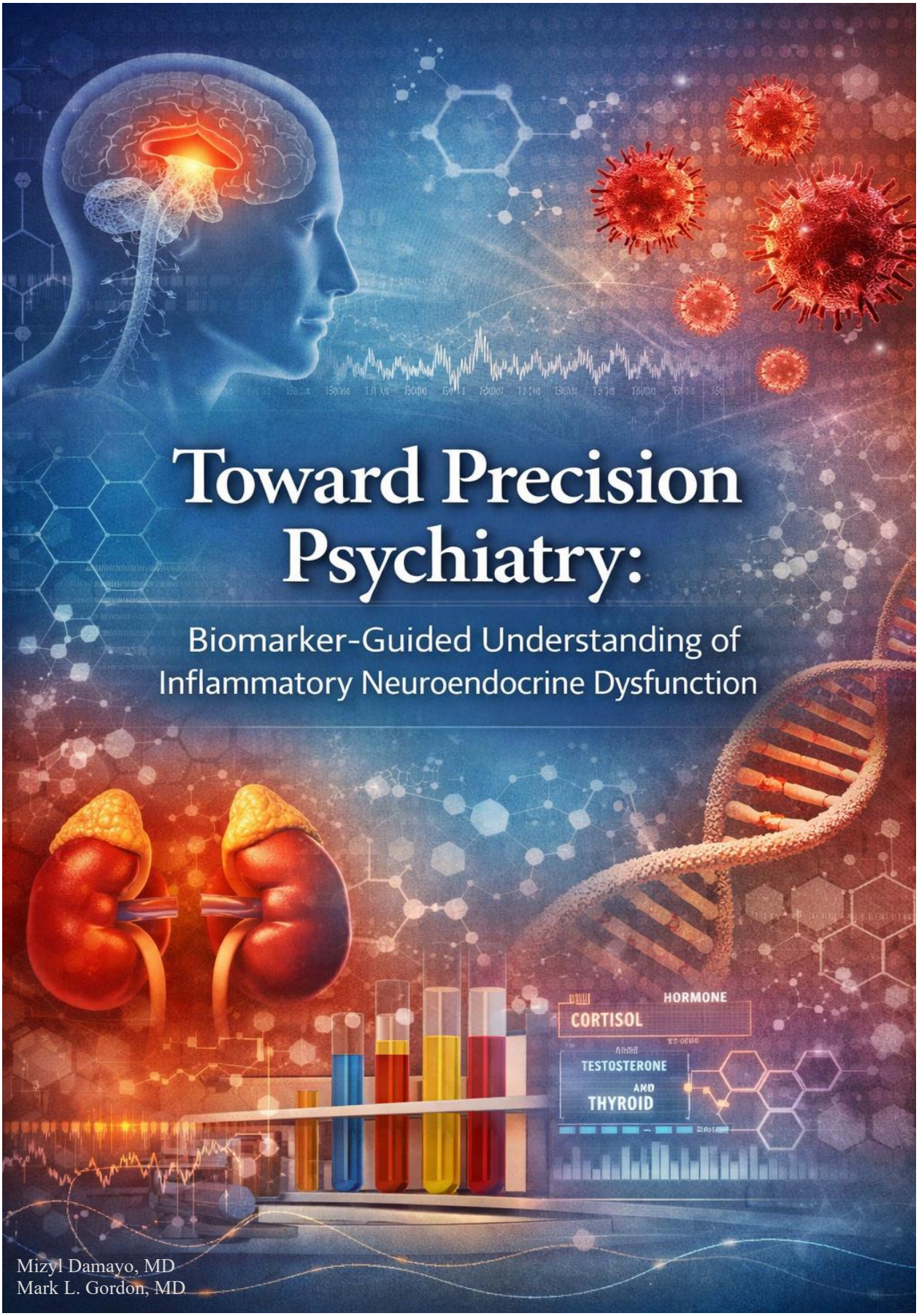

Toward Precision Psychiatry:
Biomarker-Guided Understanding of Inflammatory Neuroendocrine Dysfunction
HORMONE
CORTISOL
TESTOSTERONE
AND
THYROID
Mizyl Damayo, MD
Mark L. Gordon, MD

Toward Precision Psychiatry: Biomarker-Guided Understanding of Inflammatory Neuroendocrine Dysfunction

