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From Mechanism Discovery to Intervention: Mast Cell Overactivation and Histamine Dysregulation in ASD and PTSD—Implications for Therapy, Environmental Design, and Support in War-Affected Populations.

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ABSTRACT

This paper explores the role of mast cell overactivation and histamine dysregulation as potential pathophysiological mechanisms underlying symptoms observed in ASD and PTSD. Evidence from reviews, meta-analyses, and observational studies suggests a significant association between MCAS, HIT, environmental triggers, and a broad spectrum of those symptoms. Mast cells, as key components of the immune system, play a central role in inflammatory signaling and neuroimmune communication. When over activated, they release also histamine acting through H1-H4 receptors, influencing multiple systems, including immune, gastrointestinal, cardiovascular, respiratory, and central nervous system functions, affecting GABAergic and glutamatergic signaling, blood-brain barrier integrity, and neuroinflammatory pathways. Histamine degradation is primarily regulated by DAO and HNMT; genetic polymorphisms or acquired deficiencies in these enzymes may impair histamine clearance, leading to systemic accumulation and exacerbation of neurological and behavioral symptoms. A notable clinical overlap exists between MCAS, HIT, ASD, and PTSD, including gastrointestinal disturbances, sensory hypersensitivity, cognitive impairment, emotional dysregulation, sleep disturbances, and chronic neuroinflammation. Environmental and physiological triggers—such as infections, allergens, mold exposure, toxins, dietary histamine, and sensory stressors (light, noise, vibration, temperature, and humidity)—may further contribute to mast cell activation and symptom severity. Preliminary evidence indicates that interventions targeting mast cells regulation by design of low-trigger, supportive indoor environments, may help reduce symptom burden. These findings underscore the importance of interdisciplinary approaches and highlight the need for controlled clinical trials to evaluate the efficacy of integrated therapeutic dietary, supplementation and environmental strategies, particularly in vulnerable populations, including individuals affected by war-related trauma stress.

Keywords: *ASD; PTSD; mast cells; histamine; DAO; neuroinflammation, neuroarchitecture; MCAS, HIT, H1 receptor; H2 receptor; H3 receptor; neuroimmune disorders*

Introduction:

The missing link in neuropsychiatry.

According to the World Health Organization (WHO, 2025), approximately 1 in 127 children worldwide is estimated to have autism spectrum disorder (ASD). In the United States, data from the Centers for Disease Control and Prevention indicate that 1 in 31 (3.2%) children aged 8 years were identified with ASD in 2022 (CDC, 2025), compared with approximately 1 in 59 children in earlier estimates (CDC, 2020). Around 70% of people globally will experience a potentially traumatic event during their lifetime, people exposed to violent conflict or war are more than three times (15.3%) higher to develop PTSD (WHO, 2024). Autism spectrum disorder (ASD) as well as post-traumatic stress disorder (PTSD) are complex conditions characterized by a heterogeneous symptom profile, encompassing cognitive, behavioral, and physiological impairments. Despite extensive research worldwide, their underlying pathophysiology remains incompletely understood due to the multiplicity of symptoms, the same limiting the development of targeted and effective therapeutic strategies. Growing evidence suggests that neuroimmune interactions may play a key role in both neurodevelopmental and neuropsychiatric disorders. Questions remain about their cause and the underlying inflammatory processes observed in both conditions. Scientists are increasingly exploring the role of immune-mediated processes in body and brain function and their impact on behavior. Until now, traditional diagnostics have differentiated these conditions into entirely separate categories: ASD was classified as neurodevelopmental, PTSD as psychiatric, MCAS as immunological, and HIT as immune/metabolic.

In this article, the author develops her earlier hypothesis that mast cell overactivation and histamine metabolic dysfunction may constitute a common, yet underestimated or

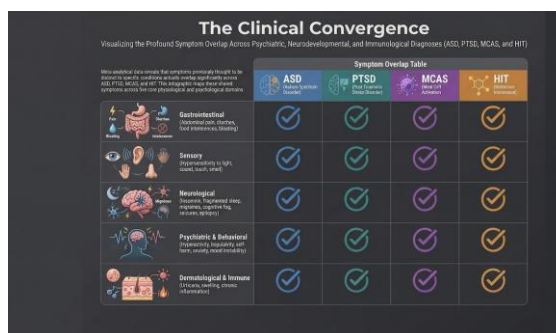
simply overlooked, pathophysiological mechanism contributing to the development of multiple symptoms in certain groups of individuals with ASD and PTSD. This hypothesis integrates findings from immunology, neurobiology, neuroarchitecture, safety engineering, design, the environment, and published clinical observations evidence, highlighting the potential role of mast cells and histamine signaling in neuroinflammation and systemic dysregulation.

The author conducted an extensive review of clinical and experimental studies, noting significant overlap between mast cell activation syndrome (MCAS), histamine intolerance (HIT), ASD, and PTSD—a phenomenon not previously recognized or linked. Common symptoms, especially somatic ones, include: sensory disturbances (hypersensitivity to sound, light, smell, and touch), gastrointestinal disturbances (abdominal pain, diarrhea, flatulence, food intolerance), autonomic (tachycardia, palpitations, flush), neurological disturbances (sleep regulation disorders, insomnia, cognitive fog, headaches, migraines, muscle spasms, tics, seizures, and epilepsy), psychiatric and behavioral disturbances (hyperactivity, impulsivity, anxiety, mood instability, emotional instability, internal tension, self-harm, cognitive impairment, difficulty concentrating, memory), and dermatological and immunological disturbances (allergy, hives, edema, and chronic skin inflammation).

Additionally, she notices that external environmental and physiological stressors—such as infections, allergens, molds, toxins, temperatures, emotional and chronic stress—can act as triggers for mast cell activation, which may contribute to increased inflammatory and neuroimmune responses. These factors may represent potential neurobiological correlates of symptom expression in ASD and PTSD, and may be considered as exploratory biomarkers in

research aimed at understanding underlying mechanisms.

In this context, the present paper proposes an integrated conceptual framework and synthesis of observations in which mast cell activation and histamine dysregulation may contribute to symptom expression in ASD and PTSD in a subset of individuals. By integrating molecular and biological mechanisms with clinical manifestations and environmental influences, this approach seeks to provide a basis for further hypothesis generation and the development of multimodal research directions. These may include interventions targeting modulation of mast cell activity and histamine pathways, also design of supportive, low-trigger environments intended to reduce environmental stressors and sensory load.



Pic. 1. The same or very similar symptoms occurring in ASD, PTSD, MCAS, HIT.

2. Literature Review

A. Mast Cells: Beyond Classical Immunity

Mast cells have traditionally been associated with allergic reactions and innate immunity, but numerous studies have revealed their crucial role in regulating the interface between the immune and nervous systems (Kempuraj et al. 2017). Mast cells are key components of the immune system, but they are difficult to precisely define because they originate in the bone marrow, circulate in the blood as precursor cells, and mature in peripheral tissues. They are found in barrier tissues throughout the body, including the skin, gastrointestinal tract, mucous

membranes, blood vessels, nerves, endothelium, respiratory system, and nervous system (Ribatti 2026). They can be compared to soldiers standing guard between the external and internal environments: the skin (the first responders to external physical and environmental stimuli), the lungs (monitoring and responding to physical and environmental stimuli transmitted through the air), the intestines (mediating the modulation of dietary histamine levels and microbiome signaling), and the brain (the blood-brain barrier—a critical link between systemic immunity and the health of the central nervous system). Importantly, mast cells lie at the interface between the immune and nervous systems. They are considered key regulators of innate and adaptive immunity, vascular permeability, tissue homeostasis, neuroimmune communication, and allergic reactions. Reported triggers of mast cell degranulation include environmental exposures as well as neuroimmune and physiological stressors, such as emotional stress (via corticotropin-releasing hormone (CRH) and neuropeptides), psychological trauma, and microbial products.

