Neuroendocrine Regulation of Mirror Neurons: Linking Hypothalamic–Pituitary–Thyroid Axis Dysfunction to Autism

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Abstract

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by impairments in social interaction, communication, and restricted or repetitive behaviors. One promising line of research points to dysfunction in the mirror neuron system, which normally supports imitation, empathy, and understanding of others' actions. Despite its potential importance, the biological basis of mirror neuron impairment remains poorly understood. Here, we propose that dysregulation of the hypothalamic–pituitary–thyroid (HPT) axis provides a mechanistic link between endocrine imbalance and mirror neuron dysfunction, thereby contributing to the social and cognitive deficits observed in ASD. To explore this idea, we developed a minimal mathematical model that couples HPT axis dynamics with mirror neuron activity. The model integrates classical feedback regulation of thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone (TSH), and thyroid hormones (T3/T4), with an additional term describing thyroid-dependent mirror neuron growth. Simulations revealed that acute suppression of HPT input leads to transient decreases in thyroid hormone levels and mirror neuron activity, whereas chronic suppression produces sustained impairments that persist even after endocrine input is restored. Phase-space analysis showed that mirror neuron maturation is highly sensitive to thyroid hormone thresholds, indicating that small endocrine fluctuations can have disproportionate neural effects. Furthermore, we identified two pituitary dysfunction pathways—reduced cell production and accelerated cell removal—that both converge on diminished T3/T4 availability and impaired mirror neuron function. Finally, we linked these endocrine effects to metabolic vulnerability by highlighting reduced succinate dehydrogenase activity in the Krebs cycle as a factor that could further compromise neural energy balance. Together, these findings suggest that systemic thyroid and metabolic regulation plays a critical role in shaping neural circuits underlying social cognition and may represent a key axis of vulnerability in ASD.

Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by impairments in social interaction, communication, and restricted/repetitive behaviors[3]. Despite decades of research and studies, the exact neurobiological foundations of the social difficulties stay elusive. This leaves a gap in understanding that inhibits both the diagnosis and treatment. One hopeful line of research focuses on the role of mirror neurons. Mirror neurons[4] are specialized cells that are triggered when an individual performs an action and when they observe the same action that's performed by other individuals. Dysfunction within the system might support the deficits in imitation, social cognition, and empathy, which are all commonly observed in people with autism. By looking into how biological and hormonal factors contribute to mirror neuron dysfunction, researches can deepen the understanding of autism's origin mechanisms and potentially discover new directions for early intervention.

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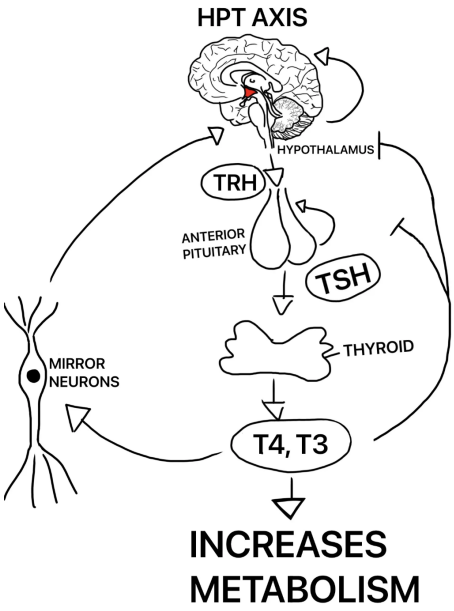

Figure 1: The hypothalamic–pituitary–thyroid (HPT) axis regulates thyroid hormone production (T4, T3), which is essential for mirror neuron development. Maternal thyroid hormone deficiency may impair these circuits, increasing vulnerability to autism spectrum disorder (ASD).