Abstract

For over a century, psychiatry has classified mental illness according to symptom clusters, depression, anxiety, bipolar disorder, schizophrenia, while neurobiology has searched for neurotransmitter imbalances to explain them. Increasing scientific evidence now challenges this reductionist view. A growing body of research demonstrates that many psychiatric conditions reflect downstream neurochemical manifestations of upstream immune activation and neuroendocrine dysregulation. Pro-inflammatory cytokines alter hypothalamic-pituitary signaling, impair mitochondrial energetics, disrupt neurosteroid production, and destabilize synaptic transmission. The resulting changes in serotonin, dopamine, glutamate, and GABA are not primary defects but adaptive responses to inflammatory stress.

This paper proposes a mechanistic framework in which psychiatric disease is understood as immune-driven neuroendocrine inflammation. Integrating evidence from neuroimmunology, endocrinology, trauma research, and biomarker-guided clinical observations, we explore how inflammation reshapes brain chemistry and behavior. We examine three highly prevalent psychiatric disorders, major depressive disorder, anxiety disorders, and bipolar disorder, to illustrate the translational implications of this model. Recognizing psychiatric symptoms as biological consequences of systemic and central inflammation may redefine diagnostic and therapeutic strategy, shifting clinical focus from neurotransmitter modulation to restoration of neuroimmune-endocrine equilibrium.

Introduction

Traditional psychiatric models emphasize neurotransmitter dysregulation, serotonin deficiency in depression, dopamine excess in psychosis, and GABA imbalance in anxiety. While pharmacologic modulation of these systems can reduce symptoms, this approach does not explain why neurotransmitter disturbances arise in the first place.

Over the past two decades, evidence has mounted that immune activation profoundly alters brain function. Elevated levels of interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) are consistently observed in patients with major depression and other psychiatric disorders [1–3]. Experimental administration of inflammatory cytokines induces depressive and anxiety symptoms in previously healthy individuals [4]. Conversely, anti-inflammatory interventions show antidepressant effects in subsets of patients with elevated inflammatory markers [5].

Parallel research demonstrates that inflammation disrupts hypothalamic-pituitary-adrenal (HPA) axis regulation, thyroid signaling, gonadal steroid production, and neurosteroid synthesis [6–8]. These endocrine shifts directly influence neurotransmitter synthesis, receptor sensitivity, and synaptic plasticity. Thus, psychiatric symptoms may represent the integrated output of immune-driven neuroendocrine perturbation.

This paradigm does not deny psychological contributors to mental illness. Rather, it asserts that persistent psychiatric syndromes often reflect measurable biological processes, particularly immune-based inflammation, that can be objectively evaluated and treated.

Mechanistic Framework: From Immune Activation to Neurochemical Symptoms

1. Peripheral Immune Activation and Cytokine Signaling

Inflammation may arise from infection, trauma, chronic stress, metabolic dysfunction, environmental toxins, or gut barrier disruption. Peripheral cytokines access the brain through multiple routes: active

transport across the blood-brain barrier (BBB), vagal nerve signaling, or passage through regions lacking tight junctions [9]. Chronic inflammation increases BBB permeability, facilitating immune cell trafficking into neural tissue [10].

Microglia, the resident immune cells of the brain, respond by adopting a pro-inflammatory phenotype (M1), releasing IL-1β, IL-6, and TNF-α. Sustained microglial activation alters synaptic pruning, dendritic architecture, and neurotransmitter metabolism [11].

2. Tryptophan Metabolism and Serotonin Depletion

Inflammation activates indoleamine 2,3-dioxygenase (IDO), diverting tryptophan from serotonin synthesis toward the kynurenine pathway [12]. This shift reduces serotonin availability and generates neuroactive metabolites such as quinolinic acid, an NMDA receptor agonist that promotes excitotoxicity [13]. Thus, the "serotonin deficiency" observed in depression may be secondary to cytokine-driven metabolic redirection rather than primary neurotransmitter failure.

3. Glutamate Excitotoxicity and Oxidative Stress

Inflammatory cytokines increase extracellular glutamate through impaired astrocytic reuptake and increased presynaptic release [14]. Elevated glutamate stimulates NMDA receptors, increasing intracellular calcium influx and reactive oxygen species (ROS) production. Excessive ROS combine with nitric oxide to form peroxynitrite, damaging mitochondrial membranes and impairing ATP generation [15].

