Review Article

Revisiting Thyroid Hormones in Schizophrenia

Nadine Correia Santos,1,2 Patrício Costa,1,2 Dina Ruano,1,3 António Macedo,4 Maria João Soares,4 José Valente,4 Ana Telma Pereira,4 Maria Helena Azevedo,4 and Joana Almeida Palha1,2

1 Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal
2 ICVS-3Bs PT Government Associate Laboratory, Braga, Guimarães, Portugal
3 Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands
4 Institute of Medical Psychology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

Correspondence should be addressed to Joana Almeida Palha, japalha@ecsaude.uminho.pt

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1. Introduction

In 1888 a report by the Committee of the Clinical Society of London explored the association of hypothyroidism with psychosis [1]. Not surprisingly, given the essential role of thyroid hormones for mammalian brain development, the effect of thyroid hormones (THs) in the modulation of affective illness and behavior continues to be an avenue of research in the pathophysiology of mood disorders [2–12]. Complementarily, research has revealed the TH modulation of crucial brain neurotransmitter systems [12–15] including the dopaminergic, serotonergic, glutamatergic, and GABAergic networks [14, 16–20]. As elaborated on throughout this paper, the misregulation of these pathways, as well as the participation of myelination and of cytokines, is of particular relevance in the schizophrenic brain [18, 21–23].

Schizophrenia is one of the most severe psychiatric disorders with an estimated prevalence of 0.7–1.0% in the population worldwide. It often runs a chronic and debilitating course, with many patients responding poorly to medication and suffering frequent and disrupting relapses. Furthermore, it is accompanied by a great social cost in terms of productivity loss and treatment-related expenses [21]. Its core features include cognitive impairment, delusions, hallucinations, altered volition and emotional reactivity and disorganized behavior. It is now clear that the heterogeneity and complexity of schizophrenia is both at the clinical and aetiological levels and that this complex disorder arises from the interaction of a range of deviant genetic traits and environmental “insults,” which may begin to act in the prenatal period [21]. The clear understanding of schizophrenia’s molecular mechanism(s) is elusive, and no biological marker has been identified. In effect, a biomarker may be difficult to find if the disease results from a subtle deregulation in a biological network with impact on mental health and behavior. In this context, modulators of transcriptional activity and their carriers/receptors are good candidates in bridging the genetic and environmental determinants of schizophrenia. Among these are TH [24].
Circulating THs, the prohormone thyroxine (T₄) and the active metabolite 3,5,3’-triiodothyronine (T₃), are lipophilic molecules carried by plasma or cerebrospinal fluid (CSF) proteins. These molecules exert their function mostly via thyroid receptors that bind T₃ with high affinity, acting as ligand-inducible transcription factors that regulate expression of T₃-responsive genes. Nonetheless, TH may also act through fast nongenomic actions [25]. The timing and adequate amount of TH’s action is crucial for the normal neurodevelopment and maturation of the central nervous system (CNS) and for proper functioning of the adult brain [6]. Given their described roles, it is not entirely unexpected that a link between TH and psychiatric disease may be considered [24, 26]. In the adult, TH fluctuations are associated with mood alterations, such that changes in TH levels are common in psychiatric patients across all ages [27–34]. Clinical case reports reveal that hyperthyroid individuals may manifest psychosis and depression [34–38]. Additionally, the prevalence of clinical hypothyroidism in psychiatric patients ranges from 0.5% to 8% [34, 38]. In fact, hypothyroid patients, or those with hypothyroxinemia, display mood impairment, as well as decreased motivation and increased depressive symptoms, such that the prevalence of depressive symptoms is close to 50% in people with hypothyroidism [34, 38]. In this regard, studies have evidenced the impact (correlation) of TH fluctuations in depression, including the relation between TH levels and depressive state and treatment outcome and/or response time to treatment [39–50]. “Of notice, TH seem important for the mood improvement” ability of antidepressants, since about 50% of treatment-resistant patients become responsive when TH are coadministered. In particular, T₃ administration has been recognized to hasten recovery [51, 52], although adjunctive supraphysiological doses of T₄ have proven especially efficacious in women with unipolar or bipolar disease and refractory to standard medication [13]. In addition, dementia has been reported in cases of severe hypothyroidism [34, 38].

In this paper, data on TH circulating levels in cohorts of schizophrenic patients will be summarized. Also, we will explore the interplay between TH and main biological networks implicated in schizophrenia.