The mirror neuron hypothesis of autism[7, 5, 6, 2] assumes that disabilities in the system disrupt the neural basis for social learning, contributing to central ASD symptoms such as reduced joint attention, decreased empathy, and difficulties in understanding the intentions of other individuals. Our research will build on this hypothesis by proposing a neuroendocrine mechanism. We suggest that a lack of maternal thyroid hormone during pregnancy might impair the development of mirror neuron circuits in the embryo's brain, which increases the vulnerability to autism. Since thyroid hormones are needed for the maturation of neural networks involved in imitation and social cognition, disruptions in their availability during critical phases of gestation might represent a biological link between endocrine dysfunction and mirror neuron deficits in ASD.
The hypothalamic pituitary thyroid (HPT) axis[8] plays a crucial role in regulating neurodevelopment through its control of thyroid hormone synthesis and release. Thyroxine (T4) and triiodothyronine (T3), which are the principals of thyroid hormones, influence the processes of neuronal proliferation, migration, synaptic formation, and myelination. Deficiencies in maternal thyroid hormones can lead to changed cortical organization and abnormal synaptic connectivity in the growing fetus. Since mirror neurons are highly dependent on accurate timing of neuronal migration and synaptic plasticity, thyroid hormone deficits might specifically balance the structural and functional integrity of these systems, which lays a biological base for social impairment. Combining the mirror neuron hypothesis with the role of the HPT axis provides a compelling neuroendocrine structure for autism (see Figure 1). This perspective highlights that ASD is not only a disorder of neural connectivity or genetics, but also one that might come from systemic hormonal imbalances during important developmental periods. By defining autism as a condition created by both mirror neurons and thyroid hormones or endocrine dysregulation, we can make a connection between neuroscience and endocrinology. This versatile model will offer a more comprehensive understanding of the disorder and suggest that early screenings for thyroid dysfunction in pregnant women could represent a obstructive strategy against specific autism risk factors. In the following sections, we first review the neuroendocrine foundations of the hypothalamic–pituitary–thyroid (HPT) axis and summarize existing evidence linking thyroid hormone dysregulation to autism. We then present a minimal mathematical model that couples HPT axis dynamics with mirror neuron activity, designed to explore how endocrine disturbances may impair neural circuits underlying

Parameter	Value	Unit
q_1	244.8	-
q_2	50.4	-
q_3	12.384	-
α_1	244.8	min
α_2	50.4	min
α_3	12.384	min
a_p	0.05	days
b_p	0.05	days
a_m	0.047	-
b_m	0.047	-
a_a	0.1	days
b_a	0.1	days
a	1.0	-
b	1.0	-
T	1.5	-

Table 1: Parameter values used in simulation

social cognition. Using this model, we simulate scenarios of thyroid dysfunction and analyze their impact on mirror neuron maturation and activity. Finally, we discuss the implications of these findings for understanding autism's neurobiological basis, propose directions for early screening and intervention, and highlight open questions for future research.

Methods

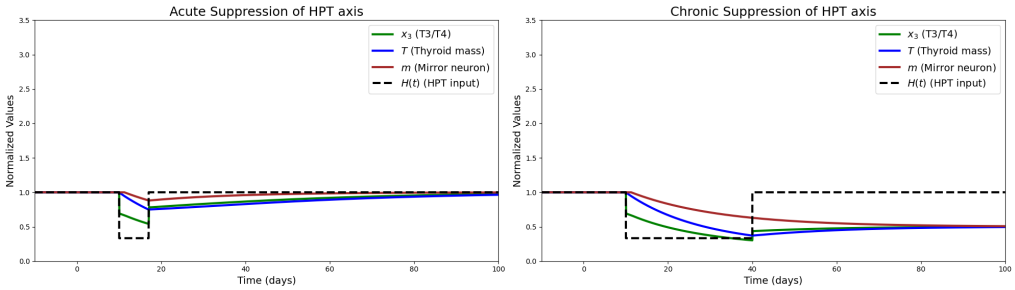

Figure 2: Dynamic responses of the hypothalamic–pituitary–thyroid (HPT) axis and mirror neurons under acute (left) and chronic (right) suppression of hypothalamic input. In the acute suppression model, thyroid hormones (T3/T4, green), thyroid mass (T, blue), and mirror neuron activity (m, red) transiently decrease but recover toward baseline following restoration of input (H(t), dashed black). In contrast, chronic suppression produces sustained reductions in thyroid hormones and mirror neuron activity, even after HPT input returns, suggesting long-term impairments in neural systems dependent on thyroid regulation.