Mitochondrial dysfunction reduces neuronal resilience, diminishes synaptic plasticity, and contributes to cognitive impairment and mood instability. Functional neuroimaging studies demonstrate altered metabolic activity in frontal and limbic circuits in inflammatory depression [16].

4. HPA Axis Dysregulation

Pro-inflammatory cytokines stimulate hypothalamic corticotropin-releasing hormone (CRH), increasing adrenocorticotropic hormone (ACTH) and cortisol release [17]. Acute activation is adaptive; chronic elevation leads to glucocorticoid receptor resistance, blunting negative feedback and perpetuating hypercortisolemia [18].

Excess cortisol impairs hippocampal neurogenesis, reduces brain-derived neurotrophic factor (BDNF), and contributes to memory and mood disturbances [19]. Over time, compensatory adrenal fatigue or hypocortisolism may emerge, further destabilizing emotional regulation.

5. Neurosteroid and Gonadal Hormone Disruption

Inflammation suppresses hypothalamic-pituitary-gonadal signaling, reducing testosterone, estradiol, and DHEA levels [20]. Neurosteroids derived from these hormones, pregnenolone, allopregnanolone, and others, modulate GABAergic and glutamatergic tone. Reduced neurosteroid availability diminishes inhibitory signaling, contributing to anxiety, irritability, and mood swings [21].

This interplay underscores that psychiatric symptoms often reflect endocrine consequences of immune stress.

Biomarker-Guided Evidence of Neuroendocrine Inflammation

Clinical observations from large patient cohorts assessed with structured biomarker panels reveal consistent patterns: elevated inflammatory markers (CRP, IL-6), disrupted cortisol rhythms, suboptimal thyroid signaling, and suppressed gonadal hormones correlate with psychiatric symptom severity.

Optimization of these parameters toward physiologic quartiles observed in healthy young adults is frequently associated with improvement in mood, cognition, and physical vitality. While correlation does not establish causation, these findings align with mechanistic data linking inflammation to neuroendocrine dysregulation.

Importantly, such assessments shift the diagnostic focus from subjective symptom reporting alone to objective biological measurement. Psychiatry may benefit from incorporating standardized inflammatory and endocrine evaluation into routine assessment, particularly in treatment-resistant cases.

Clinical Correlates: Three Prevalent Psychiatric Disorders

1. Major Depressive Disorder (MDD)

Depression affects over 280 million people worldwide [22]. Numerous meta-analyses demonstrate elevated CRP, IL-6, and TNF-α in depressed individuals [1,2]. Cytokine administration in oncology patients induces depressive symptoms, reinforcing a causal relationship [4].

Inflammation-induced IDO activation reduces serotonin synthesis, while kynurenine metabolites impair neuroplasticity [12,13]. Elevated cortisol and reduced BDNF further compromise hippocampal integrity [19].

Patients with higher inflammatory burden often respond poorly to standard SSRIs but may benefit from adjunctive anti-inflammatory strategies [5]. Recognizing inflammatory subtypes of depression allows for precision medicine rather than uniform pharmacologic escalation.

2. Anxiety Disorders

Anxiety disorders are among the most common psychiatric conditions globally [23]. Elevated inflammatory markers are associated with generalized anxiety and panic disorders [24].

Reduced allopregnanolone, a GABA-modulating neurosteroid, is observed in anxiety states [21]. Chronic stress amplifies CRH signaling and sympathetic activation, perpetuating inflammatory loops [17].

Restoring neurosteroid balance and reducing inflammatory load may stabilize GABAergic tone, offering mechanistic rationale for integrative interventions beyond benzodiazepines or SSRIs.

3. Bipolar Disorder

Bipolar disorder is characterized by oscillations between depressive and manic states. Inflammatory markers are elevated during both phases, with greater cytokine activity during mania [25].

Inflammation-related mitochondrial dysfunction may destabilize neuronal energy metabolism, contributing to mood cycling [26]. HPA axis abnormalities and oxidative stress are also well documented [27].

These findings suggest that mood instability may reflect fluctuating neuroimmune activity rather than isolated neurotransmitter excess or deficiency.