2. Thyroid Hormones and Schizophrenia: Relationship with Neurotransmitter Systems and Neural Networks

The link between TH and schizophrenia is pertinent [24, 26, 53]. In point of fact, several groups have measured TH levels, and other thyroid-related parameters, in schizophrenic patients (hospitalized and outpatients), reporting on several abnormalities. A compilation of these studies is presented in Table 1. For the collection of the presented reports the PubMed database was searched using key terms such as “psychiatric disease,” “schizophrenia,” and “thyroid hormones [levels],” and/or designation of each thyroid hormone specifically [total and free thyroxine (TT₄ and FT₄) and triiodothyronine (TT₃ and FT₃)], and thyroid stimulating hormone (TSH)]. Subsequently, for the generation of the final list, the PubMed-generated list was cross-referenced with that derived from the bibliography in articles on schizophrenia and/or psychiatric disease and TH. From our analysis, to date, 15 independent studies of human population cohorts have been published addressing the role of TH in schizophrenic patients, with assessments and/or measurement of TH status [28, 33, 54–66]. It is of mention that prior to the mid-1980s the lack of high-sensitivity assays for measurement of TH, specifically for free TH, was a handicap. Nonetheless, earlier reports already made mention of thyroid function abnormalities in schizophrenic patients and their families, as well as on the resemblance between the psychotic symptoms of people with severe hypo- and hyperthyroidism and those of schizophrenic patients [67–69].

Altogether, from the literature analysis, a dynamic relationship emerged. For example, a connection between Brief Psychiatric Rating Scale (BPRS) values, TT₄ and FT₄ levels and clinical recovery in male psychiatric patients was reported [58]. Also, a study by Roca and colleagues [60] evidenced that 49% of psychiatric patients, in their study population, exhibited significant changes in one or more TH levels, with a significant positive correlation between severity of illness and elevations of TH levels. Furthermore, clinical case reports indicate that hyperthyroid individuals may manifest psychosis [35–37], a characteristic of the positive symptoms observed in schizophrenic patients [21], and that hypothyroid individuals display mood impairment, such as decreased motivation and increased depressive symptoms, a presentation similar to the negative symptoms in schizophrenic individuals [21]. Adding to these, unpublished work from our laboratory indicates that, even within normal range, FT₃ levels in Portuguese schizophrenic male and female patients were significantly lower when compared to controls and that FT₄ levels were significantly lower in male patients when compared to mentally healthy individuals (data presented in meeting proceedings [70]).

Despite difficult interpretation, methodological limitations, and heterogeneity of patients, including complex history of antipsychotic medication, overall observations indicate that TH level fluctuations may have clinical meaning. Such observations are pertinent given that the interaction between the pituitary-thyroid axis and the dopaminergic, serotonergic, glutamatergic, and GABAergic systems, together with any correlation with myelination and proinflammatory response, are relevant in schizophrenic patients in light of their implications in the etiology of the disease [14, 16–20, 22, 23, 71]. In the schizophrenia context, each of these neural networks will be next addressed.

2.1. Dopaminergic System. Dopamine was the first neurochemical to be associated with schizophrenia, in part due to the efficacy of antipsychotic drugs that block dopamine D₂-like receptor in alleviating the hallucinations and delusions of patients (review [19]). Additionally, neuroimaging studies have revealed enhanced activity of the nigrostriatal dopamine system, albeit a hypofunctionality of the mesoprefrontal cortical system, in schizophrenic individuals [72, 73]. Thyroid hormones have been shown to regulate the levels of dopamine receptors [74, 75] and the activity of
Table 1: Literature review of studies on thyroid hormone levels in schizophrenic patients.

