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The relation between thyroid dysregulation and impaired cognition/behaviour: An integrative review

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Abstract

Despite decades of research on the relation between thyroid diseases and cognition, the nature of this relationship remains elusive. An increasing prevalence of cognitive impairment and thyroid dysfunction has been consistently observed with ageing. Also, there appears to be an association between thyroid disorders and cognitive decline. Given the increasing global burden of dementia, elucidating the relationship between thyroid disorders as a potentially modifiable risk factor of cognitive impairment was the main goal of this review. We summarise the current literature examining the relationship between thyroid hormonal dysregulation and cognition or behaviour. We present the available imaging and pathological findings related to structural and functional brain changes related to thyroid hormonal dysregulation. We also propose potential mechanisms of interaction between thyroid hormones, autoantibodies and cognition/behaviour. Effects of gender, ethnicity and environmental factors are also briefly discussed. This review highlights the need for long-term prospective studies to capture the course of brain functional changes associated with the incidence and progression of thyroid dysregulations along with the confounding effects of non-modifiable risk factors such as gender and ethnicity. Moreover, double-blind controlled clinical trials are necessary to devise appropriate treatment plans to prevent cognitive consequences of over or undertreatment of thyroid disorders.

Keywords

autoimmune; behaviour; cognition; elderly; hyperthyroidism; hypothyroidism; T1AM

1 | INTRODUCTION

Prevalence of cognitive impairment and dementia substantially increases with ageing, especially in the oldest old population.[1] Thyroid disorders are also prevalent in the elderly

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AUTHOR CONTRIBUTIONS

Manizhe Eslami-Amirabadi: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing. **Seyed Ahmad Sajjadi:** Conceptualisation; Supervision; Validation; Writing – review & editing.

PEER REVIEW

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population, with the prevalence of hypo- and hyperthyroidism reaching 30% and 10% respectively.[2,3] It has been long noted that disorders of thyroid function can lead to cognitive impairment. Therefore, thyroid dysfunctions are important and potentially modifiable risk factors of cognitive impairment in the older individuals.[4]

Thyroid dysfunctions can be categorised based on the serum levels of thyroid hormones (thyroxine [T4] and triiodothyronine [T3]) and thyroid-stimulating hormone (TSH) level as: overt hypothyroidism: decreased T4/T3 levels and increased TSH; overt hyperthyroidism: increased T4/T3 and decreased TSH; subclinical hypothyroidism: normal T4/T3 levels with increased TSH; and subclinical hyperthyroidism: normal T4/T3 levels and decreased TSH level.[4] The association of hypo- or hyperthyroidism with cognition and behaviour has been investigated in many experimental animal studies,[5–7] and also in human observational and experimental studies, as well as clinical trials.[8–11]

The objectives of this review are:

- To provide a summary of the spectrum of cognitive and behavioural impairments related to thyroid disorders
- To review the difference between the manifestations of autoimmune thyroid disorders with other causes of thyroid hormonal dysregulation
- To review the potential mechanisms of the association between thyroid disorders and cognition based on the available serological biomarkers, structural and functional imaging studies, as well as post-mortem brain pathological evaluation
- To evaluate the effects of non-modifiable variables including gender and ethnicity on the association of thyroid disorders and cognition/behaviour
- To provide evidence-based suggestions regarding the optimal treatment of thyroid disorders and to clarify the limitations of the available evidence
- To propose directions for the future studies

We searched various combinations of these key words: thyroid, hyperthyroidism, Graves, Hashimoto, hypothyroidism, mechanism, environment, gender, elderly, age, cognition, behaviour, 3-Iodothyronamine (T1AM) in PubMed, Science Direct and Google scholar. After screening the studies based on their title, we read the abstracts and only included studies that discussed cognitive/behavioural effects of thyroid diseases as their main focus of the study. In total, we included 106 studies and 23 reviews. We then compared and summarised the research characteristics of the studies and their findings. Based on this gathered information, we compiled an integrative review to provide an overview and to identify the weaknesses and strength of the available evidence.

2 | COGNITIVE AND BEHAVIOURAL SYMPTOMS OF THYROID DYSFUNCTION

2.1 | Overt hypothyroidism

Previous studies have reported an association between hypothyroidism and impairment in general cognition, memory, attention/concentration, perceptual function, language, psychomotor speed and executive function. Impaired verbal memory is the most consistently reported impairment.[9,12] Hypothyroidism associated behavioural symptoms are similar to those seen in primary depressive and anxiety disorders.[8,9,13,14] There are also rare cases of severe hypothyroidism that manifest with agitation and frank psychosis.[15–17]

Improvement of cognitive and behavioural symptoms have been reported after treatment with T4,[18–20] although other studies have reported residual behavioural/cognitive difficulties. This includes poor results in mental health summary scales, lower performance in complex attention and poor verbal memory.[20–23] These finding might suggest nonreversible effects of thyroid hormonal deficiency on brain structures, or lower efficacy/central nervous system (CNS) bioavailability of pharmacologically replaced thyroid hormone compared to normal pituitary thyroid axis function.[4]

