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The Influence of Reverse Triiodothyronine on Neuropsychiatric Disorders: A Narrative Review

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ABSTRACT

Introduction:

Reverse triiodothyronine (rT3) is traditionally regarded as a biologically inactive isomer of triiodothyronine (T3), produced primarily via peripheral deiodination of thyroxine (T4). Although T3 binds to nuclear thyroid hormone receptors and regulates transcription of genes essential to neuronal development, synaptic plasticity, and myelination, rT3 lacks such agonist activity. Recent studies suggest rT3 may competitively inhibit T3 at receptor sites and influence thyroid hormone bioavailability by modulating deiodinase enzyme activity. These effects position rT3 as a potentially significant contributor to the pathophysiology of various neuropsychiatric conditions.

Materials and Methods:

A comprehensive literature review was conducted through 2024 using biomedical databases including PubMed, Scopus, and Google Scholar. Inclusion criteria targeted peer-reviewed studies investigating rT3 regulation, deiodinase enzyme function (particularly type 3 deiodinase, D3), and clinical correlations between altered thyroid hormone profiles and psychiatric illnesses. Key terms included "reverse T3," "thyroid metabolism," "deiodinase activity," "functional hypothyroidism," and various neuropsychiatric diagnoses. Articles emphasizing both molecular mechanisms and clinical outcomes were prioritized.

Results:

Increased D3 activity during physiological stress, trauma, chronic inflammation, or psychiatric illness shifts T4 metabolism away from active T3 and toward inactive rT3. This leads to a biochemical state described as "functional hypothyroidism," where serum T4 and thyroid-stimulating hormone (TSH) levels may appear normal, yet intracellular T3 action is diminished. Elevated rT3 and reduced T3/rT3 ratios have been identified in patients with depression, bipolar disorder, generalized anxiety, cognitive impairment, and schizophrenia. These alterations correlate with symptom severity and treatment resistance in some individuals. Additionally, rT3 has shown promise as a biomarker for disrupted thyroid signaling in neuropsychiatric contexts, potentially guiding more personalized treatment approaches.

Conclusions:

Reverse T3, long viewed as a passive by-product, may play an active regulatory role in neuropsychiatric disorders by interfering with T3 signaling at the cellular level. Functional hypothyroidism driven by excess rT3 represents a distinct biochemical phenotype contributing to mood, cognition, and behavioral dysfunction. Recognition of this mechanism underscores the need for expanded thyroid assessment beyond standard TSH and T4 testing in psychiatric populations. Future research should focus on the therapeutic implications of correcting rT3 dominance and restoring optimal intracellular thyroid hormone activity.

INTRODUCTION

Thyroid hormones—thyroxine (T4), triiodothyronine (T3), and reverse triiodothyronine (rT3)—are crucial for normal brain development, synaptic activity, and neuroplasticity.[1,2] Triiodothyronine is the primary bioactive hormone, acting on nuclear thyroid hormone receptors (TRα and TRβ) to regulate the expression of genes involved in neuronal differentiation, neurogenesis, mitochondrial biogenesis, and neurotransmitter modulation.[3] Thyroxine functions largely as a prohormone that is converted into T3 or rT3 by deiodinase enzymes in peripheral tissues, including the brain.[4]

Reverse triiodothyronine (rT3), although structurally similar to T3, ***lacks significant intrinsic activity*** at thyroid hormone receptors. Nevertheless, it plays a regulatory role through competitive inhibition of T3 binding and allosteric modulation of deiodinase activity.[5] Elevated rT3 levels are observed in pathological states such as euthyroid sick syndrome, chronic inflammation, trauma, severe infections, caloric restriction, and prolonged psychological stress.[6,7] These conditions upregulate type 3 deiodinase (D3), promoting the conversion of T4 into rT3 over T3 and diminishing intracellular thyroid hormone

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action in key brain regions such as the prefrontal cortex, hippocampus, and amygdala.[8,9]

This thyroid imbalance—where circulating hormone levels may appear normal but tissue-specific hypothyroidism persists—***can impair neurotransmitter regulation*** (including serotonin, dopamine, and norepinephrine), reduce mitochondrial function, and alter neuroplasticity.[10,11] These disruptions are increasingly being linked to a spectrum of neuropsychiatric disorders. Therefore, the role of rT3 in modulating central nervous system (CNS) function warrants closer clinical scrutiny and a shift in diagnostic paradigms that often rely solely on thyroid-stimulating hormone (TSH) and T4 measurements.

