The Healthcare Review
VOL 2: Article X
GSR
Beirut, LB

The Biological Roots of Behavior: Neurological and Metabolic Basis of Self-Injury in Lesch–Nyhan Syndrome

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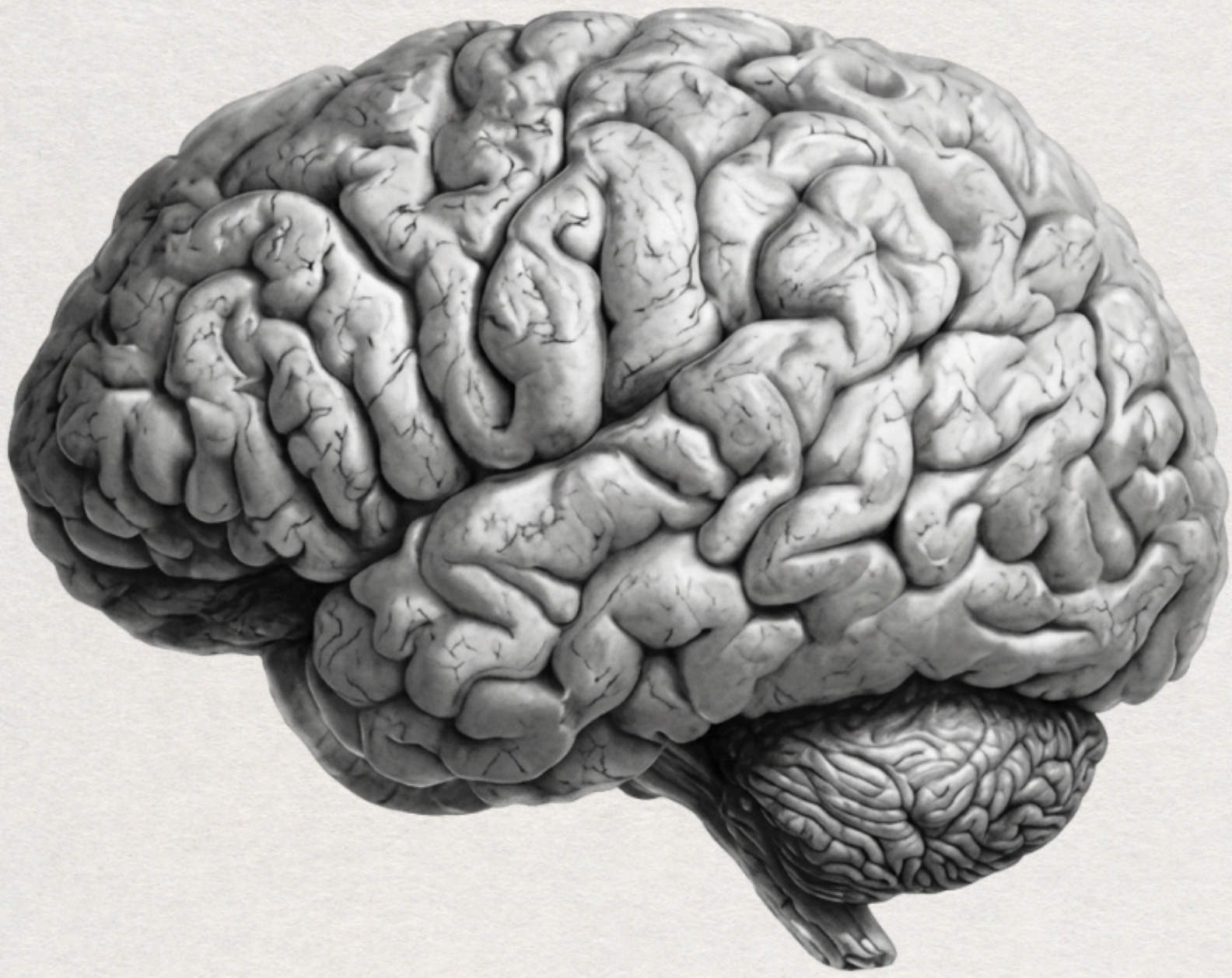

Abstract

Lesch–Nyhan syndrome (LNS) is a rare X-linked metabolic and neurodevelopmental disorder characterized by hyperuricemia, neurological impairment, and severe self-injurious behavior. Caused by mutations in the HPRT1 gene, the condition disrupts purine metabolism and leads to profound alterations in dopaminergic signaling within the basal ganglia, a neural system essential for motor control and behavioral regulation. This paper examines the biological foundations of self-injurious and dysregulated behaviors in LNS, emphasizing how metabolic dysfunction and basal ganglia pathology contribute to compulsive self-harm, aggression, and impaired impulse control. By synthesizing findings from genetics, neurochemistry, and behavioral neuroscience, the paper highlights the limitations of approaches that rely exclusively on either biological or psychological frameworks. Furthermore, it underscores the clinical value of interdisciplinary understanding for managing complex behaviors, integrating medical treatment with behavioral strategies and caregiver support. Through this lens, Lesch–Nyhan syndrome serves as a compelling model for illustrating how deeply biological mechanisms can shape behavior and how holistic perspectives are essential for effective clinical care.