| Serum analysis | Other parameters | Number of patients and controls | Diagnosis criteria |
|----------------|------------------|--------------------------------|-------------------|
| TT₄            | FT₄              | TT₃                           |                   |
| No significant difference between controls and drug-free. Decreased after chlorpromazine, trifluoperazine, or clozapine treatments | No significant difference between controls and drug-free. Decreased after chlorpromazine and clozapine treatments | 41 drug-free (for at least 3 weeks) SZ female (28) and SZ male (13) patients; 24/41 treated (6 weeks), random attribution, with chlorpromazine (10), trifluoperazine (9), or clozapine (5) | Feighner criteria 1972 and BPRS |
| Notes and Conclusions. FT₄I calculated from multiplication of serum T₄ and radioactive T³ uptake. Calls for investigation of serum TH levels before and after neuroleptic treatments (Rinier et al., [54]). | | | |
| Basal within normal, posttreatment normal | Basal within normal, posttreatment normal | 25 males drug-free SZ patients; treated (6w) with chlorpromazine (14) or fluspirilene (11) | Gorham criteria 1962 and DSM-III |
| Notes and Conclusions. Prolactin values higher (above normal range) posttreatment. Diagnosis of subclinical hypothyroidism in neuroleptic-treated SZ patients. Higher TSH basal level, and augmented TSH response to TRH, compared to pretreatment (Martinos et al., [56]). | | | |
| 75% paranoid-SZ increased when compared with total 4% change (decrease) in the other groups | 50% paranoid-SZ increased when compared with total 14% change (decrease) in other groups | 29 males: 8 paranoid-SZ, 6 undifferentiated-SZ, 7 bipolar, and 8 major depression (chronic or subchronic patients) | SADS interview |
| Notes and Conclusions. Hospitalized patients. Measurement at admission and every 2 weeks thereafter (average 4 samples/patient). Analysis of variation within groups. Calls for longitudinal assessments of thyroxine trends even when within normal range levels (Mason et al., [57]). | | | |
| Overall falling levels during recovery. A subgroup with initial low levels that increased to middle-range values. | Falling levels during recovery. A subgroup with initial low levels that increased to middle-range values. | 80 males: 6 undifferentiated-SZ, 9 paranoid-SZ, 18 schizoaffective, 15 bipolar disorder, 16 major depressive, 9 posttraumatic stress disorder, 7 others (chronic or subchronic) | BPRS and DSM III |

Notes and Conclusions. Levels of prolactin, and L-thyroxine decreased in SZ patients, whereas dopamine was elevated. Authors conclude that increased dopaminergic activity affects pituitary secretory function, and may result in decreased TSH (Rao et al., [55]).
| Serum analysis | Other parameters | Diagnosis criteria |
|----------------|------------------|--------------------|
| TT₄ | FT₄ | TT₃ | FT₃ | rT₃ | TSH | Antiperoxidase, Tab, or TBG | Number of patients and controls |

**Notes and Conclusions.** Measurement of TT₄ and FT₄ at admission and at 2-week intervals. Indication that the existence of a change in TT₄ and FT₄, irrespectively of the direction, seems to be the most important parameter in recovery. No difference between diagnostic groups or treatments (Southwick et al., [58]).

| | No significant difference between drug-naïve and drug-withdrawn, and controls |
| | No significant difference between drug-naïve, drug-withdrawn, and controls |
| | 23 drug-naïve SZ patients, 67 SZ with 2-3 days drug withdrawn, 67 SZ with neuroleptics; 90 controls |

**Notes and Conclusions.** Drug-naïve and drug-withdrawn groups combined due to similar hormone levels. Smokers removed only from controls. Dopamine increased in drug-free SZ patients compared to controls. Norepinephrine, epinephrine, and prolactin higher in neuroleptic-treated, compared to drug-free and controls. Agrees with hypothesis of dopaminergic overactivity in schizophrenia (Rao et al., [59]).

| Increased on day of hospitalization | Increased on day of hospitalization | Increased on day of hospitalization | Normal | TBG: Normal | 15 male SZ and 34 female SZ patients; age-matched controls, 19 males and 34 females |
|------------------------------------|------------------------------------|------------------------------------|--------|-------------|---------------------------------|

**Notes and Conclusions.** Measurements on day of hospitalization and after. Levels decreased later. Suggests that increases are due to increased T₄ secretion by the thyroid (Roca et al., [60]).

| Significantly lower in those with low or high TSH | FT₄ significantly lower in patients with normal TSH values | FT₃ significantly lower in those with low or high TSH | 60% normal, 5% elevated, 17% low | TAb: 20% of total patients (28% SZ female to 13% control; 14% SZ-male to 7% control) | 249 patients with chronic SZ (136 males, 113 females; median age 36 years old) |