2.2 | Overt hyperthyroidism

Most of the studies have reported impaired attention/concentration, verbal memory and executive function that could be reversed with treatment.[10,24] However, residual attention deficit following successful treatment has been reported.[25] Patients are usually irritable, agitated and jittery; they might have a clinical picture similar to mania, although a fully developed mania is rare. Thyroid storm, a rare manifestation of severe hyperthyroidism, might present with agitation, delirium and restlessness.[26] A higher incidence of behavioural disorders such as depression, generalised anxiety and bipolar mood disorders have been reported in patients with hyperthyroidism.[27–30] Less commonly, thyrotoxicosis might lead to apathy. This happens most commonly but not exclusively in the elderly population. These patients present with apathy, lethargy, weight loss and depressed mood.[26]

Beta adrenergic blockers can rapidly control irritability and anxiety related to this condition and the behavioural symptoms are reversible with more definitive treatment.[10]

2.3 | Subclinical hypothyroidism

Subclinical hypothyroidism has a less clear association with cognitive and behavioural impairment. Large population-based studies have failed to show cognitive impairment in those with subclinical hypothyroidism,[31–34] although smaller studies that used more sensitive cognitive assessment tools, have reported impairment in memory and executive function.[9,35,36] A systematic review and meta-analysis provided evidence for a significant association between subclinical hypothyroidism and cognitive impairment in patients younger than 75 years old but not older participants.[37] This finding might point to a possible age difference in the effects of thyroid hormonal dysregulation on the brain structure or function. An alternative explanation came from a large population-based study in the US (15,277 disease-free individuals older than 12 years). It showed that TSH distribution

progressively shifts toward higher levels with advancing age.[38] Therefore, the lack of association between cognition and dichotomised (normal/abnormal) TSH in patients older than 75 years might be the result of a higher TSH cut-off value in this group. Also, double-blind, placebo-controlled clinical trials that used detailed cognitive assessments failed to demonstrate improvement of cognitive performance after 12 months of T4 treatment in subclinical hypothyroidism.[39,40] Selection bias is a potential explanation for this outcome because these studies had only selected very mild cases of subclinical hypothyroidism (TSH median 7.1 [6.2–9.7 mIU L^{-1}) in the first study and TSH mean ± SD [5.57 ± 1.68 mIU L^{-1}] in the second).

Regarding behavioural symptoms, some studies have reported higher prevalence of depression and anxiety in subclinical hypothyroidism compared to normal population[41,42] and an improvement with T4 treatment,[42] whereasothers have failed to show increased symptoms in those with subclinical hypothyroidism.[32,43]

2.4 | Subclinical hyperthyroidism

Similar to subclinical hypothyroidism, some studies have shown cognitive impairment in these patients[44–46] and some have not.[32,34] Most consistently, studies have reported an association between development of dementia in elderly patients and subclinical hyperthyroidism.[47,48] However, a double-blind placebo-controlled cross-over study of 56 well-controlled hypothyroid patients (52 females) who were treated with different doses of T4 to induce subclinical hypo- or hyperthyroidism,[49] as well as another similar study on 19 hypothyroid patients, failed to demonstrate a decline in cognitive performance with either condition after 8–12 weeks.[21]

Similar to subclinical hypothyroidism, some studies have suggested irritability, depression and anxiety-related symptoms are prevalent in subclinical hyperthyroidism[14,44] but others have not found any significant difference in those symptoms between subclinical hyperthyroid and euthyroid subjects,[31,32] Meanwhile, randomised double-blind, placebo-controlled clinical trials did not report any improvement in those symptoms with treatment.[39,40]

3 | THYROID HORMONAL ALTERATIONS WITHIN THE EUTHYROID RANGE

Because the correlation between overt hypo and hyperthyroidism and cognition/behaviour has been described extensively in the literature and the correction of overt abnormalities is part of the routine practice, we put more emphasis on the alterations of thyroid hormone levels within normal range. Given that recent studies have shown that T3, T4 and TSH normal levels might change with ageing,[50] investigating continuous rather than dichotomised values might be more relevant especially in the older population. Based on the available evidence, the serum concentration of total and free T4 (fT4) remains relatively stable but the T3 level shows a decline, whereas the production of both T3 and T4 decreases with ageing. This might be a result of slower degradation of T4 in older individuals.[51] At the

same time, the distribution of TSH concentration shifts toward higher levels despite the relatively stable concentrations of fT4.[38,52]

Some previous studies have shown a decrease in cognitive abilities with higher levels of T4 within the reference range,[50,53–56] although others have failed to show any significant association.[57,58] Table 1 summarises the available literature on the subject.

In summary, studies have shown different and often conflicting results. Each study used a unique sample population, methodology, and end point, which might be one reason for the observed discrepancies. It is also conceivable that thyroid impairments might affect degenerative brain diseases differentially and therefore more selective studies might be required to characterise the effects of thyroid impairments on different neurodegenerative pathologies. Also, even if the subjects do not have known thyroid disease, they might have genetic variability in their thyroid hormone receptors that causes this discrepancy in cognitive function (see the discussion in the section on possible mechanisms further below). Genetic variants of thyroid hormone receptors can cause unresponsiveness to treatment with T4 as discussed in section on pathological findings further below. Also,there might be some irreversible damage related to hypothyroidism that does not resolve with hormone replacement, based on animal studies suggesting excessive gliosis and impaired response to injury in brain during period of hypothyroidism. Genetic variation in the enzyme responsible for activation of thyroid hormone in brain cells also might be a contributing factor. Moreover, considering noticeable changes of TSH level distributions with ageing, using an age-specific TSH reference range or measuring fT4 levels instead of TSH might prevent over diagnosis of subclinical hypothyroidism and the potential hazard of over treatment with thyroid hormones in the elderly population.

