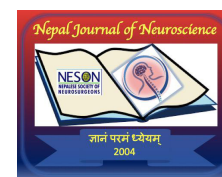


A Neurocircuit–Molecular Pathway Framework For Psychiatric Classification: Clinical And Translational Implications

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Abstract

Contemporary psychiatric diagnostic systems are predominantly symptom-based, contributing to substantial heterogeneity within diagnostic categories, frequent comorbidity, and limited guidance for mechanism-based treatment. Advances in neuroscience increasingly indicate that psychiatric disorders arise from dysfunction within specific neurocircuits, modulated by molecular and cellular pathways. However, these insights remain insufficiently integrated into clinical classification. In this article, we propose a neurocircuit–molecular pathway–based framework intended to complement existing diagnostic systems. The framework assigns individuals to dominant dysfunctional neurocircuits and associated molecular pathways, supported by graded levels of clinical and neurobiological evidence. Using schizophrenia spectrum disorders, bipolar disorder, and obsessive–compulsive and addictive disorders as exemplars, we illustrate how this approach may account for clinical heterogeneity, overlapping symptom dimensions, and differential treatment response. We further discuss implications for mechanism-informed pharmacological and neuromodulatory interventions, as well as for research stratification and future validation. While acknowledging current limitations in biomarker availability and circuit specificity, this framework provides a clinically interpretable and scalable approach to integrating neuroscience into psychiatric classification.

Keywords: psychiatric classification; neurocircuits; molecular pathways; precision psychiatry; translational psychiatry

Introduction

Despite major advances in neuroscience, psychiatric diagnosis continues to rely largely on descriptive symptom-based classifications. Systems such as DSM-5-TR and ICD-11 have achieved high diagnostic reliability and clinical utility, but their ability to reflect underlying neurobiological mechanisms remains limited^{1,2}. As a result, substantial heterogeneity exists within diagnostic categories, comorbidity across disorders is common, and prediction of illness trajectory or treatment response remains challenging.

Converging evidence from neuroimaging, neurophysiology, genetics, and molecular neuroscience suggests that psychiatric disorders reflect dysfunction in distributed

brain networks rather than abnormalities confined to isolated brain regions or single neurotransmitter systems. Research frameworks such as the Research Domain Criteria (RDoC) initiative have advanced dimensional and neurobiological perspectives on psychopathology; however, these frameworks were not designed to function as clinical diagnostic systems^{3,4,5}. Consequently, a translational gap persists between neuroscience research and routine psychiatric practice.

The present article proposes a neurocircuit–molecular pathway–based framework intended as a complementary and heuristic model rather than a replacement for existing diagnostic systems. By integrating dysfunctional neurocircuits with dominant molecular mechanisms, this framework aims to enhance clinical understanding of heterogeneity, comorbidity, and treatment resistance across psychiatric disorders.

Limitations of Current Diagnostic Systems

Symptom-based diagnostic categories were developed primarily to improve reliability and communication rather than biological validity. Although this approach has facilitated standardization, it has also resulted in diagnostic boundaries that poorly map onto underlying neurobiological mechanisms. Similar symptom dimensions, such as psychosis, mood instability, or compulsivity, occur across multiple diagnostic categories, complicating etiological inference and treatment selection.

Dimensional and transdiagnostic models have attempted to address these limitations. The Hierarchical Taxonomy of Psychopathology (HiTOP), for example, has provided valuable insights into the structure of psychopathology by organizing symptoms into empirically derived dimensions based on covariation^{6,7}. While such models improve characterization

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of phenotypic overlap and severity, they remain primarily phenomenological and do not aim to identify underlying neurobiological mechanisms or guide mechanism-based treatment selection. This highlights the need for a complementary framework that integrates biological mechanisms with clinical classification.

Here, we argue that the next phase of psychiatric classification requires neither abandonment of existing diagnostic systems nor exclusive reliance on dimensional research constructs. Instead, psychiatry requires a clinically interpretable, mechanism-oriented framework that bridges symptom-based diagnosis with contemporary neuroscience. We propose a neurocircuit–molecular pathway framework that complements existing nosologies by organizing psychopathology around dominant dysfunctional neural circuits and their associated molecular pathways. This framework is intended not as a replacement for DSM or ICD, but as a translational scaffold that links clinical presentation to underlying mechanisms, enabling biologically informed treatment selection and research stratification.