**Notes and Conclusions.** Thyroid function normalized with increased doses of medication. Managed hypothyroidism leads to decreased hospitalization. Hypothyroidism as a concurrent illness in SZ (Walch et al., [61]).
| Normal (daily mean): drug free lower than controls | Mesor (daily mean): SZ drug-free equal to treated and both lower than controls. Acrophase (daily higher), less than half in both SZ groups compared to control | 89 drug-free SZ patients (21 never received drugs, remaining over 3 days free), and 25 typical neuroleptic-treated SZ (for at least 5 days); 34 controls | Notes and Conclusions. Spectrum of thyroid function test abnormalities, but interpretation not clear (Othman et al., [33]). |
| Increased in the acute SZ, normalized with perazine with 4-week treatment. Normal in all other SZ patients. | Normal | Normal | Normal | 31 acutely ill SZ patients, 19 in remission without drugs, 20 in remission with different drugs, 24 with residual-SZ (negative symptoms); 24 controls | Notes and Conclusions. Three independent psychiatrists. No age difference in TH measurements. TSH decrease might be caused by the hyperdopaminergic state of these patients as the group reported before. None on Li+; no more information on medication. Suggests involvement of the noradrenergic receptor system (Rao [62]). |
| Higher in patients with mild or major syndrome | Higher in patients with mild or major syndrome | BPRS | Notes and Conclusions. Does not differ female from male. The higher T₄ the higher the severity of illness, and the better the response to treatment. Concludes that function of T₃ is altered as a consequence of neuroleptic therapies (Baumgartner et al., [63]). |
| Higher in RP compared to controls | Higher in RP compared to controls | Mental deterioration battery (at regular intervals for 1 year) | Notes and Conclusions. No clinical thyroid illness. 34% of patients with thyroid function tests abnormalities, and no correlation found with neuroleptic use. Calls for careful interpretation of thyroid function tests in SZ patients (Sim et al., [28]). |
Table 1: Continued.

| TT₄ | FT₄ | TT₃ | FT₃ | rT₃ | TSH | Antiperoxidase, TAb, or TBG | Number of patients and controls | Diagnosis criteria |
|-----|-----|-----|-----|-----|-----|-----------------------------|-----------------------------|------------------|
|     |     |     |     |     |     |                             |                             |                  |

Notes and Conclusions. Basal prolactin higher in RP, but not NRP, compared to controls. Basal growth hormone (GH) higher in NRP than RP SZ patients. Dexamethosone Suppression Test (DST) nonsuppression higher in RP than NRP and controls. Indicates that higher basal TSH and GH levels may be related with poorer treatment response. Higher TT₃ and FT₃, and blunted TSH response to TRH and nonsuppression in DST indicate better response in SZ patients (Yazici et al., [64]).

2/22 (9%) baseline abnormal values

|     | 4/22 (18%) baseline abnormal values | 4/30 (13%) baseline abnormal values | 38 treatment-resistant SZ patients receiving 6-weeks quetiapine, risperidone, or fluphenazine treatment |
|-----|-----------------------------------|-----------------------------------|---------------------------------------------------|

Notes and Conclusions. Little change in thyroid function except for a significant decrease in TT₄ in quetiapine treatment possibly due to UDP-glucuronosyltransferase competition with the drug. No hypothyroidism noted. At baseline no TH differences between treatment groups. No control group.

No monitoring of TH function in patients receiving quetiapine recommended. Probably no effect of risperidone or fluphenazine on TH (Kelly and Conley [65]).

|     | Normal | Normal | Normal | Normal | Antiperoxidase: normal |
|-----|--------|--------|--------|--------|------------------------|
|     |        |        |        |        |                        |

Notes and Conclusions. Even though atrophy is present in demented patients, the presence of atrophy does not necessarily lead to dementia. Lower TSH with anti-TPO associated with 4 times higher risk of dementia but P > 0.05. No association of serum TSH, FT₄, TT₃, rT₃, anti-TPO with dementia. Higher FT₄ and rT₃ related with higher hippocampus and amygdala atrophy (de Jong et al., [66]).

BPRS: Brief Psychiatry Rating Scale; DSM: Diagnostic and Statistical Manual of Mental Disorders; SADS: Schedule for Affective Disorders and Schizophrenia; TTR: transthyretin; TBG: thyroxine-binding globulin; TAb: thyroid antibodies; SZ: schizophrenia.
tyrosine hydroxylase [76–78], the rate-limiting enzyme of the
catecholaminergic pathway. Moreover, it has been suggested
that dopamine may be inhibitory of TSH secretion [59], as
treatment with dopamine blockers lead to increase in TSH
level or to subclinical hypothyroidism [79], and that hypo-
thyroidism can lead to increased dopamine receptor sensitiv-
ity [74]. In a human study of acutely ill schizophrenic pa-
tients, Rao et al. [55] analyzed the interrelation between
serum levels of dopamine, prolactin, TSH, and T4. The serum
levels of dopamine were found to be elevated in schizo-
phrenic patients, while levels of the other parameters were
decreased. The increased dopaminergic activity was hypothe-
sized to affect the pituitary secretory function, and decreased
beta-adrenergic activity was inferred as consequence of de-
creased serum TSH concentration. This is of further interest as
α1- and β-adrenergic catecholamines are involved in main-
taining deiodinase activity, and thus brain thyroid status
[80]. As such, type-1 deiodinase impairment may result in
a drop in T3 levels, with unchanged T4, and type 2 or 3
deiodinase impairment may be reflected in decreased T4
metabolization.