MATERIALS AND METHODS

This narrative review was conducted to examine the association between rT3 and neuropsychiatric disorders, including depression, bipolar disorder, anxiety, schizophrenia, cognitive dysfunction, and related conditions. A comprehensive literature search was performed using PubMed and Google Scholar, focusing on articles published between January 1970 and July 2025.

The following Boolean search logic was employed:

"reverse T3" OR "rT3" AND "psychiatric conditions" OR "neuropsychiatric disorders" OR "mental health."

Articles were selected based on the following inclusion criteria:

- Peer-reviewed publications.
- Human studies or studies involving human-derived data, including post-mortem, imaging, and observational cohorts.
- Narrative reviews, systematic reviews, meta-analyses, and original research articles from neuroendocrinology, endocrinology, psychiatry, neurology, internal medicine, and psychoneuroimmunology.
- Articles addressing the biochemical, clinical, or therapeutic roles of T3 and rT3 or the T3: rT3 ratio in psychiatric illness.

Exclusion criteria included:

- Animal-only studies without direct human correlation.
- Non-English language publications.
- Conference abstracts, unpublished dissertations, and editorial opinion pieces lacking empirical evidence.

The initial search yielded over 250 references, of which approximately 90 were reviewed in full. Ultimately, 77 peer-reviewed sources were selected for inclusion based on relevance to the scope of this review and their contribution to the mechanistic or clinical understanding of reverse T3 in psychiatric illness. Articles were prioritized for inclusion if they presented mechanistic insights, discussed diagnostic implications of rT3 levels, or explored therapeutic modulation using thyroid hormone replacement strategies.

This methodology was designed to ensure a comprehensive, cross-disciplinary synthesis of emerging evidence while maintaining scientific rigor and clinical relevance.

Biochemistry of Reverse Triiodothyronine

Reverse triiodothyronine is synthesized through the enzymatic activity of type 3 iodothyronine deiodinase (D3), which catalyzes the removal of an iodine atom from the inner ring of T4.[12] This reaction renders rT3 structurally similar to T3 but devoid of meaningful biological activity at thyroid hormone receptors. The generation of rT3 is part of a finely tuned mechanism that allows the body to regulate metabolic activity in response to environmental cues.[9] See **Figure 1** for a comparison between the structural differences between T3 and rT3.

Under conditions such as psychological stress, systemic inflammation, malnutrition, infection, and chronic illness, D3 activity is upregulated. This upregulation shifts the peripheral conversion of T4 away from the formation of active T3 and toward the production of rT3.[7,13] This enzymatic redirection is believed to serve as an adaptive response, conserving energy, and modulating cellular metabolism during states of physiological burden.[14]

Functionally, rT3 is not an inert metabolite. Though it does not activate thyroid hormone receptors, it may compete with T3 for receptor binding sites, particularly in the hypothalamus and pituitary gland, thus impacting the negative feedback loop

