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Review

Circuit mechanisms of psychotic symptoms across disorders

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SUMMARY

Psychotic symptoms, including hallucinations, delusions, and disorganized thought, occur across psychiatric and neurological disorders, yet their underlying mechanisms remain poorly integrated across scales. Here, we propose a transdiagnostic framework in which disturbances in dopamine, glutamate, GABA, serotonin, and acetylcholine alter neuronal gain and synaptic efficacy, disrupting the precision weighting of sensory evidence, prediction errors, and internally generated representations. These local disturbances propagate through cortico-striato-thalamo-cortical circuits and large-scale functional networks, producing abnormal integration-segregation dynamics and unstable attractor states. This multilevel model links molecular and cellular perturbations to circuit dysfunction, network instability, and symptom expression while allowing distinct biological pathways to converge on shared computational vulnerabilities. Emerging neuroimaging, dynamical systems, and artificial intelligence approaches may enable individualized tests of these mechanisms and support more precise, circuit-informed interventions for psychotic symptoms.

PSYCHOTIC SYMPTOMS BEYOND SCHIZOPHRENIA: TOWARD A TRANSDIAGNOSTIC FRAMEWORK

In psychiatry, the term *psychosis* does not refer to a diagnostic entity but to a constellation of symptoms—including hallucinations, delusions, disturbances of self-experience, and disorganized thought—that reflect profound disruptions in perception, belief, affect, and behavior, often culminating in a distorted relationship with reality.[1,2]

Despite decades of research, the central question of how these diverse symptoms arise from underlying brain mechanisms remains open. Current accounts have identified not only key neurobiological correlates, most prominently dopaminergic dysfunction, but also a lack of a framework linking molecular alterations to large-scale brain dynamics and behavior, in particular one applicable across the range of disorders in which psychosis is encountered.

We propose that psychotic symptoms emerge from partly distinct biological perturbations in neuromodulatory and synaptic systems—including glutamate, GABA, serotonin, acetylcholine, and prominently dopamine—that are differentially affected across psychiatric and neurological disorders (NDs) and individuals. Rather than converging on a single biological pathway, these perturbations may alter related computational operations, including neuronal gain and the precision weighting of sensory inputs, prediction errors, and internally generated representations. Aberrant precision assignment may bias salience attribution, destabilize cortical-subcortical network interactions, and promote the emergence of hallucinations, delusions, disorganization, altered self-experience, and related psychotic symptom dimensions.

In this framework, neuromodulatory systems contribute in complementary and partially dissociable ways to the regulation of neuronal gain, synaptic efficacy, and information flow across hierarchical circuits. Dopaminergic signaling is particularly well positioned to influence the precision of prediction-error signals, while glutamatergic, GABAergic, serotonergic, and cholinergic mechanisms shape the excitability, gating, and integration of neural representations across hierarchical circuits. Alterations in these mechanisms may shift the relative influence of internally and externally driven (sensory) representations. This imbalance may allow internally generated representations to become pathologically dominant or insufficiently constrained by sensory or cognitive signals, giving rise to hallucinations, delusions, and other psychotic symptoms. At the system level, such alterations are expected to manifest as changes in the coupling and integration of large-scale brain networks and, from a dynamical system perspective, lead to instabilities in the attractor landscape governing perception and cognition (Figure 1).

While the pathophysiology of psychotic symptoms has historically been investigated primarily within schizophrenia spectrum disorders (SSDs), psychotic phenomena are transdiagnostic and dimensional features that occur across a broad range of severe mental illnesses (SMI). Beyond SSD, psychotic symptoms are

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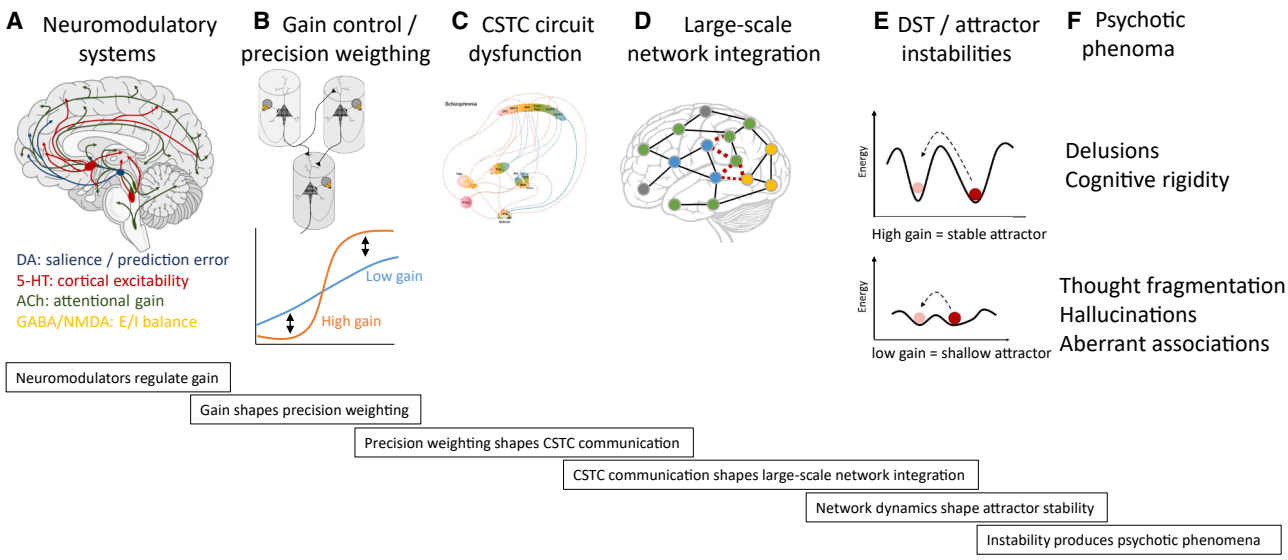


Figure 1. Multiscale cascade model of psychotic symptom emergence across disorders

(A) Neuromodulatory systems (dopamine, glutamate, GABA, serotonin, and acetylcholine) regulate cortical and subcortical processing by modulating neuronal gain and synaptic efficacy. Dopamine is linked to precision of prediction errors and salience signaling, serotonin to cortical excitability, acetylcholine to attentional gain, and GABA/NMDA mechanisms to excitation-inhibition balance.

(B) These modulatory influences converge on gain control and precision weighting mechanisms in cortical microcircuits, implemented through the balance of excitatory pyramidal neurons and inhibitory interneurons. Aberrant precision assignment leads to inappropriate weighting of sensory inputs and internally generated representations.

(C) At the circuit level, dysfunction propagates to cortico-striato-thalamo-cortical (CSTC) loops, including ventral (limbic) and dorsal (associative) circuits. Altered effective connectivity within these recurrent loops contributes to dysregulated salience assignment and impaired cognitive control.

(D) These circuit-level abnormalities scale to disruptions in large-scale brain networks, including the salience network, DMN, and frontoparietal control network, resulting in impaired network switching and aberrant integration of internally and externally oriented processing.

(E) At the system level, these disturbances are expressed as attractor instability in dynamical brain-state space, characterized by reduced stability of neural and cognitive states, flattened attractor landscapes, and increased transitions between metastable states.

(F) These multilevel abnormalities culminate in psychotic symptom dimensions, including hallucinations, delusions, disorganization, altered self-experience, and salience distortions, which are presented as transdiagnostic phenomena across psychiatric and NDs.

frequently observed in mood disorders, borderline personality disorder (BPD), and neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD), as well as in encephalitis and delirium states, suggesting partially overlapping but potentially distinct neurobiological mechanisms across diverse clinical conditions. Importantly, psychotic experiences (PEs) also occur in approximately 7% of the general population.[3,4] There, they span a spectrum ranging from mild perceptual distortions to fully developed, structured hallucinations and delusions, differing in their quality, duration, and modalities.[5,6] Thus, PEs are best conceptualized as dimensional phenomena that vary in expression, persistence, and clinical context across individuals and conditions. Within our framework, this transdiagnostic distribution can be understood as reflecting shared computational disturbances that can arise from diverse biological pathways.