2.2. Serotonergic System. Serotonin (5-hydroxytryptamine,
5-HT) is an essential neurotransmitter. Curiously, it was first
thought to have a role in schizophrenia given its similarity to
lysergic acid diethylamide (LSD), a compound that competes
for and occupies serotonin’s receptor sites, resulting in psy-
chotic symptoms [81]. Since then, perhaps the strongest
evidence of serotonin’s involvement in schizophrenia is the
role that its receptors play in the mechanism of atypical
antipsychotic drugs which, besides their high receptor selec-
tivity, show a weak direct dopaminergic antagonist effect
[82]. According to the current view, serotonergic signaling
may have a modulatory influence on central dopamine trans-
mmission, which may significantly contribute to the ther-
apeutic effects of atypical antipsychotics [83]. Altogether,
observations led to a serotonin hypothesis of schizophrenia.
Enhanced serotonergic signaling, especially via serotonin
type 2A receptors, is thought to be involved in the pathology
of schizophrenia specifically during the early phases of psy-
choes ([84] and review [20]). On the other hand, deficient
central 5-HT functions may underlie some of the negative
symptoms in schizophrenic patients [83,85].

Establishing a link between the serotonergic system and
TH modulation, Strawn et al. [86] measured CSF concen-
trations of 5-hydroxyindoleacetic acid (5-HIAA) and homo-
vanillic acid (HVA), major metabolites of serotonin and
dopamine, as well as plasma concentrations of various THs.
The concentration of 5-HIAA was significantly and nega-
tively correlated with plasma TSH and TT3, while that of
HVA was significantly and negatively correlated with plasma
TSH, TT3, and FT3. Such findings, indicative of monoamine-
thyroid interactions, are significant as studies have shown
diminished 5-HT activity in hypothyroid patients [87,88]
and a negative correlation between TSH and CSF concentra-
tions of 5-HIAA in patients with unipolar depression [89].
Of note, in a separate population of patients diagnosed with
major depressive disorder, no correlation was found bet-
ween TSH and 5-HIAA [90]. Nonetheless, as reviewed by

Bauer et al. [13], most human studies in hypothyroid pa-
tients evidence a reduced 5-HT responsiveness, that is, rever-
sible with TH replacement therapy. Furthermore, studies in
hypothyroid-state-induced animals showed that 5-HT turn-
over is increased in the brainstem and that its levels, as well
as those of its precursors, are decreased in the cortex/whole
brain [91–94]. Also, reports indicate an increase in cortical
5-HT concentrations and desensitization (no change in den-
sity) of autoinhibitory 5-HTT receptors in the raphe area,
resulting in disinhibition of cortical and hippocampal 5-HT
release, and in increased cortical 5-HT2 receptor sensitivity
[95–97]. Altogether, there is evidence that thyroid status
impacts the serotonin system in the adult brain and vice versa
[13].

2.3. Glutamatergic System. The glutamatergic hypothesis of
schizophrenia is based upon the observation that psycho-
tomimetic agents, such as ketamine and phencyclidine, in-
duce neurocognitive deficiencies and psychotic symptoms,
similar to those of schizophrenia, through blockage of the
neurotransmission at N-methyl-D-aspartate-(NMDA-) type
glutamate receptors [98]. Given that the glutamate/NMDA
receptors are ubiquitously distributed in the brain, gluta-
matergic models of schizophrenia predict widespread corti-
cal dysfunction, in particular hypofunctionality of the fore-
brain glutamate system (review [16, 99]). Furthermore, sup-
porting the model in which reduced NMDA receptor activity
may result in schizophrenic-like behavior, animal data have
shown that mice expressing only 5% of normal levels of
the NMDA Ri receptor subunit display behavioral abnormalities
similar to those observed in pharmacologically induced ani-
mal models of schizophrenia [100]. The phenotype can be
ameliorated by treatment with antipsychotic drugs (dopa-
minergic and serotonergic receptors antagonists). Altogether,
the literature corroborates a link between the glutamatergic-
dopaminergic-based systems, particularly considering
that the NMDA receptors are colocated on brain circuits that
regulate dopamine release [99].

