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Letter to the Editor

One unified hypothesis of neuropsychiatric disorders: Transdiagnostic common staging models

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Much like physicists perpetually seek a grand unified theory capable of making predictions for particles within the same theoretical framework, the idea that diverse clinical presentations of psychiatric disorders might be explained by common biological mechanisms is of interest to those in the field of biopsychiatry. Despite the attempts made by the Research Domain Criteria (RDoC) to develop a more physiologically oriented diagnostic concept, departing from phenotype-driven diagnostic systems such as the Diagnostic and Statistical Manual of Mental Disorders (DSM), the complexity of the RDoC matrix has made it challenging for those accustomed to conventional approaches. In this paper, I endeavor to integrate the diathesis-stress model, the allostatic load model, and the kindling model into what I term "transdiagnostic common staging models." From this model, shared aspects among different traditional diagnostic categories become apparent, encompassing concepts such as excitatory-inhibitory imbalance, inflammation, inflexibility, and sensitization. While it is possible that different traditional categories may lean towards different neurocircuits or neurotransmitters, I also propose the potential for cross-system interactions. This approach may offer a promising avenue for understanding the complex interplay of biological mechanisms underlying psychiatric disorders, shedding light on their commonalities and differences.

Dear Editor,

The complex clinical presentations of psychiatric disorders, despite their shared heritability,[1] have long perplexed clinicians. Although the diathesis-stress model and allostatic load model offer some insights into disease onset and progression, they fail to bridge the gap between phenotype and genotype. Therefore, gaining a deeper understanding of the underlying biological mechanisms of psychiatric disorders is essential for clinical translation. In this letter, I would like to introduce the concepts of sensitization and the kindling model.

The term "sensitization" was originally coined in pain research to describe the learning process by which an individual's response to repeated stimuli becomes increasingly stronger, in contrast to habituation, where the response weakens. It was later discovered that hyperalgesia, the phenomenon wherein small pains amplify, is not only linked to the spontaneous activation of peripheral nociceptors due to inflammation, but also to abnormal regulation within the central nervous system, referred to as central sensitization.

Around the same time, the kindling model was used to describe epilepsy patients who became increasingly susceptible to subsequent seizures after each seizure. This model was later applied to substance-induced psychosis[2] and mood episodes in emotional disorders.[3] In these cases, the initial onset of the disorders was associated with psychosocial or physical stress. However, as the disease progressed, patients experienced spontaneous attacks even without substance use or external stress. The concept of sensitization was also applied to schizophrenia[4] and the staging model for post-traumatic stress disorder (PTSD).[5]

In light of these considerations, Table 1 presents a unified hypothesis encompassing psychiatric diseases and chronic functional pain. This hypothesis incorporates two dimensions: different stages of the diseases (e.g., ultra-high risk for psychosis to full-blown psychosis) and different traditional categories (e.g., psychosis, depression, trauma-related, addiction, and pain). The staging perspective does not imply that all subjects progress towards the end, as individual susceptibility and allostatic load may play a role. Additionally, the intensity, nature, time course, and timing of stress experienced by individuals can activate different brain systems.[6]

When considering shared aspects, both stress and substance use can increase dopamine synthesis capacity, which serves as a shared pathophysiologically based biomarker in schizophrenia, bipolar psychosis, delusional disorder, and sub-chronic ketamine use.[7] Moreover, increased dopamine levels in psychosis may result from the disinhibition of GABAergic interneurons,[6] which also plays a key regulatory role in chronic pain.[8] This excitatory-inhibitory imbalance (E/I imbalance) is also observed in depression[6] and PTSD, accompanied by changes in the reactivity of inflammatory systems.[5]

Table 1. Unified hypothesis in psychiatric disease and chronic functional pain

	Psychosis	Depression	Trauma-related	Addiction	Pain
Diathesis (nature)	genetic vulnerability (shared common variant risk between disorders [1]), some deficits in habituation [2] or extinction [3].				
Stress (nurture): enduring…	stress or substance [4-6]	stress [7], drug, substance	stress (threatened death) [8]	substance or behavior	acute pain
Allostatic load increases with **deregulated** neurotransmitter or cytokine levels, where **disinhibited** receptors are more easily triggered	glial cells activation → loss of synapses [5] → hippocampus GABA↓ →overactivation →VTA glutamate↑ →NAc dopamine↑ [9] →D_1 / $\mathbf{D_2}$ ratio↓	initial VTA activation → long-duration downregulation of dopamine [9], 5HT, and norepinephrine	HPA axis, amygdala↑ → inflammatory cytokine↑ [8]	direct (stimulant) or indirect (cannabis, PCP, opioid may inhibit GABA) → NAc dopamine↑ → $\mathbf{D_1}$ activation [10]	peripheral sensitization → glial cells activation → inflammatory cytokine↑→glutamate↑, GABA↓→**nociceptor** [11]
Attention bias, impaired flexibility	doesn't ignore perceptual bias	ruminate on negative thought/feeling	doesn't forget, recurrent memories	binge without compete **positive** reinforcement	doesn't shift attention from pain
Potentially reversible **sensitization**, may involve cross-system	dopamine system → functional hallucination	limbic system → **evolving** dysphoria [7]	frontolimbic circuit → **anxious** avoidance [8]	reward/ limbic/pain system →cue/ hyperkatifeia/ opioid-induced hyperalgesia	pain modulatory system →**hyperalgesia**
Spontaneous attacks	extraordinary phenomenon	**autonomous** episode [7]	**generalized** avoidance [8]	**negative** reinforcement →compulsive behaviors	**allodynia**
Entrenched **sensitization**	perceptual abnormality	unremitting episode	unremitting PTSD [8]	substance dependent	chronic functional pain