The hypothalamic pituitary thyroid (HPT) axis is a critical neuroendocrine feedback circuit that arranges metabolism, neurodevelopment, and growth. This starts with the hypothalamus releasing thyrotropin releasing hormones, also known as TRH, which will trigger the anterior pituitary to secrete thyroid stimulating hormone, also known as TSH. TSH will stimulate the thyroid gland to produce the hormones thyroxine (T4) and triiodothyronine (T3). This will exhibit some large systemic effects and exert the negative feedback on both TRH and TSH secretion, which is a tightly regulated system that's necessary for homeostasis. Thyroid hormones are also crucial for proper neuronal proliferation, migration, differentiation, myelination, and as well as synaptic

formation. The deficits in these hormones are linked to disrupted cortical layering, which alters neurotransmission. The most notable ones glutamate mediated pathways. Not only that, but abnormal synaptic plasticity also implies autism spectrum disorder. Epidemiological studies also suggest that maternal hypothyroidism or subclinical thyroid dysfunction during pregnancy might raise the risk if ASD in the offspring, which emphasizes the vulnerability of the devloping brain to thyroid hormone shortage. In addition, some studies reported a higher generality of thyroid dysfunction in people with ASD. Instances of autoimmune thyroiditis in families of children with autism also suggest potential shared genetic or immunological procedures which connect thyroid regulation and ASD pathology. Together, these findings imply dysregulation of the HPT axis, most significant the disrupted thyroid hormone signaling, as credible neurodevelopmental pathways contributing to the cause of ASD.

Model

We developed a minimal mathematical model of the hypothalamic–pituitary–thyroid (HPT) axis coupled to mirror neuron activity[1]. The variables x_1, x_2, x_3 represent TRH, TSH, and thyroid hormone (T3/T4) levels, respectively, while P denotes pituitary activity, T represents thyroid mass, and m corresponds to mirror neuron activity. The equations (1)–(5) describe the classical feedback dynamics of the HPT axis, in which hypothalamic input H regulates hormone release through nonlinear interactions and degradation terms. Equation (6) introduces the coupling between thyroid hormone levels and mirror neuron development, where m grows in proportion to thyroid hormone availability and decays otherwise. This minimal model provides a tractable framework to explore how thyroid dysfunction can impair mirror neuron maturation and thereby contribute to autism-related phenotypes.

$$\frac{dx_1}{dt} = \frac{q_1 H}{x_3} - \alpha_1 x_1 \tag{1}$$

$$\frac{dx_2}{dt} = \frac{q_2 P}{x_3} - \alpha_2 x_2 \tag{2}$$

$$\frac{dx_3}{dt} = q_3 T - \alpha_3 x_3 \tag{3}$$

$$\frac{dP}{dt} = b_P \frac{P}{x_3} - \alpha_P P \tag{4}$$

$$\frac{dT}{dt} = b_T x_2 T - \alpha_T T \tag{5}$$

$$\frac{dm}{dt} = a_m(a + b\Theta(x_3 > T)) - b_m m \tag{6}$$

The steady state values for the hormones is given by:

$$\frac{dP}{dt} = 0 \to x_3 = \frac{b_P}{a_P}$$

$$\frac{dT}{dt} = 0 \to x_2 = \frac{a_T}{b_T}$$

$$\frac{dx_1}{dt} = 0 \to x_1 = \frac{q_1 a_P H}{\alpha_1 b_p}$$

Results

Dynamic Responses of the HPT–Mirror Neuron System

Figure 2 shows that acute suppression produces only temporary deficits, while chronic suppression yields long-lasting reductions in both thyroid hormone levels and mirror neuron activity. This dis-