4 | AUTOIMMUNITY AGAINST THYROID AND ITS ASSOCIATION WITH COGNITIVE/BEHAVIOURAL ABNORMALITIES

Anti-thyroid peroxidase (TPO) and anti-thyroid-stimulating hormon receptor (TSHR) antibodies (Ab) are the most common thyroid autoimmune Ab. These Ab are associated with relatively distinct clinical syndromes of Hashimoto thyroiditis (anti-TPO) and Grave's disease (GD) (anti-TSHR).

Hashimoto's encephalitis (HE) or steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT) is characterised by high levels of thyroid autoantibodies (TAA) in blood/cerebrospinal fluid (CSF) and response to glucocorticoid treatment.[59] A population-based cohort reported increasing annual incidence of Hashimoto's thyroiditis (HT) from 6.5/100 000 in 1935 to 69/100 000 in 1967 in the female population.[60] The largest review of patients with neurological or psychiatric symptoms of SREAT (n = 251) revealed the most prevalent symptoms were seizures (47% of patients), confusion (46%), speech disorders (37%), memory impairment (43%) and persecutory delusions (25%). Chronic memory impairment and psychiatric symptoms were the only presenting feature of 11% and 10% of the cases, respectively. Some 73% of patients were female and 32% had history of thyroid disorder (78% HT and 22% GD). Of those with available Ab results, 34% and 7%, respectively, were seropositive only for anti-TPO or anti-thyroglobulin (Tg), and

69% were positive for both Ab. In CSF (available for 53 patients), anti-TPO, anti-Tg or both had been found in 19%, 4% and 53% of the patients, respectively. Serum or CSF results for anti-TSHR Ab were not reported. Some 82% of patients showed electroencephalogram abnormalities (mostly generalised slowing). Most of the cases had normal TSH levels (median TSH of 2 mU L^{-1}).

GD is the other known thyroid auto-immune condition with cognitive/behavioural complications. GD is characterised by the presence of TSHR Ab and is the most prevalent cause of hyperthyroidism in iodine-sufficient countries such as the USA.[2]

A study showed significantly higher anxiety and depressive symptoms in 31 untreated GD patients (age range 18–60 years) compared to their age-matched controls, which resolved on treatment with methimazole. They also had considerably worse cognitive abilities in block design, picture agreement and forced face recall tests that, despite a relatively large effect size, did not reach statistical significance after correction for multiple comparisons because the study had a small sample size.[10] A functional magnetic resonance imaging (MRI) study of GD patients with a similar cognitive profile showed abnormal spontaneous activity of the left medial frontal gyrus that correlated positively with anxiety score and negatively with processing speed compared to healthy controls. All of the participants were seropositive for TSHR Ab and also anti-TPO Ab.[30]

Both TPO and TSHR Ab are also common in euthyroid individuals with no clear clinical impairment. The prevalence of anti-TPO Ab positivity increases with age, even in a healthy population; anti-TPO Ab is positive in 13% of the healthy population overall, although the prevalence increases from 6% in a teenage population to more than 24% in individuals older than 80 years.[61] Previous studies investigating the relevance of these Ab to development of cognitive or behavioural impairments in euthyroid individuals have produced conflicting results. Some studies have shown worse cognition and behaviour in euthyroid patients with anti-TPO Ab. One study found euthyroid patients with history of HT (n = 26, age: 46 ± 1.9 years) had worse executive function, visual, verbal and working memory, and attention/concentration than euthyroid patients receiving T4 treatment for goiter or surgical thyroid resection (n = 25, age: 49.8 ± 1.9 years).[62] In other studies and compared to general population, HE patients with positive anti-TPO had worse results in evaluation of somatisation, obsessive-compulsive symptoms, depression,[63] social isolation, physical, emotional and social role functioning, general health perceptions and pain.[64,65] Adopting a different approach, another study found that, among a small group of participants with controlled thyroid disease, patients with abnormal cognitive test results had significantly higher levels of anti-TPO Ab (13 HT patients and 12 cases with other thyroid disorders; mean ages of 43 and 47 years, respectively).[66] Also, the presence of anti-TPO predicted poorer psychosocial well being as measured by the 36-Item Short Form Survey questionnaire.[65] It is noteworthy that one study found the presence of anti-TPO Ab to be associated with increased grey matter density in the right amygdala and enhanced connectivity between the subcallosal and parahippocampal areas.[67]

By contrast, in another study (n = 11, age range: 22–82 years), euthyroid patients with higher anti-TPO-titers and Hashimoto's had better long-term outcomes based on the

Glasgow Outcome Scale Extended score.[68] Moreover, a large population-based cross-sectional study (n = 3253, age range: 55–85 years),[69] as well as a prospective study on elderly population (n = 255, mean age:80 years),[70] showed no association between anti-TPO seropositivity and cognitive decline, both at baseline and after 13 months of follow-up.