[1] Brainstorm Consortium. *Science*. 2018 Jun 22; 360(6395): eaap8757. *migraine is the sole neurological disorder that exhibits a significant correlation with psychiatric disorders in terms of common genetic risk. This correlation might potentially extend to other chronic functional pain disorders.
[2] Pass et al. *Genes Brain Behav*. 2022 Apr;21(4):e12799. *gene *DLG2*
[3] Wu et al. *Transl Psychiatry*. 2020 Jun 30;10(1):209. *gene *SORCS3*
[4] Yui et al. *Mol Psychiatry*. 1999 Nov;4(6):512-23.
[5] Howes and Onwordi. *Mol Psychiatry*. 2023 Apr 11.
[6] Post and Kopanda. *Am J Psychiatry*. 1976 Jun;133(6):627-34. *kindling
[7] Post. *Pharmacopsychiatry*. 1990 Jan;23(1):3-17. *sensitization
[8] Nijdam et al. *Acta Psychiatr Scand*. 2023;147:65–80. *staging model
[9] Grace. *Nat Rev Neurosci.* 2016 Aug;17(8):524-32.
[10] Brady et al. APA Textbook of Substance Use Disorder Treatment. 2021.
[11] Ji et al. *Anesthesiology*. 2018 Aug; 129(2): 343–366.

Inflammation further contributes to the loss of flexibility at two levels: the loss of flexible homeostatic reactivity (known as allostatic load) and the loss of flexible information processing (known as attention bias).[5] The latter can manifest in various clinical presentations, including an inability to ignore perceptual bias, rumination on negative thoughts or feelings, recurrent memories without forgetting, excessive substance use without competed positive reinforcement, or an inability to shift attention from pain.

Moving forward, the kindling model becomes relevant, as mentioned earlier, which starts with event-related and reversible attacks initially, progressing to spontaneous attacks and eventually unremitting symptoms.[2-5,8] When observed chronologically, patients appear to exhibit different trajectories despite receiving similar treatments. However, from a dimensional perspective, patients can be classified into various disease stages that require specific interventions.[5] Nevertheless, it is important to note that this unified hypothesis alone may not fully explain delayed reactions or delayed onset.

Current medications suggest the existence of specific neurocircuits underlying different traditional diagnostic categories; nevertheless, sensitization processes could potentially extend across multiple systems. For instance, individuals with opioid use disorder not only display hypersensitivity to addiction-related cues but also heightened sensitivity to emotional distress, known as hyperkatifeia, and may develop opioid-induced hyperalgesia. These phenomena may be associated with reward, limbic, and pain modulatory systems, respectively. The cross-system neuro-

biological basis could potentially involve inflammation, as evidenced by studies demonstrating that knockout of *TLR4* genes enhances analgesic effects, reduces tolerance, and prevents morphine-induced neuroinflammation and cytokine-induced enhancement of pain.[9]

Upon closer examination, although increased dopamine in the nucleus accumbens (NAc) underlies the neural mechanisms of both psychosis and addiction, they may interact with different receptors and result in various clinical presentations. Activation of the D1 receptor is crucial for the rewarding effects observed in addiction,[9] whereas activation of D2 receptors may be specific to psychosis, given that most antipsychotic drugs block dopamine D2 receptors at clinically effective doses.[6] These differences might arise from tonic and phasic firing, respectively activating D2 receptors and D1 receptors in the affinity-based model, but further research is warranted.

This unified hypothesis may provide an explanation for the widespread use of cognitive-behavioral therapy in psychiatric disorders, particularly in relation to attention bias, and it holds the potential to guide the identification of new targets for treatment. In addition to stage-based interventions,[5] a growing body of research has explored the use of microglia inhibitors or TNF-alpha inhibitors for the treatment of neuropsychiatric disorders. Considering the common excitatory-inhibitory imbalance observed in psychiatric disorders, balancing the entire system may prove more effective than solely targeting specific neurotransmitter pathways.

ETHICAL CONSIDERATIONS

Formal ethical approval for this work was not required.

DISCLOSURES

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