They can be activated by a range of internal and external stimuli:

- physical stimuli (temperature, pressure, vibration, electromagnetic field, radiation),
- biological (molds, fungi, bacteria, viruses, microbial products),
- chemical (heavy metals (mercury, aluminum), venoms, poisons, toxins, certain medications, narcotics, alcohol, opioids),
- IgE-dependent factors (such as allergens),
- metabolic: foods high in histamine, oxidative stress (Forsythe 2019), (Kucharik & Chang 2020),(Theoharides 2024),(Renkielska 2014).

Upon activation, mast cells rapidly undergo degranulation, releasing preformed mediators stored in cytoplasmic granules,

including histamine, tryptase, chymase, and other bioactive substances. These mediators contribute to the immediate phase of the inflammatory response. In particular, they may increase vascular permeability, induce vasodilation, and promote the recruitment and activation of other immune cells. During subsequent stages of activation, mast cells de novo synthesize and secrete lipid mediators, such as prostaglandins and leukotrienes, as well as pro-inflammatory cytokines (e.g., IL-6, TNF- α). These subsequent mediators sustain and modulate the inflammatory response, influencing its intensity and duration. (Theoharis et al. 2023). The released mediators

can act both locally and systemically—directly or by activating specific receptors on target cells. Their effects extend not only to the immune system but also to the central nervous system. Mast cell mediators, specially histamine, can affect neurons, glial cells, and the structure and function of the blood-brain barrier, influencing its permeability and promoting the development of neuroinflammation. In this way, mast cells constitute a crucial link in the communication between the immune system and the nervous system the so-called immune-neuronal axis (Theoharides et al. 2024).

The importance of these mechanisms is underscored by the discoveries that won the 2021 Nobel Prize in Physiology or Medicine, awarded to, among others, David Julius and Ardem Patapoutian for identifying receptors responsible for the perception of temperature and mechanical stimuli. These discoveries concerned, among others, ion channels such as TRPV1 and Piezo1 and Piezo2, which enable the conversion of physical stimuli (temperature, touch) into neural signals. These mechanisms are also relevant to the interaction between inflammation and the nervous system, as inflammatory mediators can modulate the activity of these receptors, influencing the perception of pain,

itch, and sensory hypersensitivity (Nobel Prize 2021).

B. Mast Cell Activation Syndrome (MCAS), Mastocytosis, Histamine Intolerance (HIT)

First, it's important to clarify the differences between MCAS and mastocytosis, which are often confused. Mastocytosis and MCAS are distinct, though partially overlapping, mast cell disorders. The former is characterized by clonal proliferation and an increased number of mast cells, while the latter is characterized by abnormal mediator release in the absence of significant proliferation. Underlying Mechanism: Mastocytosis is a proliferative (clonal) disease characterized by an increased number of mast cells (accumulation in tissues), often accompanied by a KIT mutation (e.g., D816V) (Valent et al 2017), (Pardanani 2016).

Mast Cell Activation Syndrome (MCAS) is a functional disease in which mast cell numbers are usually normal, but their excessive activation/degranulation is a problem. (Ozdemir et al. 2024). Symptom Dynamics: Mastocytosis presents more persistent/chronic symptoms associated with a mass of cells, possibly with organ changes. The response to stimuli is less dependent on triggers, with more continuous activity and less dynamic. MCAS presents more episodic/fluctuating symptoms triggered by: stress, food, and the environment, often with a heterogeneous symptom profile. The response to stimuli is strongly dependent on triggers, and the system is overreactive. The presented hypothesis points to MCAS because it involves a cascade of mediators (specially histamine), explains the variability of symptoms, and aligns with multi-organ symptoms and neuroimmunology. (MCAS : A primary care guide), (Castells et al. 2024).

Histamine can act not only as an inflammatory mediator and neurotransmitter but also as a central integrator of neuroimmune signaling, linking environmental stimuli, immune activation,

and neural network dynamics. In this context, histamine serves as a key interface through which endogenous (from mast cells and neurons) and exogenous (from diet and microbiota) signals converge, generating a cumulative regulatory burden on the body. (Maintz & Novak 2007). Histamine intolerance (HIT) is a condition in which the body has a reduced ability to break down histamine degradation (primarily from food), most often due to a deficiency or reduced activity of the enzyme diamine oxidase (DAO) (Matysiak 2022), (Hakl & Litzman 2023). This leads to histamine accumulation and symptoms such as headaches, hives, intestinal discomfort, skin flushing, or allergy-like symptoms, despite the absence of a classic IgE-mediated reaction. Its cascading action, including through H1-H4 receptors, causes similar observed symptoms as in the case of MCAS (diagnosed on the basis of various diagnoses). To diagnose HIT, the consumption of histamine-rich foods must be accompanied by a DAO deficiency, otherwise, the condition should be diagnosed as histamine poisoning (Comas-Baste 2020).

A vicious cycle of chronic sensitization may influence the development of ASD and PTSD symptoms. Once sensitized by injury or severe stress, immune cells in the barrier tissue require significantly less environmental or chemical stimuli to trigger overactivation, leading to a state of chronic inflammation and a disproportionate inflammatory response. (Yang et al. 2025).

Mast cells can spin the inflammation, affect the brain through mediators, and exacerbate neurological and sensory symptoms. Emerging evidence suggests that mast cell activation may contribute to ASD through neuroinflammatory pathways mediated by histamine, prostaglandins, and leukotrienes, particularly by modulating blood-brain barrier (BBB) permeability and microglial activation. (Mast Cells and Autism 2022), (Kempuraj et al. 2019).

C. Histamine Metabolism: DAO & HNMT

Histamine originates from both endogenous sources—primarily mast cells, basophils, and neurons—and exogenous sources, including dietary histamine and microbiota-derived histamine (Shulpekova et al. 2021), (Patel & Rahimi 2026).

Histamine metabolism is mainly mediated by two enzymes: DAO, primarily active in the gut, and histamine N-methyltransferase (HNMT), which operates in intracellular compartments, including the brain.

(Tan et al. 2023). Deficiencies of these enzymes may have a genetic basis (polymorphisms in the AOC1 or HNMT genes) or acquired (intestinal inflammation, drugs, intestinal dysbiosis) (Ferrer-Garcia et al. 2025), (Preuss et al. 1998). Disturbances in histamine degradation lead to an increase in its level, which contributes to its accumulation in the body, intensifying systemic, multi-organ and neurological symptoms (Smolinska et al. 2022). Such impairments have also been observed in patients with ADHD (Blasco -Fontecilla et al., 2024), ASD (Chung et al. 2007), as well as in individuals carrying polymorphisms in AOC1 and HNMT genes (Kadiyska et al., 2025).

D. Histamine as a Neuroimmune Mediator

Histamine functions not only as an inflammatory mediator and neurotransmitter but also as a key integrator of neuroimmune signaling, mediating bidirectional communication between environmental stimuli, immune activation, and central neural network regulation (Bernardino 2022).

Endogenous and exogenous histamine levels are cumulative, and with reduced absences of DAO/HNMT enzyme activity, their biological effects are cumulative and intensified (Keskinel 2025). This dysregulation can lead to a state of chronic, low neuroimmune activity, in which histamine signaling shifts from an adaptive, protective mechanism to a maladaptive amplifier of inflammatory and stress-related pathways. Importantly, this shift does not necessarily reflect classic

autoimmunity, but rather a form of functional neuroimmune dysregulation, potentially underlying the symptom clusters observed in conditions such as ASD and PTSD (anxiety, brain fog, gastrointestinal symptoms, hypersensitivity, heart problems) (Carthy & Ellender 2021). Furthermore, histamine interacts with four subtypes of its receptors (H1, H2, H3, H4), each of which mediates distinct physiological effects.

