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GUEST EDITORIAL

Psychiatric disorders at the crossroads of neurovascular, immune, and metabolic dysregulation: Examining comorbidities from a biopsychosocial and dimensional perspective across the lifespan

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COMORBIDITIES IN PSYCHIATRY

Psychiatric disorders frequently co-occur with both other psychiatric conditions and systemic diseases. For instance, nearly 40% of individuals with bipolar disorder (BD) experience anxiety disorders, while comorbid attention-deficit/hyperactivity disorder (ADHD) increases the risk of panic disorder, obsessive-compulsive disorder (OCD), and social anxiety disorder in BD (1). In children with BD, anxiety disorders affect 44.7% of cases, with ADHD further increasing the risk of generalized anxiety disorder and separation anxiety disorder (2). Beyond psychiatric conditions, psychiatric disorders often coexist with neurological disorders such as Alzheimer's disease, Parkinson's disease, epilepsy, migraine, and stroke. They are also frequently comorbid with obesity, diabetes, cancer, and rheumatological diseases (3, 4). Obesity increases the risk of depression by 1.33 times. Moreover, depression predicts future obesity, as demonstrated in a 10-year prospective study (5). Women with polycystic ovary syndrome (PCOS), a condition commonly associated with insulin resistance, have a significantly higher prevalence of depression, anxiety, and eating disorders, with a 2.6-fold increased risk of depression independent of body mass index (BMI) (6).

Additionally, several disorders, including Alzheimer's disease, Parkinson's disease, and autism spectrum disorders, are linked to microbiota disruption and increased inflammatory processes, which may trigger neurodegeneration. Chronic low-grade inflammation plays a key role in psychiatric disorders, with elevated inflammatory markers such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) frequently observed in depression and schizophrenia (7). Meta-analyses confirm that individuals with depression exhibit significantly higher C-reactive protein (CRP) levels (>3 mg/L), particularly in cases characterized by fatigue and anhedonia, linking systemic inflammation to symptom severity (8). Peripheral inflammation affects the brain by disrupting the blood-brain barrier (BBB), activating microglia, and altering neurotransmitter metabolism. Metabolic disturbances may also compromise blood brain barrier integrity, leading to cognitive changes (9). Pro-inflammatory cytokines contribute to serotonin depletion via the kynurenine pathway, increasing quinolinic acid, an N-methyl-D-aspartate (NMDA) receptor agonist associated with neurotoxicity and excitotoxicity (10, 11). Inflammation further impairs neuroplasticity, reduces brain-derived neurotrophic factor (BDNF) signaling, and contributes to neurovascular dysfunction and oxidative stress (10, 11). These findings suggest a

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bidirectional relationship between psychiatric disorders and immuno-metabo-vascular dysregulation, reinforcing the need for an integrated mind-body approach.

The Mind-Body Interface in Psychiatry: The Need for Dimensional Models

Individuals with mental disorders constitute a significant portion of the adult population, yet 60% also have coexisting medical conditions, indicating shared biopsychosocial mechanisms. However, traditional diagnostic models, such as the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), classify disorders based on symptom clusters, whereas neuroscience reveals overlapping biological pathways (12). Psychiatric symptoms, similar to those categorized in the DSM-5, often overlap across multiple disorders. A single symptom can manifest in several conditions, and changes in behavior can lead to different psychiatric diagnoses. For instance, eating disturbances are observed in depression, obesity, and cognitive deficits, highlighting the need for classification systems based on etiology rather than diagnostic categories.

