is voluntary and you do not have to participate. The decision to not participate will not affect your clinical care now or in the future.”

6.0 Study Design and Procedures

All participants will be treated for their hypothyroidism according to the standard of care as reflected in recent guidelines from the American Thyroid Association (27). As part of the initial screening, after informed consent is obtained, all participants will receive the following clinical tests/instruments: 1) The Cumulative Illness Rating Scale (CIRS-G;(28)); 2) The Cerebrovascular Risk Factor Scale (CVRF (29)); (stroke risk factor)

developed by the American Heart Association; 3) Patient Health Questionnaire (PHQ-9) (30)); 4) The Inventory of Depressive Symptomatology (IDS-C/IDS-SR;(31)); 5) the Montreal Cognitive Assessment (MoCA (32)); 6) Relevant laboratory studies such as complete and differential blood counts, serum chemistry, thyroid function tests; 7) A brief neuropsychological protocol focused on cognitive domains of executive function, attention, and psychomotor processing (33). *Thyroid Status Assessment:* All participants will have blood work done to obtain thyroid functions tests (TFTs): thyroid stimulating hormone (TSH), Free T4, T3, anti-thyroglobulin and anti-thyroid peroxidase (TPO) antibodies. All participants will receive *the same treatment* (levothyroxine, a synthetic T4 hormone replacement) at a dose that will be titrated using serum thyrotropin (TSH) levels as a goal, according to the American Thyroid Association Task Force recommendations (27). *Behavioral Assessment:* Depression severity will be assessed with the PHQ-9 and the IDS. Global cognitive function will be measured with the MoCA. Executive function, attention and processing speed will be assessed using the following tests from the NIH Toolbox: Dimensional Change Card Sort Test, Flanker Inhibitory Control and Attention Test and the Pattern Comparison Processing Speed Test (33). These tests have been shown to have good test-retest reliability and standardized effect sizes for practice effects (34). We will examine whether performance improvements at subsequent assessment time points exceed what would be expected due to practice effects.

All assessments will be completed at baseline (within one week of initiating treatment), 3 months follow-up and 6 months follow-up (Table 1). PHQ-9 will be administered biweekly in between behavioral/MRI sessions. It is important to note that since levothyroxine has a long half-life (6-7 days), measurements within one week are appropriate for baseline assessments. Additionally due to this long half-life, there are no acute effects of treatment that would be missed at baseline. Assessment time points at 3 months and 6 months were chosen based on preclinical and clinical studies. DTI measures normalized in the aforementioned animal studies 3 months after TH administration (4). In clinical settings, patients might require several dose adjustments to achieve the thyrotropin goal. The usual dose adjustment intervals used in clinical

practice are 6-8 weeks. In a study by Duyff et al. evaluating the neuromuscular findings in thyroid dysfunction, hypothyroid patients reached biochemical euthyroidism in an average of 19 weeks (range 7 - 41 weeks) (35). Most studies to show improvement in mood and/or cognition had a follow-up time of 6 months (24).

Baseline	3 months	6 months
TFTs	TFTs	TFTs
Behavioral assessment	Behavioral assessment	Behavioral assessment
MRI	MRI	MRI

Table 1. Timeline for clinical, behavioral and neuroimaging assessments

7.0 Expected Risks/Benefits

7.1 Risks: Diagnostic/Assessment Procedures

The diagnostic interviews (and questionnaires) are time consuming and may be boring to some individuals. These are, however, necessary in order to determine eligibility for the study. In addition, questions about alcohol/drug use, interpersonal relationships, abuse/trauma history, and questions related to history of suicidal and/or homicidal behavior may be considered sensitive by some subjects. The collection of such data poses a potential risk of loss of confidentiality around sensitive information such as psychiatric status, history of substance abuse, etc. Subjects will also be informed in the consent document that confidentiality will be limited in cases where the subject reveals intentions to harm themselves or others, and the investigator feels that the proper authorities may need to be notified in order to prevent the occurrence of harm to the subject or others. Interviews will be conducted by experienced mental health workers who will maintain confidentiality and all data from interviews and questionnaires will be numbered so as to conceal the identity of the subject.

Other Tasks

There is little risk to participating in the behavioral tasks, other than boredom or mild subjective anxiety; the PI and/or other members of the research staff who

are either MD psychiatrists, psychiatrists in training - psychiatry resident or fellow (Post-Graduate Year/PGY 1 and beyond) or clinically trained masters or PhD level therapists will be available during all behavioral tasks in order to evaluate and recommend treatment for the emergence of any anxiety/panic attack or elevated levels of anxiety.