D.1 Effects on the Central Nervous System

In the central nervous system, histamine acts through four receptor subtypes—the H1 receptor, the H2 receptor, the H3 receptor, and the H4 receptor—which together constitute a distributed regulatory network (Zhou et al. 2024). „The posterior hypothalamus is the sole source of histamine-containing neurons that innervate the whole central nervous system and are active exclusively during waking.” (Leurs, et al. 2012). This may explain why lying down facilitates sleep, as central histaminergic activity declines; however, excessive histamine levels may disrupt sleep onset and contribute to sleep disturbances (Filcek & Vats, 2023)

Chemically, histamine is 2-(4-imidazolyl) ethylamine. The ethylamine “backbone” is a common feature of many of the amine transmitters (e.g., dopamine, norepinephrine, and serotonin).” (Leurs et al. 2012), (Nuutinen et al. 2012). Interactions with other aminergic and peptidergic systems create an integrated network that connects fundamental homeostatic processes with higher brain functions, including the regulation of wake-sleep cycle (Diez-Garcia & Garzon, 2017), energy balance, feeding and drinking behaviors, as well as synaptic plasticity, memory and learning (Leurs et al. 2012). Mast cells and excessive histamine can contribute to: neuroinflammation, excitotoxicity, and disruption of the BBB. (Kempuraj et al. 2019), (Theoharides 2016). In particular, activation of H3 receptors plays a role in the release or inhibition of various neurotransmitters and

may play a role in chronic neuroinflammatory conditions. For example, H3 activation reduces GABA levels, promoting excessive glutamate activity, which consequently leads to excitotoxicity and neuroinflammation (El-Ansary & Al-Ayadhi, 2014), (Takei et al. 2017). Chronic neuroinflammation manifests as impaired memory and cognitive function, emotional, mood and sleep disturbances, agitation, and behavioral changes (Szukiewicz 2024).

D.2. Effects from the Histamine and its receptors on the body

Histamine acts as a signaling compound not only in nervous system but also in the skin, stomach, immune system. In normal, physiological concentrations, performs many beneficial and even essential functions in the body—problems arise only when it is excessive or unregulated. Sufficient amounts of histamine: in the brain and central nervous system, support wakefulness and concentration, improve attention and cognitive function (Leurs et al. 2012).

As a support for the immune response: it helps the body respond quickly to threats (infections, injuries), increases blood flow to the site of injury, and facilitates the influx of immune cells, an important element of the body's early defenses. Aids in digestion: stimulates gastric acid secretion (via H2 receptors) and supports the proper digestion of proteins. Without histamine, digestion would be less efficient. Regulates blood vessels: dilates them and regulates local blood flow, aids in wound healing and nutrient delivery. It helps maintain the body's homeostasis: it acts as a signaling molecule between the immune and nervous systems, helping body adapt to changes (stress, infection, environment) (Bernardino 2022).

Excessive levels of histamine in the blood cause tachycardia, increased blood clotting, gastric acid secretion, bronchospasm, vasodilation, increased capillary permeability, edema, inflammation, and adrenaline

secretion. Histamine can cause similar symptoms in allergy, anaphylactic shock, pseudoallergy, and HIT, but the mechanisms of their development and the severity of the reaction differ (Thangam et al. 2018).

The influx of histamine leads to systemic disturbances because histamine activates its H1, H2, H3, and H4 receptors. Some of the concerns: H1 receptor - responsible for skin reactions (hives), sensory hypesthesia, and smooth muscle spasms (including in the lungs and uterus). H2 receptor - in larger amounts, it disrupts the functions of the digestive system (abdominal pain, excessive acid secretion) and the circulatory system (heart palpitations). H3 receptors - modulate the central nervous system by altering neurotransmission. H4 receptor - drives systemic inflammatory responses of the immune cascade. Storm of histamine and simultaneous reactions of all receptors can lead in worst scenario to SIRS and sepsis (Filcek et al. 2021).

E. Symptom Overlap Between MCAS, HIT, ASD, and PTSD

There is a clear overlap between the symptoms of MCAS/HIT and those seen in ASD and PTSD (Hirota & King 2023), (Filcek 2025).

Common Clinical Symptoms:

Gastrointestinal: Food intolerances, abdominal pain, bloating, diarrhea.

Neurological and Cognitive: Attention deficits, brain fog, memory impairment.

Behavioral and Psychiatric: Mood instability, anxiety, aggression, impulsivity, self-harm.

Sensory: Hypersensitivity to sound, light, touch, and smell.

Sleep: Interrupted sleep, nightmares, insomnia.

Systemic: Migraines, headaches, heart palpitations, skin reactions (flushing, hives), muscle spasms, tics, seizures (Jennings et al. 2021), (Zhao et al. 2022), (Katrinli et al. 2022).

This symptom overlap suggests a common underlying mechanism involving immune system dysfunction and histamine signaling.

F. Mast Cells in ASD and PTSD

Emerging evidence supports the involvement of mast cells in ASD particularly in the context of neuroinflammatory involvement:

- ▣ Increased mast cell density and activation have been observed in brain tissue of individuals with ASD
- ▣ Mast cell mediators may disrupt the BBB
- ▣ Neuroinflammation is a consistent finding in ASD (Priego- González et al. 2025), (Mast Cells and Autism), (Kovacheva et al. 2024).

Mast cells, located in the central nervous system primarily within the meninges and adjacent to blood vessels, interact closely with neurons and glial cells, predisposing them to act as regulators of the neuroimmune environment. Their activation can be induced by stress factors, including neuropeptides such as corticotropin-releasing hormone (CRF) and neurotensin, elevated levels of which have been observed in individuals with ASD (Theoharides et al., 2019). As well as environmental factors playing the important role (Filcek 2025), (Baronio et al. 2015).

Activated mast cells release a wide spectrum of pro-inflammatory and neuromodulatory mediators, including histamine, proteases (tryptase, chymase), and cytokines. These mediators have been shown to affect the integrity of the BBB by increasing its permeability, which promotes the influx of pro-inflammatory factors into brain tissue and the secondary activation of microglia (Theoharides et al., 2019). Consequently, local inflammation and impaired neuronal function, including synaptic processes and brain plasticity, may occur (Kempuraj et al., 2019).

A growing body of evidence points to chronic, low-grade neuroinflammation as a significant component of ASD (Eissa et al. 2020). Increased activation of microglia and astrocytes, as well as elevated levels of pro-inflammatory cytokines in the central nervous system, has been observed, which may impact the development and functioning of neuronal networks. In this context, mast cells may serve as a key link between the immune and nervous systems, initiating and modulating the inflammatory response (Theoharides et al., 2019), (Kempuraj et al., 2019), (Sánchez-Pérez et al. 2022). Additionally, clinical observations indicate a possible co-occurrence of ASD with disorders associated with mast cell overactivity, such as MCAS or mastocytosis, which may suggest shared pathophysiological mechanisms (Theoharides et al., 2009). However, it should be emphasized that the available data are largely correlational in nature and do not allow for a definitive causal relationship.

Currently, there is no specific treatment for PTSD because the mechanisms of its development are unknown (Katrinli et al. 2022). Chronic stress associated with PTSD activates mast cells, which play a key role in the development of peripheral inflammation and neuroinflammation, which may exacerbate neurodegeneration in the pathogenesis of diseases such as Parkinson's and Alzheimer's (Kempuraj et al. 2017). Although the role of mast cells in ASD has not yet been clearly established, a growing body of research indicates their potential importance as regulators of neuroimmune processes. These mechanisms fit into a broader model of the pathophysiology of ASD and PTSD, encompassing a complex interaction of immunological, genetic, and environmental factors (Kovacheva et al. 2024), (Theoharides et al. 2019).