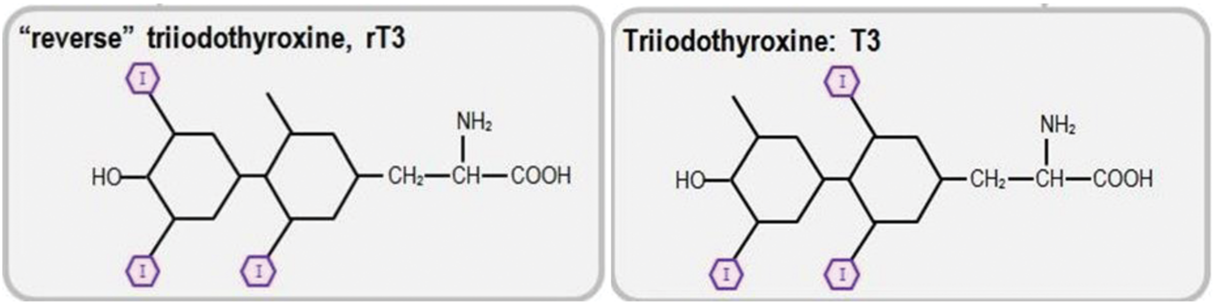

Figure 1. Thyroxine uses the enzyme D1 to remove the 5′ iodine to become triiodothyronine while the enzyme D3 removes the 5-iodine generating reverse triiodothyronine.

that regulates thyroid hormone homeostasis.[1,3] Moreover, elevated rT3 can influence the intracellular thyroid hormone landscape by inhibiting the activity of deiodinase enzymes that are critical for converting T4 into T3. These effects may culminate in a relative deficiency of T3 within neurons, impairing the genomic and non-genomic actions of thyroid hormones essential for cognitive function, mood regulation, and neuronal plasticity.[9,14]

Neuropsychiatric Implications of Reverse Triiodothyronine Elevation

Depression

Elevated levels of rT3 have been consistently observed in individuals with major depressive disorder (MDD), particularly among those who are resistant to conventional pharmacologic interventions such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).[15,16] In these patients, the peripheral conversion of T4 is increasingly shifted toward rT3 rather than the bioactive T3, often in response to chronic stress, inflammation, or dysregulated hypothalamic-pituitary-adrenal (HPA) axis activity.[7,10]

This metabolic adaptation results in elevated rT3 and a concurrent reduction in free T3 (fT3) levels, leading to diminished thyroid hormone signaling in key mood-regulating brain regions such as the prefrontal cortex, hippocampus, and anterior cingulate cortex.[11,17] Although serum TSH and T4 levels may remain within reference ranges, this phenomenon reflects a form of "tissue-level hypothyroidism" where intracellular thyroid hormone availability is insufficient to meet neurobiological demands.[18]

Neuroimaging and neurochemical studies suggest that inadequate T3 activity in the CNS contributes to reduced serotonergic tone, altered dopamine transmission, mitochondrial dysfunction, and neuroinflammation—all hallmarks of depressive pathophysiology.[19,20] Importantly, several randomized and open-label clinical trials have demonstrated that supraphysiological T3 supplementation (typically liothyronine) can improve depressive symptoms in patients who fail to respond to antidepressants, even when standard thyroid hormone panels appear normal.[21,22] This supports the idea that functional thyroid hormone resistance or rT3-mediated antagonism may underlie certain cases of refractory depression, warranting consideration of thyroid hormone modulation as an adjunctive treatment.

Bipolar Disorder

Thyroid dysfunction—particularly in the form of altered peripheral conversion of thyroid hormones—has long been implicated in the pathophysiology of bipolar disorder, especially in individuals with treatment-resistant or rapid cycling presentations.[23,24] Several studies have documented elevated rT3 levels and concurrently reduced T3 in bipolar patients during depressive phases, even when TSH and T4 levels remain within normal limits.[25,26] These findings suggest a dysregulated thyroid hormone metabolism at the tissue level, likely involving increased activity of type 3 deiodinase (D3), which favors the production of rT3 from T4 at the expense of biologically active T3.[12]

This peripheral shift toward rT3 may have downstream consequences on neurotransmitter systems, particularly dopamine and serotonin, which are heavily implicated in mood regulation. Additionally, thyroid hormone receptors are expressed in the limbic system and prefrontal cortex—areas associated with emotional processing and executive function—making them susceptible to even subtle alterations in intracellular thyroid hormone signaling.[27]

One of the most well-documented therapeutic observations in psychiatry is the efficacy of supraphysiologic doses of T3 in the treatment of rapid cycling bipolar disorder. Studies have shown that T3 augmentation can stabilize mood, reduce depressive symptoms, and even help prevent cycle acceleration, especially in women.[28,29] In some cases, patients with bipolar disorder demonstrate partial or complete remission only after thyroid hormone therapy has been optimized—supporting the view that underlying functional hypothyroidism or rT3 dominance may exacerbate affective instability.[30]

These clinical findings underscore the importance of assessing the full spectrum of thyroid function—including rT3—in patients with bipolar disorder, particularly those with mood instability, treatment resistance, or rapid cycling. Targeted intervention with T3 therapy may correct metabolic blocks in thyroid hormone action, thereby contributing to more effective and sustained mood stabilization.