Magnetic Resonance Imaging

Magnetic resonance imaging is non-invasive, widely used, and safe. The potential risks, such as static magnetic field, radio-frequency field, magnetic field gradients, and acoustic noise, are rarely dangerous or life threatening. Additional minor and/or rare risks include: (a) discomfort or anxiety from being in the confined space of the MRI scanner; (b) fast imaging sequences, such as those employed in this study, have the potential to induce peripheral nerve stimulation (PNS). PNS can be described as a light touching sensation on the skin surface and may cause mild discomfort, but is not harmful to the subject; (c) risks of hearing damage due to loud noises produced by the scanner; (d) risk that the magnetic resonance image will reveal a minor or significant lesion in the brain, e. g. a tumor, previously unknown to the subject, and requiring additional follow-up; (e) risk of injury from objects accelerated by the strong magnetic field of the magnet, striking the subject; or metallic substances on the skin or foreign bodies implanted deliberately or accidentally in the subject that acquire kinetic or thermal energy from the magnetic or radiofrequency emissions of the MRI, causing tissue injury to the subject; (f) sometimes, subjects report a temporary, slight dizziness or light-headedness when they come out of the scanner; (g) potential risk for pregnant women: According to the NIMH Council Workgroup on MRI Research and Practices (September, 2005), “there is no known risk of MR brain scanning of a pregnant woman to the developing fetus for scanning at 4T or less, and no known mechanism of potential risks under normal operating procedures.” Nevertheless, subjects should be warned about potential risks not yet discovered. Discovery and disclosure of incidental finding or abnormality on MRI scans: During the formal consent process, all subjects will be informed about the

potential risks of discovering an incidental finding or abnormality on their MRI scan. If an abnormality is found in a subject's MRI scan, the PI will contact the subject and refer the subject for medical follow-up for the problem if the subject requests, including a referral to a primary care physician. If a subject has a primary care physician, the PI will contact the subject's doctor, at the request and with verbal permission from the subject, to inform him/her of the finding on the MRI scan and to help him/her get the subject appropriate follow-up. The decision as to whether to proceed with further examination and/or treatment lies solely with the subject and his/her primary care physician.

7.2 Benefits: There is no immediate direct benefit for the participant. With the enormous economic and psychosocial costs resulting from neuropsychiatric disorders related to impaired white matter integrity, furthering our understanding about the impact of thyroid treatment on myelination is important. It is expected that this information will lead to better brain-based treatments that restore or repair structural brain connectivity. Given that the risks are minimal and the benefits substantial, the benefits greatly outweigh the risks.

8.0 Data Collection and Management Procedures

Each subject is given a unique number and there is a password-protected master key database separate from the study to data link the subject to the code. This is only accessible to the PI. Coded data set with indirect identifiers and key stored separately and re-identified only when in use.

9.0 Data Analysis

Statistical Analysis: The initial analysis will be descriptive and will characterize the study groups in terms of study variables such as age, gender, education, and measures of overall medical burden etc. Categorical variables, nominal and ordinal, will be summarized by frequencies. Continuous variables will be summarized by the mean, standard deviation, 95% confidence intervals, median, and range. Where continuous variables cannot reasonably be considered to be

normally distributed, transformations (e.g. log, square root, or cube root transformation for skewed data) to achieve a normal distribution will be explored. Care must be taken to avoid placing too much emphasis on chance associations. As noted below, both unadjusted and false discovery rate p-levels will be reported basing the adjustment on the numbers of tests performed within each area. Specific Aims 1 and 2 will be analyzed using a repeated-measures analysis of variance (ANOVA) with FA, RD, and MWF as dependent variables. Specific Aim 3 will be analyzed using bivariate correlations and partial correlations (controlling for age) between changes in FA, RD, and MWF and changes in executive function and processing speed performance scores.

Sample Size/Statistical Design: There will be a total of 30 participants by the end of the study period. Data from this initial sample will be used for power calculations to determine the appropriate sample size for future studies.

10.0 Regulatory Requirements

10.1 Informed Consent

Informed consent will be obtained by the PI at the study site in the Neuropsychiatric Institute at study entry. Risks and benefits will be thoroughly explained. The voluntary nature of the project will be thoroughly explained. The participant will be have as much as needed to consider whether or not to participate.

10.2 Subject Confidentiality

All electronic data will coded so that subjects cannot be readily identified. All data will be secured with password protection.

10.3 Unanticipated Problems

Any unanticipated problems will be immediately reported to the IRB and the sponsor as indicated.

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