F.1 Gut-Brain Axis Evidence in ASD / PTSD

Documented DAO deficiency has been found in certain groups of children with ASD. Reduced DAO activity (e.g., genetic, intestinal

disease, inflammatory conditions, increased intestinal permeability) is associated with gastrointestinal dysfunction and histamine intolerance (Maintz & Novak, 2007). This results in an impaired ability to degrade dietary histamine in the gut, which may lead to increased histamine bioavailability and local inflammatory reactions. Gastrointestinal abnormalities, including increased intestinal permeability (leaky gut), are widely described in individuals with ASD (El-Ansary, et al. 2012), (Al-Ayadhi, et al. 2021), supporting the hypothesis that impaired barrier function may facilitate systemic immune activation and disrupt the nervous system via the histamine pathway and its receptors. Furthermore, mast cells in the gastrointestinal tract interact with the microbiota, enteric neurons, and immune cells (Cryan & Dinan, 2012). Dysregulation within this network can lead to a cascade of gastrointestinal (e.g., dysbiosis, inflammation, motility disorders), immunological, and neurological symptoms observed in ASD (including sensory hypersensitivity, anxiety, and cognitive impairment) (Lewandowska-Pietruszka et al. 2023), (Priego-González et al. 2025). Research (Theoharides et al., 2012) reveals physically increased mast cell activity in the brains of children with ASD. Neuroinflammatory processes within the central nervous system are increasingly recognized as a hallmark of ASD. This directly exacerbates neuroinflammatory mechanisms, potentially leading to excitotoxicity. Autopsy and imaging studies have shown activation of microglia and astrocytes, along with elevated levels of pro-inflammatory cytokines (Vargas et al., 2005), (Theoharides et al. 2013).

Mast cells in the gastrointestinal tract occupy a central position in the gut-brain axis and dynamically interact with multiple systems through the release of mediators (Katiraei et al. 2026). Research consistently demonstrates a high degree of comorbidity between post-traumatic stress disorder (PTSD), depression, and gastrointestinal symptoms (Menon et al.

2013), (Heymann et al. 2025). Veterans with PTSD are up to eight times more likely to experience gastrointestinal symptoms, such as irritable bowel syndrome (IBS), diarrhea, constipation, nausea, vomiting, constipation, abdominal pain, peptic ulcer disease, and gastroesophageal reflux disease (often related to the overproduction of stomach acid caused by anxiety and stress) (Kearney et al. 2022), (Kuefner et al. 2008). Data from research shows that veterans suffering with PTSD are 77-81% more likely to require upper gastrointestinal tests, such as endoscopy (Crawford et al. 2023). Higher PTSD symptom severity is directly linked to more serious digestive problems. Chronic stress disrupts the gut-brain axis, causing inflammation and altering the microbiome (Schink et al. 2018).

PTSD could be presented as a neuro-immuno-endocrine disorder in which classic HPA axis dysregulation may coexist with mast cell activation, creating a feedback loop between psychological stress and the inflammatory-histamine response (Maturkar et al. 2025), (Trauma). Growing evidence indicates that alterations in this gut-brain axis may contribute to both the systemic and neurological features of the disorder, linking gastrointestinal physiology with central nervous system function in ASD (Gonçalves et al. 2024).

F.2. Vagus Nerve

The most important link is the vagus nerve, which acts as a bidirectional cable between the gut and the brain. It sends signals about gut health (e.g., distention, presence of food, intestinal problems → inflammatory and neural signals → worse mood, fatigue, anxiety). It also relays information from the brain to the gut (e.g., stress response in the brain → signal via the vagus nerve and hormones → slowed digestion, „stomach knot“) (Ma et al. 2025).

Physical evidence supports bidirectional communication of neuroimmune dysfunction in PTSD (Sumner et al. 2020) in ASD in which

peripheral and central processes are closely intertwined (Fang et al. 2025), showing that the gut-brain axis is an important mechanism underlying the systemic nature of ASD and a potential target for therapeutic intervention (El-Ansary et al. 2013).

G. Trauma, Stress, Environment and Mast Cell Sensitization in PTSD and ASD

Chronic stress and exposure to traumatic events are potent activators of mast cells, actively sensitizing them, chronically lowering their activation threshold (Bhuiyan et al. 2021).

Mechanisms activating mast cells in stress:

- Chronic stress influences mast cell activity through neuroendocrine and autonomic pathways:
- Chronic stress lowers mast cell activation thresholds
- Sympathetic nervous system activation increases inflammatory signaling
- Corticotropin-releasing hormone (CRH) can directly activate mast cells

This can lead to:

- increased histamine release
- persistent, low-grade inflammation
- increased sensory and emotional reactivity

Therefore, both traumatic experiences and chronic stress in PTSD may be associated with mast cell hypersensitivity, which contributes to symptom persistence. This suggests a trauma-driven feedback loop in which psychological stress sensitizes mast cells, leading to increased basal degranulation (including histamine release) and a state of sustained immunological overactivity. A

systemic histamine surge occurs, with histamine entering the bloodstream, activating histamine receptors (H1-H4), which also cross the blood-brain barrier, causing chronic neuroinflammation, and activating H3 receptors in the central nervous system, which lowers GABA and increases glutamate, causing excitotoxicity. (El-Ansary & Al-Ayadhi, 2014). This, in turn, increases anxiety and fight-or-flight mode. This emotional dysregulation makes the brain more susceptible to perceived environmental and emotional stress, starting the loop all over again. Breaking this vicious cycle may involve creating a low-trigger environment as a preventive or therapeutic strategy, which over time may contribute to a reduction in PTSD symptom severity.

H. Environmental and Lifestyle Factors as Triggers of Mast Cells

Many environmental factors can increase mast cell activation and histamine accumulation (MCAS: Identifying and Understanding), (Emberti et al. 2019) here some examples:

Environmental constraints:

- extreme temperatures (hot/cold)
- fluctuations in atmospheric pressure
- heavy metals (mercury, aluminum) and toxins (El-Ansary et al. 2017).
- constant sounds, noise, vibrations, alternating electromagnetic field, radiation and ionizing radiation (Gangi & Johansson, 2000), (Nicole et al. 2006).
- body pressure (e.g., elastic bands in socks)

Stress factors:

- emotional trauma (related to PTSD),

- psychological stress, anxiety,
- physical stress (intensive exercise)
- prenatal stress
- oxidative stress

Pathogens and flora:

- allergens
- bacteria, viruses
- mold, fungi

Dietary factors:

- foods high in histamine
- alcohol and fermented foods
- factors that block DAO receptors

Chronic exposure to these factors locks mast cells into a state of persistent oversensitivity. In susceptible individuals, these factors can perpetuate a cycle of chronic activation and neuroinflammation. (Mast Cells and Autism), (El Ansary 2024), (Kern & Jones 2006).

Histamine + Glutamate = Amplifying Loop

3. Objectives of the Study

The primary aim of this study is to investigate and evaluate the therapeutic potential of low-stimulation environments and their role in modulating mast cell activity, with a particular focus on lowering histamine levels. The study aims to determine whether such environments can be a complementary intervention strategy for alleviating pathophysiological symptoms in individuals with ASD and PTSD, as well as whether they can support stress reduction and regaining a

sense of safety in individuals experiencing trauma, including war trauma.

A secondary aim is to assess the impact of these interventions on the well-being of people with PTSD, and caregivers, particularly mothers and therapists supporting individuals with ASD, as those mothers experiencing chronic trauma and have an increased risk of PTSD symptoms due to chronic stress and stressful experiences. The study aims to determine whether exposure to regulated, restorative environments can contribute to the recovery of physiological and emotional resources, including reducing fatigue, restoring calm, and improving overall energy levels. Specifically, the intervention will be assessed to determine whether it reduces stress, which is often long-term in caregivers and leads to depletion of body resources. It will also support restorative processes by improving the quality of rest and sleep, as well as restoring a sense of control and security—key factors for increasing resilience to stress and improving the ability to cope with the daily challenges of caregiving.