Anxiety Disorders

The association between thyroid hormone imbalance and anxiety has gained increasing attention in recent years, particularly in the context of altered T3:rT3 ratios and their influence on neuroendocrine function. Although less extensively studied than in depression or bipolar disorder, mounting evidence suggests that elevated rT3 and relative reductions in T3 may contribute to the pathophysiology of generalized anxiety disorder (GAD), panic disorder, and post-traumatic stress disorder (PTSD).[31,32]

Anxiety states, particularly chronic or trauma-related forms, are known to activate the HPA axis and trigger an increase in cortisol secretion. Elevated cortisol, in turn, enhances the activity of type 3 deiodinase (D3), the enzyme responsible for converting T4 into rT3 instead of active T3.[7,33] This stress-adaptive mechanism, although beneficial in acute physiological threats, becomes maladaptive under persistent psychological stress or trauma, potentially leading to a pseudo-hypothyroid state at the tissue level despite normal TSH readings.

T3 plays a critical role in modulating neurotransmitters implicated in anxiety, including gamma-aminobutyric acid (GABA), serotonin, and norepinephrine. A deficiency of intracellular T3 in limbic structures such as the amygdala and hippocampus may impair inhibitory control over the fear circuitry, exacerbating hypervigilance, restlessness, and anticipatory anxiety.[10,34]

Emerging clinical findings also suggest that patients with anxiety disorders may exhibit elevated rT3 values, especially in the context of comorbid conditions such as depression or chronic fatigue syndrome. In PTSD, for instance, studies have shown increased rT3 and suppressed free T3, accompanied by symptoms of detachment, insomnia, and cognitive intrusions.[35,36]

Although data are still limited, a growing number of case reports and small observational studies have noted symptom improvement in anxiety disorders following low-dose T3 therapy, particularly in individuals with abnormal T3: rT3 ratios.[37] These findings support the hypothesis that rT3 dominance and functional T3 deficiency may underlie a subset of treatment-resistant anxiety presentations, meriting more comprehensive thyroid evaluation in such cases.

Cognitive Dysfunction and Brain Fog

Cognitive dysfunction, often described by patients as “brain fog,” is a prevalent and debilitating symptom in a wide array of neuropsychiatric and endocrine disorders. This phenomenon typically includes complaints of poor memory, reduced processing speed, attentional difficulties, and impaired executive function. Emerging evidence suggests that elevated levels of reverse T3 (rT3) may play a critical role in the pathophysiology of these cognitive complaints, particularly in patients with otherwise “normal” thyroid panels but persistent neurological symptoms[38,39]

Under conditions of physiological stress, trauma, infection, and inflammation, type 3 deiodinase (D3) activity is upregulated. This causes a preferential conversion of T4 into rT3 rather than into the bioactive T3, leading to a functional hypothyroid state at the cellular level—even if serum TSH and free T4 remain within reference ranges.[7,14] In the brain, this shift in thyroid hormone metabolism is especially problematic because neurons are highly dependent on adequate T3 for maintaining mitochondrial function, neurogenesis, myelination, and synaptic plasticity.[3]

Triiodothyronine is also involved in the regulation of intracellular calcium, glucose metabolism, and antioxidant defense systems within the CNS. A deficiency of active T3—either because of diminished production or competitive inhibition by excess rT3—can disrupt neuronal energy homeostasis, impair neurotransmitter synthesis (particularly acetylcholine and dopamine), and result in oxidative stress within vulnerable brain regions such as the hippocampus and prefrontal cortex.[40,41]

Recent studies have identified a link between elevated rT3 and cognitive decline in patients recovering from critical illness, long COVID, and chronic fatigue syndrome. In these populations, high rT3 levels have been associated with slowed processing speed, poor working memory, and impaired attentional control—symptoms that often mirror those of mild cognitive impairment and even early dementia.[42,43] In such cases, the term “non-thyroidal illness syndrome” (NTIS) is frequently used, but it often fails to capture the full neurocognitive impact of rT3-mediated thyroid dysfunction.