In terms of mechanism of action of these Ab, TSHR Ab stimulates production of TSH and thyroid hormones, whereas anti-TPO Ab block thyroid hormone synthesis.[71] An experimental study on human brain autopsies (n = 5) showed reactivity to TSHR Ab in cell bodies and axons of large neurones in frontal, motor, sensory, occipital, cingulate and parieto-occipito-temporal regions, as well as vascular endothelial cells of cingulate gyrus.[72] Some studies have suggested that thyroid dysregulation affects brain vascular system. One study showed lower perfusion of brain in hypothyroid patients[73] in regions including the frontal lobes[74] and posterior cingulate gyrus.[75] In another study, high fT4 levels and positive anti-thyroid Ab were associated with terminal internal carotid artery stenosis (n = 30, age < 65years).[76] In another study of euthyroid stroke patients younger than 55 years old, elevated anti-TPO Ab was associated with higher rates of intracranial internal carotid stenosis (odds ratio = 5.3, n = 351, 252 males, mean age = 47).[77] Furthermore, a relationship between GD and moyamoya vasculopathy (MMD) (progressive occlusive vasculopathy of internal carotid, middle and anterior cerebral arteries) has been reported. Interestingly, according to one study, aggressive treatment with anti-thyroid medication was sufficient to stop the progression of MMD and prevent its recurrence (eight females, age range 19–48 years).[78] Also, in one study, anti-TPO positivity predicted an unfavourable stroke outcome (n = 763, 121 anti-TPO + patients).[79]

Other studies have stipulated that thyroid Ab might exert their deleterious effect indirectly through activation of anti-gangliosid[80] or other anti-neuronal Ab,[81] especially those against two antigens: dimethylargininase-I (DDAHI), an enzyme regulating nitric oxide metAbolism, and aldehyde reductase-I (AKRIA), a cytoprotective enzyme. Therefore, it has been suggested that the presence of Ab against DDAHI and AKRIA can be considered biomarkers of CNS involvement in Hashimoto's patients.[82]

Changes in cytokines and related changes in neurotransmitters might also have a role in CNS dysfunction of patients with autoimmune thyroid disorders (AITD). Previous studies showed that these patients had an increased levels of monocyte cytokines (eg, monocyte chemoattractant protein-1) and T lymphocyte cytokines (eg, interferon gamma and tumor necrosis factor α), especially in patients with positive family history of hypothyroidism.[83,84] Also, it has been shown that treatment leads to decrease in interleukin-12 (a marker of T helper 1 activation).[85]

Environmental factors are also potentially important in development of AITDs and their cognitive effects. Review of studies concerning the effects of selenium (Se) on thyroid function and autoimmunity showed that Se deficiency increases the oxidative stress in the thyroid gland leading to inflammation.[86] In addition, patients with AITDs showed improvement of cognitive and behavioural symptoms after Se supplementation, as well as decreased levels of anti-TPO and anti-TSHR Ab.[87] Selenium deficiency is more prevalent in areas with low Se content in the soil such as central Africa and some European countries.

Overall studies had explained the relationship between autoimmune thyroid disorders and altered brain functions by following various mechanisms: the effect of autoantibodies on neuroglial structure, vasculopathy, interference with cytokine/neurotransmitter balance and related environmental factors. In summary, an association between autoimmune thyroid diseases and cognitive/behavioural changes has been observed, although this association is likely to be multifactorial. The worse cognitive function observed in patient with autoimmune thyroid diseases compared to those with thyroid resection indicates a causal effect for the Ab or neuroinflammation. The exact mechanism of the effect of autoimmunity is, however, difficult to establish as a result of a limited number of pathological evaluations of the brain.

5 | POSSIBLE MECHANISMS OF THE ASSOCIATION BETWEEN THYROID DYSFUNCTIONS AND COGNITION

5.1 | Pathological findings

The relationship between brain and thyroid is complex. On one hand, thyroid hormonal signalling is regulated via the hypothalamus and pituitary axis and on the other hand, thyroid hormones (mainly T3) are important players in the functions of the brain. Thyroid hormones (TH) require a complex transport mechanism to cross the blood-brain barrier (BBB) and enter their target cells. Impairment of any of these mechanisms can lead to disruption of thyroid dependent brain functions despite apparently normal blood hormonal levels. Organic anion transporter 1 (OATP1) transports T4 through the BBB and has an extensive expression in capillaries throughout the brain.[88] Also, both T3 and T4 require special transporters to enter their target cells. Brain has several TH transporters with monocarboxylate transporter8 (MCT8) being the most important with high affinity for T3. A mutation in MCT8 gene causes an X-linked disorder presenting with severe mental retardation and movement disororder.[89] The biological activity of TH in target cells is determined by intracellular levels of T3, which are mostly dependent on the activity of the iodothyronine deiodinases converting T4 to T3. A polymorphism in iodothyronine deiodinase genes had been shown in a subset of hypothyroid patients who had a suboptimal clinical response to T4 treatment alone.[90] Moreover, cognitively impaired patients carrying this polymorphism had lower circulating levels of T3.[91]