More broadly, the study also aims to assess whether restorative environments can prevent caregiver burnout by supporting their mental and physical health, thus indirectly impacting care quality for children with ASD.

4. Methodology

This study utilizes an exploratory, integrated research design that combines theoretical analysis with preliminary observational data. The research approach is interdisciplinary, drawing on findings from immunology, neuroscience, and clinical practice to develop a conceptual framework that links mast cell activity, histamine metabolism, environmental factors, and neuropsychiatric symptomatology.

Data sources include peer-reviewed literature (systematic reviews, meta-analyses,

and observational studies) on mast cell activation syndrome (MCAS), histamine intolerance (HIT), autism spectrum disorder (ASD), trauma and post-traumatic stress disorder (PTSD). These sources were used to identify converging evidence and common pathophysiological patterns.

The dataset also includes pilot observational data obtained during Vinci Power Nap® sessions with small cohorts, including children with ASD, individuals with PTSD, trauma-affected populations, and overwhelmed caregivers. Observations were based on behavioral responses, emotional state, sensory regulation, well-being and sleep-related outcomes reported by participants, caregivers, and therapists.

Analysis methods included qualitative synthesis and comparative analysis of clinical features across conditions (MCAS, HIT, ASD, PTSD), as well as the identification of common symptom clusters and potential mechanistic links. Observational findings were interpreted within the framework of the proposed neuroimmunological model, with a particular focus on environmental modulation as a therapeutic factor. Given the exploratory nature of the study and the limited sample size in the pilot observations, the results are considered hypothesis-generating. Further research using controlled experimental designs, standardized measurement tools, and biomarker-based assessments is needed to validate the proposed mechanisms and assess their clinical utility.

Research Approach:

Study Groups: Children with ASD, people with war trauma, PTSD, firefighters and caregivers.

A. Environment:

Vinci Power Nap® is a patented, non-invasive therapeutic environment designed to reduce sensory input, synchronize the body's internal rhythms, and promote deep neurophysiological relaxation. It utilizes a suspended, cocoon-like material that gently

envelops the body, allowing it to achieve an ideal ZGP reducing muscular and emotional tension during rocking, and a neuroarchitectural environment that minimizes external stimuli such as light, noise, pollutants, odors, air temperature, and tactile overload or underload.

B. First study group people with ASD

Pilot observations conducted on a small cohort of three children with ASD who traveled from a care center in Piła to Wrocław, accompanied by their mothers and therapists, to participate in respite sessions using the Vinci Power Nap® system.

B.1.Observation of Children with ASD:

After a long and stimulating four-hour journey, the children initially showed signs of increased arousal. However, upon entering the neuroarchitectural quiet environment of Vinci Power Nap®, we quickly observed noticeable calming responses, characterized by reduced arousal, increased stillness, and marked sensory relief. The children appeared to experience a state of comfort, silence, and reduced sensory load (including alternating weight-off and weight-on body motions, and the pleasant touch of the cocoon material across the entire body), regular breathing, closed eyes, birdsong, and tranquility – suggestive of acute neural regulation.

After a 20-minute calming Vinci Power Nap® session, participants went outside and explored the crowded and highly stimulating environment of a Christmas market, characterized by intense auditory, visual, and social stimuli. Upon returning, the children eagerly and enthusiastically re-engaged with the calming Vinci Power Nap® session, demonstrating a clear preference for the therapeutic, low-stimulation environment. Interestingly, during the return trip, the children clearly stated in conversations with their mothers and therapists that the Vinci Power Nap® experience was more enjoyable and beneficial than the Christmas market activity.

C. Second study group: people with trauma and PTSD and caregivers:

Additional pilot observations include sessions of Vinci Power Nap® conducted with soldiers diagnosed with PTSD (12 participants), with children and mothers affected by war trauma from Ukraine (127 participants from UNICEF project), firefighters (10 men and 5 women) and with mothers and therapists of children with ASD (7 participants).

C.1.Observations of Individuals with PTSD:

Detailed physiological and psychological parameters of the military group have been described in previous publications (Filcek 2020), (Filcek 2022), (Filcek 2023).

After the session the soldiers didn't want to go out from cocoons as they told: „It is first time, after the war, after so many years, we felt relieve and safety again”, their and firefighters reported reduction of stress, calm, bliss and fell of safety during the session, some of them fall asleep (short nap). Furthermore, evidences supporting these results are reflected in reports and recommendations from military psychologists, as well as recommendations from paramedics and firefighters experiencing secondary PTSD, as documented in the literature (Del Ben et al. 2006).

Recommendation from the Rescue Service:

„Working as a paramedic, I often ask myself why no one helps us, why no one is interested in reducing the stress of our duties. (...) there is a lack of systemic support for paramedics, rescuers of all stripes - medical, firefighters, and other uniformed services. However, there is a place that guarantees an incredible sleep experience in just a few minutes, completely resetting stress and restoring a person to factory settings - the Vinci Power Nap. I wholeheartedly recommend this wonderful sleep to all those stressed out in rescue work. It soothes the nerves, calms the body and soul, provides blissful safety, and is something that words cannot describe. This is

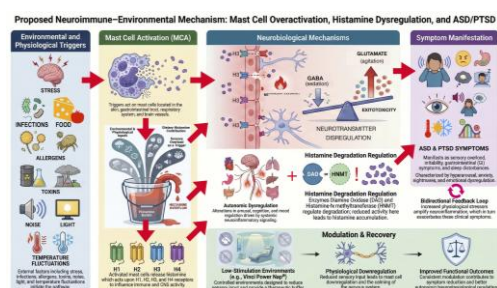
clear preference for low-stimulation environments compared to high-stimulation environments (e.g., crowded public spaces), suggesting a strong modulatory effect of environmental factors on neuroregulation. Similar patterns were observed in individuals with PTSD, including soldiers and professionals exposed to chronic stress. Reported outcomes included reduced hyperarousal, improved emotional stability, increased attention span, and increased tolerance to environmental stimuli. Observations with trauma-affected children and caregivers further supported these findings, indicating improved perceived safety, calmness, and overall well-being. All groups reported consistent improvements in sleep quality, including deeper, more restorative, and less interrupted sleep. Furthermore, symptoms commonly associated with mast cell activation and histamine intolerance, such as sensory hypersensitivity, irritability, and cognitive fatigue, were reduced. A summary of the observed results is presented in Table 1, highlighting key symptom areas and reported changes across participant groups. A conceptual model illustrating the proposed relationship between mast cell activation, histamine dysregulation, environmental factors, and symptom expression is presented in (Pic. 3). Although these results are preliminary and derived from small, uncontrolled trials, they provide consistent support for the proposed model of neuroimmune-environment interaction and warrant further investigation using standardized and controlled methodologies.

overactivation, histamine dysregulation and ASD/ PTSD.

A. Therapeutic Implications

Given the evidence demonstrating the efficacy of antihistamines in alleviating allergic, gastrointestinal, and sleep-related symptoms, as well as the benefits of a low-histamine diet, regulating the histaminergic system becomes an important therapeutic target (Al-maamari et al. 2025). Our pilot results further support this perspective. Reduction in stress and environmental factors induces mast cell activation, combined with exposure to the Vinci Power Nap® environment, which facilitates increased levels of DAO (Filcek & Vats 2023)- all of which suggest an enhanced ability to reduce high histamine levels. This effect may be mediated by the synchronization of key physiological parameters, including respiration, heart rate, and brainwave activity, along with the influence of a low-stimulation neuroarchitectural environment, which may reduce mast cell activation.

