Journal of Integrative Neuroscience

J. Integr. Neurosci. **2023**; 22(4): 95
https://doi.org/10.31083/j.jin2204095

Commentary

Dysthyroid Optic Neuropathy: Short- and Long-Term Effects on Brain Circuitry

Stefan Reuss[1,*]

[1]Department of Nuclear Medicine, University Medical Center, Johannes Gutenberg-University, 55131 Mainz, Germany
*Correspondence: reuss@uni-mainz.de (Stefan Reuss)

Academic Editor: Gernot Riedel
Submitted: 3 April 2023 Revised: 23 April 2023 Accepted: 25 April 2023 Published: 13 July 2023

Common disorders of the thyroid gland in adults include hypo- and hyperthyroidism (thyroid hormone deficiency or excess) with typical physical and neurological symptoms. These are usually the result of autoimmune processes leading to inflammation of the thyroid gland. A typical epiphenomenon of immune hyperthyroidism (Graves' disease or Morbus Basedow) is thyroid-associated ophthalmopathy [1–4]. Dysthyroid optic neuropathy, a serious complication of this disease, is associated with typical neuronal dysfunction, mainly in the visual system (optic nerve to visual cortex).

Despite the importance of the pathophysiology of visual brain regions in patients with dysthyroid optic neuropathy, data are scarce. In a manuscript in the *Journal of Integrative Neuroscience*, Dr. Jiang and coworkers [5] compared patients with thyroid-associated ophthalmopathy with and without dysthyroid optic neuropathy. They utilized resting-state functional MRI (rfMRI), a widely used standard diagnostic tool for brain function, to investigate possible consequences of optic nerve damage. Spontaneous brain activity was assessed using the regional homogeneity technique, which aims to "characterize multimodal local features of the brain connectome" [6], to identify possible brain regions that are differentially affected by optic neuropathy but are not prominent in thyroid-associated ophthalmopathy. The results indicated that dysthyroid optic neuropathy in adult patients is associated with altered patterns of spontaneous brain activity (and likely structure and connectivity) in distinct regions. The authors [5] observed significantly less regional homogeneity at the corpus callosum/cingulate gyrus in patients with dysthyroid optic neuropathy. Pathological changes in these brain sites, some of which are part of the limbic system, have been associated with disturbances in consciousness, behavior, pain perception and visceral motor functions. In particular, the posterior aspect of the cingulate gyrus is critical for eye movement and visuospatial processing, and has also been implicated in visual hallucinations [5].

Reduced regional homogeneity levels have also been found in the parietal lobe/middle frontal gyrus in dysthyroid optic neuropathy patients [5]. The parietal areas are part of the dorsal visual pathway that mediates motion and spatial visual information ("where" = parietal stream), and the middle frontal gyrus mediates interactions between the dorsal and ventral streams ("what" = form and color information, inferotemporal stream) [7].

In the few studies that have examined the human brain in patients with thyroid-associated ophthalmopathy, thinning of gray matter has been observed in several brain regions. Compared to healthy controls, regional homogeneity scores were decreased in parts of the visual pathway, such as the occipital lobe, superior temporal gyrus, and cuneus [8,9]. These regions host and connect striate (V1) and extrastriate visual cortices and are involved in visual information processing. In addition, evidence of reduced connections between brain hemispheres [10] may reflect dysfunction within the visual pathway.

Dysthyroid optic neuropathy is one of the most serious complications of thyroid-associated ophthalmopathy, occurring in 5–9 percent of cases. It is diagnosed by edema of the optic disc, i.e., the exit of retinal ganglion cell axons, and relative afferent pupillary defect (reduced pupil constriction in response to light, a clinical sign of optic nerve damage). In addition, patients suffer from impaired visual acuity and visual field, color recognition [11], and eventually even blindness. Damage to the optic nerve can lead to retinal damage, particularly in the ganglion cell layer, as well as orbital blood flow impairment and optic nerve atrophy. As reported by Jiang *et al*. [5], symptoms in dysthyroid optic neuropathy occur predominantly in regions involved in or related to visual processing, or are related to consciousness and behavioral parameters. Notably, regional homogeneity scores were negatively correlated with the "Hospital Anxiety and Depression Scale" along with disease duration. These findings suggest that patients with dysthyroid optic neuropathy are more prone to anxiety and depression, and that reduced parietal lobe/middle frontal gyrus function is observed with disease duration and progression. Because subclinical dysthyroid optic neuropathy is common in patients with autoimmune thyroid disease, there is agreement that early diagnosis and medical treatment of this disease are helpful in these patients [12].