Thyroid hormones have nuclear receptors (TR) with six isoforms with three of them having prominent expression in the brain. TRs are ligand-activated transcription factors that have three T3-binding isoforms: TRβ1, β2 (alternatively spliced product of one gene) and TRα1 from a separate gene. TRα2 has a different C-terminal extension and does not bind to T3; it acts as a dominant inhibitor for other TRs by competing for DNA binding sites.[92] In rats, TRα1 is expressed predominantly in brain, heart and skeletal muscle. TRβ2 is expressed in the brain, retina and inner ear. TRβ3 is present in kidney, liver and lung, whereas TRβ1 is more widely expressed.[93] Based on immunoreactivity to T3R, different parts of the brain are categorised into three groups: (i) strong: olfactory bulb, hippocampus, dentate gyrus, amygdala and neocortex (layers III to VI), Purkinje cells, internal granular layer and some cells in the molecular layer of cerebellum and lateral mammillary nucleus; (ii) intermediate: hypothalamus and central grey matter of brain stem; (iii) weak: thalamus, caudate, pallidum,

substantia nigra and the interpeduncular nucleus. TRs are also present in astrocytes, oligodendrocytes and epithelial cells in white matter and choroid plexus.[94]

T1AM, a thyroid hormone metabolite, has been shown to be influential on the effects of thyroid hormone in the CNS. It inhibits T4 uptake by OATP1C1, a transporter of T4 through the BBB, in a dose-dependent manner. It also inhibits transport of T4 >T3 via MCT8, a most specific thyroid hormone transporter, through the BBB. This suggests a regulatory role on thyroid hormone delivery to CNS for this protein.[95] T1AM is not a nuclear thyroid hormone ligand but activates trace amine-associated receptor1 (TAAR1) and also binds to alpha A2 adrenergic receptor, apolipoprotein B100, mitochondrial ATP synthase and membrane monoamine transporters,[96] which suggests a role for T1AM in 'orchestrated signalling events and physiological responses'.[97] Based on animal models, TAAR1 is widely expressed in the brain tissue responsible for cognition and emotions, including the prefrontal cortex, hippocampal formation and amygdala. It modulates learning and memory process with pro-learning effects and might have a neuroprotective effect against amyloid toxicity in a mouse model of Alzheimer's disease (AD).[98] Studies using recombinant selective agonist of TAAR1 showed that TAAR1 activation reduced the basal firing activity of dopaminergic neurones in the ventral tegmental area with a close functional link to D2 dopamine receptor.[97] T1AM is distributed throughout various organs, including the CNS. Systemic administration of T1AM increases the levels in the CNS, suggesting that it crosses the BBB. Its cerebral level is critically regulated within the brain likely through metabolism by the enzyme monoamine oxidase B.[99] These findings suggest that thyroid hormone metabolites other than T3/T4 also have important effects on brain function and might need to be taken in account when explaining the association of thyroid hormones with cognition/behaviour.

Animal studies have further helped identify potential biological implications of thyroid hormones. In one study, thyroidectomised rats showed impaired late-phase long-term potentiation (L-LTP) in the CA1 region of hippocampus. Immunoblot analysis of area CA1 illustrated the reversal of hypothyroid-induced reduction of signalling molecules (eg, cyclic AMP) with treatment. Such signalling is essential for L-LTP, learning and memory.[100] Moreover, experimental rodent studies have shown that the combination of T3-TRα is required for the progression of neural stem/progenitor cells toward neuroblasts. These cells are present in adult brain in the subventricular zone and dentate gyrus of the hippocampus to support memory formation, as well as affect modulation and the response to brain injury (eg, trauma) by proliferation, and also survival and differentiation to migrating neuroblasts. Therefore, their deficiency can explain decreased neuronal plasticity in the dentate gyrus and a loss of hippocampus dependent memory formation in adult hypothyroid rodents.[101,102] An absence of TRα2 leading to overexpression of TRα1 had also been shown to reduce the survival rate of postmitotic neuroblasts, suggesting that unliganded TRα1 might have a role in decline of hippocampal neurogenesis in hypothyroid adults.[103] Short-term hypothyroidism resulted in a reduction of the number of proliferating cells in the subgranular zone of the dentate gyrus and hypoplastic dendrites in neuroblasts, which was reversible with T4 treatment.[104] Some hippocampal functions such as classical conditioning were reversible after treatment of short-term hypothyroidism in rats, although some synaptic plasticity during memory formation was not reversible.[6]

In addition, T3, via TRα1, appears to exert a bimodal effect on oligodendrocyte precursor cells (OPC); in the early postnatal period, its effect on Purkinje cells and astrocytes results in the secretion of neurotrophic factors indirectly promoting the maturation of proliferating OPCs. Later and in adult mice, T3 causes complete arrest of OPC proliferation.[105] OPC reactivation can be seen in demyelinating incidents.[106] OPCs also remain capable of proliferation in ALS, although they can only differentiate to oligodendrocytes, and not neurones or astrocytes.[107]

Changes in the neurotransmitter composition of specific parts of the brain is another mechanism proposed for the cognitive and behavioural symptoms of TH dysregulation. Animal studies have reported changes in the release pattern of acetylcholine and monoamines in hippocampus and frontal cortex of experimentally induced hypo-and hyperthyroid rats along with the related functional changes.[7,108]

Elevated levels of monoamines such as noradrenaline in hyperthyroidism were also observed to be associated with neuropsychiatric manifestations.[109] Elevated levels of these metabolites are seen at symptom onset and their level decreased along with clinical an improvement in those with hyperthyroidism with psychosis.