Though larger controlled trials are still needed, some clinicians have reported symptomatic improvement in patients with cognitive dysfunction following low-dose T3 supplementation—particularly in those with high rT3 and low-normal free T3 levels.[37] These findings support a growing consensus that rT3 should be considered not just a marker of metabolic stress, but a potential modulator of brain health and cognitive performance.

Schizophrenia

Schizophrenia is a complex psychiatric disorder characterized by positive symptoms (hallucinations and delusions), negative symptoms (anhedonia, social withdrawal, and flattened affect), and cognitive dysfunction. Although traditionally regarded as a dopamine-driven illness, recent research has explored the role of endocrine-metabolic abnormalities—particularly thyroid hormone dysregulation—in its pathophysiology. Among these, elevated reverse T3 (rT3) levels and diminished T3 availability have garnered increasing attention.[16,44]

Multiple studies have reported abnormal thyroid hormone profiles in individuals with schizophrenia, particularly during acute psychotic episodes and in chronic, treatment-resistant cases. These abnormalities often include low serum T3, normal or low-normal TSH, and elevated rT3, suggesting a peripheral-to-central conversion defect or an adaptive stress-induced deiodinase shift favoring rT3 production.[45,46] Increased activity of type 3 deiodinase (D3) in the brain may impair local T3 availability, contributing to functional thyroid hormone deficiency at the neuronal level—even in the presence of euthyroid lab values.

This thyroid hormone imbalance has direct implications for the brain regions implicated in schizophrenia. Triiodothyronine modulates dopaminergic transmission, regulates GABAergic tone, and supports myelin integrity and mitochondrial metabolism—key pathways involved in the cognitive and affective dysfunctions observed in schizophrenia.[27,47] Animal studies have shown that T3 deficiency can impair prefrontal cortex development and hippocampal plasticity, which parallels the structural and functional deficits seen in patients with schizophrenia.[48]

Notably, a subset of patients with predominant negative symptoms appears to show the most profound thyroid hormone dysregulation. These individuals often exhibit cognitive slowing, affective blunting, and low motivation, symptoms that may reflect impaired T3 signaling in the frontal-striatal circuits.[49] Elevated rT3 may further exacerbate these deficits by competitively inhibiting T3 receptor binding and disrupting gene transcription critical for neuroplasticity and energy metabolism.

Although research in this area is still developing, preliminary studies have explored the therapeutic potential of T3 supplementation in schizophrenia. Some case reports and small trials suggest that adjunctive T3 may enhance response to antipsychotic medication, particularly in patients with negative or cognitive symptoms and abnormal thyroid panels.[50] Future research is warranted to clarify the mechanistic links between rT3, neuroendocrine dysfunction, and clinical presentation in schizophrenia.

Low Triiodothyronine Syndrome

Low T3 syndrome, also referred to as NTIS, is characterized by reduced serum levels of T3 without overt hypothyroidism (i.e., without an elevation in TSH or marked drop in T4). It is a common adaptive response to systemic illness, metabolic stress, malnutrition, or trauma, and it reflects a downregulation of thyroid hormone activation and cellular metabolism under conditions where conserving energy is prioritized.

