Effect of Experimental Thyrotoxicosis on Brain Gray Matter: A Voxel-Based Morphometry Study

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Key Words

Hyperthyroidism · Functional magnetic resonance imaging · DARTEL · n-back working memory task · Working memory · Voxel-based morphometry

Abstract

Background: Hyper- as well as hypothyroidism have an effect on behavior and brain function. Moreover, during development thyroid hormones influence brain structure. **Objectives:** This study aimed to demonstrate an effect of experimentally induced hyperthyroidism on brain gray matter in healthy adult humans. **Methods:** High-resolution 3D T1-weighted images were acquired in 29 healthy young subjects prior to as well as after receiving 250 µg of T₄ per day for 8 weeks. Voxel-based morphometry analysis was performed using Statistical Parametric Mapping 8 (SPM8). **Results:** Laboratory testing confirmed the induction of hyperthyroidism. In the hyperthyroid condition, gray matter volumes were increased in the right posterior cerebellum (lobule VI) and decreased in the bilateral visual cortex and anterior cerebellum (lobules I–IV) compared to the euthyroid condition. **Conclusions:** Our study provides evidence that short periods of hyperthyroidism induce distinct alterations in brain structures of cerebellar regions that have been associated with sensorimotor functions as well as working memory in the literature.

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Introduction

Hyperthyroidism is a condition in which the thyroid gland produces excessive amounts of free triiodothyronine (fT₃) and free thyroxine (fT₄). Thyrotropin [i.e. thyroid-stimulating hormone (TSH)] is suppressed. A lack of thyroid hormones during development has a profound impact on the brain development resulting in cretinism. Indeed, thyroid hormones influence a variety of processes including neurogenesis, development of glia, myelination, synaptogenesis and dendritic proliferation [1–5]. Not having enough thyroid hormones also leads to cognitive dysfunctions in a variety of cognitive domains even if hypothyroidism occurs in adulthood [6–12]. Hypothyroidism during adulthood also leads to morphological changes in the brain [13].

To date, the effects of excess thyroid hormones on the brain have been less extensively described. It is known that hyperthyroidism leads to involvement of the central nervous system, including clinical symptoms such as reduced concentration and memory performance, nervousness, irritability, and tremulousness [7, 14, 15]. However, these studies have mostly been obtained in clinical populations and thus a number of confounds, such as the direct impact of autoimmune disease on the brain, have to be considered. It is therefore desirable to analyze the influence of an excess of thyroid hormones on brain mor-

phology and cognitive functions in an experimental setting. Such studies have been performed only rarely. One study from our own group employed event-related brain potentials and neuropsychological measures [16], and could show an effect of T₄ on both.

With regard to morphological changes, there has been a recent study using voxel-based morphometry (VBM) analysis [14] that investigated a large group of 51 patients suffering from hyperthyroidism and reported altered gray matter volumes (GMV) in a number of brain regions (see Discussion). As stated above, the use of patients might be problematic, as a number of reports have suggested an autoimmune component contributing to neurological/neuropsychological symptoms in Graves' disease [17, 18].

To exclude such other factors and to check whether a short-term excess of thyroid hormones exerts an effect on brain morphology, we investigated healthy subjects before and after ingesting 250 µg of T₄ per day for 8 weeks. This dosage has been shown to reliably induce mild thyrotoxicosis, i.e. elevated T₄ and suppressed TSH with little or no clinical effects, and has been used as a comedication in depression in psychiatry in recent years [19].

Materials and Methods

Subjects

The Ethics Committee of the University of Lübeck approved all procedures prior to the experiment. All subjects gave their written informed consent prior to participation. In total, 29 healthy male right-handed subjects (median age: 30 years, range: 21–49) were recruited. One participant had to be excluded due to extensive body-building and the resulting impact on the thyroid gland. All subjects were screened prior to the study for general health, medicines, drug abuse, thyroid status (hormone level and antibodies, including antithyroid peroxidase antibody, thyrotropin receptor antibody and thyroglobulin antibody) and mood and cognitive disorders. All subjects that were included in the study had normal structural brain images as revealed by examination by a neuroradiologist, normal thyroid hormone levels and no detectable antibodies.

Blood samples were collected intravenously in serum tubes. The tubes were transported unrefrigerated, but storage was refrigerated. Laboratory analyses of TSH, fT₃ and fT₄ were performed using ELISA (enzyme-linked immunosorbent assay). The standard values of hormone levels were as follows: fT₃ 3.4–7.2 pmol/l, fT₄ 10–20 pmol/l and TSH 0.3–4.0 mU/l. Hormone blood levels at both time points (before and after intervention) were only available for 24 subjects due to freezer problems.

A number of neuropsychological tests were administered to check for overt effects of T₄ on behavior. The test-battery comprised the Attention Network Task (ANT) [20], Go/No Go, divided attention, task switching and n-back working memory tasks as implemented in the computerized 'Testbatterie zur Aufmerksamkeitsprüfung' (Battery for Attention Testing) [21], the

Trail Making Test (TMT) [22], the German version of the Auditory Verbal Learning Test (AVLT) [23], the Beck Depression Inventory II (German version) [24], the Symptom Checklist SCL 90R [25] and the German version of the 'Profile of Mood State' scale (POMS) [26].