Human brain autopsy studies have shown conflicting results regarding TH dysregulation and associated pathological changes. Autopsy of male Japanese participants of The Honolulu-Asia Aging Study (age range of 71–93 years at inclusion) reported an association between high normal fT4 levels and an increased risk of dementia overall, including AD. The study also reported increased neocortical amyloid plaques and neurofibrillary tangles in participants with high normal fT4 but did not find any association between TSH levels and dementia or Alzheimer's pathology.[56] An important limitation of the study was that it only included men, especially considering the fact that both dementia and TH dysregulations are more common in women. On the other hand, a study based on the National Alzheimer's Coordinating Center's uniform dataset, which included almost 30 000 elderly participants, did not find an association between history of treated hypothyroidism and AD pathology. The only brain pathological finding associated with treated hypothyroidism was severe atherosclerosis. There was also a significant association between treated hypothyroidism and vascular risk factors comprising hypercholesterolaemia and atrial fibrillation, and also pathological evidence of gross infarcts in autopsied brains.[110] A clear limitation of the study was the lack of an evaluation or reporting of serum T4/T3 levels.

The T3 level in the CSF was higher in patients with pathological diagnosis of hippocampal sclerosis of ageing compared to AD patients and control subjects in an autopsy study despite no significant serum T3 level difference between the subjects.[111] One study compared CSF levels of thyroid hormone derivatives between 15 AD, 10 frontotemporal dementia patients, and 10 control subjects with normal cognition. Serum thyroid hormone levels were normal in all of the subjects. There was a significant negative correlation between reverse T3 level and the reverse T3/T3 ratio and Mini-Mental State Examination score in AD patients.[112] An evaluation of serum and CSF concentration of T3/T4 and TSH in 14 hypothyroid patients before and after treatment showed a comparable increase in serum and CSF levels of T4 but the T3 level in the CSF remained unchanged despite increase in serum levels.[113] Overall,

these studies suggest that serum thyroid hormone levels do not correlate with CSF levels in a linear fashion and this might have a role in the residual CNS dysfunction observed in patients with thyroid disease despite successful treatment based on serum hormone levels.

5.2 | Imaging findings

In a population-based longitudinal study of 489 elderly participants, there was no relation between TSH levels and MRI-measured hippocampal or amygdala atrophy, although higher levels of T3/T4 were associated with more severe atrophy of the hippocampus and amygdala.[114]

A fluorodeoxyglucose-positron emission tomography (FDG-PET) study of 12 hyperthyroid (untreated GD) patients showed decreased glucose metabolism in the uncus and inferior temporal gyrus (limbic system) compared to 20 age- and gender-matched controls. Moreover, the posterior cingulate gyrus showed increased metabolism that was positively correlated with free T3 (fT3)/fT4 levels and both anxiety and depression scores.[115] In another FDG-?PET study on 10 untreated GD patients (mean ± SD age, 38.7 ± 9.3 years; five women) and 20 healthy controls, severity of depression and anxiety correlated positively with inferior temporal and parietal gyri hyper-metabolism.[116] In addition, lower grey matter volumes in the bilateral hippocampus, parahippocampal gyrus and left temporal pole had been shown in 51 untreated hyperthyroid adults compared to 51 normal control using voxel-based morphometry of 3D high resolution MRI (mean age 30 years).[117]

Another PET study (14 cases and 10 controls; age range 1855 years) showed lower glucose metabolism in the bilateral hippocampus, amygdala, peri-genual anterior cingulate cortex and right posterior cingulate gyrus in patients with hypothyroidism experiencing cognitive and behavioural symptoms. The changes reversed after treatment.[118]

An MR spectroscopy study evaluated 18 patients with hypothyroidism, 18 with hyperthyroidism, and 18 age- and gender-matched healthy controls. It showed elevated levels of glutamate in the posterior cingulate cortex of hypothyroid patients and the opposite pattern in hyperthyroidism. Glutamate levels in the cortex correlated with total and fT3 levels in serum. Hypothyroid patients also had elevated choline levels in these cortical areas. Glutamate is an excitatory neurotransmitter and its clearance by astrocytes is necessary for neuroprotection. An increase in choline level might be a sign of astrocyte proliferation.[119] T3 had been shown to modulate gene expression of glutamate transporters, causing an increase in clearance of glutamate by astrocytes in rats.[120] In another study of 11 euthyroid, 16 hyper-and 11 subclinical hypothyroid patients (age range 17–47 years), functional MRI in subclinical hypothyroid patients with impaired working memory showed loss of activation of the bilateral middle/inferior frontal gyri, bilateral dorsolateral prefrontal cortex, supplementary motor area and anterior cingulate cortex during the n-back task compared to normal and hyperthyroid patients. These changes normalised after 6 months of treatment with T4.[121] In summary, the T3/T4 level has a more clear association with changes in brain structure and function compared to TSH. Moreover, both high and low T3/T4 levels are associated with unfavourable changes.