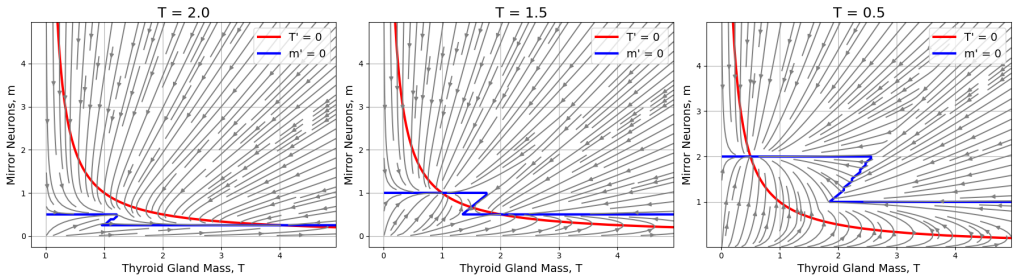

Figure 3: Phase portraits illustrating the coupled dynamics of thyroid gland mass (T) and mirror neuron activity (m) across different threshold coefficients ($T = 0.5, 1, 2$).

tinction highlights the potential for persistent neurodevelopmental consequences when endocrine dysfunction is prolonged during critical developmental windows.

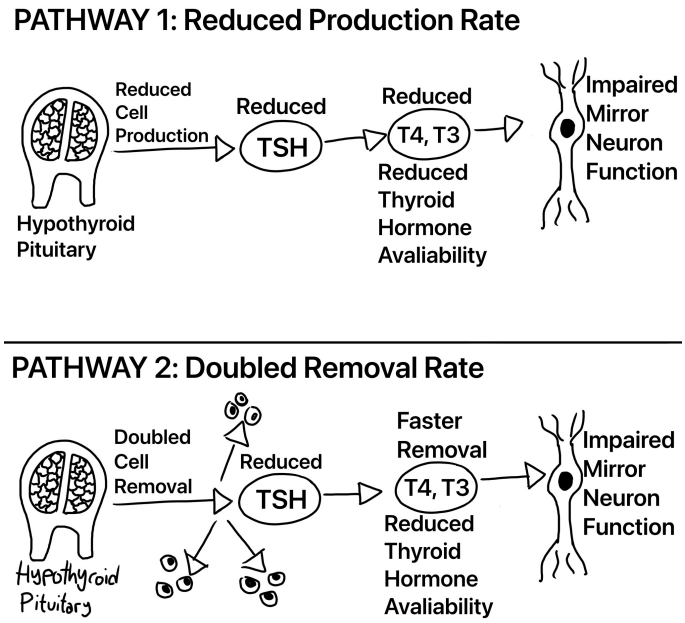

Figure 4: Pathway 1 (top): Reduced pituitary cell production decreases thyroid-stimulating hormone (TSH) secretion, lowering thyroxine (T4) and triiodothyronine (T3) availability for neuronal development. Pathway 2 (bottom): Increased pituitary cell removal accelerates TSH decline and hormone clearance, similarly reducing T4/T3 levels. In both cases, impaired thyroid hormone signaling compromises mirror neuron function, providing a potential neuroendocrine mechanism for autism spectrum disorder.

Phase-Space Dynamics of Thyroid and Mirror Neurons

As illustrated in Figure 3, mirror neuron activity is highly sensitive to threshold parameters governing thyroid hormone availability. Lower thresholds ($T = 0.5$) support stable oscillatory activity, whereas higher thresholds ($T = 2$) drive mirror neuron activity toward near-zero values. These results suggest that relatively small variations in endocrine regulation may critically shape mirror neuron maturation.