Recent dimensional frameworks, such as the Hierarchical Taxonomy of Psychopathology (HiTOP) psychosis superspectrum,[7,8] formalize this continuity by conceptualizing psychosis as a transdiagnostic continuum rather than a discrete category. Measurable intermediate constructs might help to link specific circuit dynamics and neuromodulatory processes underlying hallucinations, delusions, and related experiences across disorders. However, the explanatory value of these dimensions is contingent upon the degree to which they can be explained by underlying neural and computational processes, as proposed in the present framework.

Across mental and NDs, psychotic symptoms are a key clinical target. They often signal illness presence and track disease severity with prodromal non-psychotic symptoms preceding psychosis[9,10] and symptom worsening over disease proregression in neurodegenerative disorders.[11] Psychotic symptoms often impair everyday function and social adaptation[12] and are often highly distressing to patients and caregivers.[13,14] Although drugs blocking dopamine D2 receptors treating psychosis are available, their significant side effects and variable long-term benefits highlight the need for mechanism-informed personalization of treatment.[15,16]

While the distinct phenomenological profiles of psychotic symptoms across different mental and NDs suggest a degree of disease-specific pathophysiological mechanisms, none of these associations are exclusive, and emerging evidence supports a transdiagnostic perspective. For instance, visual hallucinations are predominantly observed in ND, such as PD and Lewy body dementia, whereas grandiose delusions are characteristically associated with the manic phase of bipolar disorder. Within the proposed precision-weighting framework, such phenotypic patterns may reflect different biological perturbations affecting related computational operations, rather than entirely distinct mechanisms.

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Bridging dimensional models with neurodevelopmental and circuit-based perspectives is essential to understand how diverse genetic, environmental, and experiential factors shape the maturation or degeneration of neural systems implicated in psychosis.

Importantly, psychotic symptoms in SMIs and NDs are often preceded by other clinical symptoms and latent neurobiological disturbances. This suggests that genetic predispositions, early-life experiences, and environmental exposures interact to shape the maturation, plasticity, or degeneration of neural systems involved in perception, salience attribution, affect regulation, and cognition. Within our framework, these factors may alter neuromodulatory tone and excitation-inhibition balance, thereby biasing neuronal gain control and the precision weighting of sensory inputs, prediction errors, and internally generated representations. For example, adverse childhood experiences increase the risk and severity of psychotic symptoms in BPD[17] and SSD.[18] They may also shape the content and trajectory of PEs through cognitive-affective mechanisms, such as negative self- and other-related schemata ("poor me, bad me"), which influence appraisal, coping, and interpersonal expectations.[19,20] From a precision-weighting perspective, such schemata may increase the salience of threat-related interpretations and shift the balance between external evidence and internally generated beliefs. Understanding developmental trajectories in relation to psychosocial and environmental factors is therefore critical for identifying both shared and disorder-specific biological pathways to psychotic symptoms across SMI and NDs.

Despite this progress, transdiagnostic approaches that investigated psychotic symptoms across disorders remain limited. Such studies are crucial for identifying shared or distinct circuit mechanisms underlying psychosis across disorders.[21] This knowledge could have direct clinical implications; for example, while antipsychotic treatments are often effective for psychosis in SSDs, they yield limited success in managing similar symptoms in delirium or AD. Understanding circuit-based dysfunctions associated with psychosis could enable patient stratification based on underlying neurobiological mechanisms, potentially guiding more targeted and effective treatments.

In this review, we integrate evidence across molecular, circuit, and system levels within this framework, linking perturbations in neuromodulatory systems (dopamine, glutamate, GABA, serotonin, and acetylcholine) to disruptions in large-scale brain networks and dynamics, and ultimately to psychotic phenomena. Importantly, we do not propose a single biological mechanism underlying psychotic symptoms.[22] Instead, we consider dysregulated precision weighting as a candidate computational principle that may be implemented through multiple, partially distinct neurobiological pathways and expressed at the systems level through altered network organization and dynamics.

We will explore established micro- and macroscale circuit disruptions within these groups, highlight shared themes and overlapping concepts, and introduce two neuroimaging frameworks that can help integrate molecular and system-level insights. These frameworks provide a comprehensive system-level perspective on the circuit mechanisms driving psychotic symptoms, while allowing for heterogeneity in their biological implementation across different mental and neuropsychiatric disorders. Finally, we highlight current methodological, analytical, and conceptual developments that have the potential to transform research on psychotic symptoms.

By integrating computational principles, neuromodulatory mechanisms, and large-scale brain dynamics, this framework offers a mechanistic and empirically testable account of psychotic symptoms, with the potential to guide experimental models, biomarker development, and more personalized clinical interventions.

A MULTISCALE MECHANISTIC FRAMEWORK OF PSYCHOTIC SYMPTOMS: NEURAL GAIN AND PRECISION WEIGHTING ACROSS BRAIN SYSTEMS

The evolution of theories underlying the emergence of psychotic symptoms has progressed significantly from localized brain region hypotheses to comprehensive circuit-level models, reflecting a growing understanding of the complex nature of psychotic disorders and their underlying neural mechanisms. Initial theories focused on specific brain regions, including the hippocampus,[21,23,24] prefrontal cortex (PFC), and most prominently striatal dopamine abnormalities.[25,26] Across these developments, a key unresolved question is how alterations at different spatial and biological scales, ranging from local synaptic processes to large-scale network dynamics, can be understood within a common mechanistic framework. In this review, we interpret this progression through the lens of dysregulated precision weighting, implemented neurobiologically as alterations in neural gain across hierarchical brain systems and diverse neurotransmitter systems.

Local striatal dopamine abnormalities have been most extensively studied in SSD, providing one of the most extensively characterized biological mechanisms associated with the emergence of PEs in this disorder group. Dopaminergic projections from the midbrain to the striatum are increasingly understood not only as encoding prediction errors[27] but also as modulating their precision—that is, the postsynaptic gain assigned to prediction-error signals. These prediction errors, related to both reward and perception in distinct striatal regions, are widely considered to be the neurobiological underpinning of perceptual disturbances proposed by various computational models.[28–30] According to these models, alterations in perceptual processing lead to assigning maladaptive salience to stimuli.[31] In computational terms, aberrant salience can be interpreted as a consequence of misallocated precision, whereby certain representations are assigned excessive gain relative to competing cognitive or external inputs, which, together with an increased reliance on prior expectations, precipitates delusions and hallucinations.[32,33] In SSD, there is multiple evidence from genetic, molecular, and imaging studies showing direct local striatal abnormalities like increased dopamine synthesis capacity and release in striatal areas.[34] While dopamine is thought to be a major contributor to the development of psychotic symptoms in PD, temporal lobe epilepsy, substance-induced psychosis, and bipolar disorder, the exact role of striatal dopaminergic dysfunction seems to be more complex. For example, in PD psychotic symptoms were historically attributed to dopamine agonist treatment. However, recent findings suggest that psychosis in PD is associated with more widespread

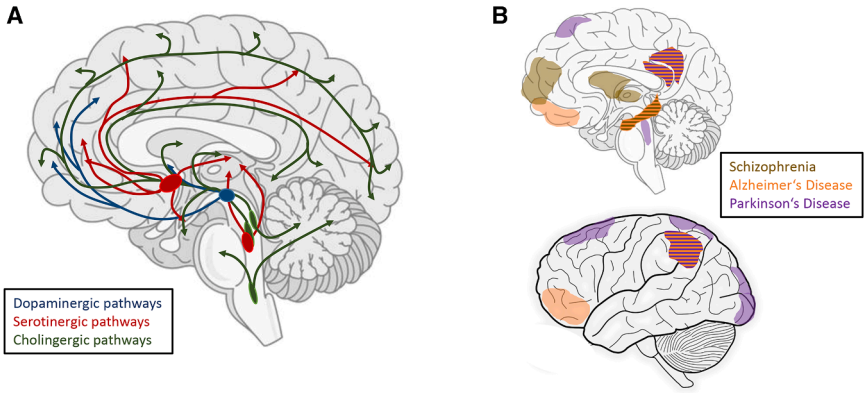


Figure 2. From local dysfunctions to large-scale circuit models of psychosis
(A) Transmitter systems involved in psychotic symptoms across different brain disorders.
(B) Brain areas implicated in psychotic symptoms in schizophrenia, AD, and PD.

disruptions in brain circuit function.[35] These include degeneration of dopaminergic neurons in the substantia nigra, as well as imbalances in serotonin-dopamine interactions and cortical serotonergic dysregulation. In delirium, elevated dopamine might contribute to the development of the delirium state and may be associated with psychotic symptoms in particular,[36] though anti-dopaminergic treatment does not significantly affect clinical outcome.[37]

As such, the present literature suggests a transdiagnostic model in which striatal dopamine dysregulation represents one important integrative mechanism among several interacting contributing to the development of psychotic symptoms[38] (Figure 2). These pathways may converge on partially shared computational vulnerabilities while retaining disorder- and symptom-specific biological implementations. In the following sections, we outline how striatal dopaminergic signaling both modulates and is modulated by other brain systems across neuropsychiatric disorders exhibiting psychosis and how these interactions may shape precision weighting within a broader, multilevel framework.