Mendes-de-Aguiar et al. [15] studied the role of T3 in
the CNS, specifically on regulation of glutamate uptake. The
team showed an increased neuronal viability against tox-
icity when neurons were cultured in the presence of T3-
treated astrocytes. Altogether, the authors concluded that
T3 is capable of regulating extracellular glutamate levels by
modulating the astrocytic glutamate transporters and, con-
sequently, by promoting neuronal development and neuro-
protection. In another study, male rats were treated with glu-
tamate receptor agonists and antagonists and serum TH
levels were assessed [101]. The results indicated that agonist
administration increased TSH concentrations, while antag-
ons decreased TSH and TH serum levels, indicating that
endogenous excitatory amino acids may play a part in the
regulation of TH secretion [102]. These studies are in agree-
ment with reports on glutamate and other endogenous exci-
tatory amino acids, such as L-aspartate, N-methyl-D-aspar-
tate, kainate, and amino-hydroxy-5-methyl-4-isoxazole pro-
pionate, in their ability to regulate the secretion of anterior
pituitary hormones as well as in the neuroendocrine regula-
tion of the hypothalamic-pituitary axis (review [103]).
2.4. GABAergic System. The role for the GABA (δ-amino-
butyric acid)-ergic system in the pathogenesis of schizophre-
nia derives mostly from neuropathologic studies [104]. Spe-
cifically, the chandelier neurons, a subtype of GABA inter-
neurons, have decreased immunostaining for the GABA
transporter, possibly related to decreased BDNF signaling
or NMDA receptor hypofunction. Furthermore, upregula-
tion of the postsynaptic GABA-A receptors, together with
reduction of both glutamic acid decarboxylase (GAD) 67
and reelin (a protein that colocalizes with GABAergic inter-
neurons), was described in schizophrenic patients [105].
GAD67 and reelin are involved in the glutamate conversion
to GABA and in synaptic plasticity and/or neuromigration.

The possibility that TH affects the GABAergic system
was first put forward in the 1960s and since then multiple
studies have examined various aspects of this relationship,
altogether suggesting that some human nervous disorders
involving GABAergic systems are related to thyroid dysfunc-
tion. Overall, as expertly reviewed by Wiens and Trudeau
[14], the effect of TH on the GABAergic system can
take place at multiple levels, including circuit formation,
enzymes involved in synthesis and metabolism of GABA and
 glutamate, GABA release and reuptake, and GABA receptors.
For example, in rat models, thyroid status has been
shown to influence the development of inhibitory cortical
GABAergic circuits [106]. Also, neonatal hypothyroidism
was evidenced to result in decreased GAD activity in various
brain regions of the neonate brain [107, 108], although not
in the adult brain. In addition, T3 administration was shown
to accelerate the developmental increase in GAD activity in
both in vivo and in vitro models [109, 110]. Furthermore,
other studies revealed lower activity of other two enzymes
in GABA metabolism, GABA aminotransferase and succinic
semialdehyde dehydrogenase, in hypothalamic animals [111],
and that T3 replacement restored activity back to control
levels [112]. At the GABA concentration level, neonatal rats
rendered hypothyroid have reduced whole brain glutamate
and GABA concentrations, from within 2 hours of birth to
postnatal day 30 [113]; interestingly, levels were not found to
be increased in animals rendered hyperthyroid [114]. In con-
trast, whole glutamate and GABA levels were found elevated
in hypothyroid animals [115] (rendered hypothyroid when
adults) and, in accordance, with the increase GAD activity
also noted. These observations point for the possible diverse
influence of TH depending on the developmental stage. Data
for animals rendered hyperthyroid are discordant between
studies. Overall, evidence continues to indicate a correla-
tion, although a positive correlation between TH levels and
GABAergic function in the developing brain and a negative
correlation in adult animals is not always a consistent finding
[14]. Adding to these observations, studies indicate that TH
affects GABA release and reuptake. For example, in in vitro
preparations of synaptosomes, from adult rat cerebral cortex,
low concentration of T3, but not of T4 or rT3, increased depo-
larization-induced GABA release by a direct nongenomic
mechanism [116]. At the GABA receptor level, studies
indicate that TH have direct nongenomic effects on the
GABA_A receptor complex, specifically that, in the presence
of GABA, T3 inhibits GABA-stimulated Cl− currents in rat
forebrain membranes and in its absence it induces the Cl−
current [117, 118]. On the other hand, GABA can affect TH
function; GABA can inhibit TSH-stimulated TH release from
the thyroid gland and affect TSH secretion from the pituitary.

On the role of adequate functioning of the maternal thy-
roid gland in offspring thyroid status development, the
report by Ahmed et al. [119], on hypo/hyperthyroidism ani-
mal models in dams, is especially noteworthy regarding the
TH-GABAergic system interplay. The study revealed that
maternal hypothyroidism induced decreases in both mono-
amine levels and in acetylcholinesterase activity and increases
in the GABA content of the offspring. This was accompanied
by suppression of Na+, K+-ATPase, Ca2+-ATPase, and Mg2+-
ATPase activity in different brain regions. On the other hand,
maternal hyperthyroidism produced reverse effects. The
authors concluded that maternal hypothyroidism and hyper-
thyroidism might induce inhibitory and stimulatory effects,
respectively, on the excitability and synaptic neurotransmis-
sions in the progeny’s brain [119].