In the healthy visual system, the optic nerve transmits the signal by fiber tracts primarily to the image-forming structures such as the lateral geniculate body, superior colliculus, and Brodmann areas 17–19. Not surprisingly, the

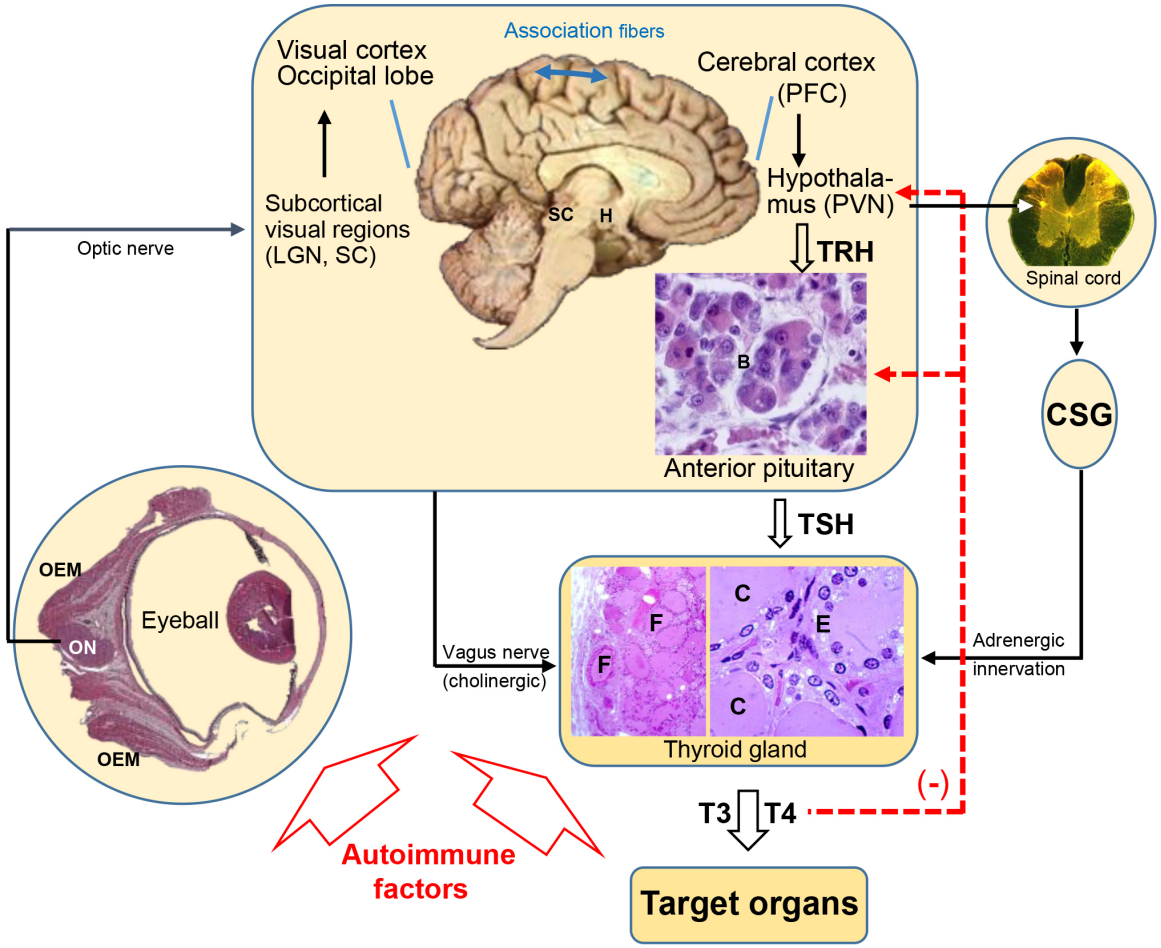

Fig. 1. Some aspects of the complex interactions between brain and thyroid gland. Solid black lines: axonal projections. Open arrows: hormonal influences. Broken red lines: feedback regulation. Abbreviations: B, basophil cells; C, colloid; CSG, cervical sympathetic ganglia; E, epithelium; F, follicle; H, hypothalamus; LGN, lateral geniculate nucleus; OEM, outer eye muscle; ON, optic nerve; PFC, prefrontal cortex; PVN, paraventricular nucleus; SC, superior colliculus; T3, triiodothyronine; T4, tetraiodothyronine = thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid stimulating hormone.

occipital (visual) cortex is among the regions found to be affected in all of the studies mentioned. The study by Jiang *et al.* [5], the first to differentiate patients with thyroid-associated ophthalmopathy with and without dysthyroid optic neuropathy, also shows that rfMRI combined with regional homogeneity analysis demonstrates clear differences between the two groups of patients. These results were recently confirmed by similar analysis methods based on rfMRI data [13]. Although the study by Jiang *et al.* [5] has limitations such as small sample size, the results indicate a risk of regional brain dysfunction in dysthyroid optic neuropathy. It also demonstrates that regional homogeneity analysis may be useful for the early diagnosis of dysthyroid optic neuropathy and thus be helpful for the prevention of the disease.