At the system level, alterations in precision weighting are expected to manifest in changes of effective connectivity within the context of anatomically and functionally embedded circuits, particularly specific subcircuits of the cortico-striato-thalamo-cortical (CSTC) loops[39,40] and large-scale functional networks.[41]

Two CSTC circuits have been most consistently implicated in the emergence of psychotic symptoms. First, a ventral, limbic circuit linking the ventral striatum, ventromedial PFC, orbitofrontal cortex, hippocampus, and amygdala that is thought to regulate salience attribution and emotional valuation, influencing ventral striatal dopamine signaling through both cortico-striatal and hippocampal-striatal pathways. This circuit regulates the precision assigned to affective and motivational signals.[42] Second, a dorsal cognitive circuit connecting the dorsal striatum (caudate and putamen) with the dorsolateral PFC and anterior cingulate cortex (ACC) supports associative learning and executive and cognitive regulation of dopaminergic tone. This circuit may support higher-order regulation of precision, including the contextual modulation of belief updating and cognitive control.

The thalamus plays a crucial integrative role within and between these CSTC circuits. As a key relay hub, it regulates the flow and filtering of information between cortical and striatal regions and coordinates activity across large-scale networks.[43] From a computational perspective, the thalamus acts as a central hub for precision control across hierarchical processing streams and is therefore ideally positioned to regulate the gain of sensory and cortical signals.[44] It is dynamically impacted by dopaminergic signaling: altered thalamic relay and inhibition can modulate midbrain dopaminergic firing patterns,[45] while dopamine in turn regulates thalamocortical transmission, creating a reciprocal loop that shapes salience assignment across multiple system.[46] Disruptions in thalamic function may therefore directly contribute to aberrant precision weighting, affecting both sensory gating and large-scale network integration.[47,48]

In SSD both the ventral and dorsal CSTC circuits have been implicated. For example, reduced functional connectivity (FC) has been described between the hippocampus and striatum and the dorsal striatum and ACC and dorso-lateral PFC.[49] Consistent with dorsal CSTC abnormalities, functional neuroimaging evidence shows correlations between dorsolateral prefrontal cortex (DLPFC) activity and striatal dopamine synthesis (Meyer-Lindenberg et al.[50]). Thalamic dysconnectivity—particularly within mediodorsal and pulvinar nuclei—has been consistently reported in schizophrenia[51,52] and related psychotic states,[53–55] including PD with psychotic symptoms.[53,56] Rather than reflecting isolated relay dysfunctions, these thalamic disturbances likely index impaired gain control in thalamocortical circuits, leading to aberrant sensory precision, aberrant attentional control, and altered integration of perceptual and cognitive information.

These functional abnormalities are paralleled by convergent structural alterations in key CSTC-limbic nodes. Gray matter volume decrease in the hippocampus has been reported for SSD,[23] BPD,[57] bipolar disorder,[58] PD,[35] and AD.[11] In the latter, the evidence suggests that frontal and parietal regions also display volume reductions.[59] Importantly, structural alterations in regions such as the hippocampus are not merely regional deficits but are thought to be correlates of functional perturbation in circuit-level gain regulation, for example, by altering hippocampal drive onto striatal dopamine systems,[23,60] thereby biasing salience assignment.

Together, these findings suggest that structural and functional vulnerabilities converge within overlapping CSTC circuits to disrupt the regulation of neural gain across distributed networks, supporting a transdiagnostic model in which psychotic symptoms emerge from shared disruptions in integrative network architecture and aberrant precision weighting. Importantly, this framework does not imply a single biological route to psychotic symptoms. Rather, similar phenomenology may arise when

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distinct molecular and circuit-level perturbations alter related computational operations, such as the balance between internally generated representations and sensory evidence. Auditory verbal and visual hallucinations provide an illustrative example of this principle.

Structural brain abnormalities have also been linked directly to auditory verbal hallucinations (AVH) in both SSD and BPD, converging on regions involved in language and cognitive control, such as the superior temporal gyrus, inferior frontal gyrus, and orbitofrontal cortex.[61,62] These regional alterations may reflect abnormal amplification of internally generated representations (e.g., inner speech), resulting from increased precision assigned to top-down predictions relative to sensory input.[63,64] In BPD, alterations in cortical thickness, gyrification, and folding complexity suggest a morphometric vulnerability to AVH.[65] By contrast, in SSD, these structural deviations are accompanied by widespread functional network disruptions involving frontostriatal, frontoparietal, temporal, and sensorimotor circuits.[66–68] Thus, in AVH, alterations in cortical gain and frontotemporal network function may increase the influence of internally generated representations while weakening their distinction from externally driven auditory input, providing a mechanistic link from local circuit dysfunction to the phenomenology of hearing voices. This pattern suggests that similar phenomenology (e.g., AVH) may arise from different points of perturbation within a shared gain-control architecture, rather than disorder-specific mechanisms alone,[69] although evidence for this convergence across disorders remains limited.

A contrasting example is provided by visual hallucinations in PD, where evidence points to a biological route involving degeneration of cholinergic and serotonergic neuromodulatory systems, altered dopaminergic modulation, and dysfunction of posterior visual, attentional, and default-mode network (DMN) interactions.[35] In patients with PD and minor visual hallucinations (e.g., passage or presence hallucinations and visual illusions), gray matter loss and hypometabolism have been related to the posterior neocortex, while structured hallucinations additionally involved the visuoperceptive processing stream.[56,70,71] Neuroimaging studies of PD patients experiencing visual hallucinations have further shown that these symptoms are not confined to dysfunction within visual cortices alone but involve altered interactions between visual processing systems, dorsal attention networks, and the DMN.[72–74] Together with dopaminergic, serotonergic, and cholinergic dysfunction, these circuit alterations may reduce the effective precision of sensory evidence and destabilize the balance between externally driven and internally generated activity, thereby allowing internally generated visual representations to intrude into conscious perception. In SSD, by contrast, alterations in connectivity between default-mode, salience, and frontal networks have been repeatedly identified,[41,75] likely being the macroscopic expressions of dysregulated precision weighting, where aberrant salience signals linked to dopaminergic dysfunction bias network interactions and destabilize ongoing cognitive states. Thus, AVH in SSD and visual hallucinations in PD may converge phenomenologically on aberrant precision weighting while arising from partially distinct biological pathways—illustrating how shared computational vulnerabilities can emerge from different molecular, circuit, and network-level perturbations.

Across disorders, a convergent pattern emerges whereby brain abnormalities associated with psychotic symptoms are not confined to regions processing the dominant sensory modality of hallucination but extend into transmodal association areas and large-scale control networks. This distributed pattern is consistent with the view that psychosis reflects a systems-level disorder of gain regulation, in which imbalances in precision weighting are expressed across hierarchical networks, rather than a deficit localized to specific sensory or cognitive modules.

Having described the involvement of specific CSTC subcircuits implicated in psychotic symptoms, it is critical to understand how local microcircuit disturbances and neuromodulatory systems converge to regulate neural gain and precision weighting within these circuits, ultimately shaping mesocortical dopamine signaling and the emergence and expression of psychotic phenomena.

A widely studied mechanism linking local cortical abnormalities to circuit dysfunction and dopamine dysregulation is excitatory-inhibitory (E/I) imbalance. Most cortical long-range communication is transmitted via glutamatergic neurons, arising from layers II–VI for cortico-cortico- and infragranular layers for cortico-subcortical connections. The firing pattern of these neurons is tightly regulated by a feedback loop involving parvalbumin-positive GABA-ergic interneurons and metabotropic NMDA receptors. Here, E/I balance refers to the relative contribution of excitatory and inhibitory synaptic inputs to these local regulatory circuits that impact long-range information processing. Importantly, E/I balance not only regulates overall cortical excitability but also determines neuronal gain, temporal precision, and oscillatory synchrony, thereby shaping which neural representations are amplified, stabilized, or suppressed across distributed cortical networks.[76] Therefore, it may mediate aberrant precision weighting at the microcircuit level.