The hallmark of Low T3 syndrome is decreased peripheral conversion of T4 to T3, often accompanied by an increase in reverse T3 (rT3), a metabolically inactive isomer that competes with T3 for receptor binding and transporter entry into target cells.[7,14] Elevated rT3 levels are driven primarily by upregulated activity of type 3 deiodinase (D3), which is induced by inflammatory cytokines (e.g., IL-6, TNF-α) and glucocorticoids during periods of physiological stress.[51,52]

This state of reduced tissue-level T3 availability may exist despite normal circulating levels of TSH and T4, and it frequently goes unrecognized by conventional thyroid panels. However, in critically ill patients, individuals with chronic fatigue syndrome, fibromyalgia, and certain psychiatric disorders such as major depression and PTSD, Low T3 syndrome is a recurring biochemical pattern associated with worse functional outcomes.[42,53]

In the brain, Low T3 status impairs neuroplasticity, neurotransmitter production, and mitochondrial efficiency. As a result, patients may present with fatigue, memory lapses, low mood, and a decline in cognitive performance—symptoms often misattributed to primary psychiatric or neurologic conditions.[54]

Although Low T3 syndrome is often regarded as an adaptive, protective mechanism during acute illness, chronic suppression of active T3 levels can have deleterious effects, particularly on the CNS and immune regulation. Clinical trials have begun to explore the potential benefits of T3 supplementation in select patients with documented Low T3 syndrome, with early findings suggesting improvement in mood, energy, and cognition when rT3 is high and T3 is low despite normal TSH.[37,55]

Recognition of Low T3 syndrome, including rT3 evaluation, can provide important diagnostic and therapeutic insights in neuropsychiatric and chronic multisystem disorders. See **Figure 2** for a summary of the Thyroid panel results in different neuropsychiatric conditions.

Nutritional Cofactors in Triiodothyronine Metabolism

Optimal thyroid hormone metabolism and regulation rely heavily on specific micronutrients that function as enzymatic cofactors or structural supports. Selenium, iron, vitamin B12 (cobalamin), and folate (vitamin B9) are among the most critical in modulating T3 production, receptor activity, and minimizing pathological elevations in rT3.

Comparartive Summary of Thyroid Profiles in Neuropsychiatric Disorders

Psychiatric Disorder	TSH	Free T4	Free T3	Common Thyroid Patterns	Key Clinical Features
Major Depression	Normal / ↑	Normal	↑	Low T3 syndrome, high rT3	Fatigue, anhedonia, sleep issues, low motivation; treatment-resistant depression responds to T3
Blpolar Disorder	Normal I	Normal	↑	Low T3 with elevated rT3, especially in depressive or rapld cycling pha-	
Anxiety Disorders	Normal ↓	Normal	↑ / N	Stress-induced D3 activation elevates rT3	Panic, hypervigilance, restlessness, insomnia GABA/serotonin dysregulation
Cognitive Dysfunction / Brain Fog	Normal ↓	Normal	↑/ Low-N	Functional hypothyroidism, high rT3 despite euthyroid labs	Memory deficits, poor focus, mental fatigue, "slow thinking;" common post-illness or in chronic fatigue
Schizophrenia	Normal ↓	Normal	↑	Impaired T3 aviailability, possible receptor resistance	

Figure 2. An elevated level of reverse triiodothyronine has been found in numerous psychiatric conditions with concurrent normal levels of thyroid-stimulating hormone and thyroxine. Adding triiodothyronine testing can provide an additional marker to further define causation for treatment resistance conditions.

Selenium is an essential trace element that serves as a cofactor for iodothyronine deiodinases—particularly D1 and D2—which are responsible for converting T4 into biologically active T3. Selenium also supports glutathione peroxidase enzymes that defend thyroid tissue from oxidative damage during hormone synthesis. Selenium deficiency has been associated with decreased T3 production, elevated rT3, and impaired T3 receptor binding in multiple tissues.[56]

Iron is vital for thyroid peroxidase (TPO), the heme-dependent enzyme that catalyzes iodination of tyrosine residues during T4 and T3 synthesis. Iron deficiency disrupts TPO activity, resulting in reduced thyroid hormone synthesis and impaired conversion of T4 to T3, which may promote rT3 accumulation. Additionally, iron plays a crucial role in neurotransmitter biosynthesis, and iron-deficient individuals may experience concurrent cognitive and mood impairments alongside thyroid dysfunction.[57]