Rationale for a Neurocircuit–Molecular Approach

Brain function is organized at the level of interacting neural circuits that support cognition, emotion, motivation, and behavior. Dysregulation within these circuits produces characteristic clinical phenotypes^{8,9}. Molecular and cellular mechanisms—including neurotransmitter systems, synaptic plasticity pathways, inflammatory processes, and circadian regulators—modulate circuit function and influence vulnerability, symptom expression, and treatment response. Traditional monoaminergic models have been insufficient to explain several core features of psychiatric disorders, particularly cognitive impairment, negative symptoms, and treatment resistance. A neurocircuit–molecular framework allows these diverse findings to be integrated into a coherent structure that aligns with contemporary neuroscience while remaining clinically interpretable^{10,11}.

Unlike dimensional models such as HiTOP, which are derived from statistical analyses of symptom structure, the present framework is explicitly mechanistic in orientation. It organizes psychopathology around dysfunctional neurocircuits and associated molecular pathways, with symptoms conceptualized as downstream expressions of these disturbances.

4. Description of the Proposed Framework

4.1 Axis A: Neurocircuit Domains

Five core neurocircuit domains are proposed:

1. Cortico–limbic circuit – affect regulation and emotional processing
2. Cortico–striatal–thalamo–cortical (CSTC) loop – psychosis and compulsivity
3. Salience network – detection and attribution of relevance and threat
4. Reward circuitry – motivation, reinforcement, and pleasure
5. Cognitive control network – executive function and working memory

Individuals may exhibit primary and secondary circuit involvement, reflecting the distributed nature of brain

dysfunction¹².

4.2 Axis B: Molecular and Cellular Pathways

Key molecular pathways modulating circuit function include dopaminergic, glutamatergic (NMDA-related), and GABAergic signaling, as well as neurotrophic and synaptic plasticity mechanisms, inflammatory–immune processes, and circadian rhythm regulation. These pathways interact dynamically and are not mutually exclusive. (Table No.1)

Table No.1: Axis including A - Neurocircuit & B – Molecular pathways

Axis	Domain	Description
Axis A	Cortico–limbic circuit	Affect regulation and emotional processing
	CSTC loop	Psychosis and compulsivity
	Salience network	Threat and relevance attribution
	Reward circuitry	Motivation and reinforcement
	Cognitive control network	Executive function and working memory
Axis B	Dopaminergic pathway	Salience and reward signaling
	Glutamatergic pathway	NMDA-mediated synaptic integration
	GABAergic pathway	Cortical inhibition and network stability
	Neurotrophic pathway	Synaptic plasticity and resilience
	Inflammatory pathway	Immune–microglial activation
	Circadian pathway	Sleep–wake and rhythm regulation

4.3 Evidence Grading

Circuit–pathway assignments are probabilistic and supported by graded evidence:

- Level 1: clinical phenotype and cognitive profile
- Level 2: neuroimaging, electrophysiological, or digital phenotypic data
- Level 3: molecular, genetic, or epigenetic markers

This grading system emphasizes flexibility and acknowledges current limitations in biomarker availability. (Table No.2)

Table No.2: Evidence levels mapped with DSM/ICD diagnosis

DSM/ICD Disorder	Primary Circuit	D o m i n a n t Pathway(s)	E v i d e n c e Level	Clinical Implication
Schizophrenia spectrum	CSTC loop	Glutamatergic ± Dopaminergic	Level 1–2	Explains partial antipsychotic response
Bipolar disorder	Cortico–limbic	Neurotrophic, Circadian	Level 1–2	Accounts for episodicity and lithium response
Major depressive disorder	Cortico–limbic	Neurotrophic, Inflammatory	Level 1	Supports plasticity-based interventions
Obsessive–compulsive disorder	CSTC loop	Dopaminergic, GABAergic	Level 1–2	Rationale for neuromodulation
Addiction	Reward circuitry	Dopaminergic	Level 1–2	Mechanism-based relapse prevention

5. Disorder Exemplars

5.1 Schizophrenia Spectrum Disorders

Schizophrenia may be conceptualized as primarily involving CSTC loop dysfunction, with dominant glutamatergic NMDA hypofunction and secondary dopaminergic dysregulation. This framework explains partial response to dopamine antagonists, persistent cognitive deficits, and the rationale for glutamatergic and neuromodulatory interventions^{13,14,15}.