Pathways Linking Pituitary Dysfunction and Mirror Neuron Impairment

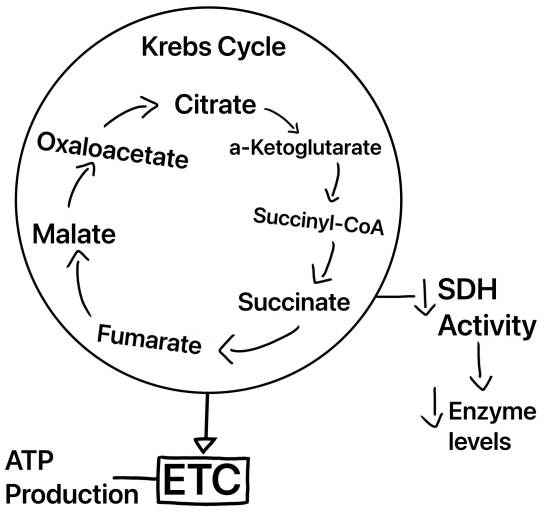

Figure 5: Schematic of the Krebs cycle highlighting impaired succinate dehydrogenase (SDH) activity, which reduces the conversion of succinate to fumarate and lowers ATP production via the electron transport chain (ETC).

Figure 4 presents two hypothetical pathways showing how pituitary dysfunction may impair mirror neuron circuits. In Pathway 1, reduced pituitary cell production lowers TSH release, decreasing thyroid hormone synthesis. In Pathway 2, accelerated pituitary cell removal hastens TSH decline and thyroid hormone clearance. Both mechanisms converge on reduced T3/T4 availability, thereby compromising mirror neuron function.

Metabolic Correlates: Krebs Cycle Deficits

Figure 5 depicts the Krebs cycle and its role in sustaining cellular energy production. Key intermediates progress through citrate, α-ketoglutarate, succinyl-CoA, succinate, fumarate, malate, and oxaloacetate. Impaired activity of succinate dehydrogenase (SDH) decreases conversion of succinate to fumarate, diminishing ATP yield from the electron transport chain. Since ATP availability is essential for synaptic transmission and plasticity, reduced metabolic efficiency may further exacerbate vulnerabilities in mirror neuron function already compromised by thyroid hormone deficits.

These results demonstrate that: (1) chronic suppression of the HPT axis produces long-lasting impairments in mirror neuron activity; (2) mirror neuron development is highly sensitive to thyroid hormone thresholds; (3) pituitary dysfunction can reduce hormone availability through multiple convergent pathways; and (4) impaired mitochondrial energy metabolism may compound endocrine-driven deficits. These findings suggest a mechanistic link between thyroid dysfunction, metabolic vulnerability, and social-cognitive impairment relevant to autism spectrum disorder.

Conclusion

We set out to investigate how dysregulation of the hypothalamic–pituitary–thyroid (HPT) axis could impair mirror neuron development and thereby contribute to social and cognitive deficits

characteristic of autism spectrum disorder (ASD). By integrating neuroendocrine physiology with a minimal mathematical model, we demonstrated that thyroid hormone availability is a critical determinant of mirror neuron activity. Our simulations revealed that while acute suppression of the HPT axis produces transient deficits, chronic suppression results in long-term reductions in thyroid hormone levels and sustained impairment of mirror neuron function. Sensitivity analyses further showed that mirror neuron maturation is highly dependent on thyroid hormone thresholds, underscoring the vulnerability of these circuits to subtle endocrine imbalances.

We also identified two distinct pituitary-related pathways—reduced cell production and accelerated cell removal—that converge on decreased thyroid hormone availability. Both mechanisms provide a plausible neuroendocrine route to mirror neuron dysfunction. Additionally, the incorporation of metabolic considerations, particularly deficits in succinate dehydrogenase activity within the Krebs cycle, highlights how reduced ATP production may exacerbate neural vulnerabilities.

These findings support a broader view of ASD as a disorder influenced not only by neural connectivity and genetics but also by systemic hormonal and metabolic regulation. The results emphasize the potential value of early thyroid function screening during pregnancy and in infants at risk for ASD. Future research should validate these predictions with empirical data from hormone assays, neuroimaging of mirror neuron circuits, and longitudinal clinical studies.

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