Vitamin B12 (cobalamin) plays an indirect but essential role in thyroid function through its involvement in one-carbon metabolism, myelin integrity, DNA synthesis, and mitochondrial energy production. Inadequate B12 levels can impair methylation-dependent enzyme activity, potentially diminishing T3 receptor sensitivity and exacerbating neurocognitive symptoms common in hypothyroid or high-rT3 states. B12 deficiency is also associated with elevated homocysteine, a marker linked to thyroid autoimmunity and cerebral inflammation.[58]

Folate (vitamin B9) functions synergistically with B12 in methylation reactions that regulate gene expression and neurotransmitter biosynthesis. It influences thyroid function indirectly by supporting metabolic detoxification and methyl-dependent enzymatic activity. Low folate levels have been associated with impaired T4-to-T3 conversion and may exacerbate the buildup of rT3 under metabolic stress.[59]

Together, these micronutrients contribute to the biochemical environment necessary for effective thyroid hormone activation and signaling. Identifying and correcting deficiencies in selenium, iron, B12, and folate should be considered a foundational therapeutic approach in individuals with elevated rT3 and neuropsychiatric symptoms.

Clinical Implications and Treatment Considerations

From a clinical standpoint, the implications of elevated reverse T3 levels necessitate a broader perspective on thyroid function testing and treatment strategies in patients presenting with neuropsychiatric symptoms. Traditional reliance on serum TSH and T4 levels may overlook subtle but functionally significant imbalances, particularly those characterized by high rT3 and low-normal T3.

Diagnosis requires a comprehensive thyroid panel that includes free T3, free T4, and reverse T3, alongside TSH. This approach enhances the ability to detect tissue-level hypothyroidism or imbalances that would otherwise remain undiagnosed under conventional paradigms.

Management strategies may benefit from targeted thyroid hormone replacement, especially with liothyronine (T3), in patients with neuropsychiatric symptoms and demonstrable rT3 elevations. Such interventions have shown promise in alleviating symptoms of depression, bipolar disorder, and cognitive dysfunction in cases resistant to standard therapies.

Research needs remain significant, as more robust, controlled clinical trials are essential to define optimal diagnostic thresholds, therapeutic windows, and long-term outcomes of rT3-targeted interventions. Further elucidation of the molecular mechanisms by which rT3 affects neuronal function may also open new therapeutic avenues for psychiatric and cognitive disorders.

CONCLUSION

The growing recognition of reverse T3 as more than an inert by-product of thyroid hormone metabolism invites a fundamental reassessment of how we evaluate and treat neuropsychiatric conditions. Once dismissed as merely a deactivation product, rT3 is now emerging as a significant modulator of CNS function, capable of influencing mood, cognition, and behavior through its effects on thyroid hormone signaling pathways.

By competing with T3 for receptor binding and reflecting the physiological consequences of chronic stress, inflammation, and illness, rT3 serves as both a biomarker of systemic dysfunction and a potential contributor to psychiatric disease pathology. This dual role positions rT3 at the intersection of endocrine and neuropsychiatric health.

Accurate diagnosis necessitates comprehensive thyroid profiling that includes rT3 levels alongside traditional markers. Therapeutic strategies aimed at optimizing T3 availability, particularly in individuals with elevated rT3 and resistant neuropsychiatric symptoms, may hold promise for improving outcomes where conventional treatments fall short.

Ongoing research is vital to further clarify the mechanistic pathways through which rT3 exerts its influence and to refine treatment approaches based on individual thyroid hormone dynamics. As clinical awareness expands, integrating rT3 into standard diagnostic and therapeutic frameworks could represent a transformative step in addressing the unmet needs of patients with complex neuropsychiatric presentations.

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DATA AVAILABILITY

The data that support the findings of this review article are provided in the references with linked access. All data sources are freely accessible.

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INDIVIDUAL AUTHOR CONTRIBUTION STATEMENT

M.L.G., A.M.G., and A.B.P. all assisted in formatting the manuscript with literature compilation, review, and revisions. M.L.G. assisted in manuscript formulation, insights, and review. A.M.G. assisted in review, revisions, and insights. A.B.P. assisted in manuscript formulation, review, and revisions. All authors read and approved of the final manuscript.

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