Experimental Design, Data Acquisition and Analysis

One experimental session was performed before and one after the ingestion of 250 µg of T₄ per day for 8 weeks. No treatment other than T₄ was allowed between the two sessions in all of the subjects. Testing was always done at mid-afternoon approximately 2–3 h after lunch.

MR images were acquired on a 3.0-tesla MR scanner (Philips Achieva; Philips BV, Eindhoven, The Netherlands). High-resolution structural images were obtained with a T1-weighted 3D turbo gradient echo sequence. Repetition time = 2,250 ms, echo time = 2.36 ms, flip angle = 9°, field of view = 256 × 256 mm, matrix size = 256 × 256, 176 sagittal slices with 1-mm thickness, voxel size = 1 × 1 × 1 mm. The first 10 images were removed from each data set. This was conducted for magnetization equilibrium and the subjects were thereby able to adjust to the environment of the scanner. The structural image data were processed using Statistical Parametric Mapping 8 (SPM8; <http://www.fil.ion.ucl.ac.uk/spm>), implemented in MATLAB 7.11.0 (MathWorks, Natick, Mass., USA). A standard tool for examining structural changes in gray matter is VBM analysis [27]. We applied Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra (DARTEL), which is implemented as a toolbox for SPM8 and enables the creation of a set of group-specific templates. Data processing steps were performed according to Ashburner [28] (<http://www.fil.ion.ucl.ac.uk/~john/misc/VBMclass10.pdf>). The brain images were segmented, normalized and modulated by using these templates. They were also modulated, smoothed (by using a 6-mm full width at half maximum Gaussian kernel) and spatially normalized into stereotactic Montreal Neurological Institute (MNI) space.

A within-subject comparison of euthyroid versus hyperthyroid state was performed. Significance was accepted at a threshold of $p < 0.001$, uncorrected, at the voxel level.

Results

After 8 weeks, the intake of T₄ led to a significant increase in fT₄ [pretreatment: 15.77 pmol/l (SD 2.33), post-treatment: 31.33 pmol/l (SD 8.17), $t(23) = -10$, $p < 0.001$]. fT₃ was increased as well [pretreatment: 4.63 pmol/l (SD 0.83), posttreatment: 7.44 pmol/l (SD 2.49), $t(23) = -5.7$, $p < 0.001$]. TSH was suppressed after treatment [pretreatment: 2.07 mU/l (SD 1.20), posttreatment: 0.02 mU/l (SD 0.02), $t(23) = 8.4$, $p < 0.001$].

Neither systolic (average change: +3.6 mm Hg) nor diastolic blood pressure (average change: -0.02 mm Hg) showed a significant impact of treatment. Heart rate rose from 68.8 beats/min (SD 4.5) to 74.8 beats/min (SD 7.5) [$t(28) = -2.8$, $p = 0.016$]. There was no change in body weight [$t(28) = 0.12$, n.s.].

Fig. 1. T-statistic maps contrasting hyperthyroid vs. euthyroid conditions. **a** Areas that showed significantly decreased GMV in the hyperthyroid condition included the bilateral visual cortex and the anterior cerebellum (lobuli I–IV). **b** The GMV was significantly increased in the hyperthyroid condition in the left posterior cerebellum (lobule VI). Bars represent t values, $p < 0.001$, uncorrected.

Of the neuropsychological tests, only the alerting measure of the ANT showed an effect of treatment [pretreatment: 27.9 ms (SD 17.9), posttreatment: 40.2 (SD 16.6), $t(28) = 3.8$, $p < 0.001$], whereas all other neuropsychological tests did not.

Significant increases in GMV were seen in the left posterior cerebellum (lobule VI) in the hyperthyroid state, whereas a decrease in GMV was seen in the bilateral visual cortex and the anterior cerebellum (lobuli I–IV; fig. 1).

Discussion

The aim of this study was to demonstrate whether short-term application of thyroid hormones resulting in mild thyrotoxicosis, i.e. marked elevation of thyroid hormones and suppressed TSH without marked clinical effects, results in morphological changes in the brain. Because hyperthyroidism is often associated with other conditions including fibromyalgia [29] and depression [30] among others, the experimental application of thyroid hormones appeared warranted. Using a recent incarnation of VBM employing DARTEL to improve intersubject registration [31], we found predominantly changes in GMV of the cerebellum. The cerebellum is a brain area