2.5. Myelination and Cytokines. The TH involvement in
the regulation of myelination and/or oligodendrocytes’ func-
tionality, central processes in the modulation of neural net-
works, is of interest in schizophrenia, where involvement
of white matter has been implicated [22, 71, 120–123].

Associations between TH levels and myelination have
been reported. Hypothyroidism is associated with delayed
myelination in several brain regions [124, 125]. Further-
more, myelin-related genes, shown to be downregulated in
postmortem schizophrenic brain, including cyclic nucleotide
phosphodiesterase, myelin-associated glycoprotein, transfer-
rind, and v-erb-b2 erythroblastic leukemia viral oncogene
homolog 3 [122], are regulated by TH. Also, changes ob-
served in the identified cell cycle genes, from microarray ana-
lysis of schizophrenic patients [123], are particularly inter-
esting given that two genes, cyclin D1 and cyclin-dependent
kinase inhibitor 1C (P57), central to oligodendrocyte differ-
entiation, have been shown to be among the early regulated
cell cycle genes after exposure to TH, a “cue” essential to
trigger oligodendrocyte differentiation [126, 127].

Myelin abnormalities in the neurological/psychiatric-
diseased brain are often presented with an inflammatory
component. In schizophrenia, evidence from clinical data
supports a potential pathogenic role of elevated cytokine
expression. Both childhood and adult schizophrenia are
characterized by elevated expression of IL-1, IL-6, and TNF-
α in the CSF; along with altered cytokine or cytokine receptor
expression [23, 128]. While many cytokines may be virtually
undetectable in a healthy noninflamed system, their induc-
tion (abnormal or in a response to an inflammatory trigger)
in immune and glial cells, such as astrocytes and microglia,
may play a significant role in the deregulation of neural cell
homeostasis, with vast consequences at the level of oligoden-
drocyte function and myelination (review [71]). In this line,
it is relevant to mention that whereas THs play an important
role in the regulation of deiodinases activity under normal
metabolic conditions, other regulating mechanisms might
be involved in TH metabolism during pathophysiological
conditions, which may overlap with those known to be
relevant for the development of schizophrenia. During these conditions, a state of altered TH metabolism can occur [non-thyroidal illness (NTI)], which is characterized by a fall of serum T$_4$ [129, 130], due to decreased extrathyroidal conversion of T$_4$ into T$_3$ by type 1 deiodinase, without an increase in serum TSH [131, 132]. In these studies, TRβ1 has been found to be downregulated (in an animal model of NTI), and type 3 deiodinase activity shown to be upregulated in liver and skeletal muscle of critically ill patients. Correspondingly, what renders these observations of particular interest, in the schizophrenia-TH-inflammation interrelation, is that in sites of local inflammation, induced in animal models by site-directed bacterial endotoxin (lipopolysaccharide) administration, deiodinase type 3 activity in inflammatory cells is strongly increased, suggesting enhanced local degradation of T$_3$ [132].

2.6. Thyroid Hormones as Neurotransmitters. The role of TH in the pathophysiology of schizophrenia is more so noteworthy when considering the possible function of TH as neurotransmitters. The breakthrough hypothesis of a neurotransmitter role for T$_3$ was put forward in the endocrinology field in the 1970s by Dratman and collaborators [133], based on the colocalization of TH with the noradrenergic system [134]. Given the vast roles of T$_3$ in the brain, this is hardly unexpected. Among others, T$_3$ promotes differentiation in astrocytes, mediates cerebellar astrocyte and neuronal proliferation, and participates in the organization of extracellular matrix molecules via astrocytes [15, 135]. Recently, Scanlan and team (review [136]) have explored a similar neurotransmitter function for 3-iodothyronamine (T(1)AM), a molecule proposed to result from a unique biosynthetic deiodination pathway starting from the decarboxylation products of either T$_4$ or rT$_3$. The hormone T$_3$ is reported to accumulate in nerve endings reaching high concentrations in the synaptosome [137, 138] and being released from it in a Ca$^{2+}$-dependent mechanism [139]. In in vitro studies T1AM has been found to block the transporters for the amines/neurotransmitters dopamine, norepinephrine, and serotonin. Interestingly, T1AM interacts with high affinity to the trace-amine-associated receptor (TAAR) [136, 140], a class of G-protein-coupled receptors, and genetic linkage studies have shown a significant association between the TAAR gene and susceptibility to schizophrenia [141].