A dimensional approach to psychiatry acknowledges that symptoms exist on a continuum rather than as discrete categories. This model suggests that mental health traits vary in severity across individuals, without clear-cut distinctions between pathology and normality. Compared to traditional categorical models, the dimensional approach aims to enhance biomarker identification and address the heterogeneity of psychiatric disorders. The DSM-5, published in 2013, significantly expanded psychiatric classifications, increasing from 128 diagnoses in the DSM-1 (1952) to 541 categories (12). However, psychiatric symptoms remain highly variable—depression alone has 16,400 possible symptom permutations, while post-traumatic stress disorder (PTSD) has 636,120—contributing to diagnostic complexity (13). The International Classification of Diseases, 11th Revision (ICD-11), an alternative classification system, differs from the DSM-5 by incorporating 19 unique diagnostic categories while omitting 70 DSM-5 categories (14). Despite these classification efforts, psychiatric diagnoses often fail to fit neatly into discrete categories, underscoring the need for alternative models. Among these, the Psychodynamic Diagnostic Manual (PDM) emphasizes individual differences, personality organization, and relational factors, providing a holistic perspective that considers life history, affect regulation, and interpersonal dynamics rather than rigid diagnostic labels (15). Similarly, the Hierarchical Taxonomy of Psychopathology (HiTOP) (16) seeks to overcome the arbitrary boundaries of the DSM-5 and the ICD-11 by organizing symptoms into broad dimensions, such as internalizing disorders (e.g., depression, anxiety, PTSD), externalizing disorders (e.g., substance use, antisocial behavior), and detachment disorders. The Research Domain Criteria (RDoC) framework shifts the focus from categorical diagnoses to biological and psychological constructs, identifying key domains such as negative valence systems (fear, anxiety, loss), positive valence systems (reward learning, motivation), and cognitive and social processes (17). These approaches acknowledge that psychiatric symptoms are dynamic, evolving across neurodevelopmental stages, aging, and environmental influences. This perspective provides a more precise and individualized understanding of mental health. The dimensional approach also highlights cognitive, emotional, and behavioral dimensions that can improve understanding of mind-body disorder comorbidities.

FROM NEURAL CIRCUITS TO FUNCTIONAL CONNECTIVITY: UNDERSTANDING MIND-BODY INTERACTIONS

Neuroscience continues to explore the intricate neuronal, glial, and vascular networks that shape cognition, emotion, and psychiatric conditions. The brain's cortical layers are organized with specific neurons forming distinct connections (18), while synaptic transmission occurs through excitatory and inhibitory potentials that regulate neural signaling. Additionally, metabotropic receptor activity plays a crucial role in neuromodulation. Neurons, along with glial cells such as astrocytes, oligodendrocytes, and microglia, interact with vascular structures, including endothelial cells and pericytes, to maintain brain homeostasis (18). Disruptions in neuronal excitatory-inhibitory balance, synaptic plasticity, and connectivity have been linked to schizophrenia, mood disorders, and neurodevelopmental conditions. Glial dysfunction contributes to depression, neurodegenerative diseases, and stress-related disorders, while neurovascular abnormalities affect cerebrovascular integrity, leading to cognitive and emotional impairments.

Beyond structural networks, neuromodulators influence multiple brain regions, shaping functional connectivity patterns that explain psychiatric symptoms and their comorbidities with medical disorders. Leptin and ghrelin, two key metabolic regulators, function as neuromodulators influencing feeding behavior, immune function, and stress responses. Both hormones regulate dopaminergic circuits in the hypothalamus, hippocampus, and amygdala, affecting social behavior, impulsivity, and emotional processing (19). Chronic stress and social isolation can disrupt their balance, impairing decision-making and cognitive control. High impulsivity and novelty-seeking behaviors increase susceptibility to unhealthy eating, altering gut microbiota and affecting immune and metabolic function (20). The vagus nerve transmits these signals, modulating both functional and structural brain connectivity. Glucagon-like peptide-1 (GLP-1) and insulin, key metabolic sensors, regulate food intake, reward learning, and motivation. GLP-1 receptor polymorphisms have been linked to deficits in reward processing, anhedonia, and psychiatric disorders (20).

At the systems level, dysregulation of the prefrontal cortex (PFC), hippocampus, and amygdala contributes to mood and anxiety disorders. Chronic overactivation of the hypothalamic-pituitary-adrenal (HPA) axis leads to cortisol dysregulation, metabolic dysfunction, and immune dysregulation (21). For example, in polycystic ovary syndrome, a condition characterized by hyperandrogenism, insulin resistance, and HPA axis dysregulation, elevated cortisol levels contribute to hippocampal atrophy, amygdala hyperactivation, and mood disorders. Inflammatory cytokines such as IL-6 and TNF-α further exacerbate psychiatric symptoms by impairing synaptic function and neuroplasticity (6).

Biopsychosocial Stress Dynamics in Cognitive, Emotional, and Behavioral Alterations Affecting Mind-Body Interaction

Psychosocial triggers, particularly stress exposure, play a central role in the interaction between mental and physical disorders, bridging various dimensions of psychopathology. Psychiatric symptoms should be understood from a lifespan perspective, incorporating developmental, neurobiological, and environmental influences. Stress exposure at different life stages—early childhood, adolescence, or adulthood—affects cognitive, emotional, and behavioral regulation, as well as physical health. Even when stress is not consciously perceived, its biological imprints persist, shaping long-term mental and physical health outcomes (22).