Introduction

The relationship between biological processes and human behavior is a central concern in both neuroscience and psychology. While many behavioral disorders are studied primarily through psychological frameworks, certain rare genetic conditions reveal how deeply behavior can be shaped by underlying biological mechanisms. Lesch–Nyhan syndrome (LNS) is one such condition, with an estimated prevalence ranging from approximately 1 in 235,000 to 1 in 380,000 live births (Hung-Hsiang et al., 2024), offering a clear example of how metabolic and neurological abnormalities can result in severe behavioral outcomes. Individuals with LNS display a distinctive pattern of symptoms that includes motor impairment (Mecchella & Burns, 2022), neurological dysfunction (Mileti & Baleja, 2025), and extreme self-injurious and compulsive behaviors (Zhang et al., 2025), reflecting the complex relationship between brain function and behavioral control. Understanding why such actions emerge requires moving beyond surface-level descriptions and examining the biological systems that govern impulse control, reward processing, and motor regulation. By examining LNS through an interdisciplinary lens, and by focusing on dopamine pathway dysfunction and abnormalities in purine metabolism, the study aims to clarify how neurobiological factors account for maladaptive self-directed behaviors. In doing so, the paper highlights the importance of integrating biological and psychological perspectives to better understand complex human behaviors and to inform more holistic approaches to care.

Biological Basis of Lesch–Nyhan Syndrome

A) Genetic Cause: HPRT1 Deficiency

To understand the biological basis of Lesch–Nyhan syndrome, it is necessary to begin at the genetic level. Inherited as an X-linked recessive trait and thus primarily affecting males—although females are usually carriers and few may manifest the disease symptoms if Barr body inactivation results in the expression of the defective X chromosome (Hung-Hsiang et al., 2024)—the disorder is caused by mutations in the *HPRT1* gene, which result in an abnormal—severe reduction or absence—activity of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT) (Ropper et al., 2023). Under normal conditions, HGPRT is responsible for salvaging purine bases—adenine and guanine—which are nitrogen-containing molecules that serve as fundamental building blocks of nucleotides essential for DNA, RNA, and cellular energy molecules such as ATP. Indeed, purine metabolism relies heavily on salvage pathways because synthesizing purine nucleotides from scratch requires significantly more energy than recycling existing purine bases (Raivio et al., 2019). In typical cellular conditions, hypoxanthine—the most abundant purine breakdown product, mainly produced from normal adenine nucleotide turnover—is recycled back into nucleotides by HGPRT, forming inosine monophosphate (IMP) (Raivio et al., 2019), which can then be converted into other nucleotides such as AMP or GMP. HGPRT also salvages guanine derived from guanine nucleotide breakdown, making it a key enzyme in conserving purines and maintaining metabolic balance. When this salvage pathway is disrupted, hypoxanthine and guanine are instead directed toward oxidation, ultimately leading to increased uric acid production (Ropper et al., 2023) and causing hyperuricemia. In humans, uric acid is the final product of purine degradation, and its accumulation reflects a failure of efficient purine

reutilization, making it the defining biochemical feature of the disorder. However, although this overproduction of uric acid can be managed with treatments such as allopurinol, a xanthine oxidase inhibitor, behavioral symptoms seen in Lesch–Nyhan syndrome remain unchanged (Grosser et al., 2023; Ropper et al., 2023).

B) Consequences of Uric Acid Accumulation

As we have just seen, as a result of impaired purine salvage, the normal balance of purine metabolism is disrupted in Lesch–Nyhan syndrome, redirecting hypoxanthine and guanine toward degradation and excessive uric acid production. This accumulation in the bloodstream leads to hyperuricemia and increased urinary excretion of uric acid, known as hyperuricosuria (Urinary stones as the initial presentation, 2025), resulting in a range of clinical complications. Indeed, uric acid can crystallize in the kidneys, causing nephrolithiasis, and in the lower urinary tract, causing urolithiasis—together leading to progressive kidney damage, severe flank pain, painful urination, and recurrent urinary tract infections (Jodorkovsky et al., 2024; Mecchella & Burns, 2022). Gouty arthritis, another possible complication, results from urate crystal deposition in joints (Mecchella & Burns, 2022) and leads to intense pain, swelling, and restricted mobility. Therefore, hyperuricemia, kidney stones, and gouty arthritis, collectively, represent the primary systemic complications of Lesch–Nyhan syndrome, underscoring the serious physiological burden of disrupted purine metabolism.