3. Thyroid Hormones and Schizophrenia: Human Studies Considerations

Thyroid hormones are widely distributed in the brain, with a multitude of effects on the CNS including a putative effect in the pathogenesis of psychiatric disorders. Indicating this interrelation, the successful treatment of affective disorders often includes the coadministration of TH. Despite these observations, the molecular action(s) that may underlie the mood-modulating properties of TH in the adult brain has only fairly recently become of greater interest. As such, when reporting on this type of analysis, three main aspects are of essence for the neuropsychiatric community to incorporate and/or consider in current and future studies: (i) the effect of antipsychotic medication, (ii) determination of CSF levels of TH, and (iii) the introduction of longitudinal studies of prenatals, neonatal, and/or childhood TH status, related to propensity to develop schizophrenia at the adult age, particularly in at-risk offspring (e.g., familial history of schizophrenia), as well as familial TH level correlations. These will next be summarily discussed.

3.1. Effect of Antipsychotic Medication on Thyroid Hormone Status. The literature reports on the effect of neuroleptic medication on deiodinases activities, as well as on the N-glucuronidation of TH, and by consequence on TH levels. Namely, the commonly used antipsychotic haloperidol can enhance type 2 deiodinase, while clozapine decreases type 2 but increases type 3 deiodinase activity in several brain regions [142]. In addition, some antipsychotics, such as clozapine, are piperazine-containing drugs that undergo N-glucuronidation. Given that the enzyme UDP-glucuronosyltransferase is responsible for the glucuronidation of TH and of certain psychotropic medications [143], a competitive mechanism may be conducive to TH level changes [65]. Finally, it may also be worthy of consideration that, even in cases where no change in circulating levels of TH is observed, deregulated deiodinase activity may affect the spatiotemporal distribution and local regulation of TH [144, 145].

3.2. Serum and CSF Thyroid Hormone Level Assessments. The measurement of TH levels in CSF samples would be more likely to represent TH brain homeostasis. Not only would this type of analysis add to ones already done to identify schizophrenia disease markers (e.g., [146] and review [147]), but it would also fill in a gap regarding the measurement of TH levels in the CSF of schizophrenic patients as such study is lacking in the field. This could be done in a manner similar to a study in an Alzheimer’s disease population, which revealed rT$_3$ level alterations in the CSF that were not reflected in the sera samples [148].

3.3. Familial, PreNatal, Neonate, and Early Childhood Thyroid Status. During development TH play a crucial role in CNS development, including in cerebral cytoarchitecture, neural growth, and synaptogenesis [149–151]. Consequently, it follows that the thyroid status and timing during development, including neonatal, has a significant impact on behavior, locomotor ability, speech, and cognition [2–8, 152]. Furthermore, given that the fetus relies on the mother for the adequate supply for TH, it is relevant to consider maternal thyroid status during pregnancy; for example, maternal hypothyroxinemia leads to decreased T$_3$ availability for the fetal brain, that is, associated with neuropsychological impairments of the child [153]. Neurodevelopment can be restored to within the normal range upon TH supplementation in case of neonatal hypothyroidism [154], although subtle abnormalities remain in these children. Such observations are further correlated with animal work findings that indicate how TH status, even prenatally, may impact on neuronal excitability and synaptic transmission within the CNS [119]. Altogether, TH status seems relevant in the pre- and postnatal periods, and there are critical periods during which
different parts of the brain and/or aspects of the CNS development are sensitive to TH supply [155]. Thus, to further understand the impact of TH on behavior, it would be of interest not only to investigate TH status in adulthood in mood and cognitive disorders, but also how alterations in the hormonal milieu during development might impact on adult behavior (as has been recently shown to be case for other hormones, such as glucocorticoids [156, 157]). In this regard, it would be further interesting to broaden thyroid assessment studies to include mentally healthy siblings of schizophrenia patients.

4. Conclusions

Thyroid hormone assessment in schizophrenic patients presents a particular challenge. Often, the heterogeneity of patients, including many with a complex history of antipsychotic medication, renders impossible a “clean” TH basal determination in disease state. Deregulations of the pituitary-TH axis continue to be of interest given the interaction between the pituitary-thyroid axis and the dopaminergic, serotonergic, glutamatergic, and GABAergic systems, together with relationships with myelination and proinflammatory response, which are strongly implicated in schizophrenia. The fine-tuning of these networks and their precise implication on disease etiology certainly warrants further investigation.

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