Neuroimaging in the Era of Precision Psychiatry: The Need for Molecular Specificity

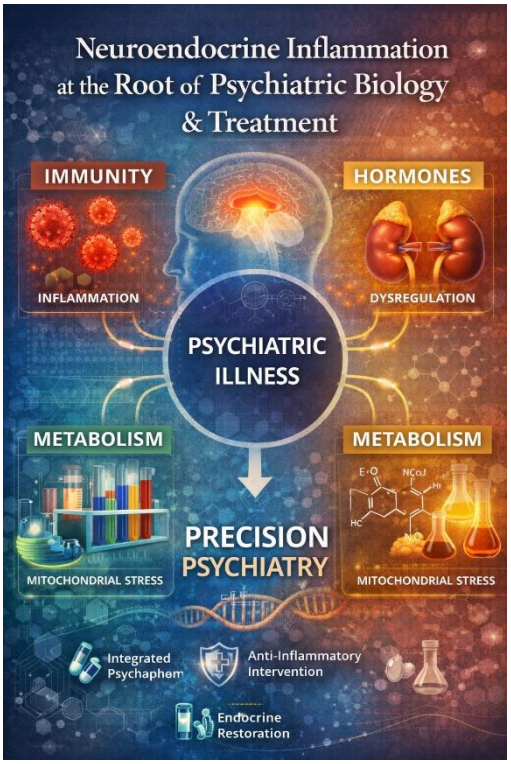
Neuroinflammation is fundamentally a cellular and molecular process characterized by microglial and astrocytic activation, cytokine signaling, blood–brain barrier and endothelial alterations, immune-cell trafficking, oxidative stress, and mitochondrial dysfunction (28–30). In contrast, standard neuroradiographic technologies primarily measure macroscopic proxies, brain structure, water diffusion, perfusion, oxygenation, or glucose metabolism—and therefore rarely provide a specific diagnosis of neuroinflammation, particularly in psychiatric conditions where changes are subtle, diffuse, and dynamic (31,32). The imaging signal is typically indirect and non-specific: edema, gliosis, demyelination, ischemia, infection, medication effects, aging, or even normal inter-individual variation may produce overlapping patterns on conventional MRI, CT, or perfusion/metabolic studies (33). Moreover, inflammatory processes often occur at microscopic scales involving synapses, microvasculature, and glial cells, while clinical imaging averages signals across millimeter-sized voxels, effectively diluting focal cellular activity (34).

Neuroimmune activity is also temporally variable, fluctuating with stress, sleep, hormonal rhythms, and injury phase, making single time-point imaging a limited snapshot that may miss active inflammatory states

(35). Psychiatric syndromes themselves are biologically heterogeneous, with similar symptoms arising from distinct pathophysiologic pathways and similar neuroimmune changes producing different clinical expressions, reducing the likelihood that any single imaging pattern will be diagnostically definitive (36). Even inflammation-targeted modalities such as TSPO PET have specificity constraints, as TSPO expression is not exclusive to pathologic microglial activation, can involve astrocytes and macrophages, and is influenced by genetic polymorphisms and quantification challenges (37).

Assessment and Treatment: Integrating Comprehensive Biomarker Panels in Precision Psychiatry

Precision psychiatric assessment begins with the premise that mood, anxiety, and cognitive disorders often reflect measurable neuroimmune and neuroendocrine dysregulation rather than isolated neurotransmitter abnormalities. Building on the mechanistic evidence linking cytokines to altered tryptophan metabolism, glutamatergic excitotoxicity, HPA-axis disruption, and neurosteroid depletion (1,8,12,14,17), a structured, multi-domain laboratory evaluation becomes central to clinical decision-making. A comprehensive 28-point biomarker panel allows simultaneous assessment of inflammatory indices, oxidative stress markers, metabolic integrity, thyroid signaling, adrenal rhythm, and gonadal hormone status—domains repeatedly implicated in psychiatric pathophysiology (2,6,7,20,25).



Complementing this physiological assessment, the iXpressGenes inflammatory panel provides genomic insight into cytokine regulation, immune activation patterns, and individual susceptibility to persistent inflammatory signaling. Together, these tools allow stratification of patients according to biological subtype—distinguishing primarily inflammatory presentations from endocrine-dominant or metabolically driven dysfunction.