It is important to determine what factors cause damage to the visual system in the course of immune hyperthyroidism. A likely pathophysiological mechanism involves the recruitment of B-cells to the thyroid gland, and the production of antibodies against thyroid antigens, leading to an inflammatory response. These autoantibodies bind to receptors on thyroid cells, mediating a chronic growth stimulus that eventually leads to hyperthyroidism, but also bind to receptors on pluripotent connective tissue cells in the orbit. This leads to inflammation, fibroblast activation, proliferation of orbital fat, and swelling of the external eye muscles, dislocating the eye and often compressing the optic nerve.

Although the pathophysiological progression of the disease appears to be unidirectional from the thyroid to the eye to the visual system, the overall situation is rather complex. It is characterized by bidirectional and parallel connections between the thyroid and brain that should be mentioned. A schematic overview of the basic anatomical and functional relationships (Fig. 1) shows neural interfaces and relay stations, as well as hormonal feed-forward and feed-back pathways that are likely to work in concert under physiological conditions. First, a humoral pathway activates thyroid metabolism. Thyrotropin-releasing hor-

mone is produced by neuroendocrine cells of the paraventricular hypothalamus and secreted into the portal blood. This peptide hormone stimulates basophil cells of the anterior pituitary to release thyrotropin into the vasculature, from where it exerts its stimulatory influence on the thyroid gland. The thyroid effector hormones triiodothyronine (T3) and tetraiodothyronine (T4, thyroxine) act on their target organs and also provide feedback inhibition to the anterior pituitary and hypothalamus. Second, the gland is subject to nervous control via its autonomic innervation. Notably, the autonomic nervous system plays a key role in integrating signals related to the body's energy homeostasis [14]. Parasympathetic vagal fibers, with acetylcholine as the main transmitter, enter the gland as branches of the laryngeal nerve [15]. Sympathetic fibers arise from the cervical ganglia [16], and there is evidence that the sympathetic nervous system controls human thyroid function via adrenergic innervation of follicular cells. Complementary to its role in hormonal stimulation of the pituitary gland, the paraventricular nucleus also sends fibers to the intermediolateral column of the spinal cord which in turn innervates the cervical sympathetic ganglia [17], which provide the adrenergic stimulation of the thyroid gland. Interestingly, the paraventricular nucleus is under the direct control of the prefrontal cortex [18], a mechanism responsible for psychological influences on endocrine and autonomic parameters. The prefrontal cortex itself receives information from cortical areas such as the striate and peristriate cortices (the regions affected by thyroid-associated ophthalmopathy and dysthyroid optic neuropathy) through extensive connections provided by association fibers.

An interesting approach would be to investigate non-image-forming pathways originating in the retina. It is not known whether additional optic fiber targets serving other needs, such as the hypothalamic suprachiasmatic nucleus (endogenous clock), the pretectal area (pupillary reflexes, optokinetic response), or the tegmental terminal nuclei of the optic tract (control of eye movements), are also functionally impaired by dysthyroid optic neuropathy. It cannot be excluded that the spatial resolution of the current methods utilized is not sufficient to image these relatively small structures. In the context of possible hypothalamic damage in dysthyroid optic neuropathy, it would be interesting to know whether the distinct circadian rhythm of pituitary thyrotropin secretion [2] persists in dysthyroid optic neuropathy.

In summary, the effects of thyroid-associated ophthalmopathy and dysthyroid optic neuropathy on functional parameters of visual and further brain regions have been investigated by Jiang and colleagues (2021) [5] and by studies from other groups. The structural changes in the human brain detected by MRI and regional homogeneity analysis are consistent with and explain many clinical signs in these patients. The complex mechanisms underlying thyroid-brain interactions are emerging. Further studies are needed to clarify these interactions and other related issues, such as the putative associations between autoimmune thyroiditis and movement disorders and dementia [19,20] and their underlying pathological mechanisms.

Author Contributions

SR wrote the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

The author thanks Pia Baqué, MD (Department of Nuclear Medicine, University of Mainz) for critical reading of the manuscript.

Funding

This research received no external funding.