We have summarised our proposed mechanisms of relationship between thyroid dysregulations and cognition as a conceptual model in Figure 1. Thyroid hormone levels change in a spectrum and, even within the normal limits, changes in T4/T3 levels have been shown to be associated with changes in brain structure and function. These changes are more pronounced in both overt hypo- and hyperthyroidism. A higher level of thyroid hormone is associated with increased sympathetic tone and brain atrophy. It can also be associated with vascular narrowing and moyamoya type vasculopathy causing stroke in the right genetic/epigenetic context. On the other hand, low thyroid hormone is associated with other vascular risk factors and might cause atherosclerosis, independently leading to cerebrovascular events. Animal studies on brain changes in the setting of hypothyroidism showed impaired response to brain injury such as traumatic events, impaired memory formation and excessive gliosis even in the adult brain. Furthermore, hyper- and hypothyroidism have been shown to be associated with inflammatory response that can be influential in the observed brain dysfunction. Thyroid autoantibodies are present in euthyroid population and patients with autoimmune thyroid conditions regardless of thyroid function based on thyroid hormone level. These Ab are present in the CSF of patients with cognitive /behavioural symptoms in the context of autoimmune thyroid diseases. Observational pathological studies have shown receptors for some of these Ab in brain tissue. Therefore, there might be a role for them in the observed neurological dysfunctions related to autoimmune thyroid diseases. However, this has been subject to ongoing debate considering the possibility of other, unknown autoimmune CNS diseases that can merely be coexistent with autoimmune thyroid disease in the subset of patients with neurological dysfunctions.

6 | THYROID HORMONES AND COGNITION IN WOMEN

As discussed, AITDs and thyroid hormonal dysregulation in general are more prevalent in women.[59,110] Collectively, various types of dementia are also more prevalent in women.[1] Therefore, further sex-specific exploration of the relation between thyroid dysregulation and cognition is warranted.

A cross-sectional study evaluated the correlation between fT4, TSH and anti-thyroid Ab levels and cognitive function in 383 postmenopausal women aged 50–65 years who were at least 2 years past their last menstruation. Their TSH and T4 levels were within the normal range (mean = 1.91 mU L^{-1} and 14.76 pmol L^{-1}, respectively). The mean neurocognitive scores of the study population were below normal average. Their worst performances were in executive function, processing speed and complex attention. More than 50% of them had lower than normal scores in more than one domain of cognition. There was a significant negative correlation between the level of anti-thyroid Ab and cognitive ability, as well as a negative correlation between fT4 level and cognitive function.[122] In an elderly female population (aged 65 years and older), 82% of the population had cognitive deficit in at least one domain.[123]

6.1 | Effect of ethnicity

Although the vast majority of the studies have been on Caucasian population, studies on other ethnic groups have also shown similar associations between thyroid hormonal

dysregulation and cognition/behaviour. The main difference compared to Caucasians appears to be in the prevalence of thyroid dysregulation and other related conditions. A population-based cross-sectional study on apparently normal Mexican participants (n = 1750, 40% female, age over 60 years), showed an increased risk of mild cognitive impairment in patients with hypo- and hyperthyroidism.[124] Also, a study on 10 362 Brazilian participants without known thyroid dysregulation reported lower executive function in participants with low-normal TSH levels.[125] In a study on Chinese participants (77 cognitively normal, 64 mild cognitive impairment and 154 AD patients, aged > 50 years), fT3 levels were significantly higher in patients with Alzheimer type dementia and the odds ratio of AD was significantly higher in those with low-normal TSH levels.[48] Moreover, moyamoya vasculopathy, which is reported to be associated with hyperthyroidism in general and GD in particular, is more prevalent in Asian and Mexican populations.[78] Except for one population-based study to develop an ethnicity specific TSH reference range,[38] no large study on African or African-Americans could be found concerning thyroid hormonal dysregulation and its brain related consequences.

6.2 | Future direction of research

In conclusion, based on the available evidence, higher levels of thyroid hormones even within the normal range are associated with cognitive and behavioural changes and a detectable structural change in the brain. Hypothyroidism has also been shown to be associated with vascular pathologies of the brain. In addition, because the fT4 level remains stable with ageing but the normal TSH level is age-dependent, it is reasonable to use fT4 for screening and monitoring treatment of thyroid hormonal dysregulation instead of TSH.

Moreover, the presence of anti-thyroid Ab is another independent risk factor for cognitive/behavioural and structural changes.

A well-designed long-term cohort study on middle-aged healthy age-matched men and women in two separate groups might provide the opportunity to recognise the pattern and temporal order of the changes in TH, TSH and autoantibodies with ageing. The baseline information of those participants will help to establish possible genetic or environmental risk factors that make certain part of the population more susceptible to thyroid hormonal dysregulation and its cognitive/behavioural effects.

In addition, a double-blind clinical trial with different set goals for TH levels within a normal range will enable us to compare cognitive outcomes and determine the safest therapeutic goal for treatment of patients with thyroid hormonal dysregulation.