Importantly, E/I balance in cortical and hippocampal microcircuits directly modulates striatal dopamine release: excessive excitation or reduced inhibition can drive aberrant signaling through CSTC loops, altering midbrain dopaminergic neuron firing and ultimately contributing to the heightened striatal dopamine tone observed in psychotic symptoms.[77] Alterations in E/I balance can therefore be understood as disturbances in local gain control,[78] thereby affecting precision assignment to sensory inputs or internal representation, influencing the fidelity of neural representations and their propagation across cortical circuits.[79] Consistent with this framework, Haarsma et al.[80,81] showed that first-episode psychosis is associated with impaired dopamine-dependent precision weighting of prediction errors during learning. Their findings suggested that dopamine contributes to psychosis not only through striatal salience mechanisms but also by regulating cortical gain control during belief updating, linking neuronal gain abnormalities to maladaptive inference.

In SSD, there is extensive evidence for glutamate and GABA abnormalities.[82] This includes genome-wide association studies of SSD identifying genes that are linked to E/I balance, primarily through synaptic function and glutamate signaling pathways,[83,84] as well as neuroimaging evidence including electroencephalogram (EEG), magnetoencephalography (MEG), and

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Table 1. Psychotic symptoms across disorders—Symptoms, neurotransmitters, and circuits

Disorder	Main psychotic symptoms	Key neurotransmitter(s)	Affected brain systems	Clinical management
Schizophrenia (SZ)	hallucinations (mainly auditory), delusions, disorganized thought, paranoia, cognitive impairment	dopamine (D2 in striatum, D1 in PFC), glutamate (NMDA), GABA	PFC, hippocampus, thalamus, cortico-striato-thalamic circuits	antipsychotics (D2 antagonists, partial agonists), cognitive-behavioral therapy (CBT), psychosocial interventions
Affective disorders (bipolar disorder, major depression with psychotic features)	mood-congruent delusions (grandiosity in mania, guilt in depression), auditory hallucinations (self-referential)	serotonin (5-HT dysfunction), dopamine (reward circuits), glutamate	limbic system (amygdala, hippocampus), PFC, reward circuitry	mood stabilizers (e.g., lithium and valproate), atypical antipsychotics, antidepressants (with caution)
Primary substance-induced psychosis (PSD)	hallucinations (mainly visual), paranoia, delusions, disorganized thought (often transient)	dopamine (in stimulant-induced cases), glutamate (NMDA antagonism in ketamine/PCP use), serotonin (psychedelic-induced)	varies by substance: frontal cortex (cocaine, meth), thalamus (ketamine, PCP), serotonergic pathways (lysergic acid diethylamide, psilocybin)	withdrawal management, benzodiazepines (for agitation), antipsychotics (if persistent symptoms)
Borderline personality disorder (BPD)	transient stress-induced paranoid ideation, dissociation, micropsychotic episodes (brief hallucinations, persecutory thoughts)	serotonin (5-HT), dopamine	limbic-prefrontal dysconnectivity, amygdala hyperactivity, PFC	dialectical behavior therapy (DBT), atypical antipsychotics (if severe transient symptoms)
Delirium	acute onset fluctuating hallucinations (often visual), delusions, confusion, disorientation	acetylcholine, dopamine	diffuse cortical dysfunction, hippocampus, thalamus, brainstem	treat underlying cause, antipsychotics (e.g., haloperidol, and quetiapine), cholinesterase inhibitors (in some cases)
Parkinson's disease (PD) psychosis	visual hallucinations, minor illusions, paranoid delusions (late-stage)	dopamine (nigrostriatal pathway), serotonin (5-HT2A dysfunction), acetylcholine (cholinergic deficits)	basal ganglia, brainstem (raphe nuclei), thalamus, PFC, visual processing areas	adjusting dopaminergic therapy, 5-HT2A inverse agonists (e.g., pimavanserin), cholinesterase inhibitors
Alzheimer's disease (AD) psychosis	visual hallucinations, delusions (misidentification, paranoia), late-stage agitation	acetylcholine, serotonin, dopamine	temporal and parietal lobes, hippocampus, frontal cortex, DMN	atypical antipsychotics (low-dose), cholinesterase inhibitors

functional magnetic resonance imaging (fMRI),[85,86] consistent with aberrant gain modulation and resulting impaired coordination of hierarchical network dynamics. Altered E/I imbalance has also been observed in PD,[87] AD,[88,89] and mood disorders.[90] This convergence across disorders supports the notion that dysregulated gain control may represent a transdiagnostic mechanism contributing to psychotic symptom formation despite heterogeneous upstream etiologies. However, direct causal links between these alterations and psychotic symptoms remain to be empirically established.

Additional systemic components regulating dopaminergic signaling include other neuromodulatory influences, which have been implicated in psychosis (see Table 1). Specifically, serotonergic and cholinergic alterations have been proposed to affect CSTC function and striatal dopamine signaling with effects that may vary across disorders and circuit contexts. These pathways may contribute to the pathogenesis of psychosis, either directly or by modulating cortical excitability, sensory gain, and dopamine-glutamate coupling within specific CSTC subcircuits.

Serotonin has long been proposed to contribute to CSTC circuit dysfunction in psychosis. Mechanistically, serotonergic input modulates cortical excitability and inhibitory interneurons,[91] thus directly affecting cortical gain and precision of cortical representations. This is particularly true in dorsolateral PFC and ACC,[92] which in turn regulate midbrain dopaminergic firing and striatal dopamine release.[34] This is supported by the discovery that the 5-HT2A agonist lysergic acid diethylamide (LSD) can induce psychotomimetic states, despite clinical differences from SSD.[92,93] In SSD, post-mortem studies have reported decreased 5-HT2A receptor densities and a loss of serotonergic neurons in the raphe nuclei, findings that have been

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interpreted as early abnormalities predating the onset of psychotic symptoms.[94,95] These alterations are thought to disrupt serotonergic modulation of CSTC circuits, potentially altering E/I balance in key cortical and subcortical regions such as the ACC and dorsolateral PFC. In PD, serotonergic alterations have been linked specifically to hallucinations. PD patients experiencing visual hallucinations exhibit higher 5-HT2A and 5-HT3 receptor binding compared with those without hallucinations.[96,97] This suggests that serotonergic dysregulation contributes to psychotic symptoms in PD through mechanisms that may differ from those implicated in schizophrenia.[98] The therapeutic relevance of serotonin in psychotic symptoms of PD patients is highlighted by pimavanserin, a 5-HT2A inverse agonist, which has been approved for the treatment of psychotic symptoms in PD[99] and has also demonstrated efficacy in reducing relapse rates in psychotic symptoms in AD.[100]

Theories of cholinergic involvement in the pathophysiology of SSD suggest that decreased muscarinic M1 and M4 receptor densities in the ACC and PFC contribute to altered cortico-striatal circuit function[101] and directly modulate mesocortical dopamine release in the striatum.[102,103] Cholinergic projections from the basal forebrain and thalamic nuclei play a critical role in regulating attentional gain and arousal, stabilizing cortical network dynamics,[104] and thereby dynamically controlling precision assignment across cortical networks. In PD, loss of cholinergic neurons in the nucleus basalis of Meynert (BNM) and the pedunculopontine nucleus has been proposed as a potential driver of altered FC in the DMN and salience network, with PD patients experiencing visual hallucinations showing distinct cholinergic deficiency in the left ventral visual stream and the left superior temporal lobe.[74] Similarly, AD patients with hallucinations might exhibit reduced acetylcholinesterase activity in visual areas, indicating cholinergic denervation[11,105] that may contribute to network-level dysfunction.[106] Beyond ND, cholinergic deficiency is also a key feature of delirium,[107,108] in particular hippocampal input and potentially reciprocal interactions with dopamine and serotonin neurotransmission.[108]