The proposed neuroimmunological framework suggests several potential therapeutic pathways that address both the biological and environmental dimensions of symptom expression in ASD and PTSD. From a biological perspective, interventions aimed at regulating mast cell activity and histamine metabolism may provide symptomatic relief in selected individuals. These interventions may include dietary modifications, limiting the consumption of histamine-rich foods, diaminoxidase (DAO) supplementation, and the use of histamine receptor antagonists (H1-H4), which may contribute to improved histamine clearance and reduce neuroinflammatory burden. At the same time, the results highlight the importance of environmental modulation as a complementary therapeutic strategy. Exposure to environments with low stimulation and limited sensory activity appears to support autonomic regulation and may reduce mast cell reactivity triggered by



Pic. 2. Proposed neuroimmune - environmental mechanism: mast cell

sensory and physiological stressors. The concept of designed supportive environments, exemplified by Vinci Power Nap®, highlights a novel non-pharmacological approach that can improve emotional regulation, reduce hyperarousal, and enhance overall functional performance. Importantly, the therapeutic model proposed here aligns with an integrated, multimodal approach that combines immunological, neurological, and environmental interventions. This perspective supports a shift toward personalized care strategies that address individual differences in neuroimmune sensitivity and environmental reactivity. Although initial observations are encouraging, these therapeutic implications remain hypothetical and require validation through controlled clinical trials, standardized outcome measures, and biomarker-based studies. Nevertheless, integrating mast cell and histamine modulation with environmental design offers a promising avenue for future translational and clinical research on neurodevelopmental and neuropsychiatric disorders.

Taken together, these findings suggest that integrated neuroimmune interventions—combining environmental modulation, physiological regulation, and a low-histamine diet—may represent a promising, multifaceted therapeutic strategy for individuals with ASD, PTSD, and their caregivers. Such approaches may provide a structured respite space that supports both symptom reduction and systemic recovery.

B. Systems Medicine: implications of many medical disciplines

Mast cell dysfunction and histamine excess are increasingly recognized as a systemic mechanism with potential implications for many medical disciplines. Growing evidence suggests that abnormal mast cell activation and signaling may contribute to systemic inflammatory responses and, therefore, to a wide range of pathological conditions, including:

- Psychiatry and Neurodevelopment (ASD and PTSD),
- Gastroenterology, Obesity, and Oncology (Biliary tract cancer, gastric cancer, intestinal cancer, histamine intolerance (HIT), nonalcoholic fatty liver disease (NAFLD), metabolic syndrome),
- Nephrology and Gynecology (Chronic kidney disease, Endometriosis),
- Neurology and Immunology (Stroke, Alzheimer's disease, Parkinson's disease, Rheumatoid arthritis, MCAS),
- Cardiology and Infectious Diseases (Cardiitis and myocardial infarction, tachycardia, blood clots, chronic COVID),

Hypothetically, these observations indicate that ASD and PTSD should not be considered in isolation, but rather as part of a broader neuroimmunological continuum in which mast cell dysfunction and histamine may constitute a common underlying mechanism contributing to the dysregulation of multiple systems.

C. Potential Interventions

Based on the proposed framework of the relationship between mast cells, histamine, and neuroimmunology, several potential interventions can be considered as part of a multimodal therapeutic approach for individuals with ASD and PTSD. These interventions target both the biological mechanisms of histamine regulation and the environmental factors that influence mast cell activation. These approaches may reduce symptom burden in subgroups of individuals with ASD and PTSD.

Therapeutic measures:

1. Use protocols to check levels of DAO, histamine and inflammations levels. (Table.1, Pic. 4)

2. Reducing histamine load (dietary intervention):

- Implementation of a strict low-histamine diet to limit exogenous histamine intake

2. Supporting histamine degradation:

- Enhancement of gastrointestinal histamine breakdown through Diamine oxidase supplementation

3. Blocking histamine receptors:

- Use of targeted H1 and H2 receptor antagonists (antihistamines) to prevent downstream signaling and symptom cascades (Kou et al. 2024).

4. Environmental and trigger management:

- Reduction of sensory and emotional triggers that may activate mast cells
- Creation of a calming, low-stimulation, sensory-friendly environment to support nervous system regulation

5. Mast cell stabilization and anti-inflammatory support:

- Targeted supplementation (Vit. D3, Vit. B6, B9, B12, vitamin C, zinc, copper), quercetin (natural mast cell stabilizer), black seed oil (Witkin & Nelson, 2004).

D. Nutritional Engineering

Some individuals with ASD experience mast cell activation and increased sensitivity to histamine. From a biochemical perspective, strategies to reduce histamine burden may include dietary modification by limiting the consumption of histamine-rich or histamine-releasing foods, supplementing with (DAO) to support histamine degradation, and pharmacological modulation with histamine receptor antagonists (H1-H4). This approach may help reduce histamine levels in the body and mitigate subsequent neuroinflammatory

effects (Lackner et al. 2019). Reducing exposure to the high-risk factors identified in the categories below may support the management of behavioral and gastrointestinal symptoms.

Nutritional engineering goals:

- Minimize exogenous histamine burden.
- Total elimination of histamine-rich foods.
- Removal of artificial additives and preservatives.
- Identification and specific treatment of individual food intolerances.

A practical checklist of trigger foods:

Eliminate foods high in histamine, such as:

- aged cheeses (Parmesan/cheddar), fermented foods (sauerkraut/pickled/soy sauce), yogurt, kefir, processed meats, long-stored fish.

Eliminate histamine releasers:

Foods that trigger histamine release, such as:

- tomatoes, strawberries, citrus fruits, chocolate, nuts.

DAO blockers:

Inhibit the enzyme responsible for histamine breakdown:

- alcohol, black tea, energy drinks, coffee.

Better-tolerated options to choose:

- fresh meat, rice, oil, apples, pears, carrots, zucchini, etc. (Sánchez-Pérez et al. 2021).

Individual sensitivity: not every individual with ASD reacts the same to histamine, dietary adjustments should be tailored to individual responses. There is no one-size-fits-all diet for individuals with ASD.

E. Environmental and Safety Engineering: Neuroarchitecture

People spend a significant portion of their lives indoors, within built environments.

Neuroarchitecture is an interdisciplinary field that integrates neuroscience, architecture, biology, physiology, and psychology to

investigate how built environments—such as buildings, spatial layouts, lighting, and acoustics—influence brain function, emotions, behavior, and cognitive processes, as well as how these environments can be optimized to support human well-being. (Wanget al. 2022), (Abbas et al. 2024), (Filcek 2022, 2023). In parallel, increasing evidence points to the role of mast cell activation and immune dysregulation in mediating responses to environmental stimuli. Additional supportive strategies to reduce chronic mast cell activation can further enhance physiological resilience.

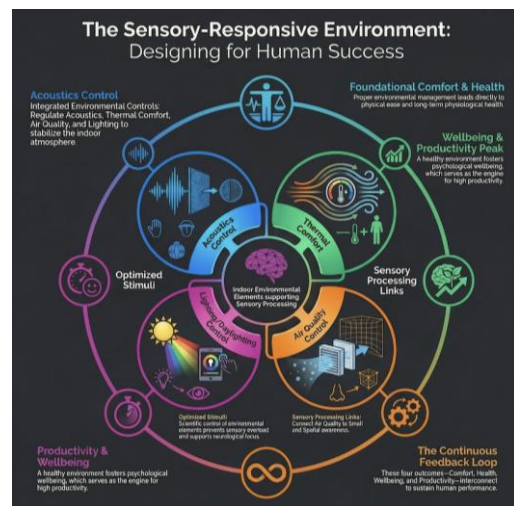
Environmental and safety engineering goals:

- Physically calm mast cell reactivity.
- Design spaces specifically to reduce sensory load, as all pollutants also the coldness and noise from AC (Ouis et al. 2025).
- Mitigate extreme temperature fluctuations.
- Control acoustics, lighting, smell, touch and taste parameters.
- Remove environmental toxins and mold.