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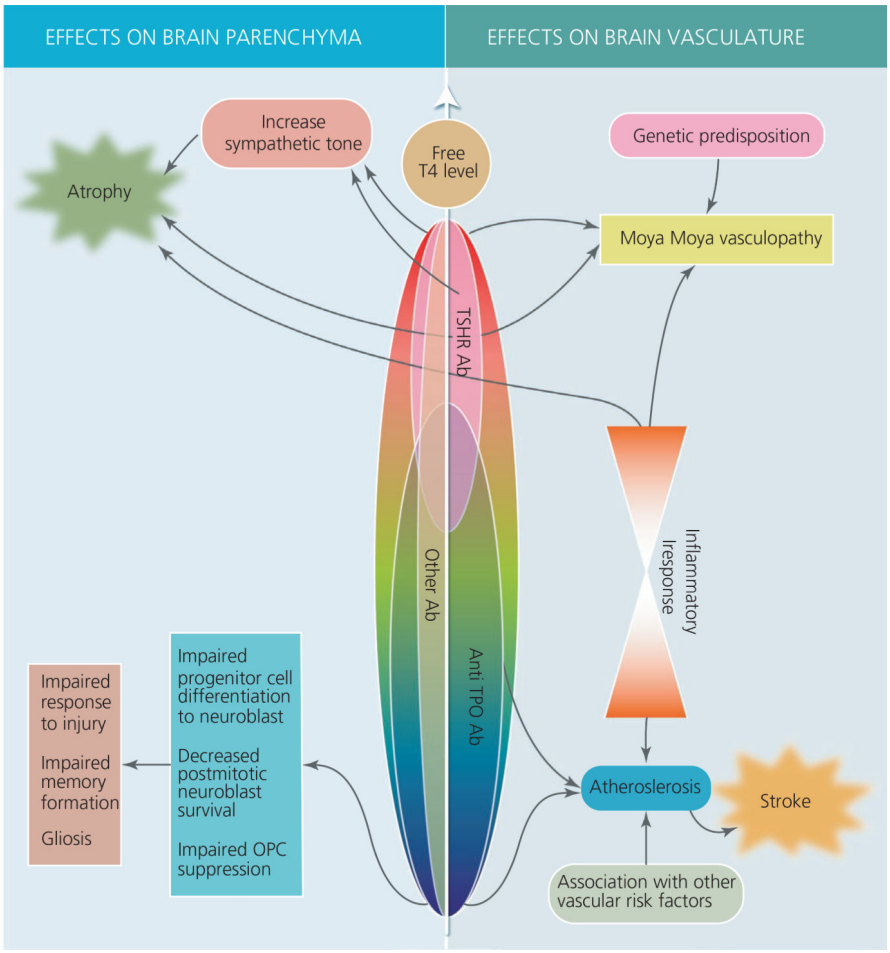

FIGURE 1.

Proposed mechanisms of the effect of thyroid dysregulations on adult brain. Left side: effects on brain parenchyma leading to cortical atrophy/malfunction, gliosis and impaired response to injury. Right side: effects on brain vasculature leading to brain vascular events. Ab, antibodies; T4, thyroxine; TPO, thyroid peroxidase; TSHR, thyroid-stimulating hormone receptor; OPC, oligodendrocyte precursor cell

TABLE 1

Studies of the relation between thyroid hormonal alterations within normal range and cognition/behaviour

Authors, publication year, citation	Type of study	Sample size	Follow-up period	Findings
Hogervorst et al (2008)[53]	Cohort	n = 1047 (mean ± SD age: 73.6 ± 6.2 years)	2 years	High normal fT4 levels were independently associated with more rapid cognitive decline
Tan et al (2008)[55]	Cohort	n = 1864 (mean age: 71; 59% women)	12.7 years	Both low and high TSH levels were associated with an increased risk of developing incident AD in women but not in men.
De Jong et al (2009)[56]	Cohort	n = 665 (men; age range: 71–93 years)	Mean 4.7 years	Every SD increase in fT4 levels was associated with a 20% increase in risk of dementia overall and a 30% increase in risk of AD
Forti et al (2012)[54]	Retrospective cohort	n = 660 (older than 65 years)	Mean 3.8 years	The highest TSH tertile had a three-fold increase in the risk of vascular dementia, no association with AD
Yeap et al (2012)[50]	Cohort	n = 3401 (community-dwelling men aged 70–89 years)	2 to 8 years	Older men with fT4 levels higher than 25th percentile of reference range were found to have a 70% higher hazard ratio of dementia compared to the lower 25%
Beydoun et al (2015)[46]	Cohort	n = 1275 (age range: 30–64 years)	5 years	Higher fT4 was associated with better verbal memory only in male participants, better visuo-spatial/visuo-construction ability in all, and better learning/memory in women and African-Americans
Castellano et al (2013)[57]	Case control	n = 62 (age range: 67–84 years)	3 years	No significant association
Booth et al (2013)[58]	Cohort	n = 659 (mean ± SD age = 69.5 ± 0.8 years)	3 years	No significant association
Cappola et al (2015)[59]	Cohort	n = 2843 (aged: 65 years and older)	10 years	High normal fT4 associated with higher mortality. High normal TSH levels had decreased incidence of dementia and better survival during 10 years of follow-up
Shrestha et al (2016)[60]	Cross-sectional	n = 2704 (age range: 55–74 years)	N/A	Higher fT4 was associated with better spatial perception, psychomotor speed and visuospatial abilities. Concurrent increases in age and fT4 were associated with deficits in memory and learning as measured by California Verbal Learning Test subtests
Szlejf et al (2017)[61]	Cross-sectional	n = 10,362 (mean ± SD age: 49.5 ± 7.4 years; 52.3% women)	N/A	Worse executive function has been reported in those with low normal TSH levels
Almeida et al (2011)[62]	population-based cross-sectional	n = 3932 (non-disabled men; age range: 69–87 years)	N/A	No association with depressive symptoms
Medici et al (2014)[63]	Cohort	n = 1503 (mean ± SD age: 70.6 ± 7.3 years)	8 years	Higher fT4 had significant association with higher depressive symptoms at baseline and higher incidence of depression

Abbreviations: AD, Alzheimer's disease; fT4, free T4; TSH, thyroid-stimulating hormone.