Together, these findings support a convergent model in which multiple neuromodulatory systems regulate hierarchical brain-network dynamics through distributed gain modulation. Rather than acting as independent contributors, dopaminergic, serotinergic, and cholinergic systems may implement complementary aspects of precision control across hierarchical brain networks,[109] modulating the relative influence of sensory inputs, internal models, and contextual information. Importantly, the relevance of these neuromodulatory systems for psychotic symptoms may not primarily lie in isolated neurotransmitter abnormalities but in their capacity to alter the stability, integration, and transition dynamics of large-scale brain networks in context. Serotonergic and cholinergic dysregulation modulate cortico-striatal dynamics, influencing both E/I balance and striatal dopamine release. In this hierarchical architecture, dopamine is suggested to occupy a central role in implementing precision weighting at the system level, effectively modulating which signals are amplified and propagated through CSTC circuits.[80] Serotonergic pathways from the raphe to prefrontal and striatal regions may perturb dopaminergic tone, thereby altering the gain assigned to the prediction-error signal and biasing perceptual inference, while cholinergic deficits within basal forebrain and thalamic nuclei further compromise network stability and sensory precision by disrupting attentional gain control and thalamocortical filtering mechanisms. Through these effects, neuromodulatory disturbances may shift the operating regime of distributed brain systems, promoting unstable transitions between internally and externally oriented processing states, impaired sensory gating, and aberrant coupling between salience, default mode, attentional, and sensory networks. More broadly, these observations underscore that neurotransmitter abnormalities are not independent drivers of psychotic symptoms but are embedded within a distributed system of gain control, in which multiple neuromodulatory systems interact across molecular, cellular, circuit, and network levels. Contemporary models of psychotic symptoms therefore require a representation of how these interacting mechanisms shape precision weighting across large-scale brain systems, rather than attributing symptom expression to any single neurotransmitter system. Dopaminergic signaling may be particularly relevant for the precision of prediction-error signals and salience attribution, but its effects are shaped by interactions with glutamatergic, GABAergic, serotonergic, and cholinergic mechanisms, as well as by the circuit and network context in which these signals operate. This perspective reconciles the apparent heterogeneity of upstream mechanisms; partially shared computational disturbances may emerge from different combinations of molecular, circuit, and network-level perturbations.

TOWARD COMPUTATIONAL SYSTEMS MODELS OF PSYCHOTIC SYMPTOMS

The evidence reviewed so far suggested that psychotic symptoms may emerge from disruptions in how brain systems regulate the amplification, integration, and selection of representation across distributed networks. Within this framework, multiple neurotransmitter systems and large-scale neural networks interact to regulate neuronal gain across CSTC circuits. Striatal dopamine signaling may be particularly relevant for the precision assigned to prediction-error signals and the attribution of salience but represents one component of a broader, distributed gain-control architecture rather than a single downstream endpoint of diverse biological disturbances. Although dopamine-dependent alterations in prediction-error signaling provide an important computational account of maladaptive salience attribution, isolated neurotransmitter abnormalities alone cannot explain the phenomenological diversity, temporal variability, and transdiagnostic nature of psychotic symptoms. Instead, dopaminergic effects are shaped by interactions with local circuit properties, other neuromodulatory systems, and large-scale network organization. Models capable of capturing the emergent properties arising from these multiscale, system-level interactions hold the promise of providing predictive insights and guiding personalized psychiatry.[110]

A second challenge for network models arises from the dynamic nature of psychotic symptoms, which fluctuates across multiple timescales. Transient subclinical experiences, attenuated or brief symptoms, and episodes of severe psychotic

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symptoms can emerge and subside unpredictably, often eluding clinical detection. This variability argues for computational approaches that incorporate non-stationarity into computational models—accounting for the temporal variability, switching dynamics, and fluctuating psychotic symptom severity seen in different mental disorders. Moreover, it emphasizes the importance of identifying developmental, genetic, and environmental factors that shape the associated CSTC circuit long before first psychotic symptoms emerge.

Finally, psychotic symptoms do not manifest as discrete, disease-specific phenomena but rather exist along a transdiagnostic spectrum that spans from transient subclinical experiences in otherwise healthy individuals to severe, chronic, and treatment-resistant illness. Mechanistic models must thus reflect this broad clinical spectrum in allowing for graded transitions between different symptom states while capturing shared mechanisms across diagnoses.

Therefore, advancing our understanding of psychotic symptoms requires novel circuit models that move beyond static localizationist or connectionist accounts and instead conceptualize hallucinations and delusions as emergent properties of unstable large-scale neural dynamics. Such models should integrate local microcircuit abnormalities, neuromodulatory influences, distributed network organization, and temporal fluctuations within a unified systems-neuroscience framework. Large-scale circuit and dynamical system models are particularly promising in this regard, as they provide a mechanistic framework for understanding how alterations in neuronal gain, precision control, and recurrent network interactions may destabilize brain states, bias perceptual inference, and ultimately contribute to the emergence of psychotic symptoms across diagnostic categories.

Large-scale network models of psychotic symptoms

Modeling the brain as an interconnected system has gained significant traction in recent years, providing a biologically grounded framework for understanding how local molecular or structural alterations can propagate through large-scale neural circuits to produce system-level dysfunction through aberrant gain regulation and disrupted network dynamics.[111–113] In this sense, network models can be viewed as the systems-level implementation of the previously described mechanistic framework of dysregulated precision weighting and aberrant gain control. The network topology of the brain, defined by the arrangement of nodes (brain regions) and edges (functional or structural connections), can be analyzed using graph theoretical methods to examine both static and time-varying network organization. These approaches have been instrumental in uncovering key features that govern the computational processes underlying psychotic symptoms.[114,115] Specifically, brain networks balance functional segregation and global integration through modular organization,[116] supporting flexible and efficient cognition.[117] From a mechanistic perspective, this balance reflects the brain's capacity to dynamically regulate neural gain and maintain stable yet flexible information processing near critical regimes.[79,118] Disruptions to this balance—particular between prefrontal, hippocampal, and striatal nodes—have been proposed to underlie the aberrant information processing seen in psychosis and described in the long-standing disconnection hypothesis of schizophrenia.[85,119,120] Crucially, these network-level disruptions can be interpreted as the macroscopic manifestation of the same precision-weighting abnormalities described at the synaptic and circuit level in predictive coding accounts. For example, hyperactivity within hippocampal and striatal circuits has been linked to biased salience assignment toward self-generated percepts or beliefs and potentially increasing the likelihood that internally generated activity is experienced as meaningful or real.[121]

Alterations in structural brain networks associated with psychosis have been extensively documented (for review, see van den Heuvel and Fornito[122]). Two consistent themes have emerged: First, a shift toward hyper-integration, which increases the global impact of local perturbations and may reduce network controllability,[123,124] making it more susceptible to increased neural noise, which in turn may contribute to the emergence of hallucinations and delusions. Computationally, such architectures may amplify small perturbations across distributed circuits, destabilizing precision weighting and salience attribution processes.[125] This may help explain how weak internally generated sensory activity can propagate through highly integrated networks and ultimately be experienced as externally real, as proposed for auditory hallucinations. Second, psychosis preferentially disrupts hub regions, particularly in striatal and hippocampal circuits that contribute to learning, salience attribution, and the regulation of larce-scale network dynamics across disorders, including AD,[126] BPD,[127] bipolar disorder,[128] PD,[129] and schizophrenia.[130] These hubs occupy positions of high centrality and are therefore critical for maintaining dynamic stability across cortical-subcortical loops—a principle that makes their dysfunction particularly consequential for psychotic symptoms.

At the FC level, psychosis has been linked to disruptions in dynamic flexibility in network configuration. In healthy brains, FC dynamically adjusts to internal and external demands across multiple timescales, maintaining near-critical dynamics that optimize information transfer and flexible transitions between integrated and segregated states.[131–135] Deviations from this time-variant balance have been observed across various disorders featuring psychotic symptoms, including schizophrenia,[136–138] bipolar disorder,[139] PD,[140] AD,[141] and delirium,[142] thereby extending the previously described mechanistic notion of unstable precision weighting into the temporal domain of large-scale brain dynamics across diagnostic categories.