The continuous cycle of environmental optimization consists of architectural sensory design, mapping the relationships between environmental factors, sensory processing, and well-being together with human performance (Assem et al., 2023), (Lee et al., 2022).

1. Effective interior design must account for the human organism as a **biological filter** (not just the mechanical or esthetically aspects), where sensory systems act as primary gatekeepers of physiological and cognitive outcomes.

2. Environmental controls constitute the physical input, while overall well-being and performance represents the systemic output. Alignment between these domains is essential and nonnegotiable.
3. The ecosystem is cyclical. Minor disturbances in fundamental parameters—such as acoustics or thermal comfort—can trigger cascading effects within the system, leading to disruptions in regulation, efficiency, and regeneration, especially when such exposures are persistent (day and night, every room) (Aslanoglu 2025).



Pic. 3. The sensory calming - responsive environment, designing for human wellbeing.

The built environment can act as a mediator between sensory input and functional outcomes. Macro-level outcomes are likely influenced by the cumulative effects of micro-level sensory experiences. Environmental interventions are increasingly recognized as complementary approaches in supportive care and stress regulation. Low-stimulation environments with controlled sensory input—such as engineered rest or recovery systems—may reduce sensory and stress load, thereby supporting autonomic nervous system regulation and physiological regeneration. Such environments have been associated with

improved emotional and muscles regulation, attention, and reduced hyperarousal (Filcek 2020), (Filcek 2022), (Filcek 2023).

These potential therapeutic interventions highlight the value of an integrated approach combining biochemical, immunological, sensory and environmental strategies. This multimodal approach aligns with emerging trends in personalized medicine and neuroimmune modulation. All proposed interventions remain in the preliminary phase and require validation in rigorously designed clinical trials to assess safety, efficacy, and long-term outcomes.

F. Case study: Vinci Power Nap® as a pioneering neuroarchitecture-based regenerative environment

The Vinci Power Nap® (VPN) is a controlled recovery environment designed to simulate aspects of a natural forest-like setting, aiming to reduce environmental stressors and bring back feeling of safety. It incorporates an enclosed cocoon-like structure intended to facilitate a transition from a state of heightened stress arousal to relaxation and recovery. The neuroarchitectural principles underlying this design are described in the available publications (Filcek, 2020, 2022, 2023, 2025). In the context of individuals experiencing stress overload, fatigue, anxiety, including symptoms of ASD PTSD and war trauma, it can act as an environmental support system to regulate stress responses, particularly in situations of persistent nervous system hyper-excitability to stimuli, emotional and muscle tension, sleep disturbances.

VPN can support self-regulation processes:

- lowering arousal levels,
- reducing sensory overload,

- short-term relief of the nervous system and a feeling of weightlessness of the body thanks to the Zero Gravity Position (ZGP),
- restoring basic psychophysiological balance,
- synchronize breathing, heartbeat and brain waves by swinging in special frequency,
- restoring feeling of safety and calm.

The author hypothesizes that targeted interventions aimed at restoring neurophysiological synchronization may represent a novel regulatory approach. The VPN system is conceptualized here as a non-pharmacological modulatory tool designed to support the regenerative synchronization of neuronal and autonomic processes. By influencing physiological states related to parasympathetic activation, sensory regulation, and neural oscillation patterns, these interventions may indirectly contribute to:

- reducing chronic stress-induced mast cell activation
- normalizing histaminergic signaling ways
- stabilizing neuroimmune communication
- restoring functional homeostasis in the central nervous system

In this context, VPN is positioned not as a direct inhibitor of histamine pathways, but as a systemic regulator, acting upstream by modulating the conditions that could drive histamine dysregulation. This integrated model suggests that histamine dysregulation and impaired neurophysiological synchronization may constitute intertwined mechanisms, and addressing them simultaneously may offer a new therapeutic perspective for complex conditions such as ASD and PTSD.

Possible applications for:

- children with ASD: Sensory regulation (Al Baalkhi & Agiel, 2021), sleep improvement,
- soldiers with PTSD: supporting trauma recovery, nervous system & sleep regulation,
- trauma care in conflict-affected populations,
- children at school: sensory sensitive regulation and improvement focus, memory, efficiency (Aguel A. & Filcek 2025).
- pilots, doctors, firefighters, policemen, teachers, astronauts, caregivers, leaders, etc.

Top organizations recommendations for VPN:
WHO recommendations in IMPLEMENTOME

(Link:<https://implementome.org/projectdetails/1a89bec26302419a944cb3ae2cc65062>)

UNFCCC recommendations during COP24
(link:
www.youtube.com/watch?v=wb2ntCU1lzA)

Further research is needed to empirically validate this model in large-scale randomized controlled trials (RCTs), in particular through studies assessing the interaction between histamine metabolism, neuronal oscillatory activity, and interventions targeting autonomic and sensory regulation.

6. Discussion

The present work advances a unifying neuroimmune framework in which mast cell overactivation and histamine dysregulation may contribute to the pathophysiology of ASD and PTSD in a subset of individuals. By integrating findings from immunology, neuroscience, and clinical observation, this perspective highlights a potentially under recognized axis linking peripheral immune activity with central nervous system function. The observed overlap in symptomatology across these diagnostic categories suggests that they may not represent isolated conditions, but rather manifestations of shared underlying pathophysiological

mechanisms. This convergence supports a shift from fragmented, symptom-based management toward a unified, mechanism-driven, systems-based treatment model. One of the key implications of this model is the recognition of mast cells as active participants in neurobiological processes beyond their classical role in allergic responses. Their strategic localization at environmental interfaces and in proximity to neural structures positions them as critical mediators of bidirectional communication between the immune system and the brain. Chronic or excessive activation of mast cells may lead to sustained release of histamine and other pro-inflammatory mediators, promoting blood-brain barrier disruption, neuroinflammation, and altered neurotransmitter balance. These processes may, in turn, contribute to the cognitive, behavioral, and sensory symptoms observed in ASD and PTSD. The proposed role of histamine dysregulation further strengthens this integrative model. Impaired degradation due to reduced activity of DAO and HNMT may result in cumulative histamine exposure, amplifying systemic and central effects. Importantly, histamine influences key neurobiological pathways, including GABAergic and glutamatergic signaling, sleep-wake regulation, and stress responsiveness, all of which are frequently altered in ASD and PTSD. This provides a plausible mechanistic link between immune dysregulation and neuropsychiatric symptom expression.

The observed clinical overlap between MCAS, HIT, ASD, and PTSD supports the relevance of this hypothesis. However, it is important to acknowledge that these associations are not necessarily universal and may define specific biological subtypes rather than entire diagnostic categories. This highlights the need for diverse approaches in future studies, including identified and proposed biomarkers related to mast cell activity and histamine metabolism. From a translational perspective, the framework suggests several potential

intervention pathways. Strategies aimed at reducing mast cell activation and regulating histamine levels—such as dietary modification, enzyme supplementation, and histamine receptor antagonism—may offer symptom relief in selected individuals. In addition, the concept of supportive environmental design represents an important and often overlooked dimension of intervention. Reducing exposure to sensory and environmental triggers (e.g., light, noise, temperature fluctuations, and airborne irritants) may help minimize mast cell activation and improve overall neurophysiological stability.

Despite its integrative value, this hypothesis remains to be validated through rigorous experimental and clinical studies. Current evidence is largely derived from associative data, preclinical models, and observations. Well-designed, controlled trials are needed to establish causality, evaluate therapeutic efficacy, and determine the extent to which mast cell-histamine pathways contribute to ASD and PTSD across different populations.