Conflict of Interest

The author declares no conflict of interest. Stefan Reuss is serving as one of the Editorial Board members of this journal. We declare that Stefan Reuss had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Gernot Riedel.

References

[1] Greer MA. Graves' disease. Annual Review of Medicine. 1964; 15: 65–78.

[2] Fisher DA. Physiological variations in thyroid hormones: physiological and pathophysiological considerations. Clinical Chemistry. 1996; 42: 135–139.

[3] Forhead AJ, Fowden AL. Thyroid hormones in fetal growth and prepartum maturation. The Journal of Endocrinology. 2014; 221: R87–R103.

[4] Solomon IL, Blizzard RM. Autoimmune disorders of endocrine glands. The Journal of Pediatrics. 1963; 63: 1021–1033.

[5] Jiang YP, Yang YC, Tang LY, Ge QM, Shi WQ, Su T, *et al*. Altered spontaneous brain activity patterns in dysthyroid optic neuropathy: a resting-state fMRI study. Journal of Integrative Neuroscience. 2021; 20: 375–383.

[6] Jiang L, Zuo XN. Regional Homogeneity: A Multimodal, Multiscale Neuroimaging Marker of the Human Connectome. The Neuroscientist. 2016; 22: 486–505.

[7] Van Essen DC, Gallant JL. Neural mechanisms of form and motion processing in the primate visual system. Neuron. 1994; 13: 1–10.

[8] Chen W, Wu Q, Chen L, Zhou J, Chen HH, Xu XQ, *et al*. Aberrant brain voxel-wise resting state fMRI in patients with thyroid-associated ophthalmopathy. Journal of Neuroimaging. 2021; 31: 773–783.

[9] Wu Q, Hu H, Chen W, Chen HH, Chen L, Xu XQ, *et al*. Morphological and microstructural brain changes in thyroid-associated ophthalmopathy: a combined voxel-based morphometry and diffusion tensor imaging study. Journal of Endocrinological Investigation. 2020; 43: 1591–1598.

[10] Qi CX, Wen Z, Huang X. Reduction of Interhemispheric Homotopic Connectivity in Cognitive and Visual Information Processing Pathways in Patients With Thyroid-Associated Ophthalmopathy. Frontiers in Human Neuroscience. 2022; 16: 882114.
[11] Saeed P, Tavakoli Rad S, Bisschop PHLT. Dysthyroid Optic Neuropathy. Ophthalmic Plastic and Reconstructive Surgery. 2018; 34: S60–S67.
[12] Poonam NS, Alam MS, Oberoi P, Mukherjee B. Dysthyroid optic neuropathy: Demographics, risk factors, investigations, and management outcomes. Indian Journal of Ophthalmology. 2022; 70: 4419–4426.
[13] Wu H, Luo B, Wang Q, Zhao Y, Yuan G, Liu P, *et al*. Functional and Morphological Brain Alterations in Dysthyroid Optic Neuropathy: A Combined Resting-State fMRI and Voxel-Based Morphometry Study. Journal of Magnetic Resonance Imaging. 2022. (online ahead of print)
[14] Seoane-Collazo P, Fernø J, Gonzalez F, Diéguez C, Leis R, Nogueiras R, *et al*. Hypothalamic-autonomic control of energy homeostasis. Endocrine. 2015; 50: 276–291.
[15] Van Sande J, Dumont JE, Melander A, Sundler F. Presence and influence of cholinergic nerves in the human thyroid. The Journal of Clinical Endocrinology and Metabolism. 1980; 51: 500–502.
[16] Romeo HE, González Solveyra C, Vacas MI, Rosenstein RE, Barontini M, Cardinali DP. Origins of the sympathetic projections to rat thyroid and parathyroid glands. Journal of the Autonomic Nervous System. 1986; 17: 63–70.
[17] Reuss S. Spinal relay neurons for central control of autonomic pathways in a photoperiodic rodent. Journal of Integrative Neuroscience. 2021; 20: 561–571.
[18] Cerqueira JJ, Almeida OFX, Sousa N. The stressed prefrontal cortex. Left? Right! Brain, Behavior, and Immunity. 2008; 22: 630–638.
[19] Schneider SA, Tschaidse L, Reisch N. Thyroid Disorders and Movement Disorders-A Systematic Review. Movement Disorders Clinical Practice. 2023; 10: 360–368.
[20] Salehipour A, Dolatshahi M, Haghshomar M, Amin J. The Role of Thyroid Dysfunction in Alzheimer's Disease: A Systematic Review and Meta-Analysis. The Journal of Prevention of Alzheimer's Disease. 2023; 10: 276–286.