While direct evidence linking these alterations to specific psychotic symptoms in patient samples remains limited, dysregulated segregation-integration dynamics have directly linked hallucinations in PD[140,143] and Lewy body dementia.[144] Mechanistically, excessive integration may reduce the functional separation between perceptual, associative, and self-referential circuits, amplifying the propagation of internally generated activity across large-scale networks, resulting in associations, hallucinations, and delusions. Conversely, excessive segregation may impair the flexible integration of distributed information, fragmenting cognitive processing and reducing contextual constraint on perception and belief formation. For instance, aberrant interactions between auditory, salience, and DMNs have been proposed to diminish the distinction between internally generated speech and externally derived auditory input,[145]

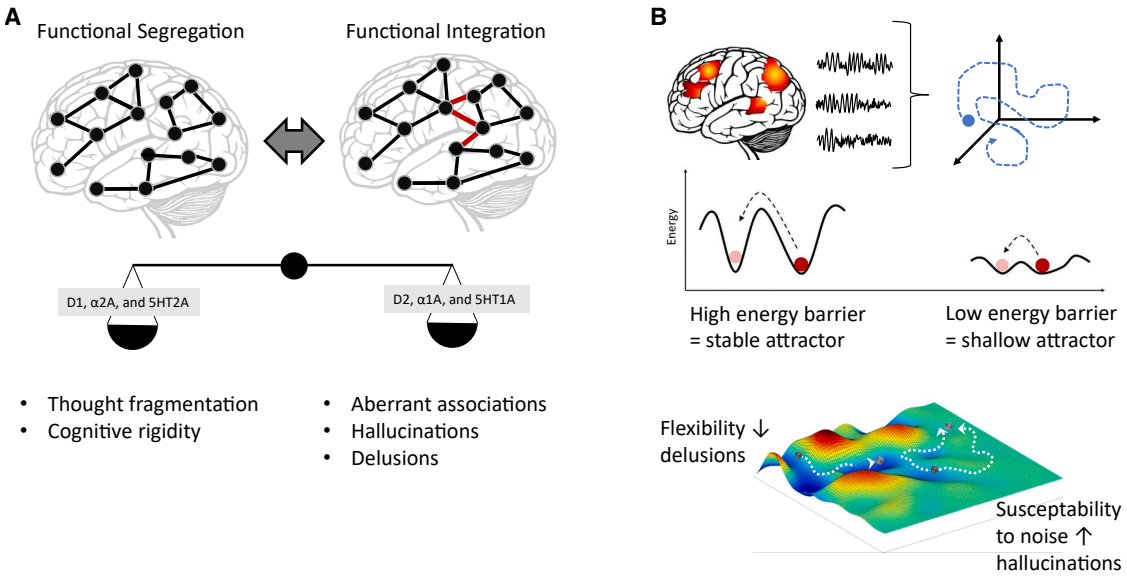


Figure 3. Network neuroscience and dynamical systems approach to psychosis

(A) Functional network integration and segregation as circuit mechanisms underlying psychotic symptoms.

(B) Dynamical system models of brain dysfunction integrate diverse levels of observations into a global explanatory framework of psychotic symptoms.

providing a plausible systems-level mechanism for auditory verbal hallucinations.

From a mechanistic point of view, the dynamic balance of brain-wide integration and segregation can be understood as reflecting network stability and gain control, processes that are modulated by interacting neuromodulatory systems, including dopamine, acetylcholine, and serotonin (Figure 3),[146–148] and thereby implement the gain-control framework introduced earlier at the system level. Specifically, dopamine and noradrenaline modulate the stability of network integration and segregation by influencing signal-to-noise ratios and gain control across cortical and striatal hubs,[146,149,150] while acetylcholine and serotonin fine-tune the flexibility and responsiveness of local circuits,[151,152] collectively shaping the brain's capacity to balance specialized processing with global integration. Accordingly, neuromodulatory dysfunction may shift large-scale brain systems away from critical operating regimes into unstable dynamical states potentially characterized by aberrant salience attribution and perceptual inference.[153]

Consistent with this framework, E/I imbalance in prefrontal and hippocampal l areas has been shown to disrupt the integration of large-scale brain networks important for cognition and attention through several mechanisms that impair visual and auditory processing.[148,154–156] By altering oscillatory synchrony, signal-to-noise ratios, and neuronal gain regulation within local microcircuits, such E/I abnormalities may impair the coordinated switching between integrated and segregated network states required for adaptive perception and cognition.[157] Notably, many substances associated with PEs—some of which are being explored for their therapeutic potential—have been shown to induce long-lasting reconfigurations of the segregation/integration balance in brain networks. This includes ketamine[158–160] as well as, more recently, LSD and psilocybin,[161,162] further emphasizing the role of network-level alterations in psychotic states. Importantly, these pharmacologically induced states provide experimentally tractable models for studying how disturbances in neural gain and large-scale network reconfiguration contribute to hallucination-like percepts and altered belief formation.[163] Together, these findings suggest that psychotic symptoms may reflect state transitions within an unstable dynamic regime, where neuromodulatory disruptions (e.g., dopaminergic, cholinergic, and serotonergic) shift the system away from criticality, producing the perceptual and cognitive disturbances characteristic of psychosis.

Dynamical systems models of psychotic symptoms

While network models are powerful explanatory frameworks for relating connectivity changes to computational processes and system behaviors, dynamical systems theory (DST) models provide a complementary and more mechanistic account of how temporal instability and nonlinear transitions in brain activity, shaped by diverse circuit dysfunctions, may contribute to psychotic symptoms across disorders.[164] Dynamical system approaches describe the temporal evolution of brain activity over time, describing trajectories through multidimensional state spaces defined by neural population activity.[125,165] Within this space, attractors represent stable configurations of neural activity, while bifurcation points mark transitions where small perturbations—such as neuromodulatory changes—can produce abrupt shifts in cognitive or perceptual states.[166]

Applied to psychosis, this framework suggests that delusions and hallucinations may reflect reduced stability or maladaptive transition between cognitive and perceptual attractor states.[164] Flattened or shallow attractor basins render neural trajectories more sensitive to noise and less constrained by prior contextual information. Consequently, transient fluctuations in sensory or

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mnemonic representations may be misinterpreted as externally generated experiences—potentially manifesting as hallucinations or delusional beliefs.[167] In this view, psychotic symptoms emerge not from isolated dysfunction within a single brain region but from a system-level alteration in the stability landscape governing large-scale brain dynamics—providing a testable hypothesis that can be evaluated using empirical measures such as reduced dwell time in stable states, increased transition entropy, or altered recurrence patterns in neural time series.[41,168]

To date, studies linking features of brain dynamics using tools from DST to specific behavior or clinical phenomena remain surprisingly limited, especially in the context of psychotic symptoms. Initial, though partially indirect, evidence that psychotic symptoms are indeed associated with altered attractors stems from studies contrasting PD patients with and without hallucinations[140] and studies on altered brain dynamics linked to dopamine signaling.[169] Nonetheless, recent years have seen substantial growth in evidence supporting the theoretical foundations of how molecular, neuromodulatory, and spatial features associated with psychotic symptoms shape the underlying global brain dynamics.

A key advantage of DST is that it provides a mechanistic bridge between molecular neuromodulation, local network disruptions, and macroscopic circuit behavior. Neuromodulatory systems such as serotonin, dopamine, noradrenaline, and acetylcholine actively shape the brain's attractor landscape by modulating the stability of attractor basins, thereby influencing overall network dynamics.[118,170] These neuromodulatory effects can be conceptualized as forms of dynamic gain control as outlined above that regulate the precision and stability of neural representations across large-scale brain systems. Broadly, their effects can be categorized by their effect on stability: D2, α1A, and 5HT1A receptor activation flatten attractor basins, enhancing flexibility but also increasing vulnerability to disorganized transitions, whereas D1, α2A, M1, and 5HT2A receptor activation deepen attractor basing, promoting persistent cognitive states.[167,170,171] For instance, an imbalance between D1 and D2 receptor activity in the PFC alters NMDA-mediated signaling, thereby reducing the signal-to-noise ratio of information processing, promoting neural instability[149,172] in line with the dual-state theory.[171] Such reductions in signal-to-noise ratio may correspond to aberrant precision assignment, whereby internally generated representations become excessively amplified or insufficiently constrained by sensory evidence.[173] This would manifest as flattened attractor landscapes and unstable transitions between cognitive states.[174] Similarly, cholinergic projections from the basal nucleus of Meynert are thought to deepen attractor basins, stabilizing cognitive states, whereas noradrenergic bursts from the locus coeruleus flatten them, increasing flexibility but also the susceptibility to disorganized thought patterns.[104]

This attractor-based perspective thus provides biophysically interpretable models of psychotic symptoms that effectively integrate local cytoarchitectural and global neurotransmitter features, in which hallucinations correspond to spontaneous transitions into aberrant perceptual attractors, and delusions to maladaptive stabilization within misattributed belief states. For example, excessive precision or gain assigned to internally generated representations may stabilize aberrant perceptual attractors, rendering them resistant to contradictory sensory input,[32] thereby contributing to persistent hallucinations or fixed delusional beliefs.[175] Crucially, these hypotheses are empirically testable: one can predict that patients with psychotic symptoms will show increased metastability,[176] reduced recurrence stability,[175] and aberrant critical slowing in neural time-series analyses—parameters that can be estimated using EEG, fMRI, or whole-brain computational modeling. Importantly, from a transdiagnostic perspective, the diverse disruptions observed in CSTC circuits across disorders may give rise to partially overlapping patterns of large-scale brain dynamics, despite differences in their underlying molecular and circuit-level origins. Establishing the extent and conditions under which such dynamic similarities occur remains an open empirical question. If supported, such findings could provide a framework for relating distinct biological perturbations to shared computational and dynamical features that bridge molecular, circuit, and systems neuroscience, with significant implications for understanding and treating psychosis.