C) Neurological and Brain Dysfunction

Although these complications reflect the systemic metabolic burden of the disorder, they do not fully account for the neurological and behavioral features of Lesch–Nyhan syndrome, suggesting that disrupted purine metabolism also affects neural function through additional mechanisms. In particular, mutations in the HPRT1 gene profoundly affect the basal ganglia, a brain region essential for motor control and behavioral regulation, by disrupting normal neurodevelopment and compromising the survival of dopaminergic neurons—neurons responsible for the production and release of dopamine (Morris et al., 2025). Indeed, dopamine plays a crucial role in the basal ganglia by regulating ‘‘motor control, motivation, reward processing and learning’’ (Muralidhara & Hardege, 2025). Thus, dopaminergic neurons, whose function depends heavily on intact purine metabolism to meet high energetic and metabolic demands, therefore represent a highly specialized neuronal population essential for normal movement and behavioral regulation (Muralidhara & Hardege, 2025). In LNS, these neurons are particularly vulnerable, with marked reductions in dopamine levels consistently reported within the substantia nigra pars compacta, reflecting impaired development or survival of dopaminergic neurons (Mileti & Baleja, 2025). Neurobiological studies further demonstrate a profound loss of dopaminergic terminals—estimated at 60–90%—within the basal ganglia of individuals with Lesch–Nyhan syndrome, a deficit that emerges early in development and coincides with the typical onset of self-injurious behaviors (Baglioni et al., 2024). This dopamine deficiency disrupts basal ganglia circuitry, leading to abnormal motor output and impaired regulation of movement and behavior. It should be noted that affected individuals typically do not exhibit overt neurological abnormalities at birth: developmental delays and neurological signs become apparent only after several months of life (Hung-Hsiang et al., 2024).

As a consequence of disrupted basal ganglia circuitry and reduced dopaminergic signaling, individuals with Lesch–Nyhan syndrome commonly develop characteristic movement disorders that

typically emerge between 8 and 12 months of age, reflecting a progressive basal ganglia involvement (Hung-Hsiang et al., 2024). For instance, choreoathetosis, marked by involuntary, irregular, and writhing movements, reflects impaired regulation of motor output and the inability to suppress unwanted movements (Mecchella & Burns, 2022). Spasticity, characterized by increased muscle tone and stiffness, further contributes to abnormal posture and restricted voluntary movement (Mecchella & Burns, 2022). Together, these motor disturbances highlight the profound impact of basal ganglia dysfunction on movement control in LNS and often appear early in development, significantly impairing motor coordination and daily functioning.

Psychological and Behavioral Features of Lesch–Nyhan Syndrome

While motor disturbances are a prominent neurological feature of Lesch–Nyhan syndrome, the disorder is most distinctive for its severe behavioral abnormalities, particularly self-injurious and compulsive behaviors. These manifestations are not attributable to reduced pain perception or lack of awareness, but instead reflect profound impairments in impulse control and emotional regulation arising from basal ganglia dysfunction.

A) Compulsive Self-Injurious Behavior

Self-injurious behavior in Lesch–Nyhan syndrome differs fundamentally from that observed in most psychiatric and neurodevelopmental conditions. Whereas self-injury in autism spectrum disorder or intellectual disability is often stereotyped and repetitive, and in psychiatric disorders is typically impulsive or emotionally driven, self-injury in LNS—rarely the initial presenting symptom and commonly developing later in infancy or early childhood (Hung-Hsiang et al., 2024)—is severe, compulsive, and biologically determined (Zhang et al., 2025). The most characteristic behaviors include repetitive self-biting of the lips, tongue, cheeks, and fingers, as well as head banging and forceful limb movements, often requiring physical protection or restraint (Baglioni et al., 2024). This onset of self-injurious behavior is variable, appearing as early as 10 months in some individuals but not until adolescence in others (Hung-Hsiang et al., 2024). Most importantly, these behaviors occur despite preserved pain perception and awareness of injury, indicating that they are not motivated by analgesia-seeking or emotional distress.