that has long been considered to be mainly important for the control of movement [32, 33]. However, the cerebellum has also been associated with attention [34], working memory [35], language [36], executive functions [37], emotion and affection [38–40]. The cerebellum can be divided into three parts: the anterior lobe (lobuli I–V), the posterior lobe (lobuli VI–IX) and the medial flocculonodular lobe (lobule X) [41]. The anterior cerebellum is polysynaptically connected to cortical motor areas via deep cerebellar nuclei and the thalamus, whereas the posterior cerebellum is connected primarily to prefrontal and association cortices [42–44]. Moreover, the anterior cerebellum shows topographically organized somatomotor representations [44]. As a consequence of this anatomical circuitry, it appears that damage to the posterior cerebellum leads to cognitive deficits, while damage to the anterior cerebellum leads to motor deficits predominantly [45]. The clinical cerebellar cognitive affective syndrome ([46]) in patients suffering from cerebellar lesions provides further evidence that the cerebellum is involved in cognitive and affective functions [47]. Additionally, analyses of resting state fMRI revealed that the cerebellum contributes to cognitive networks and is interconnected with prefrontal and parietal association areas [32]. Connections with prefrontal and parietal areas are imple-

mented via cortico-ponto-cerebellar loops and cerebello-thalamocortical loops [41, 48–50]. The sensorimotor regions of the cerebral cortex project exactly to the lobules that reacted with a change in GMV in our study. To the extent to which a decrease of GMV is indicative of a worsened functionality of the involved brain structure and, vice versa, an increase of GMV is associated with a gain of function, our results for the anterior cerebellum suggest that motor functions supported by the cerebellum should be impacted negatively. On the other hand, the increase in GMV in lobule VI, which is thought to be involved in articulatory rehearsal and visual-to-phonological encoding, i.e. processes that are necessary for working memory [32, 51], implies that working memory processes might be improved. These hypotheses need to be tested in further studies with increased treatment duration and, possibly, increased dosage of T_4 .

An important question often raised with regard to morphological changes revealed by VBM regards the underlying microstructural changes reflected by increases or decreases of GMV. Whereas long-term changes, as observed for example in aging studies [52] or in professional musicians [53], might reflect loss or increase of cells and/or dendrites, more rapid change, as observed following juggling training [54], for example, are less well understood. Several mechanisms that might well occur in parallel have been suggested, including astroglial swelling, synaptogenesis and angiogenesis [55–57]. Induced hyperthyroidism may provide an interesting test case, as this condition could be mimicked easily in animals which could be investigated using both neuroimaging and post-mortem histology.

How do the current results compare to previous morphometric results obtained in relation to changes in thyroid hormone levels? A recent VBM study [13] revealed a reduction in GMV in the left postcentral gyrus and the cerebellum in 10 hypothyroid patients compared to 10 euthyroid control participants. With regard to white matter volume, a reduction was found in the cerebellum and a number of cortical regions comprising right inferior and middle frontal gyrus, right precentral gyrus, right inferior occipital gyrus and right temporal gyrus in the patients. No changes in the cerebellum were reported by Quinque et al. [58] who studied 18 patients with treated hypothyroidism due to Hashimoto's thyroiditis with a mean treatment duration of about 4.5 years. VBM did not reveal any gray matter differences in patients compared to controls, but fT_4 levels in the patients were within the normal range. A study in adult patients with long-standing hyperthyroidism with clinical symptoms [14] revealed reduced GMV in the hippocam-

pus, parahippocampal gyrus, calcarine region, lingual gyrus and left temporal pole, and increased GMV in the supplementary motor area bilaterally. Again, no differences were seen for the cerebellum. Using metabolic imaging (18-FDG-PET), Schreckenberger et al. [59] studied 12 patients with untreated hyperthyroidism due to Graves' disease and found decreased glucose metabolism in the limbic system (uncus and inferior temporal gyrus), but no changes in the cerebellum. Likewise, Bauer et al. [60] used PET to investigate hypothyroid patients before and after T_4 replacement therapy. While lower activity (compared to control participants) was found prior to therapy in the amygdala, hippocampus and anterior cingulate cortex, these alterations were normalized after treatment. Again, no cerebellar involvement was reported.

The functional measurements with the PET technique used by Schreckenberger et al. [59] and Bauer et al. [60] depict glucose consumption. The relation of such functional measurement to the morphometric changes of the cerebellum reported in the current study and by Singh et al. [13] remains to be demonstrated. Also, the PET measurements were conducted in the resting state, i.e. during a state that did not tax cerebellar function.

There is ample evidence suggesting that the cerebellum is a major target of thyroid hormones in the brain. It has been shown that T_3 is produced in the cerebellum by deiodination of T_4 in astrocytes prior to acting on cerebellar neurons [61]. There is also evidence for an expression of β_1 , α_1 and α_2 types of thyroid hormone receptors in the cerebellum in adulthood [62]. It has also been shown that thyroid hormone leads to a differentiation of cultured oligodendrocytes precursor cells via binding to the $TR\alpha_1$ receptor [63]. While most of the evidence for an action of thyroid hormones comes from rodents, the current results suggest that the cerebellum is also a target of thyroid hormones in man. Moreover, the current findings suggest looking for effects of hyperthyroidism on functions supported by the altered regions in the cerebellum such as motor control and working memory. Unpublished results of our group suggest that these functions are indeed influenced by hyperthyroidism.

Conclusion

Short-term mild thyrotoxicosis leads to structural changes in the GMV of the cerebellum and primary visual cortex. Our results therefore suggest searching for changes in functions that are supported by the altered parts of the cerebellum.

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Disclosure Statement

The authors have no financial conflicts to report.

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