The proposed model provides a novel, theoretically and biologically plausible framework linking immune dysregulation to a spectrum of neurodevelopmental and neuropsychiatric disorders. It opens new avenues of interdisciplinary research and highlighting the potential of combining molecular, clinical, and environmental approaches to develop personalized therapeutic strategies. Integrated ecosystem intervention, prevention, and mind-body protection as therapy must address the complexity of the problem. Instead of masking individual symptoms, it should be a multi-layered strategy to stabilize the neuroimmune system. Biochemistry: Supplementation with DAO enzymes and vitamins, H1 and H2 receptor antagonists (antihistamines). Diet: A strict low-histamine diet prevents the overload and degradation of metabolic pathways. Environment: creating a space with a neuroarchitecture that reduces

stress, reduces visual and auditory stimuli, and eliminates toxins and pollutants.

A. Limitations and Future Directions

Current observations: preliminary evidence suggests significant symptom improvement with histamine-lowering protocols in ASD, PTSD, HIT, and MCAS. However, it is important to note that in some individuals with ASD and PTSD, mast cells and histamine may play a modulating role in somatic symptoms and agitation, but are not considered a cause or biomarker of the disorder. Biomarker development in RCTs: development of precise genetic (AOC1, HNMT) and metabolic testing protocols for early detection (Table 1, Fig. 4) that may inform combination therapies: targeted, multimodal interventions integrating receptor antagonists, enzymatic support, diet, and neuroarchitecture.

B. Biomarkers which could be important to measure in future clinical research

Future directions in neuroimmunological psychiatry include the identification and validation of biomarkers relevant to immune-neural interactions. Potential targets for future clinical research may include markers of mast cell activation, histamine metabolism, inflammatory cytokines, and stress-axis dysregulation, which could contribute to the stratification of biological subtypes within psychiatric disorders, for example:

- Genetic: AOC1, HNMT (Okutan et al. 2023), (Wright & Shin 2017).
- Mast cell activation involves the coordinated release of histamine: (Valent et al 2017)

Elevated levels of histamine and its metabolites (including N-methylhistamine), together with increased D-dimer concentrations and enhanced mast cell activity—reflected by serum tryptase levels (both baseline and episodic elevations)—indicate dysregulation of immune responses and inflammatory-vascular processes. This is

often accompanied by reduced activity of histamine-degrading enzymes such as DAO and HNMT, as well as low vitamin D3 levels, further exacerbating histamine imbalance. These alterations may be associated with transient histamine surges triggered by environmental factors and increased mast cell reactivity and degranulation, leading to the release of mediators such as prostaglandin D2 (PGD2), leukotrienes (e.g., LTE4), and heparin, resulting in a temporally regulated and self-amplifying inflammatory cascade that can progress from acute vascular responses to sustained, systemic inflammation.

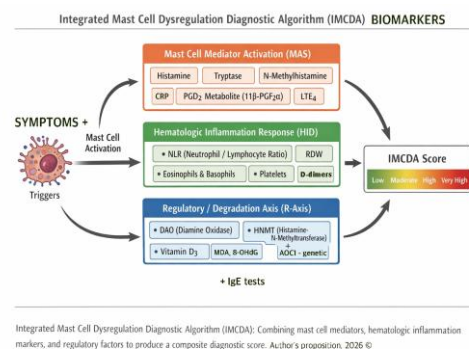
1. Histamine → triggers the reaction (ignition) (Akin 2017)
2. PGD2 → strengthens and extends (maintenance) (Hirai 2004), (Boyce 2008)
3. Leukotrienes → perpetuates and deepens (chronicity) (Minkyu et al. 2025)

At the level of coagulation and endothelial function, in addition to D-dimers, alterations may be observed in fibrinogen levels, von Willebrand factor, and other markers of endothelial activation, reflecting the impact of mast cell mediators on hemostasis and vascular function (Guilarte et al. 2017). These processes are often accompanied by redox imbalance, as evidenced by changes in oxidative stress markers such as MDA, 8-OHdG, and reduced glutathione levels. (Tab.1, Pic.4) (OXI Stress).

- Elevated stress-related mediators: and a histamine-driven stress response are observed, along with increased inflammatory markers such as CRP, IL-6, TNF- α , and IL-1 β , as well as altered cytokine and chemokine profiles. In some cases, elevated IgE levels (Galli & Tsai 2012), along with eosinophil and basophil activation, suggest a coexisting allergic or

hypersensitivity component. Long-term activation of these pathways may contribute to chronic low-grade inflammation, mast cell sensitization, exacerbated histamine response, creating cross-talk amplification loop:

1. Trigger (e.g., allergen, stress, infection, environmental stimulus/ gut problems) ↑ Mast cell activation ↑ Degranulation
2. Histamine ↑ vascular permeability → facilitates mediator diffusion
3. PGD2 ↑ immune cell recruitment → enhances inflammatory signaling
4. Leukotrienes ↑ chronic inflammation → sustain mast cell activation
5. BBB disruption + microglial activation → Neuroinflammation, ASD and PTSD symptoms, gut problems, stress,
6. → Self-amplifying feedback loop



Pic. 4. Author's proposition of integrated mast cell dysregulation diagnostic algorithm.

7. Conclusion, Implications, and Recommendations

This study proposes a novel and integrated neuroimmunological framework in which excessive mast cell activation and histamine dysregulation may contribute to the pathophysiology of ASD and PTSD symptoms in a biologically defined group of individuals. This research demonstrates that these conditions are not simply a state of mind–

they may also represent systemic responses of the body struggling to maintain biological equilibrium in an overstimulating, mast cell-activating environment (e.g., excessive, constant noise and cold air conditioning).

Systemic histamine accumulation may exacerbate mast cell activation and the inflammatory response at the blood-brain barrier, which indirectly influences the functioning of the central histamine system and modulation of H3 receptors, leading to decreased GABA, increased glutamate, excitotoxicity, chronic sleep disturbances, neuroinflammation, and behavioral dysregulation. By linking immunological mechanisms to neurodevelopmental and neuropsychiatric symptoms, the presented model offers a coherent explanation for the broad and overlapping spectrum of symptoms observed in these conditions. Preliminary observations further suggest that modulation of both biological and environmental factors may play a significant role in symptom management. In particular, pharmacological interventions targeting histamine pathways, an elimination diet, combined with the implementation of supportive, low-stimulation environments such as the Vinci Power Nap® neuroarchitecture, may contribute to improved emotional regulation, reduced sensory overload, and improved overall well-being and functioning. The observed improvements in behavioral responses, stress tolerance, and sleep quality across diverse groups—including individuals with ASD, PTSD, and war trauma exposure—underscore the potential importance of this combined approach.

Current evidence is primarily exploratory, based on associational and pilot studies. Although these results are promising, further controlled studies are necessary to establish causality and clinical effectiveness. This approach opens new avenues for personalized, integrated treatment strategies for neurodevelopmental and neuropsychiatric

disorders. In summary, this review highlights the mast cell-histamine pathway as a promising yet understudied target for neurodevelopmental and neuropsychiatric disorders. It also highlights the importance of integrating biological knowledge with environmental and therapeutic design, opening new avenues for personalized, multimodal interventions aimed at improving the quality of life of individuals affected by these disorders, including depression, ASD, PTSD, ADHD, Alzheimer and Parkinson disease.

From psychiatry to neuroimmune safety engineering, understanding the role of mast cells and histamine may help shift the current paradigm, suggesting that the future of healthcare lies not only in treating symptoms, but also in designing therapies and environments that reduce inflammatory load at its source.

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Conflict of interest statement: Author is also the creator of Vinci Power Nap® neuroarchitecture pioneering system.

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