Moreover, observational studies indicate that stress may act as an aggravating factor, intensifying the frequency or intensity of self-injury in daily life (Bozano et al., 2020). In particular, pre-clinical studies demonstrate that activation of the hypothalamic–pituitary–adrenal (HPA) axis and the release of stress hormones increase blood levels of uric acid (Logan & Mishra, 2025). Stress enhances the activity of xanthine enzymes involved in purine metabolism, thereby increasing uric acid production, which in turn feeds back into stress physiology and behavioral regulation (Logan & Mishra, 2025). In the context of Lesch–Nyhan syndrome, persistent elevation of uric acid due to a defective HGPRT may mimic aspects of stress physiology, thereby amplifying behavioral dysregulation without implying subjective psychological stress. As a result, individuals with LNS may exhibit heightened physiological stress reactivity, lowering the threshold for agitation and behavioral escalation even in response to minor environmental stressors.

Among neurometabolic disorders, Lesch–Nyhan syndrome is the condition most strongly associated with self-injurious behavior, reflecting selective dysfunction of dopaminergic pathways within basal ganglia circuits rather than learned or reactive behavior (Baglioni et al., 2024). These

behaviors are often persistent and resistant to conventional interventions, significantly affecting daily functioning and requiring substantial caregiver support (Baird-Daniel et al., 2023). This pattern of persistent, biologically driven self-injury poses major clinical and ethical challenges, often necessitating long-term protective strategies and intensive caregiver involvement.

In light of the persistence and severity of these behaviors, novel therapeutic approaches have been explored to provide symptomatic relief when conventional interventions fail. Indeed, deep brain stimulation targeting the globus pallidus internus (GPi)—a structure of the basal ganglia—has been explored as a treatment option for medically refractory cases, with several reports demonstrating reductions in both dystonia and self-mutilating behavior (Baird-Daniel et al., 2023). In pediatric patients with severe self-injury unresponsive to pharmacological and behavioral interventions, bilateral GPi stimulation has been associated with caregiver-reported improvements in compulsive self-harm and motor symptoms (Baird-Daniel et al., 2023). Although outcomes remain variable and the procedure carries unique challenges due to communication difficulties and postoperative risks related to self-injury, these findings reinforce the involvement of basal ganglia circuits in the behavioral phenotype of Lesch–Nyhan syndrome and suggest that neuromodulation may offer symptomatic relief when conventional treatments fail.

B) Impulse Control and Behavioral Dysregulation

Although self-injurious behavior is the most distinctive manifestation, behavioral dysregulation in Lesch–Nyhan syndrome extends beyond this hallmark feature and involves multiple domains of impulse control and affective regulation.

At a developmental level, the HGPRT deficiency seen in LNS may disrupt purinergic signaling and inhibitory control (Lipiński & Doroba, 2025). More specifically, purines such as ATP and adenosine play a central role in regulating neurotransmission and synaptic plasticity, and disturbances within this system are associated with impulsivity and aggressive behavioral phenotypes (Sahay et al., 2025). In parallel, elevated uric acid appears to reduce adenosinergic transmission, thereby leading to diminished inhibitory control and increased neuronal excitability (Logan & Mishra, 2025). Taken together, these alterations provide a mechanistic basis for behavioral disinhibition and emotional lability observed in Lesch–Nyhan syndrome. Consistent with this early neurobiological disruption, psychomotor delay—typically evident within the first 3–6 months of life—reflects neural vulnerability that may contribute to later behavioral dysregulation (Hung-Hsiang et al., 2024). As the disorder progresses, severe generalized dystonia, involuntary movements, and intellectual disability further constrain voluntary control (Lipiński & Doroba, 2025), potentially exacerbating impulsive and aggressive behaviors.

In fact, aggressive behaviors and suicidality have been linked to agitation and poor impulse control even in the absence of a primary psychiatric illness, indicating that impaired inhibitory regulation can emerge from underlying neurobiological dysfunction rather than emotional or cognitive pathology alone (Sahay et al., 2025). This framework is particularly relevant to Lesch–Nyhan syndrome, in which behavioral disturbances emerge from neurobiological vulnerabilities that modulate impulsivity and affective control.

At the neural level, chronically elevated uric acid can induce neuroinflammation and disrupt blood–brain barrier integrity, processes linked to behavioral dysregulation. Animal studies show that uric acid crosses the blood–brain barrier and that sustained elevation leads to neuroinflammation and cognitive dysfunction (Logan & Mishra, 2025). Human research further associates increased blood–

brain barrier permeability with aggressive and violent behavior (Logan & Mishra, 2025). Together, these findings suggest that metabolic disturbances in LNS affect brain systems governing emotional regulation and impulse control, contributing to stable patterns of aggression and dysregulated behavior.