Methodologically, the field recently has advanced along two main methodological lines: equation-based modeling[125,166] and data-driven time series reconstruction.[177–179] Equation-based models derive differential equations from biophysical principles, offering mechanistic interpretability but requiring strong a priori assumptions. Data-driven approaches extract dynamics directly from experimental (e.g., neuroimaging) data, capturing individual variability but risking overfitting. Combining both approaches enables researchers to infer the latent structure of brain dynamics and test whether specific perturbations (e.g., pharmacological, sensory, or cognitive) can move the system across bifurcation boundaries—thereby reproducing transient psychotic phenomena in silico. This is particularly valuable given that most neuroimaging data in psychosis are acquired outside of acute symptom states; simulated transitions across bifurcation points thus provide a mechanistic means to model the onset and resolution of PEs under controlled conditions.

In summary, dynamical systems models not only provide mechanistically grounded explanations for psychotic symptoms but also a quantitative, falsifiable framework for understanding psychosis as a disorder of brain-state stability and dysregulating gain control (Table 2). Thereby, the framework integrates cellular, synaptic, and neuromodulatory mechanisms with large-scale network dynamics, explaining how local receptor-level perturbations or dysconnections can propagate into macroscopic instabilities in perception and cognition. This approach thus offers a principled bridge between molecular neurobiology and clinical phenomenology, allowing for experimentally tractable predictions about when and how psychotic states emerge and resolve.

EMERGING APPROACHES TO ELUCIDATING THE MECHANISMS OF PSYCHOSIS

Precision neuroimaging of circuit dysfunction

Recent advances in multi-echo and ultra-high-field magnetic resonance imaging (MRI) are beginning to close the gap between theoretical circuit models and empirically measurable brain structure and function. Conventional field-strength

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Table 2. Testable predictions and competing explanations

#	Prediction	Competing explanation	Evidence against framework
1	Circuit-level measures of gain regulation and precision weighting should explain variance in psychotic symptom dimensions beyond regional abnormalities alone.	Psychotic symptoms primarily reflect focal or region-specific pathology, with circuit-level abnormalities largely secondary or epiphenomenal.	Regional measures consistently outperform circuit- and network-level measures in explaining symptom severity or phenomenology across independent samples.
2	Alterations in large-scale integration-segregation dynamics should track within-person fluctuations in psychotic symptoms across time and clinical states.	Psychotic symptoms primarily reflect relatively stable structural or trait-like abnormalities, with network dynamics playing a limited role in symptom expression.	Large-scale network dynamics remain stable despite substantial within-person fluctuations in psychotic symptoms, or dynamic measures fail to predict symptom changes longitudinally.
3	Individualized measures of circuit and network dysfunction should improve prediction of symptom dimensions, clinical trajectories, or treatment response beyond diagnosis alone.	Diagnostic categories capture the biologically relevant variation sufficiently well for prediction, making individualized circuit-level measures provide limited additional information.	Individualized circuit/network measures fail to improve prediction over conventional diagnostic and clinical variables across independent datasets or prospective studies.
4	Different molecular or circuit-level perturbations should be able to produce similar alterations in gain regulation, precision weighting, or network dynamics, while the same upstream perturbation may produce different psychotic phenotypes depending on circuit context.	A relatively direct mapping exists between specific biological abnormalities and specific psychotic symptoms, with limited dependence on computational or network context.	Specific psychotic phenotypes consistently map onto single upstream molecular or circuit abnormalities, or identical upstream perturbations reliably produce the same symptom phenotype across individuals and disorders.

neuroimaging has provided important insight into large-scale connectivity changes in psychosis, but its limited spatial and temporal resolution constrain interpretation at the level of specific cortical layers or subcortical nuclei. These constraints are particularly relevant for testing hypotheses centered on disturbances in CSTC loops, where psychosis-related dysfunction is thought to emerge from altered top-down and bottom-up signaling dynamics and aberrant gain regulation that can influence striatal dopamine release, thereby altering salience attribution and belief formation.

High-field imaging (>7T), especially when combined with innovations in pulse sequences and contrast mechanisms, has enabled researchers to map depth-dependent cortical and subcortical activity at submillimeter precision.[180,181] This enables the differentiation of laminar input-output patterns[182]—such as feedforward thalamocortical drive and feedback modulation from prefrontal and neuromodulatory systems—thereby allowing direct tests of predictive processing models that posit abnormal precision weighting between sensory inputs and higher-order priors. For example, layer-specific abnormalities in feedback signaling from PFC to sensory regions could indicate excessive top-down gain assignment to internally generated representations, a proposed mechanism underlying hallucinations and delusion formation. Similarly, altered thalamic gating within CSTC loops or prefrontal instability contributing to the disrupted loop dynamics could be tested as system-level mechanisms for aberrant salience attribution.[166] These approaches therefore allow direct probing of how disorder-specific alterations in laminar signaling, thalamic gating, and cortical-subcortical interactions interact with striatal dopamine signaling and broader network dynamics. This may help determine whether dopamine-dependent alterations in salience attribution constitute one component of a distributed gain-control architecture through which distinct biological perturbations can contribute to the emergence of psychotic symptoms across disorders.

Beyond connectomics, high-field magnetic resonance (MR) spectroscopy allows the simultaneous quantification of multiple neurotransmitter systems such as glutamate[183,184] and GABA,[183,185] thereby providing in vivo proxies of local E/I balance in key brain regions central to psychosis pathophysiology and neural gain regulation. Importantly, these measures can be directly incorporated into computational network and dynamical systems models to test how local alterations in excitation-inhibition balance reshape attractor stability, signal-to-noise ratios, and large-scale network transitions.[186] Together, these developments allow the field to move toward mechanistic testing by allowing researchers to examine how laminar-specific E/I imbalances, dopamine signaling, and CSTC circuit dynamics interact and whether their perturbation is reflected in large-scale altered integration-segregation dynamics or transitions across unstable attractor states.

As these techniques continue to evolve, they could provide the empirical backbone or individualized, circuit-informed models of psychosis—bridging neurotransmitter-level dysregulation, circuit instability, and clinical symptomatology.[187,188] Crucially, rather than serving as broad discovery tools, ultra-high-field MRI and dynamical modeling should be strategically deployed to test specific mechanistic hypotheses derived from our CSTC and gain control and network-based frameworks, offering a path toward falsifiable and precision-oriented models of psychosis.

ANNs for mechanistic modeling of psychosis

Since their conception, brain research has been a key inspiration for artificial neural networks (ANNs).[189] Early models mimicked binary neuronal firing in an "all-or-nothing" fashion, while

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contemporary architectures, including hierarchical, recurrent, deep, and spiking neural networks, enabled biologically inspired simulations of neural computations. Beyond advanced predictive analytics, ANNs now offer a framework to interrogate mechanisms of neural function and dysfunction, including psychotic symptoms and the computational processes underlying their emergence.