Stress arises from multiple life domains, influencing psychological well-being. Early-life adversity, including neglect and a lack of stress inoculation, increases vulnerability to depression, anxiety, and post-traumatic stress disorder (PTSD) (22). Interpersonal conflicts, social isolation, and major life transitions heighten emotional distress, while chronic health conditions and medical procedures contribute to systemic inflammation and hormonal imbalances. Economic hardships and job instability create persistent psychological strain, further reinforcing the link between stress and mind-body disorders (23).

The HPA axis, immune system, metabolic pathways, and cerebrovascular functions interact to regulate stress responses (22). Chronic stress alters serotonergic and dopaminergic signaling, contributing to mood instability and emotional dysregulation in depression and anxiety disorders. In neurodevelopmental disorders, early-life stress impairs prefrontal cortex development and impulse control (22), increasing the risk of ADHD. Severe stressors contribute to dopaminergic dysregulation in psychotic disorders, influencing the onset of schizophrenia and perceptual disturbances. Stress also plays a role in somatic symptom disorders, linking autonomic dysfunction to chronic pain and gastrointestinal disturbances (22).

Recognizing stress as a transdiagnostic factor allows psychiatric research to adopt a more integrative approach to diagnosis and treatment, targeting shared neurobiological pathways across mental and physical conditions. Stress disrupts neuronal, immune, metabolic, and vascular systems, driving the pathophysiology of both psychiatric and medical disorders (21–23). At the metabolic level, stress increases glucose availability as an adaptive survival response; however, chronic stress contributes to insulin resistance, obesity, and diabetes mellitus. The immune system temporarily enhances defense mechanisms, but prolonged stress triggers neuroinflammation and immune dysregulation (24). Neurovascular function is also profoundly affected, as glucocorticoid-induced pericyte apoptosis impairs capillary integrity and neurovascular coupling, disrupting oxygen and nutrient delivery to the brain. The sympathetic-medullo-adrenergic (SMA) system triggers gut ischemia, oxidative stress, and endothelial

injury, contributing to chronic inflammation and blood-brain barrier disruption (25). This dysfunction allows inflammatory mediators such as TNF-α and IL-6 to enter systemic circulation, exacerbating psychiatric symptoms and accelerating cognitive decline.

Neuropeptides such as oxytocin and neuropeptide Y (NPY) enhance resilience by reducing anxiety, improving social bonding, and increasing cognitive flexibility. Psychological resilience is reflected in adaptive coping behaviors, while biological resilience manifests through stress-buffering mechanisms at cellular and molecular levels (26). Factors such as optimism, humor, social support, and physical well-being reinforce dopaminergic circuits, helping individuals maintain adaptive responses to stress (27). Cognitive strategies, including cognitive-behavioral therapy (CBT), cognitive reappraisal, and emotion labeling, strengthen prefrontal control over emotional processing, reducing maladaptive stress responses (27). Enhancing resilience through pharmacological interventions (e.g., GLP-1 agonists, anti-inflammatory agents, oxytocin-based therapies) and behavioral strategies (e.g., CBT, mindfulness, physical activity) can improve stress adaptation.

CONCLUSION

By integrating a dimensional and stress-dynamics-inclusive approach, identifying immune, metabolic, and vascular biomarkers could refine psychiatric classification and guide personalized treatment strategies. Pharmacological interventions targeting neuroimmune and metabolic pathways, such as anti-inflammatory agents and GLP-1 analogs, may offer new therapeutic opportunities for modulating psychiatric dimensions and disrupting the bidirectional cycle between mind and body that reinforces comorbid disorders. In clinical practice, a transdiagnostic, dimensional approach could optimize treatment by addressing underlying pathophysiological mechanisms rather than focusing solely on categorical diagnoses. This neuro-vascular-immune-metabolic paradigm presents a promising avenue for advancing psychiatric research and clinical practice, ultimately improving patient outcomes through a more holistic and biologically informed approach.

Future research should prioritize longitudinal studies to track neurodevelopmental trajectories and age-related changes, as well as the impact of stress and resilience dynamics on the brain and body over time. This approach will provide a deeper understanding of how the neuro-vascular-immune-metabolic nexus evolves. Additionally, fostering interdisciplinary collaborations between psychiatry, neurology, immunology, and endocrinology will help bridge knowledge gaps and facilitate a more holistic approach to mental health research. The integration of artificial intelligence (AI) technologies in data analysis may enhance biomarker-driven approaches, improving diagnostic accuracy and enabling more personalized treatment strategies, ultimately leading to better clinical outcomes (28).

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