Treatment is then directed toward correction of upstream biological imbalance. Elevated inflammatory markers prompt targeted anti-inflammatory, mitochondrial, and metabolic interventions (5,15,26), while dysregulated cortisol rhythms or suppressed neurosteroids guide endocrine restoration strategies to stabilize GABAergic and glutamatergic tone (6,21). Optimization toward physiologic quartiles observed in healthy younger adults is frequently associated with improvement in mood stability, cognitive clarity, and stress resilience.

Translational Implications

Reframing psychiatric illness as a manifestation of neuroendocrine inflammation carries profound clinical implications. Expanding diagnostic assessment to include routine measurement of inflammatory and endocrine biomarkers allows clinicians to identify biologically treatable contributors to mood, anxiety, and cognitive symptoms that might otherwise be attributed solely to neurotransmitter imbalance. This broader biological lens shifts evaluation from descriptive psychiatry toward measurable physiology.

An integrated treatment strategy naturally follows. Rather than relying exclusively on psychopharmacology, therapeutic planning can incorporate targeted anti-inflammatory interventions, endocrine restoration, metabolic optimization, and lifestyle-based modulation of immune activity. Such approaches address

upstream drivers of neurochemical disruption while maintaining the stabilizing benefits of conventional medications when appropriate.

Understanding psychiatric conditions as biologically mediated disorders of immune–endocrine interaction may also reduce stigma. When symptoms are contextualized within measurable systemic processes, mental illness is more clearly recognized as a medical condition rather than a personal failing or purely psychological weakness.

Finally, this framework advances the movement toward precision psychiatry. Subtyping patients according to inflammatory burden, hormonal status, and metabolic integrity enables individualized treatment strategies tailored to biological phenotype rather than generalized symptom clusters. In doing so, psychiatry evolves from reactive symptom management to proactive, mechanism-based care grounded in objective data.

Conclusion

Psychiatric disorders may not originate primarily in neurotransmitter deficiency or excess. Instead, they may represent adaptive neurochemical responses to immune-driven neuroendocrine dysregulation. Chronic inflammation alters tryptophan metabolism, activates glutamatergic excitotoxic pathways, impairs mitochondrial energetics, disrupts HPA signaling, and suppresses neurosteroid synthesis.

The convergence of neuroimmunology and endocrinology offers a coherent framework linking systemic inflammation to psychiatric symptomatology. By integrating objective biomarker assessment with mechanistic understanding, psychiatry stands at the threshold of a paradigm shift, from symptom management to biological restoration.

Recognizing psychiatric disease as neuroendocrine inflammation does not replace psychotherapy or psychopharmacology; it deepens their foundation. It invites clinicians to look upstream, beyond serotonin and dopamine, toward the immune-endocrine interface that shapes brain chemistry and human behavior.

Dr. Mizyl F. Damayo, MD

Dr. Mizyl F. Damayo, MD is a board-certified psychiatrist and Medical Director of Paradise Behavioral Health in Punta Gorda, Florida, with more than 25 years of clinical experience in adult psychiatry and addiction medicine. She earned her medical degree from Matias H. Aznar Memorial College of Medicine and completed her psychiatry residency at Charleston Area Medical Center through the West Virginia University Charleston Division. Dr. Damayo is certified by the American Board of Psychiatry and Neurology and the American Board of Addiction Medicine and is licensed to practice in multiple states, including Florida.

In addition to her traditional psychiatric training, Dr. Damayo completed over four years of advanced clinical training with Millennium Health Centers, Inc., where she developed specialized expertise in the assessment and management of patients with neuroendocrine dysfunction. This training focused on structured biomarker interpretation, identification of inflammatory and hormonal imbalances, and implementation of physiologically guided treatment strategies for complex neuropsychiatric presentations.

Dr. Damayo's clinical philosophy centers on a precision-based, biologically informed model of psychiatric care. She emphasizes comprehensive evaluation of underlying contributors to mental health conditions, integrating laboratory analysis, hormonal assessment, genetic insight, and metabolic evaluation into individualized treatment planning. Through her Brain Well Program, she applies structured biomarker-guided approaches designed to move beyond symptom-based prescribing toward identification and correction of root physiological imbalances associated with depression, anxiety, trauma-related disorders, obsessive-compulsive disorder, and treatment-resistant conditions.

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