5.2 Bipolar Disorder

Bipolar disorder predominantly involves cortico–limbic circuit dysregulation modulated by neurotrophic and circadian pathways. This perspective accounts for episodicity, mood instability, and the therapeutic effects of mood stabilizers that influence synaptic plasticity and circadian regulation^{16,17,18}.

5.3 Obsessive–Compulsive Disorder and Addiction

Obsessive–compulsive disorder and addictive disorders prominently involve CSTC and reward circuitry dysfunction, respectively. Viewing these conditions through a circuit–pathway lens highlights shared mechanisms of compulsivity across diagnostic boundaries and supports transdiagnostic treatment approaches^{19,20,21}. (Table No.2)

6. Clinical and Research Implications

The proposed framework reframes treatment resistance as a potential mismatch between therapeutic mechanism and underlying circuit–pathway dysfunction. It supports mechanism-informed pharmacological strategies, circuit-targeted neuromodulation, and stratified clinical trials. In research settings, the framework may facilitate biologically informed subgrouping and improve reproducibility across studies^{22,23,24}. (Fig No.1)

6.1 Relationship to Existing Classification Frameworks

Symptom-based systems such as DSM-5-TR and ICD-11 prioritize reliability and clinical communication but offer limited biological specificity. Dimensional models such as HiTOP clarify symptom structure but remain phenomenological. Research frameworks such as RDoC emphasize brain–behavior relationships without providing diagnostic schemas²⁵. In

contrast, the present framework integrates neurocircuit and molecular knowledge into a clinically interpretable, mechanism-oriented classification intended to complement existing approaches.

6.2 Testable Predictions and Falsifiability

A key limitation of prior biologically informed classification models has been the absence of explicit, testable predictions. The present framework generates several falsifiable hypotheses that distinguish it from purely descriptive or dimensional systems. First, the framework predicts that patients meeting criteria for different DSM or ICD diagnoses but sharing dominant neurocircuit–molecular profiles will demonstrate greater similarity in treatment response than patients sharing a categorical diagnosis alone. For example, individuals with schizophrenia spectrum disorders and bipolar disorder who exhibit predominant cortico–limbic circuit dysfunction modulated by circadian and neurotrophic pathways should respond more similarly to mood stabilizers and circadian-targeting interventions than to dopamine-centric antipsychotic strategies.

Second, the model predicts that treatment resistance reflects, at least in part, a mismatch between therapeutic mechanism and dominant circuit–pathway dysfunction. Patients with psychotic symptoms driven primarily by glutamatergic or cognitive control network dysfunction are expected to show limited response to dopamine antagonists but greater benefit from glutamatergic modulators or circuit-targeted neuromodulation. Third, the framework predicts that neuromodulatory interventions such as transcranial magnetic stimulation or deep brain stimulation will demonstrate enhanced efficacy when targets are selected based on circuit-level dysfunction rather than categorical diagnosis. This prediction is directly testable in stratified clinical trials.

Finally, longitudinal application of the framework predicts that shifts in dominant circuit–pathway involvement over time will parallel changes in clinical phenotype, relapse risk, and treatment responsiveness, providing a dynamic alternative to static categorical diagnosis. Failure to observe these predicted convergences between circuit–pathway profiles and treatment outcomes would falsify key assumptions of the model, thereby providing a clear empirical basis for refinement or rejection.

7. Limitations and Future Directions

Neurocircuits overlap extensively, biomarkers lack specificity, and routine clinical assessment of circuit dysfunction remains challenging. The framework is intended as a heuristic model rather than a validated diagnostic system. Future work should focus on longitudinal validation, multimodal biomarkers, and pragmatic clinical implementation studies.

Conclusion

A neurocircuit–molecular pathway–based classification offers a biologically grounded and clinically interpretable approach to psychiatric diagnosis. By complementing existing symptom-based systems, this framework provides a translational bridge between neuroscience and clinical practice and supports ongoing efforts toward precision psychiatry. We argue that the future of psychiatric classification cannot remain exclusively symptom-

bound. Progress toward precision psychiatry will require models that re-integrate neuroscience into clinical reasoning without sacrificing interpretability or utility. The neurocircuit–molecular pathway framework represents one step toward that goal.

STATEMENTS AND DECLARATIONS

Competing Interests

The authors declare that they have no competing interests relevant to this manuscript.

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Ethics

Informed consent was obtained from the patient to use the radiological images. Institutional ethical approval was not required.

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