Importance of Interdisciplinary Understanding

Understanding Lesch–Nyhan syndrome, therefore, requires an interdisciplinary approach that integrates both biological mechanisms and behavioral manifestations explored previously, a strategy essential for developing a holistic and clinically relevant understanding of the condition.

As outlined above, the HPRT1 mutation disrupts purine metabolism, resulting in both overproduction of uric acid (Ropper et al., 2023) and significant neurological impairments, particularly in the basal ganglia (Morris et al., 2025). These neurobiological disruptions form the foundation for the behavioral manifestations observed in patients, such as self-injury, aggression, and compulsive actions (Zhang et al., 2025). Therefore, by examining these behaviors alongside their biological origins, researchers and clinicians can develop a more comprehensive understanding of the condition.

Moreover, linking neurobiology and psychology provides crucial insights into patient care. On one hand, biological treatments, such as managing uric acid levels with allopurinol, address the metabolic consequences of the disorder without fully alleviating the behavioral challenges (Grosser et al., 2023; Ropper et al., 2023). On the other hand, however, psychological and behavioral interventions aim to reduce harm and improve daily functioning. In a recent review of interventions for self-injurious behavior in children and adolescents with autism spectrum disorder (ASD), Labarca et al. (2025) emphasize the effectiveness of applied behavior analysis (ABA), such as functional analysis of behavior, identification of environmental triggers, and reinforcement of safer alternative responses, particularly when implemented early and grounded in systematic behavior modification and positive reinforcement. Although this evidence is derived from ASD populations, the behavioral principles underlying ABA may conceptually be applied across disorders. Nevertheless, it is essential to emphasize that Lesch–Nyhan syndrome remains a genetically determined metabolic and neurodevelopmental disorder, and therefore self-injurious behaviors cannot be fully addressed through behavioral intervention alone. Consequently, managing these behaviors is inherently complex, requiring behavioral strategies to be integrated with biological treatment, environmental adaptations, and long-term caregiver support.

Additionally, the role of caregivers and healthcare providers is central to this interdisciplinary model. Understanding the biological underpinnings of the disorder can help caregivers anticipate behavioral challenges, while psychological strategies equip them with tools to support patients safely and empathetically. Therefore, a training that emphasizes both neurological and behavioral aspects ensures care is both effective and compassionate.

Ultimately, an interdisciplinary perspective not only enhances clinical outcomes but also advances research by encouraging collaboration between neurologists, psychologists, geneticists, and other specialists. Such collaboration underscores the broader value of bridging biological and psychological sciences, particularly for rare disorders where each perspective illuminates aspects of the condition that might otherwise remain misunderstood.

Conclusion

Lesch–Nyhan syndrome provides a striking illustration of how genetic and metabolic abnormalities can profoundly shape neurological development and behavioral expression. As explored throughout this paper, mutations in the *HPRT1* gene disrupt purine metabolism, leading not only to systemic complications such as hyperuricemia but also to significant neurological impairments within the basal ganglia. These neurobiological disruptions form the foundation for the severe motor abnormalities, compulsive self-injury, aggression, and impaired impulse control that characterize the disorder. Importantly, these behaviors cannot be adequately explained through psychological or environmental models alone, as they arise primarily from biologically driven dysfunction in neural circuits responsible for behavioral regulation.

At the same time, examining behavioral manifestations alongside their biological origins highlights the importance of interdisciplinary approaches in both research and clinical practice. While biological treatments can effectively manage metabolic consequences, they offer limited relief from behavioral symptoms. Conversely, behavioral and psychological interventions, although incapable of altering the genetic basis of the disorder, can play a meaningful role in reducing harm, improving daily functioning, and supporting caregivers when integrated thoughtfully with medical care. This complementary relationship underscores the necessity of combining biological and psychological perspectives rather than treating them as competing frameworks.

Ultimately, Lesch–Nyhan syndrome demonstrates the broader value of interdisciplinary understanding in healthcare, particularly for rare and complex disorders. By bridging neuroscience, genetics, psychology, and clinical care, researchers and clinicians can develop more accurate models of behavior and more compassionate, effective strategies for intervention. Increasing awareness of conditions such as LNS not only improves patient outcomes but also deepens our understanding of the biological roots of behavior, reinforcing the need for holistic approaches within modern healthcare systems.

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