A promising framework in this regard is "neuroconnectionism," which proposes the use of ANNs to test neuroscientific hypotheses by establishing mappings between artificial and biological neural architectures.[190] Within this paradigm, trained ANN models are evaluated based on their ability to reproduce empirical data, analyzed for computational properties that give rise to task performance, and subsequently interpreted within a neurobiological context. This approach has yielded important insights into a range of cognitive domains, including vision,[191,192] audition,[193] attention,[194] learning,[195] and memory.[196] By systematically varying model architectures, objective functions, and learning algorithms, researchers have developed computational frameworks that permit causal interrogation of large-scale neural processes underlying complex behaviors in ecologically valid settings that are otherwise difficult to manipulate experimentally.[197]

Applications in psychiatric disorders remain relatively limited.[164,198] In psychosis, ANN models have been applied in relatively constrained experiments and are comparably simpler in their architecture.[172,199] Nevertheless, such models can serve as an essential bridge between theoretical constructs and empirical data—by testing how aberrant precision weighting, recurrent instability, or altered salience assignment can give rise to computational signatures associated with disorganized speech, hallucinations, or delusional belief formation. In particular, by mimicking or reproducing human behavior in silico, these models offer a pathway to causally interrogate the emergence of large-scale, circuit-level phenomena observed in patients with psychotic symptoms. Moreover, they allow researchers to link behavioral disruptions to candidate underlying mechanisms—such as CSTC loop dysfunction, dopaminergic dysregulation, and E/I imbalance—and to probe how different combinations of these perturbations may reshape neural attractor landscapes, altering cognitive stability and potentially giving rise to computational features associated with psychotic phenomena.[200]

Looking forward, integration of ANN models trained on complex behavioral data from individuals with psychosis holds the potential to provide mechanistic insights into transdiagnostic computational and system-level processes associated with hallucinations, delusions, and disorganized thought.[201–203] Particularly promising are recurrent and generative architectures capable of modeling predictive processing, hierarchical inference, and dynamical state transitions.[197,204] Models incorporating domain-specific knowledge and sensory grounding may allow data-driven exploration of circuit-level dysfunction without the need for explicitly human-interpretable parameters.[198,205] Such approaches may ultimately help identify the computational motifs through which local circuit abnormalities scale into large-scale network instability and clinically manifest psychotic symptoms.[206] A key challenge remains in balancing biological plausibility with model interpretability and computational feasibility,[198] but these approaches offer a promising route toward mechanistically informed, transdiagnostic models of psychotic symptoms that accommodate heterogeneous biological origins.

Toward a developmental and transdiagnostic framework

In addition to the technological and analytical advances previously addressed, a fundamental conceptual shift in how we approach the study of psychotic symptoms is required to substantially enhance our understanding of the circuit mechanisms underlying them. First, the transdiagnostic perspective put forward in this review is essential for shifting the focus to the diverse pathways leading to psychotic symptoms beyond SSD.[10] As a necessary initial step, researchers must improve the precision of their use of the term psychosis and clarify the concept, despite the challenges posed by its transient and heterogeneous nature. This includes focusing on the underlying cognitive and perceptual processes and neurobiologically defined circuit mechanisms—such as belief updating,[207] jumping to conclusion,[208] aberrant salience attribution, and modulation of subcortical dopamine release[38] or altered gain control and precision-weighting in CSTC loops—rather than relying on (retrospective) summary measures of symptom clusters. From a systems-neuroscience perspective, this implies conceptualizing psychotic symptoms not as static diagnostic entities, but as dynamic failures of context-sensitive inference, in which disturbances in gain control alter the balance between internally generated predictions and externally driven sensory evidence with downstream effects on system dynamics and network abnormalities. In line with this, expanding mechanistic research to encompass at-risk populations and non-clinical groups, including the "hearing voices" community[209] or induced hallucinations/delusions,[69] will help tackle the often transient phenomena of psychotic symptoms, capturing the full spectrum of PEs and their underlying neural substrates in the absence of confounding factors common in clinical populations.

Second, following this transdiagnostic approach, it is essential to model psychotic symptoms across the lifespan using normative modeling and longitudinal study designs. This approach enables the identification of critical developmental and degenerative windows of vulnerability and resilience and clarifies how risk factors—such as adverse childhood experiences, substance use, stress, sleep deprivation,[210] or hearing loss[211]—as well as resilience factors such as social contact[212] or coping styles[20] shape brain circuit development and functional network dynamics. Importantly, many of these risk factors may affect neuromodulation and gain control through partially distinct mechanisms, potentially biasing large-scale brain dynamics toward unstable attractor states and maladaptive belief updating. Developmental alterations in E/I balance,[213] dopaminergic signaling, or thalamocortical gating[214] may therefore constitute distinct biological pathways that influence related computational processes involved in vulnerability to psychotic symptoms.[77] Elucidating these dynamic interactions will not only advance the understanding of the timing and mechanisms underlying the emergence of specific psychotic symptoms but can potentially inform the development of targeted preventive and interventional strategies.[215,216]

Third, within this transdiagnostic framework, multi-omics approaches in large datasets that integrate genetic, epigenetic, molecular, and stem cell data become essential to identify shared and disorder-specific biological pathways underlying psychotic symptoms.[217,218] Mapping how they relate to both shared and disorder-specific patterns of neural circuit dysfunction remains challenging, but dynamical system approaches[219] and new transformer models hold promise to close this gap soon.[220] Such integrative approaches may be particularly valuable for explaining how molecular and synaptic alterations propagate across scales to reshape mesoscale circuit dynamics[221] and ultimately to alter large-scale gain regulation and attractor dynamics associated with psychotic symptoms. Furthermore, leveraging stem cell models alongside multi-omics data can allow researchers to directly experimentally validate these candidate mechanisms and identify novel therapeutic compounds through high-throughput screening that can be ultimately translated back to humans.[222]

In summary, adopting a transdiagnostic perspective requires a more precise and mechanistic definition of psychotic symptoms, which in turn necessitates studying symptom trajectories and associated risk factors across the lifespan in diverse populations,[223] as well as incorporating multi-omics approaches to dissect the shared and distinct biological pathways underlying psychotic symptoms. Integrating these approaches with computational models of gain control, predictive processing, and dynamical brain-state transitions may ultimately provide a mechanistic framework linking molecular dysregulation, circuit instability, and subjective psychopathology across diagnostic categories. Such a framework could enable biologically grounded and individually tailored models of psychosis, with important implications for early detection, prevention, and precision therapeutics.

CONCLUSIONS AND FUTURE DIRECTIONS

In conclusion, this review summarized evidence across psychiatric, neurological, and neurobiological research on psychotic symptoms, calling for a shift from traditional, diagnosis-related models to a transdiagnostic framework that conceptualizes psychotic symptoms as dimensional phenomena emerging across disorders. This perspective moves beyond descriptive symptom categories and isolated mechanisms by linking specific psychotic phenomena—including hallucinations, delusions, and disorganized thought—to a mechanistic framework centered on disturbances in neural gain regulation, precision weighting, and large-scale CSTC dynamics. Rather than arising from isolated neurotransmitter abnormalities alone, psychotic symptoms can be understood as emergent consequences of interactions among local circuit dysfunction, neuromodulatory imbalance, and large-scale network instability. Within this framework, network neuroscience and DST provide increasingly mechanistically interpretable models capable of explaining how disruptions in E/I balance, dopaminergic and cholinergic gain control, and altered integration-segregation dynamics destabilize perceptual and cognitive attractor states across disorders. These models generate empirically testable predictions regarding altered brain-state stability, metastability, transition dynamics, and aberrant salience processing that can be quantified using multimodal neuroimaging and computational approaches.

Recent advances in ultra-high-field MRI, computational modeling, and biologically informed AI/ANN modeling further enable direct interrogation of laminar-specific input-output signaling, attractor dynamics, and large-scale network integration-segregation stability, linking neural circuit disruptions to specific psychotic symptoms. A developmental perspective incorporating biological, contextual, and social risk and resilience factors further enriches our understanding of different trajectories of brain circuitry leading to particular psychotic symptoms in different disorders. Critically, future progress will depend on moving beyond broad clinical constructs of psychosis toward more precise characterization of individual symptom dimensions and their underlying computational and neurobiological mechanism. Collectively, these advances provide a foundation for falsifiable, mechanistically grounded, and transdiagnostic models of psychotic symptoms that bridge molecular, circuit, systems, and behavioral levels of analysis. Such an approach may ultimately enable biologically informed stratification, improved prediction of symptom trajectories, and targeted interventions tailored to specific circuit and computational dysfunctions across disorders.

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